Psychology and Disease: Unveiling Emerging Perspectives on Their Interplay

Carlos Gómez Martínez

UNIVERSITAT ROVIRA i VIRGILI

Psychology and Disease:

Unveiling Emerging Perspectives on Their Interplay

Carlos Gómez Martínez

Doctoral Thesis 2024

UNIVERSITAT ROVIRA I VIRGILI
Psychology and Disease: Unveiling Emerging Perspectives on Their Interplay
Carlos Gómez Martínez

Carlos Gómez Martínez

Psychology and Disease:

Unveiling Emerging Perspectives on Their Interplay

DOCTORAL THESIS

Supervised by Prof. Jordi Salas Salvadó,

Dr. Nancy Babio and Dr. Jordi Júlvez

Human Nutrition Unit

Department of Biochemistry and Biotechnology

Rovira i Virgili University

Reus, Tarragona

2024

UNIVERSITAT ROVIRA I VIRGILI
Psychology and Disease: Unveiling Emerging Perspectives on Their Interplay
Carlos Gómez Martínez

UNIVERSITAT ROVIRA I VIRGILI

Jordi Salas Salvadó, Full Professor of Nutrition and Food Science at the Department of Biochemistry and Biotechnology of Rovira i Virgili University.

Nancy Elvira Babio Sánchez, Associate Professor at the Department of Biochemistry and Biotechnology of Rovira i Virgili University.

Jordi Júlvez, Researcher and Group leader of NeuroEpia at the Insitut d'Investigació Sanitaria Pere i Virgili.

I STATE that the present study entitled "**Psychology and Disease: Unveiling Emerging Perspectives on Their Interplay**", presented by Mr. Carlos Gómez Martínez for the award of the Degree of Doctor, has been carried out under my supervision at the Department of Biochemistry and Biotechnology of this university and it is currently up for an international distinction.

Reus, 17 September 2024

Prof. Jordi Salas-Salvado Dr. Nancy Babio Dr. Jordi Júlvez

UNIVERSITAT ROVIRA I VIRGILI
Psychology and Disease: Unveiling Emerging Perspectives on Their Interplay
Carlos Gómez Martínez

TABLE OF CONTENTS

ACKNOWLEDGMENTS

UNIVERSITAT ROVIRA I VIRGILI
Psychology and Disease: Unveiling Emerging Perspectives on Their Interplay
Carlos Gómez Martínez

AGRADECIMIENTOS

Las etapas de la vida parecen ser un momento estático e inamovible dentro de un ciclo vital cambiante y finito. Pero si te paras a pensar, incluso en esta supuesta etapa de vida estática, transcurres por fases, altibajos. Por tanto, una etapa de tu vida es equiparable a tu ciclo vital, también es dinámico. No obstante, fechas y eventos concretos determinan una etapa, y hoy, yo, cierro una etapa de vida cambiante y finita de mi ciclo vital. Un viaje que me ha llegado hasta la redacción de estas palabras.

La motivación para realizar un doctorado se basa en la gratitud y la reciprocidad que siento que debo devolver al mundo. En una sociedad líquida, tender una mano real y no una sombra, permanecer sin esperar. Mi medio, la palabra; mi vehículo, la docencia. Como estudiante me hicieron ver la posibilidad de no observar reflejos y no solo vivir instintivamente. Ojalá pueda ser una figura que proyecte luz hacía el conocimiento y anhelo por nunca dejar de lado a su ser más interior. Mi camino es el símil de una semilla germinada, que se va desarrollando, hasta llegar el día que es una manzana, y sin esperarlo, ésta cae, y de golpe, te abre los ojos al conocimiento y te estimula a transmitir la pasión por aprender: “eureka”.

A los 18 años de edad, partí de Barcelona a Girona, y así empecé mi Grado en Psicología. Había una vida por florecer dentro de mí. Girona plantó la semilla. Madrid cultivó el afán, que yo adquirí, por querer ver la luz en vez del reflejo del conocimiento. México me regó con vivencias únicas. Y Girona volvió a mi vida para recolectar los frutos de mi etapa del Grado. Palma de Mallorca sembró con el máster mi interés por cómo la evolución filogenética humana permite no solo tener consciencia, sino que ésta tenga una identidad desvinculada del instante presente. Posteriormente, Barcelona intermedió a mi actualidad, y me hizo descubrir el autoamor compartido. Y este viaje, el cual zarpó hace ya una década, está por finalizar una etapa que deja paso a unos puntos suspensivos por descubrir…

Me gustaría mencionar a las personas que son más importantes en mi vida y han formado parte en el transcurso de mi doctorado. Estoy convencido de que habrá muchas personas que no nombraré, pero no por ello dejáis de formar parte de este camino. Gracias a todas vosotras.

Sergio, ets increïble. Tinc tant per aprendre de tu, que escrivint aquestes paraules me'n adono de lo tossut que soc per no escoltar-te més. Intento ser el millor germà amb les habilitats que tinc, però el que sí que et puc assegurar és que ets la persona per la qual més he intentat progressar amb la finalitat de poder ser un exemple per a tu. Espero que la dedicació que he tingut en la meva trajectòria acadèmica pugui ajudar-te a veure que pas a pas i com formiguetes, acaba arribant el dia en què els teus esforços es veuen recompensats. També vull que sàpigues que, passi el que passi, sempre estaré orgullós de tu i confiaré en el teu camí. Sé que a vegades puc ser exigent, arribant a centrar-me massa en els aspectes que encara queden per millorar. Tot i això, avui vull remarcar alguns dels moments més feliços de la meva vida amb tu. Encara que per a tu sigui impossible recordar-ho, un dia, tornant de l'institut, la mama em va dir que estava embarassada i que anava a tenir un germà. Recordo que contenir les llàgrimes de l'emoció no era possible, i que des d'aquest dia hi ha una il·lusió en la meva vida que sempre serà present. Aquesta il·lusió ets tu, Sergio. També recordo que, quan encara eres un nadó, jo t'agafava en braços i me n'anava a l'habitació per intentar que t'adormissis. La major part de les vegades, després de gairebé una hora, jo anava content a dir-li a la mama que ja t'havies adormit, i al cap de 5 segons et posaves a plorar. La veritat és que sovint no t'adormies, però aquests moments amb tu en braços em van donar un amor que avui dia encara porto amb mi. Quan ja vas ser una miqueta més gran, recordo que molts dies t'anava a buscar al Pau Romeva. I nosaltres, poc temeraris, baixàvem amb skate, tu de nou estant damunt dels meus braços. També recordo els partits de futbol que fèiem al parc de sota casa, o ja quan et vas fer més gran a les pistes de bàsquet. No vull oblidar totes les partides que vam fer amb les Nerfs, ni l'èpic modo carrera del FIFA que vam fer amb el Milan, amb els gols de Çalhanoglu des del mig del camp i les excursions de Romagnoli. Desafortunadament, quan vaig complir la majoria d'edat, vaig haver de marxar de Barcelona, comportant un dels aspectes vitals que més m'ha costat portar aquests anys. Estar separats. No obstant això, sempre has vingut a visitar-me allà on estigués, ja sigui Girona, Madrid, Palma de Mallorca, Reus, o fins i tot a París. Com oblidar també el nostre viatge a Portugal, i del joc de l'amagatall al parc del Senyor de Matosinhos. Com no tenir present el nostre viatge més recent per Andalusia, escoltant dia i nit a Lil Nas X. En fi, Sergio, l'amor incommensurable que sento per tu sempre viurà amb mi. No oblidis mai que ets formidable. Mama, gracias por mostrarme con el ejemplo a ser fuerte, defendiendo tus hijos como una leona defiende a su camada. Quiero que sepas que nunca voy a olvidar nuestros cafecitos. Tampoco todo lo que has hecho por mí, por como cada día de mi vida

has velado por mis necesidades, hasta el punto en el que, aunque tú no pudieras, sacabas fuerzas de donde no las había y me ayudabas igualmente, y sólo por el amor que sientes hacia tus hijos. Gracias por querernos y cuidarnos. Papa, gracias por brindarme apoyo en momentos en los que lo he necesitado, por ayudarme con todas las mudanzas que me han permitido ir de un sitio a otro y avanzar con mi carrera académica. Sin ninguna duda, tus acciones han permitido que llegue el día en el que vaya a ser doctor, y este hito en mi vida también es gracias a ti. Sé que deseas lo mejor para mí, y lo valoro mucho. Ojalá que esta tesis no solo sea un cambio en mi vida para que ésta cada vez sea mejor, sino también para la tuya. Y Balto, sé que nunca vas a leer esto, pero en tan solo poco más de un año me has cambiado la vida. En mi camino hacía ser mejor persona, trato de aprender a querer y cuidar a mis personas cercanas como tú haces conmigo. Siempre vas a estar presente en mí.

Jordi y Nancy, dejando de lado el ámbito laboral, desde el día que llegué, sentí que me acogisteis como uno más de los vuestros. Siento que, por algún motivo, encontrasteis algo en mí que, hasta incluso a día de hoy, aún me cuesta ver. En uno de los momentos más inestables de mi vida, me brindasteis un apoyo que nunca olvidaré. Sentí que lo único que os importó de verdad fue mi bienestar emocional. Mis más sinceras gracias por mostrarme ese cariño. Jordi, sempre m'ha costat posar valor a la meva persona i el que faig. Sense cap mena de dubte, tu m'has ajudat a creure'm més competent, ja que mai has posat en qüestió això. A causa de l'exigència d'aquest grup amb la recerca, em va costar una mica arrancar amb la publicació dels meus primers articles. Mai oblidaré els mals de cap que et vaig generar amb el primer paper. Jo, Carlos, un estudiant predoctoral de primer any canviant-li com havia de presentar-se la discussió a un dels millors investigadors no només a escala nacional, sinó internacional. No obstant això, ara aplico aquesta exigència en les meves preguntes de recerca i amb la forma de resoldre-les estadísticament. Em sento agraït d'haver contribuït en el PREDIMED-Plus, de les oportunitats que he pogut gaudir gràcies a tu amb el projecte PRIME, i de formar part del teu èxit. Gràcies Jordi. Nancy, primero me gustaría remarcar un aspecto de ti que es envidiable. Hacerte valer como investigadora, además en Cataluña viniendo de Argentina, y acabar siendo pionera en gran multitud de cosas, es difícil y a la vez admirable. Nunca rendirse por las cosas que crees que tienen valor, y apostar desde hace tiempo por aspectos que hoy en día son valorados como imprescindibles en el mundo de la investigación, te hacen estar en el lugar que te has ganado. Gracias por enseñarme que la dedicación da sus frutos, tanto con

tu ejemplo como con tus actos. Además, sabes que contigo he sido papá. Hemos creado un ser viviente, que ahora ya camina sin su padre. Estoy convencido de que, bajo tu supervisión, llegará igual de lejos que tú. Sus primeros pasos ya apuntan bien alto. En el ámbito personal, pocas son las cosas que me han pasado que tú ya no sepas. Gracias por darme consejo, y brindarme oportunidades siempre orientadas a lo que estoy buscando. Me has escuchado, y he sentido una reciprocidad que siempre tendré presente. A ambos, Nancy y Jordi, espero seguir colaborando en el futuro, ya que todo lo que me habéis enseñado es lo que me hace sentir con fuerzas para valorarme como un investigador más que competente para aplicar proyectos que lleguen a tener un impacto real en la sociedad. Ojalá en el futuro poder tener estudiantes predoctorales a mi cargo y ser capaz de concederles tantas experiencias tan valuables en su doctorado como las que me habéis facilitado a mí. Por esto y más, gracias a ambos. Jordi Júlvez, gràcies per aportar la teva experiència de l'àmbit de la psicologia en els nostres treballs. Les reunions que vam tenir al començament de la meva tesis han sigut enriquidores. Aquesta ajuda ha sigut imprescindible per la consecució de la meva tesis.

Sandrine, you are the most rigorous and inspiring supervisor I have ever had. I have learned from your high standards in research. I am grateful for you deleting most of my written text in our manuscripts because I have understood the importance of focusing on the core of the matter to make things easier to understand for readers. In addition, I not only felt your involvement in my research work, but also in my personal well-being during and after my internship. My sincere thanks. Pauline, my fruitful collaboration with the EREN was possible thanks to your help. You worked with me hand in hand, even while pursuing your PhD. I am very happy for the academic success we have achieved together. Thank you.

María, eres maravillosa. Admiro tu felicidad y lo buena persona que eres con todo el mundo. Te haces querer con tu sonrisa. Gracias por aceptarme en tu vida como una persona muy importante que forma parte de la misma. Los años vividos contigo ya siempre van a estar impregnados en mí. Me siento muy afortunado de haber coincidido contigo en el doctorado, y de que incluso ahora seas una compañera de vida de mí y Balto. Los dos agradecemos tu alegría en nuestras vidas.

Sara y Laura, gracias por las cenas, los juegos, y por ser las titas de Balto. Representáis en mí un eje fundamental de mi vida en Reus. Sin vosotras, romper la monotonía que

puede conllevar el trabajo sería imposible. Deseo que ambos nos llevemos para el resto de nuestras vidas una amistad que permita compartir todos los buenos momentos venideros que están por acontecer.

Sangeetha, too many feelings to describe in just a few words. You are the light guiding who I will be in the future, a kind-hearted person who, with each word, revealed her marvelous soul. Thank you for loving me the way you do. Always remember that you will be with me in my academic and personal life. All my best wishes to you.

Alberto, gracias por acompañar mis meses en París. Sentí un hermano en muy poco tiempo. Los dos hemos compartido experiencias que nos hacen entendernos sin tener que explicarnos. Tu simpleza y altruismo ante la vida me hacen querer tenerte a mi lado. Gracias por hacer de París una estancia inolvidable. Hernando, justo pensando ahora en ti, me doy cuenta de algo que en verdad es obvio y que se me había pasado desapercibido por notarlo tan natural. Me haces sentir como en casa. Poder salir del despacho e ir a verte, decir cualquier tontería, y reírnos a carcajada suelta es algo que seguro no voy a poder encontrar en ningún otro lugar. Gracias por compartir mis momentos "esquiceitor" con risas. Héctor, eres único. Defender una postura contra viento y marea, aunque todo el mundo opine diferente, es un aspecto admirable en ti. En poco tiempo, contigo y con los pájaros, he sentido que tengo un grupo de amigos con los que puedo quedar para compartir momentos agradables y distendidos, en los que siento que formo parte de un grupo a los que siempre les va bien estar conmigo. No siempre me ha sido fácil este aspecto, y por eso te doy las gracias a ti y a todos vosotros.

Susana, siempre que lo he necesitado me has escuchado. Tus consejos ante cómo afrontar la vida los he escuchado detenidamente, aunque quizás pueda dar la sensación de que no los interiorizaba. En la vida, a menudo nos complicamos más de la cuenta. La naturalidad y sencillez con la que me aconsejas sobre cómo hacer frente las situaciones es algo que siempre trato de aplicar en mi día a día. Gracias Susana.

Sonia, has sido un apoyo inconmensurable en el momento en que más lo necesité. No te dejaste llevar por mi momento, ni me juzgaste por no saber encontrar el camino. Simplemente me ofrecías quedar y me preguntabas qué tal estaba. Eres una persona con un corazón inmenso, y en el mío siempre vas a estar presente. Admiro tu resiliencia y tu valentía. Gracias infinitas. Santi, gracias por ser las risas de mis noches. Jesús, gracias por estar conmigo en esa etapa de dificultad, por ayudarme a no pensar de más en que los

momentos difíciles son difíciles, y darme tranquilidad en que todo iba a pasar. Y si, sin darme cuenta, esa etapa ya pasó. Mis más profundas gracias a todas las personas que me apoyasteis. Adrián, ya sea para hablar de estadística o de cualquier duda existencial superflua, he sentido una persona dentro del trabajo al que poder acudir y sentirme bien. Gracias.

MP, imposible no acordarme de ti. Eres una persona bellísima, y trabajadora como ninguna. Te deseo lo mejor y una vida repleta de alegrías merecidas. MA, coseta, escribiendo estas palabras me viene a la mente lo divertida que eres y lo que nos haces reír a todos con tu espontaneidad. La noche de pijamas en Croacia me hizo acordar de cuando era pequeño y estaba de campamentos. Gracias por haberme hecho sentir tan bien a tu lado.

Steph, I really enjoyed our time together. You have been so kind to me and to all of us. I am sure that all the good things that are happening in your life are well deserved. Nadine, eres muy divertida y buena persona. Para mí, eres el ejemplo de la mejor jefa que se pueda ser. Nunca tienes una palabra subida de tono con nadie, aunque puedas tener motivos para ello. Además, sabes valorar las cualidades positivas de cada una de las personas. Me siento muy feliz de haber compartido contigo estos años. Jiaqi, otra mujer de la que sigo aprendiendo sobre cómo se debe de afrontar la vida. Me fascina la facilidad con la que sabes resolver cosas complejas, y con la que siempre le pones una sonrisa a la vida. No menos importante, gracias por desvelar el secreto más bien guardado de la ciencia de los z-scores. Eres increíble tal como eres, no permitas que nada ni nadie lo cambie nunca.

Tany, gracias por acompañarme en los primeros pasos de CORALS. Me has demostrado que, con esfuerzo y dedicación, al final las cosas salen hacia adelante. Indira, gracias por ayudarme al incio con la sintaxis de cognición. También, por hacerme parte de tu cumpleaños, lo recuerdo como un día muy emotivo y agradazco haber formado parte. Estefanía e Irene, gracias por los momentos y risas aseguradas en la Unitat y en el camping de este verano, son instantes irrepetibles. Claudia, gracias por siempre alegrar con tu energía el ambiente. Confío en que tu positividad te llevará al sitio que desees. Alessandro y Carles, aunque no lo parezca, sois de los pocos que han estado aquí desde mi inicio, gracias por formar parte de mi camino. Cristina, los paseos que tuvimos al inicio de nuestro doctorado con María fueron geniales, y tu etapa final emotiva. Gracias

por compartirlos conmigo. También quiero mencionar a Nerea. No compartimos tanto tiempo, pero me sentí muy acogido por ti al inicio de mi doctorado. Gracias.

Als meus amics de Girona, Sergi, Cate, Ari, Mauri, Marc, Adrià, Júlia, Xavi, Anna, Ivan, Raül, Rajae, tots formeu part del meu camí. Amb vosaltres he viscut moments únics. Diuen que els anys de la carrera són dels millors, i jo no puc estar més d'acord amb això. Sergi, gràcies per ser el meu company de conversacions profundes, Adrià per obrir les portes d'aquestes, i Marc per tancar-les dient: "Bueno, anem a dinar". Ari, gràcies per acollir-me i fer-me sentir un més en la teva vida. Mai ho oblidaré. Cate i Mauri, impossible recordar la infinitat d'instants aleatoris que vam viure junts. Em quedo amb totes les bones experiències viscudes al nostre pis amb la Roella. Gràcies a cadascun de tots vosaltres per aportar-me un aspecte únic.

A mis amistades de México, Ali, Andrés, Nicolás, Carelí, Chisaki, Alex, Jimmy, Javi, Richard, Ander, Gracia, y Julia, con una mano en el corazón, os aseguro que me sentí profundamente conectado a todos vosotros. Sois muy especiales en mi vida. Sé que lo que vivimos es irrepetible, pero pongo mis mejores deseos en que algún día muchos de nosotros nos podamos reunir de nuevo. Infinitas gracias por formar parte de mí y de todas las aventuras y emociones que compartimos.

Cómo dejar de lado mi convivencia en Palma de Mallorca con Sandra, Germán, y Lucas. ¿Escucháis? “Tantan Tatatantan tatatan”. ¡Hora de Juego de Tronos, infusión, y chocolate! Una convivencia más que agradable la que compartí con vosotros. Gracias. Joao, gracias por las quedadas que tuvimos y por hacerme hablar portugués, aunque ahora ya no sepa decir ni una frase. Mara, gracias por aceptarme como tu hermanito pequeño. También quiero destacar la rigurosidad que aprendí del profesor Marcos Nadal sobre cómo ser crítico con la lectura de artículos científicos. Para mí, aprender todos los conceptos que me brindó el máster fue apasionante. A día de hoy, pensar en cómo a través de la filogénesis del ser humano se puede culminar en nuestra idiosincrasia cognitiva es un hobby.

Francis, me animaste a dar el paso hacia el mundo académico universitario. Y sin darnos cuenta, hoy me encuentro entregándote mi tesis doctoral. Estoy seguro que no olvidaré tu mirada el día que nos veamos y por fin sea doctor. Gracias.

Me siento muy afortunado de haber estado aprendiendo durante todo un curso académico de los profesores rigurosos y excelentes que tuve en la Universidad Autónoma de Madrid. Quiero destacar el papel de la profesora Asunción López Manjón. La asignatura que me impartió cambió mi vida. En gran parte por usted, hoy me encuentro escribiendo los agradecimientos de mi tesis. Ojalá pueda suponer un cambio en la vida de mis estudiantes como lo supuso usted para mí. También quiero darle las gracias por dejarme colaborar e involucrarme en el día a día de vuestro grupo de Psicología Básica liderado por Ignacio Pozo, fue un honor poder asistir a vuestras sesiones. Y hablando de cambios personales y la involucración de uno mismo con su ser, Nela Haedo, usted fue una luz que se cultivó en lo más profundo de mi interior y que siempre me va a acompañar en mi camino. Gracias a usted entendí la relevancia de otras disciplinas de la psicología de corrientes más humanistas. Siempre seguiré andando en el camino que usted me hizo ver. Mis más sinceras gracias Nela.

També estic orgullós del meu pas per la Fundació Mona i del meu TFG amb vosaltres. Sempre estaré molt agraït a en Miquel Llorente i la Maria Padrell per permetre que m'involucrés en el vostre dia a dia, sentir en primera persona el que comporta ser investigador, i, a més a més, recompensar-me amb una autoria. Mai oblidaré que el meu primer article és sobre lateralitat en ximpanzés.

Cristina, gràcies per fer cada una de les nostres 63 hores de docència ser un camí ple d'aprenentatges inoblidables. El que vam fer és una de les experiències més enriquidores que he tingut en la meva vida, i em sento molt afortunat d'haver-les compartit amb tu. Estic convençut que ambdós sempre recordarem aquests primers passos en el nostre camí docent per la passió per donar el nostre màxim en enriquir la vida dels estudiants. Ets un exemple a seguir por tots els docents del món. No deixis que mai ningú et tregui la teva passió innata que tens per millorar el sistema educatiu.

Anna, gràcies per estar sempre al meu costat, encara quan jo no hi podia ser. Sempre tindré en el meu cor que hagis estat amb mi en les bones, i sobretot en les dolentes. M'has demostrat al valor que té una gran amistat com la teva. Manu y Héctor, últimamente no he frecuentado tanto Barcelona y no he podido compartir el tiempo que me hubiera gustado con vosotros. No obstante, tengo muy presente los momentos que hemos compartido y ojalá podamos vernos más a menudo una vez acabe esta etapa. Vuestra visita a Reus, más el viaje con Anna a Múnich en el que compartí mi COVID con

vosotros, el arriesgado plan en la cervecería, y el aprovechar al máximo toda la pizza disponible en el restaurante, siempre formarán parte de mis recuerdos en esta ardua travesía del doctorado.

Rubén, Joan, Gimeno, David, Jorge, Víctor, Laura, gràcies per donar-me moments infinits d'improvisació i rialles. Sense vosaltres no hauria sigut possible distreure'm, gaudir, i sentir que formo part d'una segona família. Els moments amb vosaltres són increïbles. Us portaré amb mi vagi on vagi. Gràcies per acompanyar-me.

También quiero agradecer a todos los trabajadores y participantes de los estudios PREDIMED-Plus, CORALS, y NutriNet-Santé por hacer posible la consecución de este momento tan importante en la carrera de un investigador. A su vez, a todas las entidades financiadoras que han permitido el desarrollo del presente trabajo.

Y para finalizar, gracias a mí mismo por no dejarte perder en un camino que parecía que no estaba hecho para ti.

ABSTRACT, ABBREVIATIONS, LIST OF FIGURES, AND LIST OF TABLES

UNIVERSITAT ROVIRA I VIRGILI
Psychology and Disease: Unveiling Emerging Perspectives on Their Interplay
Carlos Gómez Martínez

ABSTRACT: ENGLISH

Over the past century, increases in life expectancy have been accompanied by a greater prevalence of chronic diseases such as type 2 diabetes and cardiovascular disease, significant cognitive impairments reflected in an increase in dementia, and considerable prevalence rates of mental health conditions such as depression. Moreover, personality traits such as impulsivity have been suggested to play an important role in the incidence of chronic diseases and mental disorders, as well as the unprecedented Coronavirus Disease 2019 (COVID-19) pandemic interacted with all these features. Therefore, although societies have been making efforts to improve the overall health of their people, there is still a need for further improvements in both physical and mental health conditions.

The objectives of the present doctoral thesis are to assess in adult and older adult populations if: 1) trait impulsivity is longitudinally associated with the adherence to healthy and unhealthy dietary patterns in the PREDIMED-Plus-Cognition cohort and with the incidence of type 2 diabetes and cardiovascular disease in the Nutrinet-Santé cohort; 2) glycemic-related measurements are longitudinally associated with global, trait, and behavioral impulsivity domains in the PREDIMED-Plus-Cognition cohort and with cognitive decline in the PREDIMED-Plus cohort; and 3) participants who experienced COVID-19 exhibit cognitive decline and depressive symptomatology in the PREDIMED-Plus cohort.

The main results of the current dissertation show that, firstly, higher values in the personality trait of impulsivity were longitudinally associated with increased and decreased adherence to unhealthy and healthy dietary patterns, respectively, over three years of follow-up in nearly 500 Spanish older adults at high risk for cardiovascular disease. In addition, this personality trait was positively associated with the risk of developing type 2 diabetes and cardiovascular disease over 8 years of follow-up in approximately 50,000 French adults from the general population. Secondly, insulin resistance, prevalence of type 2 diabetes, longer diabetes duration, poor glycemic diabetes control, and insulin treatment were associated with worsening cognitive function within only two years of follow-up in 6,874 Spanish older adults at high cardiovascular risk. Moreover, higher glycated hemoglobin levels, the presence of type 2 diabetes, and poor

diabetes control showed positive associations with changes in the global impulsivity composite, and those with higher glycated hemoglobin levels were further related to increases in the trait and behavioral impulsivity domains over the three years of follow-up in almost 500 Spanish older adults at high risk for cardiovascular disease. Thirdly, compared with participants who did not experience COVID-19, those who were positive cases had 62% increased odds of increased risk of depression over a median follow-up of 29 weeks after infection. In addition, participants who experienced COVID-19 did not exhibit a significant association with cognitive decline over a median follow-up of 44 weeks after infection, compared with those who did not have COVID-19. The latter two findings were examined in more than 5,000 Spanish older adults at high risk for cardiovascular disease.

In conclusion, the results of this thesis suggest the relevance of assessing levels of trait impulsivity to evaluate the risk of chronic diseases such as type 2 diabetes and cardiovascular disease. The assessment of trait impulsivity may further facilitate the identification of difficulties an individual may have in adhering to a healthy dietary pattern that can prevent the incidence of the aforementioned diseases. This may be of interest, as strategies focused on reducing impulsivity in participants with higher levels of impulsivity and at high risk for cardiometabolic diseases may reduce the incidence of these diseases through healthier dietary adherence. In addition, glycemic dysregulations were longitudinally associated with worsening cognitive function and increased impulsivity, which may indicate an increase in the burden of medical diseases, neurocognitive impairments, and some mental disorders that are more strongly associated with impulsivity. On the other hand, before the COVID-19 pandemic, the prevalence of depression was estimated to have been increasing since before the 2000s. During and after the pandemic, in the literature, positive associations between COVID-19 and depression rates have been observed. These detrimental associations have also been observed between COVID-19 and cognitive function. The current work showed that when these relationships were evaluated over longer periods of time, participants who experienced COVID-19 were more likely to exhibit an increase in depressive symptoms and risk, but not cognitive decline. However, it is important to replicate these findings in other populations and settings and to conduct additional randomized clinical control trials to validate recommendations for populations.

ABSTRACT: SPANISH

Durante el último siglo, el aumento de la esperanza de vida ha ido acompañado de una mayor prevalencia de enfermedades crónicas como la diabetes tipo 2, las enfermedades cardiovasculares, o la demencia, y de considerables tasas de prevalencia de otros trastornos de salud mental como la depresión. Además, se ha sugerido que rasgos de personalidad, tales como la impulsividad, juegan un papel importante en la incidencia de enfermedades crónicas y trastornos mentales. Además, la pandemia de la enfermedad del Coronavirus 2019 (COVID-19) interactuó con todas estas características. Por tanto, aunque las sociedades han estado realizando esfuerzos para mejorar la salud general de sus ciudadanos, aún se necesita progresar en la mejora de las condiciones de salud física y mental.

Los objetivos de la presente tesis doctoral son evaluar en poblaciones adultas y de adultos mayores si: 1) la impulsividad como rasgo de personalidad está asociada longitudinalmente con la adherencia a patrones dietéticos saludables y no saludables en la cohorte PREDIMED-Plus-Cognición y con la incidencia de diabetes tipo 2 y enfermedad cardiovascular en la cohorte Nutrinet-Santé; 2) variables relacionadas con el estado glucémico están asociadas longitudinalmente con los dominios de impulsividad global, de impulsividad como rasgo de personalidad, y de impulsividad conductual en la cohorte PREDIMED-Plus-Cognición, así como con el deterioro cognitivo en la cohorte PREDIMED-Plus; y 3) los participantes que tuvieron COVID-19 presentan deterioro cognitivo y sintomatología depresiva en la cohorte PREDIMED-Plus.

Los principales resultados de la presente disertación muestran que, en primer lugar, los valores más altos del rasgo de personalidad impulsivo se asociaron longitudinalmente con una mayor adherencia a patrones dietéticos poco saludables y una menor adherencia a patrones dietéticos saludables durante tres años de seguimiento en casi 500 adultos mayores españoles con alto riesgo de enfermedad cardiovascular. Además, este rasgo de personalidad se asoció positivamente con el riesgo de desarrollar diabetes tipo 2 y enfermedad cardiovascular durante ocho años de seguimiento en aproximadamente 50,000 adultos franceses, representativos de la población general. En segundo lugar, la resistencia a la insulina, la prevalencia de diabetes tipo 2, la mayor duración de la diabetes, el mal control glucémico de la diabetes, y el tratamiento con insulina se

asociaron a un empeoramiento de la función cognitiva tras dos años de seguimiento de 6,874 adultos mayores españoles con alto riesgo cardiovascular. Además, en casi 500 adultos mayores españoles con alto riesgo de enfermedad cardiovascular, elevaciones en la hemoglobina glucosilada, la presencia de diabetes tipo 2, y un mal control de la diabetes se asociaron a incrementos de la impulsividad global. Aquellos participantes con niveles más altos de hemoglobina glucosilada presentaron aumentos en los dominios del rasgo de personalidad impulsividad e impulsividad conductual durante los tres años de seguimiento. En tercer lugar, en comparación con los participantes que no habían experimentado la enfermedad del COVID-19, aquellos que fueron casos positivos presentaron un 62% mayor riesgo de desarrollar depresión tras 29 semanas después de la infección. Además, los participantes que tuvieron COVID-19 no presentaron declive cognitivo tras 44 semanas después de la infección, en comparación con aquellos que no padecieron COVID-19. Estos dos últimos hallazgos se examinaron en más de 5,000 adultos mayores españoles con alto riesgo de enfermedad cardiovascular.

En conclusión, los resultados de esta tesis sugieren la relevancia de evaluar los niveles del rasgo de personalidad impulsiva para el desarrollo de estrategias de prevención de enfermedades crónicas como la diabetes tipo 2 y la enfermedad cardiovascular. La evaluación del rasgo de personalidad impulsivo podría facilitar la identificación de las dificultades que un individuo puede tener para adherirse a un patrón dietético saludable y, por tanto, prevenir la incidencia de las enfermedades mencionadas anteriormente. Esto podría ser de interés, ya que en individuos con altos niveles de impulsividad y alto riesgo de desarrollar enfermedades cardiometabólicas las estrategias centradas en reducir la impulsividad podrían reducir la incidencia de estas enfermedades a través de una mayor adherencia a una dieta saludable. Además, las desregulaciones glucémicas se asociaron longitudinalmente con un empeoramiento de la función cognitiva y un aumento de la impulsividad, lo que podría indicar un aumento de la carga de enfermedades, deterioro neurocognitivo, y algunos trastornos mentales que están estrechamente relacionados con la impulsividad. Por otro lado, antes de la pandemia de COVID-19, se estimaba que la prevalencia de la depresión estaba en aumento desde antes de la década de los 2000. Durante y después de la pandemia, en la literatura, se observaron asociaciones positivas a corto plazo entre el COVID-19 y la depresión. Estas asociaciones perjudiciales también se han observado entre el COVID-19 y la función cognitiva. El trabajo actual mostró que, cuando estas relaciones se evaluaron durante períodos de tiempo más largos, los

participantes que experimentaron COVID-19 fueron más propensos a incrementar la sintomatología depresiva i el riesgo de desarrollar depresión, pero no un deterioro cognitivo más pronunciado. Sin embargo, es importante replicar estos hallazgos en otras poblaciones y contextos, y realizar ensayos clínicos aleatorizados y con grupos control adicionales para validar estas recomendaciones orientadas a la población.

ABSTRACT: CATALAN

Durant l'últim segle, l'augment de l'esperança de vida ha anat acompanyat d'una major prevalença de malalties cròniques com la diabetis tipus 2, les malalties cardiovasculars, o la demència, i de considerables taxes de prevalença d'altres trastorns de salut mental com la depressió. A més, s'ha suggerit que trets de personalitat, com ara la impulsivitat, juguen un paper important en la incidència de malalties cròniques i trastorns mentals. A més, la pandèmia de la malaltia del Coronavirus 2019 (COVID-19) va interactuar amb totes aquestes característiques. Per tant, encara que les societats han estat fent esforços per millorar la salut general dels seus ciutadans, encara es necessita progressar en la millora de les condicions de salut física i mental.

Els objectius de la present tesi doctoral són avaluar en poblacions adultes i d'adults majors si: 1) la impulsivitat com a tret de personalitat està associada longitudinalment amb l'adherència a patrons dietètics saludables i no saludables en la cohort PREDIMED-Plus-Cognició i amb la incidència de diabetis tipus 2 i malaltia cardiovascular en la cohort Nutrinet-Santé; 2) variables relacionades amb l'estat glucèmic estan associades longitudinalment amb els dominis d'impulsivitat global, d'impulsivitat com a tret de personalitat, i d'impulsivitat conductual en la cohort PREDIMED-Plus-Cognició, així com amb el deteriorament cognitiu en la cohort PREDIMED-Plus; i 3) els participants que van patir de COVID-19 presenten deteriorament cognitu i simptomatologia depressiva en la cohort PREDIMED-Plus.

Els principals resultats de la present dissertació mostren que, en primer lloc, els valors més alts del tret de personalitat impulsiu es van associar longitudinalment amb una major adherència a patrons dietètics poc saludables i una menor adherència a patrons dietètics saludables durant tres anys de seguiment en gairebé 500 adults majors espanyols amb alt risc de malaltia cardiovascular. A més, aquest tret de personalitat es va associar positivament amb el risc de desenvolupar diabetis tipus 2 i malaltia cardiovascular durant vuit anys de seguiment en aproximadament 50,000 adults francesos, representatius de la població general. En segon lloc, la resistència a la insulina, la prevalença de diabetis tipus 2, la major durada de la diabetis, el mal control glucèmic de la diabetis, i el tractament amb insulina es van associar a un empitjorament de la funció cognitiva després de dos anys de seguiment de 6,874 adults majors espanyols amb alt risc cardiovascular. A més,

en gairebé 500 adults majors espanyols amb alt risc de malaltia cardiovascular, elevacions en l'hemoglobina glucosilada, la presència de diabetis tipus 2, i un mal control de la diabetis es van associar a increments de la impulsivitat global. Aquells participants amb nivells més alts d'hemoglobina glucosilada van presentar augments en els dominis del tret de personalitat impulsivitat i d'impulsivitat conductual durant els tres anys de seguiment. En tercer lloc, en comparació amb els participants que no havien experimentat la malaltia del COVID-19, aquells que van ser casos positius van presentar un 62% major risc de desenvolupar depressió després de 29 setmanes després de la infecció. A més, els participants que van experimentar COVID-19 no van presentar declivi cognitiu després de 44 setmanes després de la infecció, en comparació amb aquells que no van patir COVID-19. Aquests dos últims resultats es van examinar en més de 5,000 adults majors espanyols amb alt risc de malaltia cardiovascular.

En conclusió, els resultats d'aquesta tesi suggereixen la rellevància d'avaluar els nivells del tret de personalitat impulsiu per el desenvolupament d'estratègies de prevenció de malalties cròniques com la diabetis tipus 2 i la malaltia cardiovascular. L'avaluació del tret de personalitat impulsiu podria facilitar la identificació de les dificultats que un individu pot tenir per dherir-se a un patró dietètic saludable i, per tant, prevenir la incidència de les malalties esmentades anteriorment. Això podria ser d'interès, ja que en individus amb alts nivells d'impulsivitat i alt risc de desenvolupar malalties cardiometabòliques, les estratègies centrades en reduir la impulsivitat podrien reduir la incidència d'aquestes malalties a través d'una major adherència a una dieta saludable. A més, les desregulacions glucèmiques es van associar longitudinalment amb un empitjorament de la funció cognitiva i un augment de la impulsivitat, la qual cosa podria indicar un augment de la càrrega de malalties, deterioració neurocognitiva, i alguns trastorns mentals que estan estretament relacionats amb la impulsivitat. D'altra banda, abans de la pandèmia de la COVID-19, s'estimava que la prevalença de la depressió estava en augment des d'abans de la dècada dels 2000. Durant i després de la pandèmia, en la literatura, es van observar associacions positives a curt termini entre el COVID-19 i la depressió. Aquestes associacions perjudicials també s'han observat entre el COVID-19 i la funció cognitiva. El treball actual va mostrar que, quan aquestes relacions es van avaluar durant períodes de temps més llargs, els participants que van experimentar COVID-19 van ser més propensos a incrementar la simptomatologia depressiva i el risc de desenvolupar depressió, però no un deteriorament cognitiu més pronunciat. No obstant

això, és important replicar aquestes troballes en altres poblacions i contextos, i realitzar assajos clínics aleatoritzats i amb grups control addicionals per validar aquestes recomanacions orientades a la població.

ABBREVIATIONS

B

BDI-II:	Beck Depression Inventory version II.
BIS-11:	Barratt Impulsiveness Scale version 11.

C

CDC:	Centers for Disease Control and Prevention.
CDT:	Clock Drawing Test.
CépiDC:	French National Mortality Registry.
CNAM:	Caisse Nationale de l'Assurance Maladie (in French).
COVID-19:	Coronavirus Disease 2019.
CPT:	Conners' Continuous Performance Test.

D

DALYs:	Disability-adjusted life years.
DASH:	Dietary Approaches to Stop Hypertension.
DSM-5:	Diagnostic and Statistical Manual of Mental Disorders, Fifth edition.
DST-b:	Digit Span Test backward section.
DST-f:	Digit Span Test forward section.

F

FFQ:	Food-frequency questionnaire.

H

HbA1c:	Glycated hemoglobin.
HDL-cholesterol:	High-density lipoprotein cholesterol.
HOMA-IR:	Homeostatic Model Assessment for Insulin Resistance.

I

IDPP-4:	Dipeptidyl peptidase-4 inhibitors.

IgG:	Immunoglobulin blood test G.
IGT:	Iowa Gambling Task.
IMPULS:	Impulsivity-Focused Group Intervention to Reduce Binge Eating Episodes.
IPAQ:	International Physical Activity Questionnaire.
L	
LDL-cholesterol:	Low-density lipoprotein cholesterol.
M	
MIND:	Mediterranean-DASH Intervention for Neurodegenerative Delay.
MMSE:	Mini-Mental State Examination.
MoCA:	Montreal Cognitive Assessment.
P	
PREDIMED-Plus:	PREvención con DIeta MEDiterránea (in Spanish).
S	
SARS-Cov-2:	Severe Acute Respiratory Syndrome Coronavirus 2.
SNIIRAM:	Système National d'Information Inter-Régimes de l'Assurance Maladie (in French).
SWCT:	Stroop Color and Word Test.
T	
TMT-A:	Trail Making Test part A.
TMT-B:	Trail Making Test part B.
U	
UPPS-P:	Negative urgency, lack of premeditation, lack of perseverance, sensation seeking, and positive urgency Impulsive Behavior Scale.
V	
VFT-a:	Verbal Fluency Test animals version.
VFT-p:	Verbal Fluency Test letter “p” version.

LIST OF FIGURES

LIST OF TABLES

I. INTRODUCTION

UNIVERSITAT ROVIRA I VIRGILI
Psychology and Disease: Unveiling Emerging Perspectives on Their Interplay
Carlos Gómez Martínez

Psychological factors have been identified as significant contributors to the prevalence of various diseases and overall health status[1–4]. The term health status is defined as "the range of manifestations of disease in a given patient, including symptoms, functional limitation, and quality of life", with quality of life being understood as "the discrepancy between the actual and the desired function"[5]. Personality traits such as neuroticism, emotional states such as anger and hostility, and mental health conditions such as depression and anxiety, have been linked with the development and progression of several diseases, including cardiometabolic diseases, cancer, infectious diseases, and dementia[6–11]. Furthermore, these psychological factors have been linked to elevated mortality rates and a greater global disease burden[12,13]. In addition, during the development of this doctoral thesis, the COVID-19 pandemic occurred, having both physical and psychological consequences worldwide.

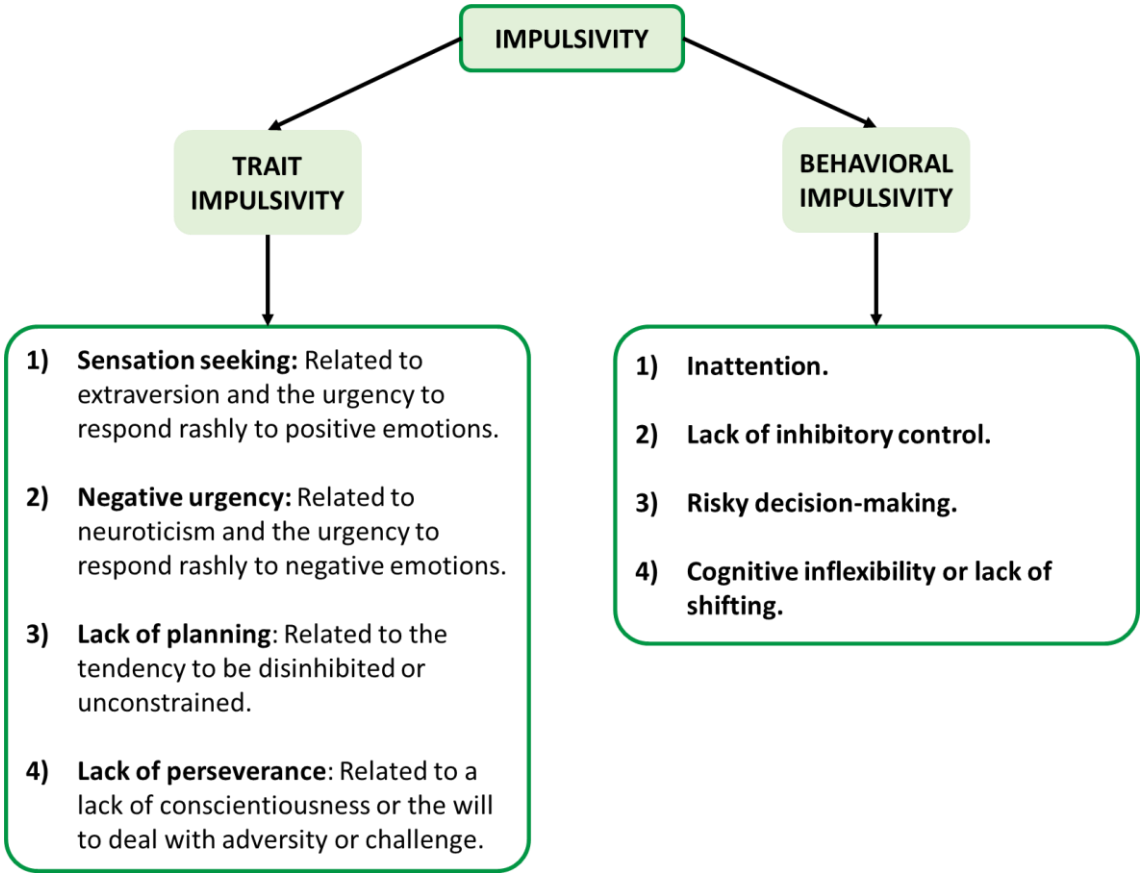
It is important to note that psychological factors are not inherently harmful. However, in some cases, an extreme manifestation of these characteristics can have a negative impact on health outcomes[14]. Conversely, the promotion of positive psychological factors, including brain reserve, well-being, social support, and mindfulness, has been demonstrated to be beneficial in the prevention of the aforementioned diseases[15–19].

The present dissertation introduces, presents findings, and discusses associations between certain psychological factors and various health status assessments from an epidemiological perspective. This doctoral thesis has focused on several specific areas, including impulsivity, cognitive function, depressive symptomatology, diet, glycemic status and disease, cardiovascular disease, and COVID-19 status. Specifically, in the following introductory section, each of the assessed topics is briefly defined, described with key epidemiological data and possible determinants, reported with findings from intervention trials, and related to lifestyle and health outcomes of interest.

IMPULSIVITY

Impulsivity is defined as "a predisposition toward rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions to the impulsive individuals or to others"[20]. These quick responses, often driven by emotions and a need to respond harshly, can be strategic or advantageous in certain contexts[21,22]. However, high to extreme levels of impulsivity have been consistently associated with poor health and psychiatric conditions[20,23–25].

Figure 1. Domains and subfactors of impulsivity.



Note. Adapted from Sharma L, Markon KE, Clark LA. Toward a theory of distinct types of "impulsive" behaviors: A meta-analysis of self-report and behavioral measures. Psychological Bulletin. 2014. doi: 10.1037/a0034418.

Impulsivity is considered a personality trait that can lead to impulsive actions[26–28]. Personality traits are defined as relatively enduring patterns of thoughts, feelings, and behaviors that reflect a tendency to respond in a specific manner under particular

circumstances or situational cues[26,27]. These traits are shaped by genetics and ontogenetic processes and are typically established prior to adulthood[29,30]. Nevertheless, trait impulsivity is more modifiable than other personality traits and can exhibit change across the lifespan[31]. This trait is characterized by an urgency to respond to emotional states, a lack of premeditation, and a high level of sensation seeking[32]. These personality features facilitate an understanding of the diverse ways in which trait impulsivity can manifest and affect behavior. Once the trait of impulsivity has manifested in an action, it can be referred to as behavioral impulsivity[33]. Behavioral impulsivity is characterized by heightened sensitivity to rewards, a propensity for risk-taking when making decisions, and impaired activity in prefrontal cortex regions that result in a diminished capacity for attention, cognitive flexibility, and inhibitory control[28,34–36]. In **Figure 1** are presented the principal domains and underlying factors of trait and behavioral impulsivity identified in the meta-analysis conducted by Sharma and collegues[28].

A substantial body of evidence indicates that elevated levels of impulsivity are associated with an increased prevalence of psychiatric conditions, including attention deficit hyperactivity disorder, antisocial personality disorder, gambling, substance abuse, eating disorders, and suicidality[20,21,37–39]. Neural substrates provide a potential explanation for this comorbidity between impaired impulsivity and psychiatric conditions. A dysfunction of the frontostriatal neural circuits has the potential to disrupt the top-down cognitive control system, which may subsequently manifest in behavioral issues such as difficulties with delayed discounting of rewards, premature responding, and motor inhibition[35]. A comprehensive overview of the neurological circuitry associated with impulsivity has been previously documented and can be found in the referenced literature[34,35,40,41].

Greater impulsivity has not only been linked with psychiatric diseases but also has been suggested to play an important role in health outcomes[1,42]. Indeed, impulsivity has been demonstrated to be positively associated with a range of risky lifestyle behaviors, including alcohol intake[43,44], cigarette consumption[45,46], and higher body mass index levels[24,47]. In fact, a meta-analysis showed a strong relationship between elevated scores on a composite measure of impulsivity and diminished quality of life[37].

The implementation of interventions designed to mitigate the impact of elevated impulsivity levels, and meta-analyses of these interventions, have proven to be an efficacious approach, indicating the potential for impulsivity to be modified[48–53]. In light

of the observed associations between impulsivity and an elevated risk of several prevalent diseases, future research is warranted in the future to investigate the potential efficacy of these interventions aimed at reducing impulsivity in individuals with high impulsivity and an elevated risk of developing diseases. In children and adolescents, a considerable number of psychological-based interventions have been demonstrated to effectively enhance self-regulation, a fundamental aspect of behavioral impulsivity [48]. This has resulted in notable improvements in academic, health, and behavioral outcomes[48]. In adults, meta-analyses of mindfulness interventions or other techniques designed to decrease delay discounting or impulsive choice have demonstrated beneficial effects in reducing behavioral impulsivity and substance abuse disorders[49,50]. Nonetheless, these meta-analyses revealed methodological limitations across the various study designs[49,50]. In individuals with binge eating disorder, where impulsivity levels are typically elevated[54], a reduction in impulsivity levels was observed over time following the implementation of a cognitive and behavioral intervention guideline, named the Impulsivity-Focused Group Intervention to Reduce Binge Eating Episodes (IMPULS)[51]. However, this reduction in impulsivity levels was not statistically significant when compared with the control group, with only a significant beneficial effect observed for depressive symptomatology[51].

The present thesis focused on examining the relationships between impulsivity, dietary patterns, glycemic status, and the risk of developing type 2 diabetes and cardiovascular disease. Prior research has indicated that impulsivity is inversely associated with healthy diets[55,56]. However, there is a paucity of studies that have evaluated the longitudinal relationships between impulsivity and both healthy and unhealthy dietary patterns. On the other hand, positive relationships have been identified along the pathway from impulsivity to dysfunctional health behaviors and subsequently to cardiometabolic risk[25,57,58]. Nevertheless, no studies were identified that performed a comprehensive assessment of various glycemic status and impulsivity measurements, nor between impulsivity and incident type 2 diabetes and cardiovascular disease events. This represents a significant gap in the scientific literature, and further research in this area is warranted. Specifically, studies have shown that when type 2 diabetes has been diagnosed, impulsivity is associated with poor diabetes control, as evidenced by the presence of lifestyle risk behaviors and uncontrolled glycated hemoglobin (HbA1c) levels[59,60]. However, further prospective studies conducted with control groups with

controlled type 2 diabetes or with participants without type 2 diabetes are required to provide more conclusive evidence.

COGNITIVE FUNCTION AND DECLINE

Cognitive functions encompass all the basic psychological processes that allow individuals to extract information from and interact with their environment in a manner that ensures optimal survivability. These mental processes are the culmination of a continuous interplay between the brain, body, and environment, throughout the phylogenetic and ontogenetic evolution of organisms with central nervous systems, allowing humans to perform all the actions of daily life[61–63]. These mental processes are organized into first-order neurocognitive domains, including perceptual-motor function, social cognition, attention, learning and memory, executive function, and language[64]. Within these domains, second-order cognitive functions represent specific abilities that underpin the broader scope of first-order cognitive domains[64].

Across the lifespan, cognitive function typically increases during childhood, reaches its peak in adulthood, and then gradually declines into old age[65]. Cognitive aging is the natural process by which cognitive functions begin to decline. However, over the past century, a multitude of medical advancements have led to a notable increase in life expectancy, and this prolonged lifespan has been accompanied by significant impairments in cognitive function[66]. When cognitive decline is discernible as a slight yet perceptible deterioration in cognitive abilities that exceed expectations for an individual's age but does not considerably impede daily life and activities, the term mild cognitive impairment has been proposed[65,66]. Mild cognitive impairment has been demonstrated to elevate the likelihood of dementia, although in some instances, this phase of cognitive impairment can be reversed[67,68]. Dementia represents the most severe form of cognitive impairment, primarily affecting older individuals, with Alzheimer's disease being the most common form and contributing to 60–70% of dementia cases[69]. Dementia has a profound impact on an individual's ability to perform activities of daily living, and is a major cause of disability and dependency among older populations globally[69].

Recent studies assessing the prevalence of cognitive impairment and mild cognitive impairment have estimated global prevalence rates of 19% and 16%, respectively[70,71]. With regard to dementia, a decline in incidence was observed in some countries from 1990 to 2019, which is likely attributable to improvements in modifiable risk factors[72]. However, global trends in total dementia prevalence have demonstrated an increase,

which is primarily attributable to population growth and aging[73]. In 2019, the estimated number of individuals living with dementia was 57 million, with projections indicating an increase to 153 million by 2050[73].

A variety of sociodemographic factors, lifestyle behaviors, and genetic markers have been identified as influencing the preservation or deterioration of cognitive function[74,75]. The most widely recognized protective factors for cognitive function include physical, cognitive, and social activity, as well as higher levels of education. In contrast, an unhealthy diet, alcohol abuse, smoking, obesity, hypertension, dyslipidemia, diabetes mellitus, and depression have been identified as risk factors for cognitive impairment[76].

Given the pivotal role of cognitive function in daily living, significant efforts have been directed toward mitigating the global health burden of cognitive impairments such as dementia. Recent meta-analytic reviews have demonstrated the beneficial effects of multidomain lifestyle interventions on the preservation of cognitive function abilities and improvement in cognitive screening tests[77]. These beneficial interventions include aerobic exercise, cognitive training, motor challenges, creative arts, storytelling groups, and social interventions[78]. These helpful intervention results have been observed to persist for up to one year in participants with mild cognitive impairment[78]. Additional meta-analytic evidence from large-scale trials with randomized, parallel control group designs indicated a significant beneficial effect only in individuals at risk of dementia, but not in the general population or in individuals with mild cognitive impairment[79]. Specifically, a beneficial effect in only one trial implementing a pharmacological intervention and another with a multi-domain intervention was described[79]. However, when this effect was assessed using small- and medium-scale randomized clinical control trials, clear benefits were shown for both general and mild cognitive impairment populations by using nutrition, physical activity, cognitive stimulation, and multidomain interventions[79]. In summary, the current evidence indicates that interventions designed to improve cognitive function in older adults may offer benefits in certain circumstances. Nevertheless, the majority of interventions are currently ongoing, and further robust evidence on the most beneficial interventions is still required.

The present dissertation focused on examining longitudinal relationships between glycemic-related measures, cognitive function, and impulsivity. The potential role of glycemic dysregulation in cognitive decline has been a topic of extensive investigation,

with a growing body of evidence indicating long-term deleterious associations. Indeed, elevated HbA1c levels have been linked to an increased risk of cognitive decline and dementia over periods of time longer than eight years in middle-aged and older adults[80–83]. Similarly, a history of type 2 diabetes was associated with a 19% greater cognitive decline over a 20-year period in a cohort of 13,351 individuals when compared to those without a diabetes diagnosis[80]. Nevertheless, there is a scarcity of studies employing shorter follow-up periods to evaluate the potential association between glycemic dysregulation and cognitive decline in individuals at cardiovascular risk. On the other hand, associations between glycemic dysregulation and higher trait and behavioral impulsivity have been described[84–89]. However, in almost all studies, results were reported using cross-sectional designs, small population sizes, or a lack of comprehensive assessment of the broad nature of impulsivity, thus necessitating more robust evidence.

DEPRESSIVE SYMPTOMATOLOGY

Depressive disorder, commonly referred to as depression, is a prevalent psychiatric condition that is characterized by a persistently low mood and a marked decrease in pleasure or interest in activities over extended periods. This mental disorder is estimated to affect between 280 and 300 million people around the world[90,91]. In contrast to ordinary fluctuations in mood and typical emotional responses to daily life, depression can have a profound impact on various aspects of life, including interpersonal relationships and functioning in family, social, and occupational contexts[90]. Additionally, depression is recognized as a universal condition that can potentially affect all individuals regardless of their background, though its prevalence is higher in high-income countries and among women[92,93].

The prevalence rates of depression between 1994 and 2014, assessed in more than 1 million adults from 30 countries, demonstrated an increase of approximately 11%[94]. In older adults, a trend increase in the prevalence of depression has been described from 2000 to 2020 globally, and the prevalence of depression in older adults has been estimated to be about 28% in 2021[95].

Depression has its etiology in a complex interplay of social, psychological, and biological determinants[90]. Individuals who have experienced adverse life events, such as unemployment, bereavement, or traumatic incidents, are at an increased risk of developing depression[90]. This risk is further compounded by the subsequent exacerbation of stress and functional impairment, which deteriorates the individual's life circumstances and intensifies depressive symptoms[90].

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) specifies the diagnostic criteria for Major Depressive Disorder, which is characterized by a set of symptoms that are present for a minimum of two weeks and significantly affect the individual's mood and lifestyle[96]. A diagnosis of major depressive disorder requires the presence of at least five of the following symptoms for a minimum of two weeks: depressed mood most of the day, almost every day; markedly decreased interest or pleasure in all or almost all activities most of the day, almost every day; significant weight loss (when not dieting) or weight gain, or decreased or increased appetite almost every day; insomnia or hypersomnia almost every day; psychomotor agitation or retardation

almost every day; fatigue or loss of energy almost every day; feelings of worthlessness or excessive or inappropriate guilt almost every day; impaired ability to think or concentrate, or indecisiveness almost every day; and recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan to commit suicide[96].

The scientific literature has extensively studied depressive symptomatology, consistently demonstrating adverse associations with numerous lifestyle factors, comorbidities, and health outcomes[91]. Depression is intricately linked to physical health, with bidirectional influences between the two[97]. This interaction results in a poor prognosis for various chronic diseases, including cardiovascular disease, cancer, and inflammatory diseases[98], due to increased smoking, physical inactivity, obesity, cognitive impairment, and the presence of type 2 diabetes, cardiovascular disease, and dementia[99–101]. Furthermore, individuals with these chronic conditions may develop depressive disorders as a consequence of the difficulties associated with managing their conditions[90].

Given the significant global health concern that depression represents, with the potential to impair the quality of life of individuals diagnosed with this mental disorder and to exacerbate the symptoms of numerous other diseases, initiatives have been undertaken with the aim of reducing its prevalence. A substantial body of evidence supports the efficacy of psychological and pharmacological treatments for the improvement and remission of depressive symptoms and major depressive disorder. These include psychological therapies, antidepressants, transcranial magnetic stimulation, modified electroconvulsive therapy, and deep brain stimulation[91]. Interventions that promote positive emotion regulation have consistently been demonstrated to be an effective method for reducing depressive symptomatology[102]. Nevertheless, a lack of awareness in society regarding the potential beneficial effects of interventions, the stigma attached to psychological and psychiatric disorders and therapies, and ineffective campaigns to treat depression represent significant barriers to successful recovery[91].

The present work examined the prospective relationship between COVID-19 status, depressive symptomatology and depression risk. In Spain, during the initial phase of COVID-19, a significant psychological impact was observed in more than 3,000 individuals, with 41% of this population exhibiting depressive symptoms[103]. Globally, the prevalence of depressive symptoms reached its highest peak between April and May

2020, subsequently demonstrating a gradual decline from June to October 2020[104]. Despite this decline, the rates of depressive symptoms remained higher than those observed between January and February 2020[104]. However, there is a paucity of evidence regarding the long-term effects of COVID-19 on the development of depression, necessitating further research to inform the establishment of evidence-based guidelines for individuals who have experienced COVID-19.

DIETARY PATTERNS

Dietary patterns are defined as the overall dietary intake of an individual, including the combinations and quantities of foods and beverages regularly consumed by individuals or populations[105].

A comprehensive approach to dietary patterns, as opposed to a narrow focus on specific food groups or nutrients, provides a more comprehensive measure for nutritional epidemiology and a more accurate representation of overall dietary habits[106]. The evidence indicates that promoting individual food components in the diet of an individual or population without considering the intake of other food components is a suboptimal approach to disease prevention[105]. The intake of nutrients within dietary patterns can exhibit synergistic or antagonistic interactions, which are often challenging to identify without consideration of adherence to overall dietary patterns[105]. These patterns have a significant impact on health outcomes and are crucial in understanding the relationship between diet and chronic diseases[107].

A healthy dietary pattern is typically characterized by an abundance of foods that promote health, including fruits, vegetables, soy, nuts, seeds, whole grains, legumes, and fish[105,108]. In contrast, a healthy dietary pattern is typically low in sodium, saturated fats, trans fats, animal-derived proteins, and added sugars[105,108]. The results of recent observational meta-analyses and reviews have consistently demonstrated a beneficial association between healthy dietary patterns and a broad range of health outcomes. For instance, young people who consume diets that are high in energy density and low in fiber are at an increased risk of becoming overweight or obese later in life[109]. In adults, adherence to healthy dietary patterns has been linked to a reduced risk of obesity[110], metabolic syndrome[106], elevated glycated hemoglobin levels[106,110,111], and the incidence of type 2 diabetes as well as improved glycemic control in individuals with diabetes diagnosis[112,113]. Moreover, these healthy dietary patterns are linked to lower systolic and diastolic blood pressure[114], a reduced incidence of cardiovascular disease[115], and a lower risk of dementia and Alzheimer's disease[116]. Otherwise, lower adherence to healthy dietary patterns is associated with higher all-cause mortality and mortality from cardiovascular disease, cancer, and neurodegenerative diseases[117].

In contrast, unhealthy dietary patterns are characterized by high consumption of processed and ultra-processed foods, red meat, refined grains, sugary beverages, and sweets, in conjunction with a low intake of nutrient-dense foods such as fruits, vegetables, whole grains, nuts, seeds, and healthy fats[118]. This shift in the rising production and consumption of ultra-processed foods has prompted the identification of new health concerns, given the established link between these ultraprocessed foods and an increased risk of type 2 diabetes and cardiovascular disease[119,120]. A representative example of an unhealthy dietary pattern is the Western diet, which is characterized by a high consumption of ultra-processed foods and has been linked to an increased prevalence of obesity, diabetes, cardiovascular disease, cancer, and impaired immune responses[121,122].

As dietary patterns have been evidenced to substantially influence health outcomes and have further been demonstrated to be modifiable through psychological and lifestyle interventions, some clinical trials have been conducted to promote beneficial dietary patterns and reduce the incidence of chronic diseases. The results of meta-analyses indicate that diets based on the Mediterranean and Dietary Approaches to Stop Hypertension (DASH) dietary patterns are associated with a reduced risk of developing type 2 diabetes, irrespective of the promotion of physical activity[123]. Furthermore, the Mediterranean diet has been linked to a lower incidence of cardiovascular disease, cardiovascular disease-related mortality, and overall mortality[124]. The evidence also suggests that healthy dietary interventions may alleviate depressive symptomatology, although inconsistency in the assessment of outcomes across studies has been noted[125].

The current doctoral thesis investigates longitudinal relationships between the personality trait of impulsivity and adherence to healthy and unhealthy dietary patterns. In the last few decades, promoting a healthy diet has been a major strategy in the prevention of numerous diseases. Nevertheless, there is still a need for further research to gain a deeper understanding of the factors that influence food choices. Some primary factors influencing food choices have been identified as interrelationships between genetic and epigenetic characteristics, personality traits, cognitive and affective patterns, cultural and social pressures, dietary determinants such as palatability and organoleptic properties of foods, and physiological mechanisms including signals from the gastrointestinal tract and adipose tissue to the brain and vice versa[126]. Concerning the focus of this dissertation, research examining the relationships between impulsivity and food preferences and intakes represents a consistent topic of investigation within the existing literature[55,127–129].

For example, one study found cross-sectional associations between the personality trait impulsivity and lower adherence to a healthy French dietary pattern, as well as positive associations with energy intake, snacking, and eating disorders[56]. However, the absence of prospective findings, the failure to adjust models for important covariates, and the absence of dietary pattern assessments represent notable limitations.

CARDIOVASCULAR STATUS AND DISEASE

Cardiovascular status is defined as the overall health and function of the cardiovascular system, which encompasses the activity of the heart and blood vessels, and the efficiency of circulatory functions is determined by these two components[130].

A suboptimal state of the cardiovascular system can result in the development of cardiovascular disease[130]. Some of the most common cardiovascular diseases include: coronary artery disease, affecting the blood vessels supplying the heart muscle; cerebrovascular disease, affecting the blood vessels supplying brain function; peripheral arterial disease, affecting the blood vessels supplying the function of the arms and legs; rheumatic heart disease, damaging the heart muscle and valves due to rheumatic fever caused by streptococcal bacteria; congenital heart disease, which is caused by malformations of the heart's structure from birth that affect the normal development and function of the heart; and deep vein thrombosis and pulmonary embolism, which cause blood clots formed in leg veins that can dislodge and travel to the heart and lungs[130]. Some of the primary mechanisms that can contribute to a cardiovascular disease event are the result of an obstruction of coronary or cerebral arteries by clots or atherosclerotic plaques, which impedes oxygenated blood flow to surrounding cells. Alternatively, a rupture of the arterial walls can lead to hemorrhage[131,132]. Both occlusion and hemorrhage typically culminate in cell death due to the disruption of blood supply, increased pressure, inflammatory responses, or the toxic effects of blood components [133].

A meta-analysis of the available evidence suggests a slight decline in the global average trend of cardiovascular disease incidence from 1990 to 2019, although the observed decrease is almost trivially[134,135]. Nevertheless, it is important to note that cardiovascular disease remains the leading cause of death from noncommunicable diseases, and efforts are warranted to further reduce the global health burden of cardiovascular diseases in the following decades[130].

Recent evidence has been discussing the detrimental effects that environmental factors, such as noise and air pollution, can have on cardiovascular disease risk[136]. However, the well-established risk factors include genetic predisposition, family history of cardiovascular disease, tobacco use, excessive alcohol consumption, poor dietary habits,

physical inactivity, obesity, hypertension, and diabetes[137–139]. Consequently, cardiovascular disease often coexists with conditions such as obesity, dyslipidemia, hypertension, metabolic syndrome, diabetes mellitus, cancer, and depression and anxiety[101,137,140–143], potentially increasing the global health burden of cardiovascular disease. A study conducted using the UK Biobank cohort, which included 135,199 adults, indicated a robust correlation between enhanced cardiovascular health and extended life expectancy[144]. This was observed not only in the absence of cardiovascular disease but also in the context of other major chronic illnesses, including diabetes, cancer, and dementia[144]. Moreover, as cardiovascular diseases impede typical blood flow to cells, including brain cells, there is a well-established comorbidity with cognitive decline and elevated rates of dementia [145,146].

Interestingly, a pooled study of 155,722 individuals from 21 high-, middle-, and low-income countries evaluated potential risk determinants of cardiovascular disease, assessing behavioral, metabolic, socioeconomic, psychological, grip strength, household, and air pollution factors[147]. The study revealed that approximately 70% of cardiovascular disease cases and deaths were attributable to modifiable risk factors. In addition, metabolic factors were identified as the predominant risk factors for cardiovascular disease, accounting for approximately 40% of cases, while behavioral risk factors were found to contribute most to cardiovascular disease mortality, accounting for approximately 25% of cases[147].

Clinical intervention trials have been conducted with the objective of reducing the incidence of cardiovascular disease and its huge impact on public health. This is due to the fact that numerous risk factors for cardiovascular disease events are potentially modifiable lifestyle characteristics. Meta-analysis of randomized clinical control trials showed that that behavioral counseling interventions designed to enhance diet and promote physical activity in individuals with elevated blood pressure and lipid levels were efficacious in reducing cardiovascular events, blood pressure, low-density lipoproteins, and adiposity-related outcomes[148]. Moreover, blood pressure-lowering medications, such as statins, have been demonstrated to be successful strategies for the primary prevention of cardiovascular disease[149,150]. In the context of secondary prevention of cardiovascular disease, the Mediterranean diet has been proposed as a noteworthy dietary pattern for the prevention of major cardiovascular events[151]. Additionally, exercise and numerous pharmacological interventions have demonstrated comparable potential benefits in the

secondary prevention of coronary heart disease, rehabilitation following a stroke, and the treatment of heart failure[152].

The current thesis aimed to study the longitudinal associations between the personality trait of impulsivity and the risk of developing cardiovascular disease. Some personality traits have been proposed to play a role in the incidence of cardiovascular disease. However, to the best of our knowledge, only two studies have assessed these relationships. One of these prospective study cohorts, comprising 4,267 individuals and conducted in Germany, demonstrated that participants exhibiting low internal locus of control over disease, in conjunction with elevated psychoticism levels, exhibited an increased risk of incident myocardial infarction[153]. The remaining study included data from six United States cohorts. The pooled study revealed that elevated neuroticism and diminished conscientiousness were linked to an increased likelihood of developing stroke[7]. Furthermore, it was postulated that severe childhood stress exerts a more pronounced influence on the incidence of cardiovascular disease in later life compared to stressor events in adult populations[154]. However, adult stress may be an important trigger for cardiovascular disease, and evidence has been giving importance to the role of stress in disease progression in individuals at high risk or with prevalent disease[154]. Accordingly, further research is required to ascertain the potential relationships between psychological factors and the incidence of cardiovascular disease. For example, impulsivity has been associated with higher cardiometabolic risk[25]. Nevertheless, the relationship between impulsivity and the risk of developing cardiovascular disease has not been previously investigated.

GLYCEMIC STATUS AND DISEASE

The term glycemic status is used to describe the level and regulation of glucose in the blood, and constitutes an important indicator of how an individual manages blood glucose, which is crucial for energy production and overall health[155].

A dysregulated glycemic status results in impaired glucose metabolism, which can lead to the development of chronic diseases such as diabetes mellitus[155]. The intermediate states between normality and diabetes are impaired glucose tolerance and impaired fasting glucose. These conditions are regarded as prediabetic states, defined by elevated glucose levels that do not meet the clinical criteria for diabetes[156]. Diabetes is a metabolic disease that is characterized by either an insufficient production or an inefficient utilization of the insulin that is produced by the organism, which ultimately results in elevated blood glucose levels[156]. Insulin is a hormone that regulates the entry of glucose into cells, which is essential for cellular energy expenditure[157]. Glycemic dysregulation in individuals with diabetes is typically associated with significant complications, including damage to the heart, blood vessels, eyes, kidneys, and nerves, and the most prevailing forms of diabetes are type 1 and type 2 diabetes mellitus[156].

Type 1 diabetes is characterized by autoimmune destruction of the insulin-producing beta cells in the pancreas, with a typical onset in childhood or adolescence[158]. Type 2 diabetes is the most prevalent form of diabetes, a principal cause of mortality from noncommunicable diseases, and is typically developed in adulthood[156]. The development of type 2 diabetes is largely attributable to factors such as excess body weight, physical inactivity, and poor dietary habits, which collectively impair the pancreas's ability to produce sufficient, effective, or even any insulin[156,158]. Furthermore, gestational diabetes mellitus is a form of diabetes that occurs during pregnancy and affects both the mother and the embryo, it is typically caused by hormonal changes and is generally reversible after childbirth[156].

In 2021, the global prevalence of prediabetic conditions was 6% for impaired glucose tolerance and 9% for impaired fasting glucose, and it was projected that by 2045 there would be a significant increase of approximately 1% in the number of cases of these prediabetic conditions[159]. A systematic review of data from 1980 to 2017 revealed that

the global prevalence of type 2 diabetes increased until 2006, followed by a subsequent decline[160]. This study highlighted the limited availability of data in low- and middle-income countries[160]. However, other studies have presented contrary evidence that is inconsistent with this conclusion. One of these studies indicated that the prevalence and incidence of type 2 diabetes increased from 1990 to 2017, and suggested that the global prevalence of diabetes may increase by approximately 8,000 per 100,000 person-years by 2040[161]. Other studies have similarly indicated positive trends in the incidence of type 1 and type 2 diabetes worldwide[162,163]. Additionally, another study using data from 195 countries estimated that the global burden of deaths and disability-adjusted life years (DALYs) due to incident cases of type 1 and type 2 diabetes will increase by 125% and 116%, respectively, from 1990 to 2025[164]. Furthermore, comorbidities of type 1 and 2 diabetes with depressive and anxiety symptoms have been documented in comparison to the general population, which has been linked to a reduction in psychological well-being and an increase in the global health burden associated with the onset of type 2 diabetes[165].

Based on an umbrella of meta-analysis and a narrative review of the Nurses Health Studies, which followed more than 200,000 participants over decades, several risk factors have been identified to increase the risk of developing type 2 diabetes[112,166]. Among these risk factors are included the presence of obesity and early and late weight gain, metabolic syndrome, sedentary time, depression, consumption of sugar-sweetened beverages and processed meats, higher levels of c-reactive protein, alanine aminotransferase and gamma-glutamyltransferase, and a genetic predisposition for an increased presence of proinflammatory biomarkers, dyslipidemia, obesity, and insulin resistance[112,166]. Protective factors for type 2 diabetes have also been identified, including adequate sleep and higher physical activity, adherence to a healthy diet, consumption of coffee and whole grains, educational level, socioeconomic status, and serum adiponectin and vitamin D levels[112,166]. Additionally, environmental risk factors have been proposed as a possible mechanism through which lifestyle risk factors may increase the risk of developing type 2 diabetes[167].

Meta-analyses of clinical lifestyle interventions aimed at preventing the incidence of type 2 diabetes by decreasing body weight and improving physical activity and/or diet quality showed a significantly reduced risk of type 2 diabetes[168,169]. These lifestyle interventions have been demonstrated to be cost-effective in populations at high risk of developing type

2 diabetes[170]. These findings are of significant importance, as type 2 diabetes has a profound impact on global health[156].

In individuals who are already diagnosed with diabetes, glycemic control is a critical feature in the prevention of further adverse outcomes. For example, both short- and long-term glycemic variability have been identified as an independent risk factor for a poor prognosis in the health status of the individual[171]. Indeed, glycemic variability has been linked to adverse clinical outcomes in individuals with diabetes, including diabetic nephropathy, retinopathy, and peripheral neuropathy, hypoglycemia, cognitive dysfunction, cardiovascular disease, and mortality[171]. It is noteworthy that the personality trait of impulsivity has been proposed as a significant factor influencing the management of type 2 diabetes. Some studies have found that higher trait impulsivity is associated with more lifestyle-related risky behaviors for the management of the disease, such as poor adherence to medication, as well as with uncontrolled levels of HbA1c[59,60]. Meta-analyses of psychological interventions have been showing significant benefits for the control of glycated hemoglobin levels in both participants having type 1 or 2 diabetes mellitus[172,173]. Moreover, the effectiveness of several types of oral glucose-lowering medication has been reported for ameliorating type 2 diabetes management, but adverse effects that result in therapy ineffectiveness present a significant challenge[174]. In addition, advancements in nanotechnology-based approaches are emerging with the potential to offer significant benefits in the management of type 2 diabetes, compared to traditional approaches[174,175].

The present study examined the relationship between trait impulsivity and the risk of developing type 2 diabetes. Moreover, this thesis further examined the relationships between glycemic dysregulations, cognitive function, and impulsivity. Firstly, there is compelling evidence from meta-analyses and large-scale observational studies with long follow-up periods indicating that glycemic dysregulations are detrimental to cognitive function. Among the glycemic dysregulations assessed were HbA1c levels and the presence and duration of type 2 diabetes. The results of these studies indicated a relationship between glycemic dysregulations and cognitive decline and impairment, as well as with the presence of mild cognitive impairment and dementia[81–83,176–182]. However, the current body of literature lacks sufficient evidence to determine whether a comprehensive assessment of multiple glycemic-related variables is associated with an adverse impact on cognitive function over a relatively brief period of two years. To the best of our knowledge, only one study has assessed longitudinal trends over a three-year

follow-up period in cognitive performance in participants with type 2 diabetes, and this study found no associations at the short-term level[183]. Accordingly, further research is required to ascertain potential relationships between glycemic dysregulations and cognitive decline over shorter periods of time. Secondly, previous research has indicated that certain psychological traits are associated with glycemic status and type 2 diabetes. These studies involved relatively small populations and mostly cross-sectional findings, indicating that glycemic dysregulations have been associated with higher impulsivity in adult populations with and without type 2 diabetes[84–89], although not all studies found significant links[184–186]. Unfortunately, despite the observation of positive relationships between impulsivity features and glycemic dysregulations, the potential association between trait impulsivity and the risk of developing type 2 diabetes was not investigated. In accordance with the Big Five personality trait model[187] and in results from pooling studies, only higher scores in conscientiousness levels demonstrated a consistently inverse relationship with HbA1c values and the risk of developing type 2 diabetes [8,188]. Thus, it is crucial to assess whether there is a link between trait impulsivity and the likelihood of developing type 2 diabetes, given that type 2 diabetes is one of the primary causes of death from noncommunicable diseases[156]. Moreover, it is noteworthy to increase the degree of evidence in the longitudinal relationships between impulsivity features and glycemic status measurements, such as the control of HbA1c levels in participants having type 2 diabetes. This will facilitate the assessment of whether future interventions aimed at reducing elevated impulsivity levels in populations at risk of developing cardiometabolic diseases or with established type 2 diabetes could be beneficial for reducing the subsequent disease burden.

COVID-19

Coronavirus Disease 2019 (COVID-19) is caused by the infection of a virus named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)[189]. The global pandemic of COVID-19 emerged in late 2019, significantly impacting public health and societies around the world[189]. The virus primarily affects the respiratory system, resulting in a spectrum of symptoms that may range from the typical symptoms of a common cold to those of a mild to moderate respiratory illness[190]. All individuals are susceptible to infection with SARS-CoV-2, with the potential for serious illness or death at any age, although the majority of infected individuals are expected to recover without the need for specialized treatment. Individuals of advanced age and those with preexisting medical conditions, including diabetes, chronic respiratory disease, cancer, or cardiovascular disease, may experience a severe form of illness necessitating medical intervention when they test positive for COVID-19[189]. This virus is transmitted between humans from an infected individual to another via liquid particles, which are typically dispersed by the mouth or nose when the infected person coughs, sneezes, speaks, sings, or breathes[189].

The number of positive COVID-19 cases reported by the World Health Organization until 7th July 2024 is around 776 million cases, with more than 7 million deaths[189]. The primary prevention for COVID-19 is vaccination, with over 13 billion COVID-19 vaccine doses administered as of June 2023, in addition to the use of face masks and proper hand hygiene[189].

The most prevalent symptoms of SARS-CoV-2 infection are to have fever, cough, tiredness, and loss of taste or smell[189,190]. However, additional symptoms such as sore throat, headache, musculoskeletal discomfort, diarrhea, and red or irritated eyes have also been commonly described[189,190]. In severe cases of COVID-19, patients have reported respiratory distress, dyspnea, speech difficulties, and chest discomfort[189,190]. Symptoms typically manifest 5 to 6 days after infection and are expected to resolve within two weeks[190]. Nevertheless, some individuals may experience symptoms for extended periods, even years after being positive cases of COVID-19. The term long COVID has been used to describe the persistence of symptoms for a minimum of three months,

encompassing a wide range of symptoms or conditions that may improve, worsen, or be ongoing[191].

The COVID-19 pandemic has exacerbated the challenges associated with the management of cardiometabolic diseases. Obesity, type 2 diabetes, chronic kidney diseases, and liver disease were reported to be significantly associated with higher risk of developing severe COVID-19 symptoms[192]. For example, individuals with type 2 diabetes and a diagnosis of COVID-19 exhibited a 6.3-fold elevated risk of mortality compared to those without diabetes[193]. Moreover, there is evidence indicating an increase in the incidence of new-onset diabetes cases during the course of the pandemic[194]. These findings have also been documented when studying associations between SARS-CoV-2 infection and cardiovascular disease. The prevalence of cardiovascular risk factors predisposes to severe COVID-19 illness, but also SARS-CoV-2 infection can impair the cardiovascular system increasing the risk for arrhythmia and heart failure, among other complications[195]. Nevertheless, the long-term impact of potential changes associated with the ongoing pandemic on the incidence of type 2 diabetes and cardiovascular disease requires further investigation in the forthcoming decades.

The psychological health after the COVID-19 pandemic has been disturbed noticeably[196]. All domains of human life were affected at some point during the pandemic, as one of the central strategies for managing the worldwide SARS-CoV-2 spread was the persuasive messaging, collective behavioral change, or restrictions imposed by government policies such as lockdowns[197]. For example, a comparative analysis of depression assessments conducted before and during the pandemic in children and adolescents across Europe revealed a 36% higher likelihood of developing clinically significant depressive disorders, along with a notable increase in the prevalence of general depressive symptoms[198]. Similar findings were observed in adolescents and young adults in the United States, indicating a heightened prevalence of depressive and anxiety symptoms during the pandemic[199]. In adult populations that had experienced an infection with the SARS-CoV-2 virus, depressive symptoms have been identified in approximately 35% of cases over short-, medium-, or long-term periods[200]. Indeed, an additional 53 (27% increase) and 76 (26% increase) million cases of major depressive disorder and anxiety disorders, respectively, within the COVID-19 pandemic period between January 2020

and January 2021 were globally estimated[201]. Furthermore, a decline in mental health and life satisfaction was documented in the United Kingdom and Spain[103,202].

Psychological-based interventions for individuals who have experienced infection with the SARS-CoV-2 virus appear to be promising in alleviating the negative psychological and social consequences of infection, including pharmacological treatments, cognitive behavioral therapy, physiotherapy, yoga, and outdoor and indoor exercise[202]. Therefore, it is imperative to continue monitoring the psychological and social components and the effects of psychological interventions with the aim of maintaining or increasing well-being in the post-pandemic era.

The present dissertation aimed to investigate whether individuals who had a positive diagnosis of COVID-19 exhibited changes in cognitive function or depressive symptoms. A novel aspect of our study was the inclusion of a control group of individuals who had not experienced a positive diagnosis of this infectious disease, along with the use of a longer follow-up period than have been employed in prior research.

II. JUSTIFICATION

UNIVERSITAT ROVIRA I VIRGILI
Psychology and Disease: Unveiling Emerging Perspectives on Their Interplay
Carlos Gómez Martínez

JUSTIFICATION

The physical and psychological health of individuals is of crucial importance for the well-being of populations and the economic growth of countries and states. Some psychological aspects, such as elevated levels of the personality trait of impulsivity, have been demonstrated to have a deleterious association with dietary components. A positive correlation has been observed between higher trait impulsivity values and the consumption of unhealthy foods, food groups, and individual dietary patterns. However, there is a paucity of studies that have assessed the longitudinal associations between trait impulsivity and both healthy and unhealthy dietary patterns. The PREDIMED-Plus-Cognition cohort has enabled the filling of this knowledge gap in the scientific field of trait impulsivity and dietary habits. Moreover, to the best of our knowledge, no study has assessed the longitudinal risk of developing type 2 diabetes or cardiovascular disease in the associations between trait impulsivity and the incidence of the two aforementioned cardiometabolic diseases. The NutriNet-Santé cohort allowed for an investigation of whether elevated levels of trait impulsivity may be associated with an increased risk of developing type 2 diabetes and cardiovascular disease.

On the other hand, the scientific literature has documented cross-sectional and positive associations between glycemic dysregulations and trait and behavioral impulsivity. The glycemic parameters assessed included insulin resistance and blood glucose levels, the prevalence of type 2 diabetes, and poor glycemic control in participants with this chronic insulin disease. Nevertheless, the lack of studies examining the prospective associations between these glycemic-related parameters and trait and behavioral impulsivity, as well as a global composite of these two impulsivity assessments, underscores the necessity for further research in this scientific field. The PREDIMED-Plus-Cognition cohort provided an opportunity to explore this novel approach by assessing a range of glycemic-related parameters and their association with global, trait, and behavioral impulsivity scores. Furthermore, there is a substantial and compelling body of evidence from the scientific literature that suggests a link between glycemic dysregulations and longitudinal changes in cognitive function. The PREDIMED-Plus study, permitted the examination of these associations in the short term, using longitudinal data from only the second year of follow-up, and the inclusion in a single manuscript of the associations between many glycemic-

related parameters and a global cognitive function composite derived from eight cognitive tests in a population of older Mediterranean adults with overweight or obesity and metabolic syndrome who were further following a lifestyle intervention. The glycemic-related parameters assessed included the evaluation of insulin resistance and blood glucose levels, the prevalence of type 2 diabetes and the duration since the type 2 diabetes diagnosis, a comparison between participants with poor and good diabetes control as assessed by HbA1c levels, and the use of multiple diabetic medications.

The ongoing COVID-19 pandemic has prompted the conduction of extensive and high-quality studies examining the relationship between COVID-19 status and cognitive function and mental health status such as depression However, the majority of studies have assessed these associations in the short term. Furthermore, some review manuscripts have emphasized the paucity of studies that have employed control groups that were not identified as positive cases of COVID-19[203]. The thesis was conducted during the ongoing pandemic, and therefore the PREDIMED-Plus study enabled the evidence to be strengthened by employing a control group and evaluating the associations over a longer follow-up period than in the majority of previous studies.

III. HYPOTHESIS AND AIMS

UNIVERSITAT ROVIRA I VIRGILI
Psychology and Disease: Unveiling Emerging Perspectives on Their Interplay
Carlos Gómez Martínez

HYPOTHESIS AND AIMS

Hypothesis 1: Higher trait impulsivity is associated with greater adherence to unhealthy dietary patterns and lower adherence to healthy dietary patterns in older adults at high cardiovascular risk.

Aim 1: To prospectively examine the associations between levels of trait impulsivity and adherence to healthy and unhealthy dietary patterns within the context of the PREDIMED-Plus-Cognition cohort (462 Spanish older adults at high risk of cardiovascular disease over three years of follow-up).

Hypothesis 2: Higher trait impulsivity is associated with an increased risk of developing cardiovascular disease.

Aim 2: To prospectively examine the associations between levels of trait impulsivity and the risk of incident cardiovascular disease within the context of the NutriNet-Santé cohort (48,377 general French adults over eight years of follow-up).

Hypothesis 3: Higher trait impulsivity is associated with an increased risk of developing type 2 diabetes.

Aim 3: To prospectively examine the associations between levels of trait impulsivity and the risk of developing type 2 diabetes within the context of the NutriNet-Santé cohort (48,135 general French adults over eight years of follow-up).

Hypothesis 4: Glycemic dysregulations are associated with increased impulsivity.

Aim 4: To prospectively examine the associations of insulin resistance, glycated hemoglobin, type 2 diabetes prevalence, and type 2 diabetes control with the global impulsivity composite, as well as with trait and behavioral impulsivity domains, within the context of the PREDIMED-Plus- Cognition cohort (487 Spanish older adults at high risk of cardiovascular disease over three years of follow-up).

Hypothesis 5: Glycemic dysregulations are associated with greater cognitive dysfunction.

Aim 5: To prospectively examine the associations of insulin resistance, glycated hemoglobin, type 2 diabetes prevalence, type 2 diabetes control, and diabetes medication use with cognitive function changes over two years of follow-up within the context of the PREDIMED-Plus cohort (6,874 Spanish older adults at high risk of cardiovascular disease over two years of follow-up).

Hypothesis 6: The presence of COVID-19 is associated with greater cognitive dysfunction.

Aim 6: To prospectively examine the associations of COVID-19 status (negative/positive) with cognitive impairment and changes in cognitive function before and after COVID-19 status ascertainment within the context of the PREDIMED-Plus cohort (50 weeks after COVID-19 status ascertainment in 5,179 Spanish older adults at high risk of cardiovascular disease).

Hypothesis 7: The presence of COVID-19 is associated with increased depressive symptomatology and risk.

Aim 7: To prospectively examine the associations of COVID-19 status (negative/positive) with depressive risk and changes in depressive symptomatology before and after COVID-19 status ascertainment within the context of the PREDIMED-Plus cohort (29 weeks after COVID-19 status ascertainment in 5,486 Spanish older adults at high risk of cardiovascular disease).

IV. MATERIAL AND METHODS

UNIVERSITAT ROVIRA I VIRGILI
Psychology and Disease: Unveiling Emerging Perspectives on Their Interplay
Carlos Gómez Martínez

THE PREDIMED-PLUS AND PREDIMED-PLUS-COGNITION STUDIES

Study Objective

The PREDIMED-Plus study (in Spanish: PREvención con DIeta MEDiterránea) aims to assess the effect of an intervention, based on the promotion of an energy-restricted Mediterranean diet and physical activity with behavioral support, on the primary prevention of cardiovascular disease. Therefore, the main objectives of this study are to assess the effect of an intensive lifestyle intervention on the incidence of cardiovascular events (non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death) and weight change (weight loss and long-term weight-loss maintenance).

As secondary objectives are evaluated the effect of the intervention on the reduction of waist circumference and acute coronary syndromes, coronary revascularization, total mortality, heart failure, peripheral artery disease, venous thrombosis, atrial fibrillation, type 2 diabetes and its complications, total cancer, cancer in main cancer sites (breast, prostate, colorectal, lung and stomach), gallstone diseases, symptomatic gout, neurodegenerative disorders (dementia and Parkinson's disease), unipolar depression, osteoporotic fractures, and eating behavior disorders. As intermediate outcomes are assessed the effect of the lifestyle intervention on the nutrient intake and overall dietary pattern, systolic and diastolic blood pressure, serum lipid concentrations, fasting glucose, glycated hemoglobin and uric acid, kidney function, liver function, C-reactive protein, medication needs of anti-hypertensive, anti-diabetic and lipid-lowering medications, electrocardiogram traits, cognitive function, quality of life, and psychopathological scales.

The PREDIMED-Plus-Cognition substudy was within the framework of the PREDIMED-Plus study and has the aim to amplify psychological and cognitive assessments.

Study Design

The PREDIMED-Plus study is an ongoing randomized, parallel-group, primary prevention clinical trial conducted in 23 centers across Spain and in adult men aged 55–

75 and adult women aged 60–75 with a BMI ≥27 and <40 kg/m2 who meet at least three criteria for the metabolic syndrome[204]. Participants allocated to the intervention group received recommendations to follow an energy-restricted Mediterranean diet, physical activity promotion, and behavioral support, whereas those participants in the control group received only usual care general recommendations to follow an energy-unrestricted Mediterranean diet. Participants were enrolled between September 2013 and December 2016 and performed the intervention program over 6 years further 2 additional years of follow-up, having a total of 8 years of follow-up.

Initially, physicians evaluated potential candidates in order to know their predisposition to be enrolled in the study. Later, they were called via telephone to explain the study and, if they had the predisposition to participate in the study a last face-to-face screening visit was done. If participants met with eligibility criteria and correctly completed the administered questionnaires and records, they were invited to attend the baseline visit in which the randomization procedure was performed. Participants were randomly allocated in a 1:1 ratio to either the intervention or control group, using a centrally controlled, computer-generated random-number internet-based system with stratification by center, sex, and age (<65, 65–70, and >70 years). Couples sharing the same household were randomized as pairs, using the couple as a randomization unit.

Participants in the intervention group were followed 3 times/month (an individual motivational interview, a telephone call, and a group session). Participants in the control group received nutritional educational sessions every 6 months (an individual visit and a group session) to follow a non-caloric reduced Mediterranean diet using the same PREDIMED study approach[205]. No specific advice for increasing physical activity or weight loss was provided to the control group. All participants received free extra virgin olive oil (1 L/month) to reinforce their adherence to the Mediterranean diet.

The PREDIMED-Plus-Cognition sub-study was performed in 4 of the 23 centers across Spain and is currently finalized with a total follow-up period of 3 years. Specialized psychological personnel administered the psychological questionnaires and cognitive tests.

Exclusion criteria for the PREDIMED-Plus study were: illiteracy or inability/unwillingness to give written informed consent or communicate with study staff,

institutionalization (the participant is a permanent or long-stay resident in a care home), documented history or previous cardiovascular disease, active malignant cancer or history of malignancy within the last 5 years (except non-melanoma skin cancer), inability to follow the recommended diet or to carry out physical activity, a low predicted likelihood to change dietary habits according to the Prochaska and DiClemente Stages of Change Model[206], inability to follow the scheduled intervention visits, inclusion in another program that provides advice on weight loss (>5 kg) in the six months before the selection visit, history of surgical procedures for weight loss or intention to undergo bariatric surgery in the next 12 months, history of small or large bowel resection, history of inflammatory bowel disease, obesity of known endocrine origin (except for treated hypothyroidism), food allergy to any component of the Mediterranean diet, immunodeficiency or HIV-positive status, cirrhosis or liver failure, serious psychiatric disorders as schizophrenia, bipolar disorder, eating disorders, or depression with hospitalization within the last 6 months, any severe co-morbidity condition with less than 24 months' life expectancy, alcohol abuse or addiction (or total daily alcohol intake >50g) or drug abuse within the past 6 months, history of major organ transplantation, concurrent therapy with immunosuppressive drugs or cytotoxic agents, current treatment with systemic corticosteroids, current use of weight loss medication, concurrent participation in another randomized clinical trial, patients with an acute infection or inflammation will be allowed to participate in the study 3 months after resolution of their condition, and any other condition that may interfere with adherence to the study protocol.

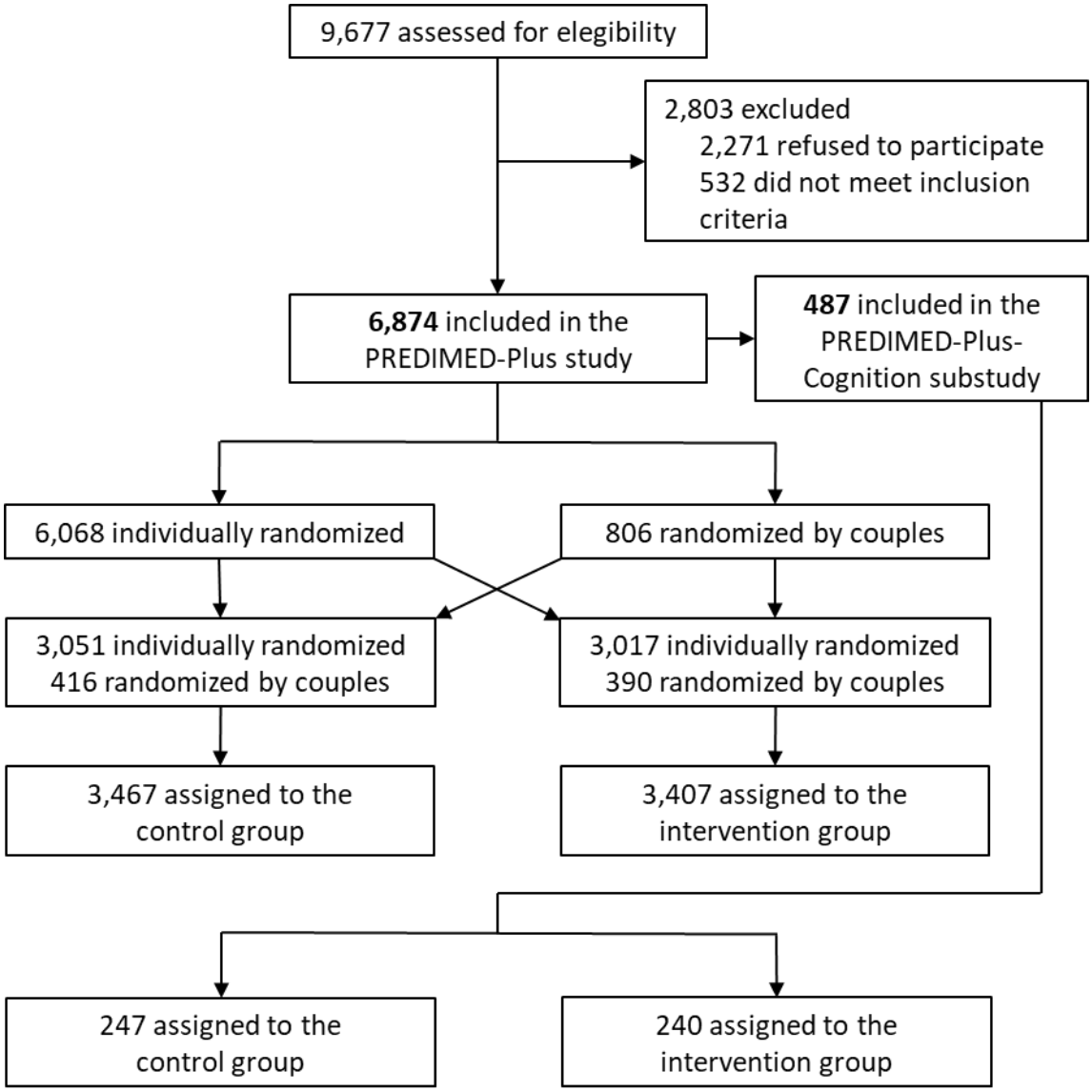
The study PREDIMED-Plus study protocol has been comprehensively described elsewhere[207,208] and can be found at http://www.predimedplus.com.

The trial was registered in the International Standard Randomized Controlled Trial registry and can be found on the website: http://www.isrctn.com/ISRCTN89898870.

Study Population

A total population of 9,677 individuals was assessed for eligibility, of which 6,874 participants were randomized. A total of 3,468 participants were assigned to the control group and 3,406 to the intervention group. A total of 487 participants were further included in the PREDIMED-Plus-Cognition study. A more detailed flowchart is presented in **Figure 2**.

Figure 2. Flowchart of the PREDIMED-Plus and PREDIMED-Plus-Cognition populations.



The ethical committees of all participating institutions approved the procedures and the study protocol following the Declaration of Helsinki standards, and all the participants signed the written informed consent.

Measurements

Several measurements were assessed and the data collection by visits of both the PREDIMED-Plus and PREDIMED-Plus-Cognition studies are described in **Table 1**. The measurements included in both studies are described in the following paragraphs of this section.

Table 1. Data collection by visits in the PREDIMED-Plus and PREDIMED-Plus-Cognition studies.

Measurements	Visits												
	S1	S2	S3	Y0	6m	Y1	Y2	Y3	Y4	Y5	Y6	Y7	Y8
Eligibility questionnaire	X												
3-day food register			X										
Anthropometric measurements	X		X	X	X	X	X	X	X	X	X	X	X
General questionnaires				X									
143-item FFQ			X		X	X	X	X	X	X	X	X	X
Mediterranean diet questionnaires				X	X	X	X	X	X	X	X	X	X
Physical activity questionnaires			X	X	X	X	X	X	X	X	X	X	X
Chair test				X	X	X	X	X	X	X	X	X	X
Accelerometers				X	X	X	X	X	X	X	X	X	X
Follow-up questionnaire					X	X	X	X	X	X	X	X	X
Electrocardiogram	X					X	X	X	X	X	X	X	X
Blood pressure	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sample				X	X	X		X		X		X	X
Urine collection				X	X	X		X		X		X	X
Nail collection				X		X		X		X		X	X
Neuropsychological tests			X				X		X		X		X
Psychopathological questionnaires			X			X	X	X	X	X	X	X	X
Quality of life questionnaires			X			X		X		X		X	
PREDIMED-Plus-Cognition questionnaires				X		X		X					
PREDIMED-Plus-Cognition tests				X		X		X					

Abbreviations: S, screening visit; m, month; Y, year; FFQ, food frequency questionnaire

Methods: Predimed-Plus

Regarding the PREDIMED-Plus study, the eligibility questionnaire selected the participants that can be enrolled in the final population with inclusion and exclusion criteria. The food register of 3 days recorded the aliments and quantity ingested in the last 3 complete days. Anthropometric measurements assessed weight, height, and waist circumference.

General questionnaires recorded medical data on medical and family history, and use of medications. The 143-item food-frequency questionnaire (FFQ), validated in Spanish populations[209], evaluates the quantities and amounts of specific aliments in their respective food groups. The validated Mediterranean Adherence Screener[210], also named the 14-point Mediterranean diet questionnaire, assessed the typical Mediterranean food pattern exclusively in the control group. The validated 17-point energy-restricted Mediterranean diet[211] assessed the Mediterranean diet with further caloric restriction. Physical activity assessment included the validated Regicor Short Physical Activity Questionnaire[212], as well as the Physical Activity Readiness Questionnaire[213], Rapid Assessment of Physical Activity[214], the Nurses' Health Study sedentary lifestyle questionnaire[215], and the 30 seconds Chair Test is a measurement of lower body strength in older adults[216]. Each participant in the intervention group received a pedometer to self-monitor the number of day steps. A total of 50% and 20% of participants in the intervention and control groups, respectively, were further provided with accelerometers for the purpose of quantifying physical activity. The follow-up questionnaires asked about clinical events during follow-ups.

Electrocardiograms were conducted at primary care centers. The collection of fasting blood samples enabled the measurement of lipid profiles (total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides), fasting plasma glucose, blood cell count, serum sodium, potassium, calcium, uric acid, urea, creatinine, albumin, C-reactive protein, erythrocyte sedimentation rate, glycated hemoglobin, liver function tests (serum bilirubin, alkaline phosphatase, alanine transaminase, aspartate aminotransferase, and gamma-glutamyltranspeptidase) and optional coagulation tests (prothrombin time, activated partial thromboplastin time and fibrinogen). Morning spot urine collection allowed us to obtain albumin and creatinine in urine, and nail sample collection was also obtained from participants.

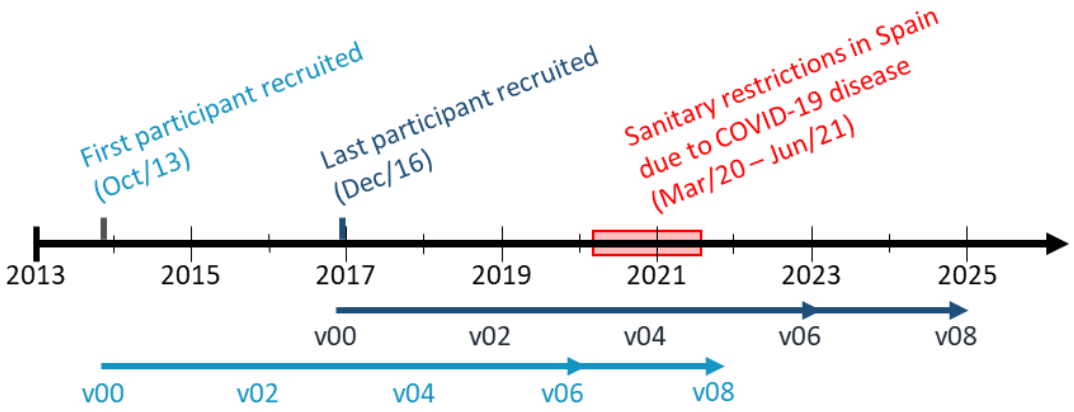
The neuropsychological evaluation included a battery of 6 cognitive tests: the Mini-Mental State Examination (MMSE)[217], the Clock Drawing Test (CDT)[218], the Digit Span Test (DST) forward (DST-f) and backward (DST-b) sections[219], the Verbal Fluency Test (VFT) animals (VFT-a) and letter "p" (VFT-p) categories[220,221], and the Trail Making Test (TMT) A (TMT-A) and B (TMT-B) sections[222]. Quality of life assessment was evaluated using the Short Form-36 Health Survey[223]. Psychopathological questionnaires included the Beck Depression Inventory-II (BDI-II)[224], the Multidimensional Scale of Weight Locus Control[225], and a screening for eating disorders[226].

Regarding the PREDIMED-Plus-Cognition sub-study, several psychological questionnaires were administered, including the lack of premeditation, lack of perseverance, negative urgency, and positive urgency (UPPS-P) Impulsive Behavior Scale[32], the Yale Food Addiction Scale[227], the Functioning Assessment Short Test[228], and the Dysexecutive Questionnaire[229]. Cognitive tests were also administered, including the Montreal Cognitive Assessment (MoCa)[230], the Stroop Color Word Test (STCW)[231], the Symbol Digit Modalities Test (SDMT)[232], the Rey Auditory Verbal Learning Test (RAVLT)[233], and the Rey–Osterrieth Complex Figure Test (ROCF)[234]. Furthermore, the computerized Iowa Gambling Task (IGT)[235] and the Conners' Continuous Performance Test Third Edition (CPT)[236] were administered.

The pandemic of COVID-19 occurred while the PREDIMED-Plus study was ongoing and all participants were being recruited. This exceptional situation changed the design of the PREDIMED-Plus study. However, an adaptation of the intervention was made during the sanitary restrictions that occurred in Spain during March/2020-June/2021, in order to adapt the way to collect data and maintain the compliance of the study[237]. **Figure 3** shows when the sanitary restrictions in Spain due to the COVID-19 disease affected the follow-up visits of the PREDIMED-Plus participants. Since PREDIMED-Plus is a multicenter study, it was susceptible to regional health regulations. Therefore, between June and July 2021, a questionnaire was sent to all principal investigators to assess the general impact of social and mobility restrictions enforced to slow COVID-19 transmission on the PREDIMED-Plus intervention and data collection. This COVID-19 questionnaire was divided into five study periods (Mar-May/2020, Jun-Aug/2020, Sep-Dec/2020, Jan-Mar/2021, and Apr-Jun/2021) and consisted of two parts. Part A included 8 questions related to the percentage of time spent in lockdown and the severity of the restrictions imposed, with responses ranging from 0% "There was no lockdown during

this period" to 100% "There was total restriction during the entire period. Part B included 7 questions related to the proportion of different methods used for contacting participants, data collection, and intervention strategies, with responses ranging from 0% "This method was not used" to 100% "This was the only method used". For intermediate situations, investigators were asked to use only the percentages 25%, 50%, and 75%[237].

Figure 3. Influence of sanitary restrictions in Spain due to COVID-19 on the follow-up of participants in the PREDIMED-Plus trial.



Abbreviations: v00, baseline visit; v02, second-year follow-up visit; v04, fourth-year follow-up visit; v06, sixth-year follow-up visit; v08, eighth-year follow-up visit. The PREDIMED-Plus intervention was conducted between the v00 and the v06 visits. No intervention was conducted and only observational data was collected between the v06 and v08 visits.

Measurements of Interest

For the purpose of this doctoral thesis, a comprehensive description of the exposures and outcomes of interest will be described in this section.

Concerning diet, a total of 10 scores assessing adherence to several dietary patterns were estimated using questionnaires and the 143-FFQ, and a brief description of all of them is described below. Plant-based diets are characterized by higher consumption of plant-based foods rather than animal sources and are typically associated with less risk of cardiovascular disease[238]. The Healthy and Unhealthy Plant-Based dietary patterns were obtained using the respective dietary scores[239]. Mediterranean diet was associated with

improved health status and especially less risk of cardiovascular disease incidence[205,240]. Mediterranean diets are based on the consumption of fruits and vegetables, whole grains, extra virgin olive oil as principal fat, nuts, white meat, and fish. The adherence to both the Mediterranean diet and the energy-restricted Mediterranean diet was evaluated using the 14-point and 17-point Mediterranean Diet Adherence Screener[210,211], respectively. The United States defined nutritional guidelines in order to reduce the incidence of cardiovascular disease. hese guidelines focus on dietary intake that includes vegetables, fruits, whole grains, nuts, legumes, long-chain omega-3 fatty acids, and polyunsaturated fats, while limiting the consumption of red meat, trans fats, and sugar-sweetened beverages. The 2010 Alternative Healthy Eating Index[241] is the dietary pattern following these recommendations and was also estimated for the present work. The Portfolio diet[242] is a plant-based dietary pattern, focusing on recognized lowering-cholesterol food intake and having as key components soluble fibers, plant sterols and stanols, nuts, and soy proteins. This diet was originally developed in Canada and was also obtained for the current work. The DASH[243] is a dietary pattern aiming to reduce hypertension and focusing on high vegetables, fruits, whole grains, lean proteins, nuts, seeds, legumes, and low-fat or fat-free dairy products consumption as well as reducing sodium and sweets and added sugars. The Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND)[244] is a hybrid of the Mediterranean and DASH diets. This dietary pattern aims to promote brain health and reduce the risk of neurodegenerative diseases by emphasizing foods believed to benefit the brain, such as green leafy vegetables, berries, nuts, olive oil, fish, poultry, and moderate wine consumption, while limiting sweets, pastries, and fried and fast foods. The EAT-Lancet developed the Planetary Healthy Diet or EAT-Lancet diet[245], a set of dietary recommendations aiming to create a diet that is not only healthy for individuals but also sustainable for the planet. The key components are established on plant-based emphasis, moderate and ecological-based animal consumption such as fish, poultry, eggs, and dairy, and limited added sugars and caloric intake according the sex. Finally, the author of this thesis developed a Western diet score[246], an unhealthy dietary pattern related to several chronic diseases[118]. A summary of the principal dietary components of this diet, as well as the methodology for calculating Western dietary patterns, is provided in **Table 2**.

Table 2. Principal dietary components of the Western diet and the methodology used to obtain the Western dietary pattern score.

Food group	Food components
Low intake	
Whole grains	Integral pasta; integral rice; integral bread; integral muesli
Fruits	Orange, grapefruit or mandarin; banana; apple or pear; strawberry; cherry or plum; peach; watermelon; melon; kiwi; grape
Vegetables	Chard or spinach; cabbage, cauliflower or broccoli; lettuce, endive or escarole; tomato; carrot or pumpkin; green bean; eggplant, zucchini or cucumber; pepper; asparagus; gazpacho; onion; garlic; boiled potato; other vegetables
Fish	White fish; blue fish; natural canned fish; oil canned fish
Nuts	Almond; pistachio; walnut; other nuts
Legumes	Lentil; bean; chickpea; pea or broad pea;
High intake	
Refined grains	White pasta; white rice; white bread
Fast/fried foods	Pizza; croquette; fried potato; chips; snacks
Red and processed meats	Calf; pork; lamb; hamburger or meatball; bacon; liver; other animal entrails; serrano ham; York ham or cocked ham; processed meats
Butters	Butter; margarine; lard
High sugar drinks	High sugar carbonated beverages; bottling or canned fruit juices
Sweets and desserts	Cookies; chocolate cookies; cake; sponge cake; croissant; donut; cupcake; churros; chocolate; nougat; marzipan

The amount of each food component was determined by considering the frequency of consumption multiplied by the standard serving amount.
Each food group was divided into quintiles: 1st quintile = 1 point; 2nd quintile = 2 points; 3rd quintile = 3 points; 4th quintile = 4 points; 5th quintile = 5 points.
The total score for each low-intake food group was reversed.
Western diet score was obtained following the formula: Western diet = refined grains + fast/fried foods + red and processed meats + butters + high sugar drinks + sweets and desserts + whole grains + fruits + vegetables + fish + nuts + legumes.

Regarding glycemic status, we will use data on insulin resistance, glycated hemoglobin, type 2 diabetes prevalence and duration, and control of diabetes in those participants with type 2 diabetes. Blood samples were collected in fasting conditions and glycated hemoglobin (HbA1c) and insulin were obtained by routine laboratory methods. Insulin was obtained by an electrochemiluminescence immunoassay using an Elecsys immunoanalyzer (Roche Diagnostics, Meylan, France), and the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) index was calculated[247]. Prediabetes and

type 2 diabetes status were defined following the Diabetes Association criteria[248]. Prediabetes status was determined by HbA1c being between 39 mmol/mol (5.7%) and 46 mmol/mol (6.4%), or having fasting plasma glucose between ≥100 mg/dl and ≤125 mg/dl. Type 2 diabetes was defined with a previous diagnosis of diabetes, HbA1c ≥48 mmol/mol (6.5%), use of antidiabetic medication, or having fasting plasma glucose >126 mg/dl in both the screening and baseline visits. Furthermore, diabetes duration was also assessed by self-reported data in less than 5 years or equal to or more than 5 years of diabetes duration. The rest of the participants who did not meet any of these criteria were categorized into the non-diabetes category. Therefore, all the possible categories of diabetes status were: no diabetes (excluding those with prediabetes); no diabetes (including those with prediabetes); prediabetes; type 2 diabetes prevalence; less than 5 years of diabetes duration; more than 5 years of diabetes duration. Control of diabetes was assessed using HbA1c cut-offs, following the Diabetes Association criteria[248]. Good control and poor control of diabetes were categorized using the following values: (HbA1c <57 mmol/mol or ≥57 mmol/mol; 57 mmol/mol = 7.4%), respectively. Moreover, diabetes treatment was also evaluated using self-reported data on insulin, sulfonylureas, metformin, or dipeptidyl peptidase-4 inhibitors (IDPP-4) medication use.

Concerning impulsivity, both trait and behavioral impulsivity were measured. Trait impulsivity was assessed using the validated Spanish version[249] of the Impulsive Behavior Scale (UPPS-P) questionnaire[32]. This scale assesses 5 impulsivity-related dimensions, including negative urgency, (lack of) perseverance, (lack of) premeditation, sensation seeking, and positive urgency. Each subscale was generated by adding their respective items and the total score was obtained by adding all the items. The UPPS-P score ranges between 0 to 236 points and higher scores indicate higher impulsivity. Behavioral impulsivity was evaluated using the CPT third edition, the IGT, and the SCWT. The CPT is a computer-based task in which participants have to press the space bar over 14 minutes in response to stimuli. The CPT reports several measurements, and the commissions and perseveration scores were the selected scores due to they were impulsivity-related assessments[236]. The commission score indicates failed targets (e.g.: responding to a non-target), whereas the perseveration score indicates random or anticipatory responses (e.g.: hit reaction time <100ms). For both assessments, higher scores reflect higher impulsivity. The IGT[250] is a computer-based task in which participants have to choose across 4 card decks. With each choice, a monetary reward or

punishment appears and the final objective is to win as much money as possible. The IGT evaluates risky decision-making, a measure related to impulsivity[28]. Higher scores on the IGT indicate lower impulsivity because participants showed better performance under a risky decision-making situation. The Spanish version of the SCWT[231] contains three different tasks in which congruent and incongruent stimuli, based on words and the color printed in the words, are presented. Each task allows for 45 seconds, and an interference score was obtained from the values of the three different tasks. This interference score assesses the participants' inhibition control capacity, a measure related to impulsivity[28]. Higher scores indicate better inhibition control and therefore, lower impulsivity.

Regarding cognitive function, it is assessed different cognitive performance assessments based on a battery of 8 cognitive tests. The MMSE[217] is a cognitive screening test validated for Spanish populations[251], being also an assessment of general cognitive function. The MMSE includes several sections, being temporal orientation, spatial orientation, registration, attention and calculation, remote memory, naming 2 objects, repeating a sentence, stage a command of mobility, writing a complete sentence, reading a sentence and obeying a command, and copy two pentagons with an intersection. The MMSE has a maximum punctuation of 30 points, and higher scores indicate better cognitive performance. The CDT[218] is a cognitive screening test and the Spanish 7-point version[252] was used. The CDT evaluates visuospatial, visuoconstruction, memory capacities, and verbal and numerical knowledge[218] asking the participant to draw a clock with a specific hour. Higher scores indicate better cognitive function. The VFT[220,221] was psychometrically assessed in Spanish populations[252,253], and the semantic VFT animals and the phonological VFT letter "p" categories for Spanish populations were assessed. For both tasks, participants have 60 seconds to say the maximum words they can concerning animals for the VFT-a and to start with the letter "p" for the VFT-p. Higher scores of the VFT-a and the VFT-p reflect better language and executive function capacities[254]. The TMT[222] consists of two different sections, existing normative data for Spanish populations[255]. In the first section, the TMT-A, participants have to connect consecutively numbers drawing a line. In the second section, the TMT-B participants have to connect consecutively and alternatively numbers and letters (1-A-2-B-3-C-…). The TMT-A assesses processing speed[255], whereas the TMT-B evaluates cognitive flexibility[256]. The time spent for each section was the total punctuation, and higher scores indicate poorer cognitive performance.

Concerning depression, it was assessed by using the BDI-II, a 21-item self-report inventory designed to quantifythe severity of depressive symptomatology in adolescent and adult populations[224]. Each item is scored on a 4-point Likert scale, with scores ranging from 0 to 3. Depressive symptomatology was assessed as a continuous variable using the total score of the BDI-II (range: 0-63 points), and as a dichotomous variable using the internationally validated cut-off for obtaining low (<14) and elevated (≥14) depression risk categories.

Regarding COVID-19 disease, the occurrence of COVID-19 (negative/positive) was defined by the PREDIMED-Plus Clinical Event Ascertainment. Clinical event adjudication was based on information from the participants' medical records, which were reviewed annually by the participating physicians. This determination was based on the Centers for Disease Control and Prevention (CDC) guidelines, which define a negative or positive COVID-19 event based on the detection of SARS-Cov-2 by polymerase chain reaction (PCR) or antigen tests such as the immunoglobulin test G (IgG)[257], or if the physician noted in the participant's Spanish medical history that they had a positive COVID-19 disease event. Participants who did not have a confirmed or probable positive case of COVID-19 disease were considered to be COVID-19 negative (i.e., presumed not to have experienced the infection). In addition, a sub-sample of the PREDIMED-Plus study underwent serologic testing using SARS-CoV-2 IgG ELISA kits (n=3,982) between 3 March 2020 and 25 December 2021.

THE NUTRINET-SANTÉ STUDY

Study Objective

The NutriNet-Santé study aims to investigate the associations between nutrition and health outcomes such as healthy aging, quality of life, obesity, hypertension, metabolic syndrome, type 2 diabetes, cardiovascular disease, cancers, depression, and mortality, among others[258]. Secondary objectives are concerned with the study of determinants of nutritional status, such as psychological, sociological, economic, and cultural factors associated with diet and the consequent nutrition-related health, as well as their interactions. Furthermore, the NutriNet-Santé study aims to study the nutritional status of the population over time, assess the level of exposure to nutritional risks, and estimate the impact of public health campaigns or activities on the population[258].

Study Design

The NutriNet-Santé study is an observational, web-based, ongoing prospective cohort study conducted in the general population in France. Participants are being recruited through an extensive nationwide multimedia initiative started between April and May 2009 using an extensive multimedia campaign including television, radio, national and regional newspapers, posters, and the internet. The aim was to raise public awareness of the study, call for volunteers, and provide information on enrollment procedures. This information is accessible through the study website: http://www.etude-nutrinet-sante.fr. The call for volunteers is The NutriNet-Santé study is an observational, web-based, ongoing prospective cohort study of the general population in France. Participants are being recruited through an extensive nationwide multimedia initiative launched between April and May 2009 using a comprehensive multimedia campaign including television, radio, national and regional newspapers, posters, and the internet. The aim was to raise public awareness of the study, call for volunteers, and provide information on enrollment procedures. This information is available on the study website: http://www.etude-nutrinet-sante.fr. The call for volunteers is prominently displayed on the websites of all institutional partners involved in the study. A poster and bulletin board advertising campaign are conducted through various professional channels, including physicians, pharmacists, dentists, and town hall administrators. Enrollment will remain open

throughout the study duration, and consists of three dietary questionnaires and a sociodemographic, lifestyle, health status, anthropometric, and physical activity questionnaire. During follow-up, additional questionnaires were administered and participants can update their self-reports of health events via the NutriNet-Santé intranet, which are validated by an expert NutriNet-Santé committee that has access to the medical information recorded in the Système National d'Information Inter-Régimes de l'Assurance Maladie (SNIIRAM) through the Caisse Nationale de l'Assurance Maladie (CNAM) of the French national health insurance system.

The inclusion criteria are adult volunteers aged with or higher than 18 years old, who have access to and ability to manage internet features and speak French fluently, with no further exclusion criteria being determined.

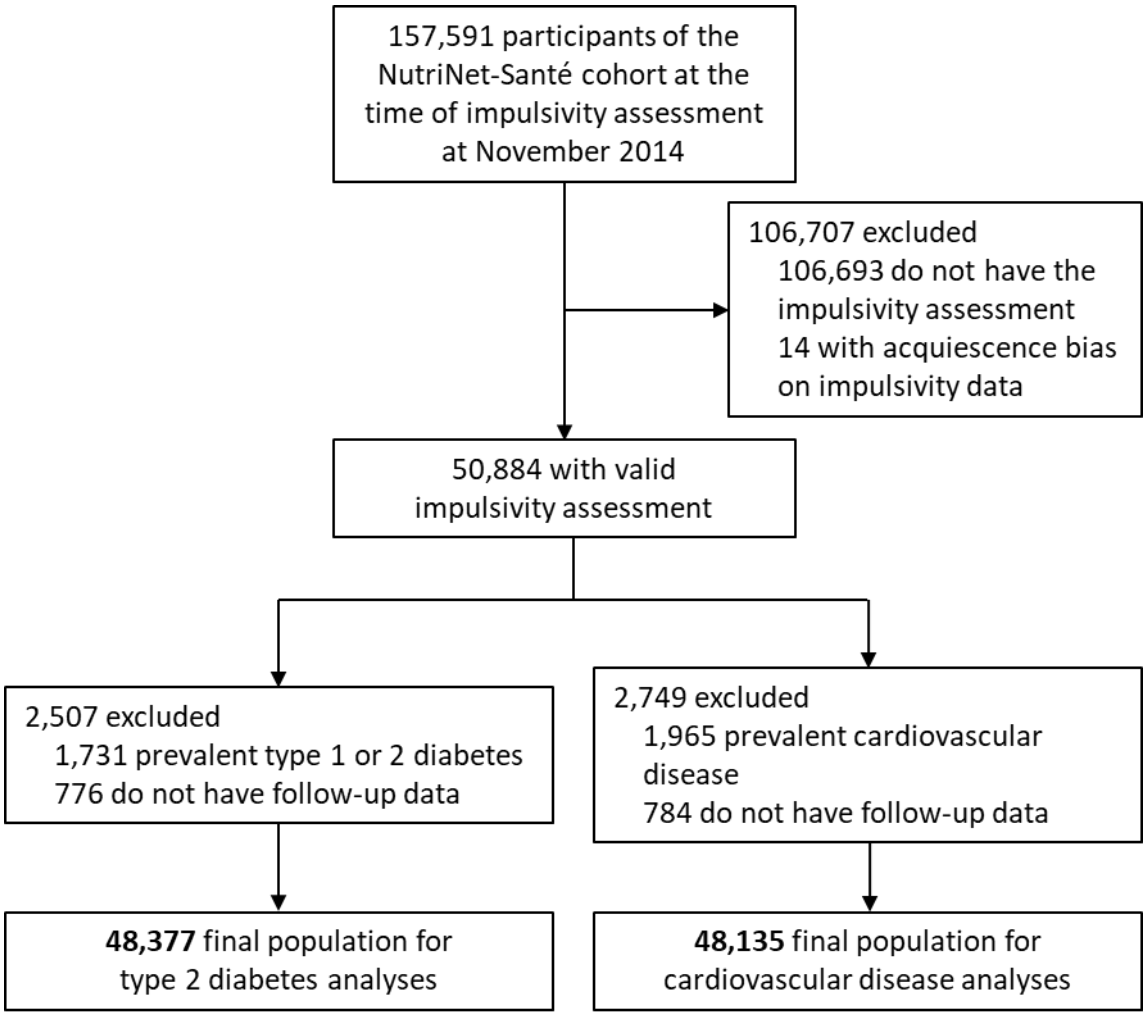
The study protocol is described elsewhere[258] and can be found at: https://www.info.etude-nutrinet-sante.fr/siteinfo/.

The cohort was registered on 11th October 2017 in the International Standard Randomized Controlled Trial registry, entitled "The NutriNet-Santé Study. A Web-based Prospective Cohort Study of the Relationship Between Nutrition and Health and of Dietary Patterns and Nutritional Status Predictors" and with a cohort registration number of NCT03335644. This information can be found at the following website link: https://www.clinicaltrials.gov/ct2/show/NCT03335644.

Study Population

It is estimated that the NutriNet-Santé study population currently consists of approximately 200,000 volunteers. For the purposes of the current work, the total population was only considered up to November 2014, when the trait impulsivity was assessed. At that time, the total population consisted of 157,611 participants, but only 32.4% of participants had a valid impulsivity questionnaire assessment. A detailed flowchart illustrating the study population is provided in **Figure 4**.

Figure 4. Flowchart of the NutriNet-Santé population.



All participants report an electronic informed consent. Procedures were approved by the Commission Nationale de l'Informatique et des Libertés (CNIL no: 908450 and 909216) and the Institutional Research Board of the French Institute for Health and Medical Research (IRB INSERM no: 0000388FWA00005831), according with the Declaration of Helsinki standards.

Measurements

The NutriNet-Santé study has an inclusion kit of questionnaires, one questionnaire for each month of follow-up, and a similar inclusion kit of questionnaires when a full year of follow-up has been achieved. The same structure was implemented for subsequent follow-up visits, with the expectation that participants would have at least 10 years of follow-up records. Additionally, from the beginning of the study to the 14th December

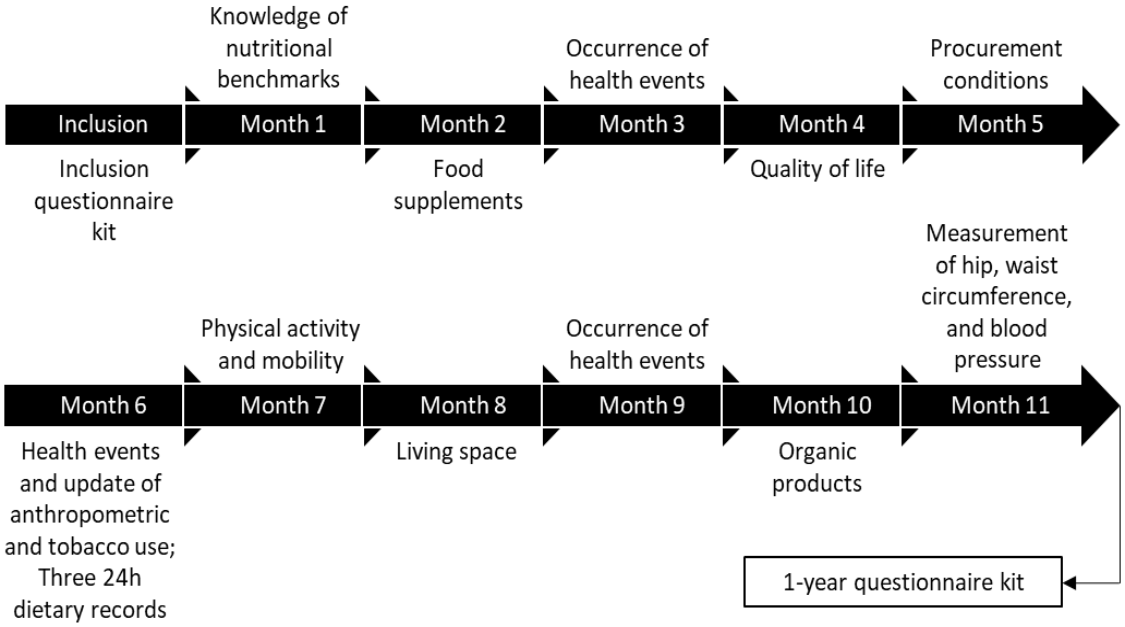
2016, and from the 15th December 2016 to the present date, the way in which the questionnaires were administered to participants presented modifications. In addition, additional questionnaires were sent out to all participants on specific dates.

Regarding the inclusion kit of questionnaires, a registration questionnaire including sex as well as date and location of birth was recorded. A sociodemographic questionnaire including household, household situation, current profession, professional status, higher education level achieved, partner situation, household income, tobacco and alcohol consumption, and seafood products were collected. A health status questionnaire asking for cardiovascular, cancers, type 2 diabetes, other diseases, healthcare, family history of diseases, blood pressure, medication use, disabilities, and reproductive history (only for women) was recorded. An anthropometric questionnaire included a self-reported weight and height measurement and also asked for recent weight change, weight fluctuation history, dieting, and intentional weight loss. Regarding the physical activity and sedentary behavior questionnaire, the International Physical Activity Questionnaire (IPAQ)[259] was administered obtaining low, moderate, and high categories of physical activity. To finish with the inclusion kit questionnaire, three 24-hour dietary records have to be completed by the participants and these records will provide a comprehensive account of their dietary habits, including the types and quantities of foods and beverages consumed, as well as the associated details such as time and location.

Subsequently, depending on the month each participant reached in the study, a specific questionnaire was sent to them. The list of questionnaires sent from the beginning of the study until December 14, 2016, can be found at the following link: https://info.etude-nutrinet-sante.fr/siteinfo/article/52. The list of sent questionnaires from the 15th December 2016 to the present date can be found in the following link: https://info.etude-nutrinet-sante.fr/siteinfo/article/53. The questionnaires sent at specific time points can be found in the latter two links mentioned at the bottom of the webpage. An example of the questionnaire administration during the first year of follow-up is shown in **Figure 5**.

The NutriNet-Santé study focuses on any minor or major health event of the participants, who can upload data on their health status at any time via the NutriNet-Santé intranet. The NutriNet-Santé Medical Expert Committee evaluated the participants' health status updates using a multi-source approach to validate the health events.

Figure 5. NutriNet-Santé questionnaire administration across the first year of follow-up.



Measurements of Interest

Trait impulsivity was assessed using the 11th version of the Barratt Impulsiveness Scale (BIS-11)[260], which was adapted from the validated French version of the BIS-10[261]. The BIS-11 is the most widely used instrument to assess trait impulsivity in both research and clinical practice[262]. This questionnaire was administered to participants between May and November 2014. The BIS-11 was a self-reported questionnaire with a 4-point Likert scale scoring, which ranges from "rarely/never" (1 point) to "almost always/always" (4 points). Item examples are: "I do things without thinking?", or "I act on impulse?". Additionally, the BIS-11 presents a total of three subfactors, being the attentional, motor, and non-planning subfactor scales. The total trait impulsivity score from the BIS-11 ranges from 30 to 120, with higher scores reflecting higher trait impulsivity. The total score showed an acceptable internal consistency displaying a 0.77 α Cronbach coefficient.

Cardiovascular disease and type 2 diabetes cases were identified through a comprehensive approach involving multiple sources. Participants were asked to report any new health status event, including type 2 diabetes and cardiovascular disease, through yearly questionnaires, the health status check-up sent every six months, or spontaneously at any time using the NutriNet-Santé intranet. These health events were reviewed by the NutriNet-Santé physician expert committee, and they asked participants, participants'

physicians, or medical institutions to complement this health status event with additional medical records, such as diagnoses, examinations, or hospitalizations. When participants did not upload information for a year or more, the physician expert committee contacted the participants' families or physicians to know about the health status of the participants. Moreover, cardiovascular disease and type 2 diabetes events were linked to the SNIIRAM database, administered by CNAM, as well as to the French National Mortality Registry (CépiDC) to identify mortality due to cardiovascular disease or type 2 diabetes events. This linkage limits the potential bias of participants who did not report a cardiovascular disease or type 2 diabetes event. The SNIIRAM uses the International Chronic Diseases Classification Clinical Modification 10th Revision (ICD-10)[263] to ascertain incident cases of cardiovascular disease or type 2 diabetes. Incident cardiovascular disease events were classified as coronary heart disease [myocardial infarction (I21), acute coronary syndrome (I20.0 and I21.4), angina pectoris (I20.1, I20.8, I20.9), and angioplasty (Z95.8)], and as cerebrovascular disease [stroke (I64), transient ischaemic attack (G45.8 and G45.9)]. Participants contributed person-time from their impulsivity assessment until the date of cardiovascular disease or type 2 diabetes event, date of last follow-up, date of death, or 8th February 2023, whichever occurred first.

STATISTICAL ANALYSES

Statistical analyses were described in detail in each chapter of the results section of the present doctoral thesis. The statistical analyses conducted were performed using the PREDIMED-Plus database in the second year of follow-up, the complete Predimed-Plus-Cognition database, and the NutriNet-Santé database which includes data regarding trait impulsivity until 8th February 2023. Briefly, the statistical analyses conducted were as follows:

- Descriptive population analyses were conducted using means and standard deviations (SD) for continuous variables and numbers and percentages (%) for qualitative variables. In the NutriNet-Santé analyses, the median and interquartile range for the follow-up period were determined. The evaluation of differences in exposure variables of interest was conducted using the t-test for dichotomous variables, the one-way ANOVA test for categorical variables, and the Pearson chi-square test for quantitative variables.
- Main prospective analyses were conducted using linear regression models and linear mixed models, with the estimation of beta coefficients. Logistic regression models were employed to calculate odds ratios. Cox regression models were utilized to estimate hazard ratios, cumulative hazard functions, and person-time contributions. Additionally, incidence rates were calculated to assess the frequency of events occurring over time. The aforementioned coefficients were presented with 95% confidence intervals.
- Interaction analyses were conducted using the likelihood ratio test, which involved comparing the primary model with a model that included an interaction term between the exposure variable and the primary covariate of interest. In instances where a significant interaction was identified, the results were stratified according to the particular covariate of interest. Some of these covariates of interest were intervention group, sex, age, or body mass index status.

All analyses were performed using STATA versions 14 and 18 (StataCorp LLC; http://www.stata.com). Statistical significance was determined at a threshold of p-value < 0.05.

V.RESULTS

UNIVERSITAT ROVIRA I VIRGILI
Psychology and Disease: Unveiling Emerging Perspectives on Their Interplay
Carlos Gómez Martínez

THESIS-RELATED PUBLICATIONS

Table 3. Details of thesis-related publications.

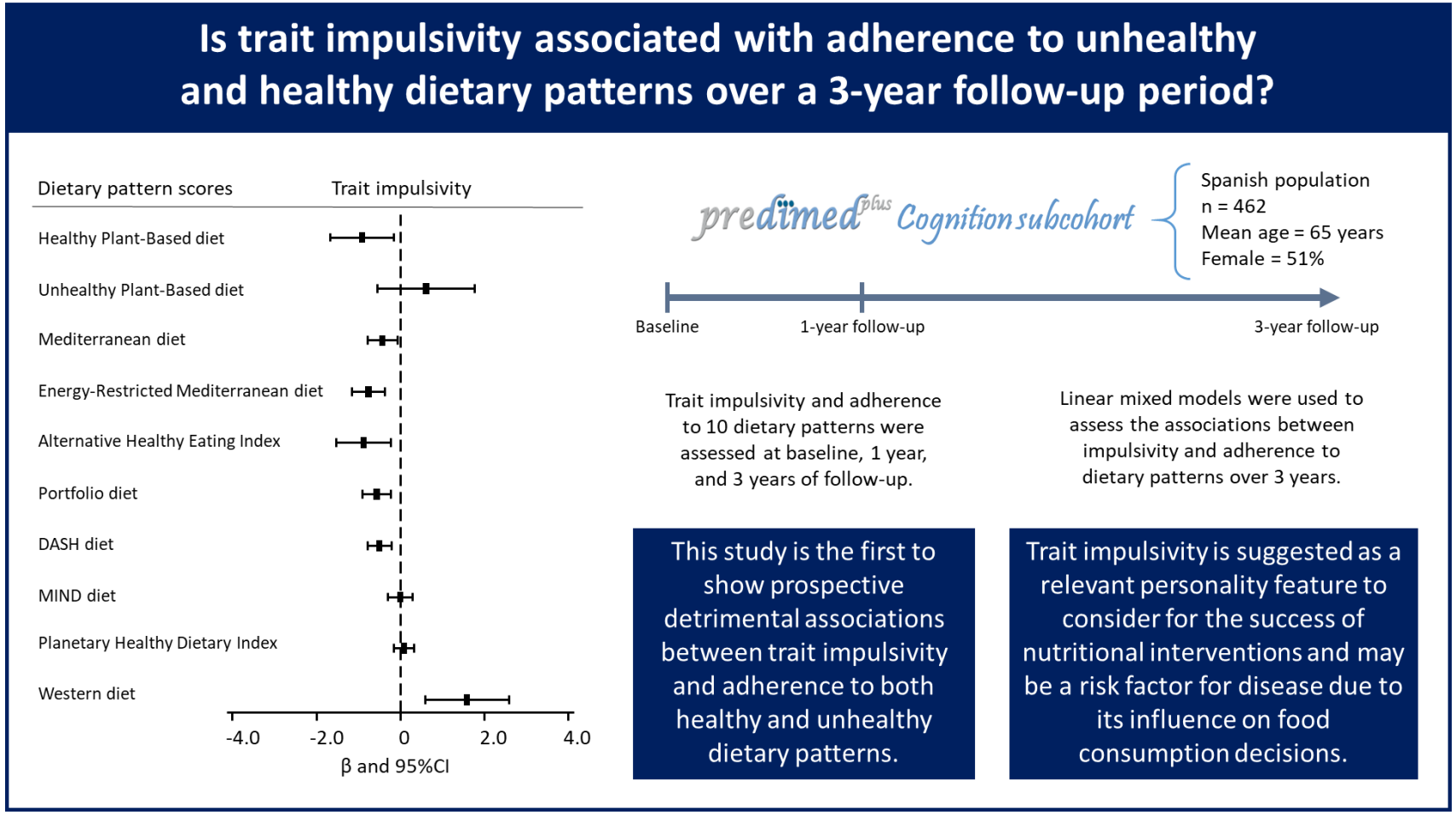
CHAPTER NUMBER AND TITLE	MANUSCRIPT TITLE (DOI)	JOURNAL (PUBLICATION DATE)	IMPACT FACTOR; POSITION IN CATEGORY
1 – TRAIT IMPULSIVITY AND ADHERENCE TO DIETARY PATTERNS	Impulsivity is longitudinally associated with healthy and unhealthy dietary patterns in individuals with overweight or obesity and metabolic syndrome within the framework of the PREDIMED-Plus trial (https://doi.org/10.1186/s12966-022-01335-8)	International Journal of Behavioral Nutrition and Physical Activity (08/Aug/2022)	8.7 (2022); 7/88 in Nutrition and Dietetics = D1
2 – TRAIT IMPULSIVITY AND INCIDENCE OF CARDIOVASCULAR DISEASE	Trait impulsivity is associated with an increased risk of cardiovascular disease incidence over 8 years of follow-up: results from the NutriNet-Santé cohort	In preparation	
3 – TRAIT IMPULSIVITY AND INCIDENCE OF TYPE 2 DIABETES	Trait impulsivity is associated with an increased risk of type 2 diabetes incidence in adults over 8 years of follow-up: results from the NutriNet-Santé cohort (https://doi.org/10.1186/s12916-024-03540-7)	BMC Medicine (15/Aug/2024)	7.0 (2023); 23/325 in Medicine, General & Internal = D1
4 – GLYCEMIC STATUS AND IMPULSIVITY	Glycated hemoglobin, type 2 diabetes, and poor diabetes control are positively associated with impulsivity changes in aged individuals with overweight or obesity and metabolic syndrome (https://doi.org/10.1111/nyas.15205)	Annals of the New York Academy of Sciences (16/Aug/2024)	4.1 (2023); 24/134 in Multidisciplinary Sciences = Q1

5 – GLYCEMIC STATUS AND COGNITIVE FUNCTION	Glycemic Dysregulations Are Associated With Worsening Cognitive Function in Older Participants at High Risk of Cardiovascular Disease: Two-Year Follow-up in the PREDIMED-Plus Study (https://doi.org/10.3389/fendo.2021.754347)	Frontiers in Endocrinology (29/Oct/2021)	6.1 (2021); 33/146 in Endocrinology and Metabolism = Q1
6 – COVID-19 AND COGNITIVE FUNCTION	COVID-19 and Cognitive Decline in Older Adults with High-Cardiovascular Risk: A Post Hoc Analysis (http://dx.doi.org/10.14336/AD.2024.0380)	Aging and Disease (21/Jul/2024)	7.0 (2023); 6/74 in Geriatrics and Gerontology = D1
7 – COVID-19 AND DEPRESSIVE SYMPTOMATOLOGY	Coronavirus disease 2019 is associated with long-term depressive symptoms in Spanish older adults with overweight/obesity and metabolic syndrome (https://doi.org/10.1017/S0033291723002313)	Psychological Medicine (05/Sep/2023)	5.9 (2023); 7/92 in Psychology = D1

Note: The impact factor of the journals was obtained using the Journal Citation Reports of the Web of Science webpage.

CHAPTER 1:
TRAIT IMPULSIVITY AND ADHERENCE TO DIETARY PATTERNS

Figure 6. Graphical abstract of Chapter 1. Trait impulsivity and adherence to dietary patterns.



International Journal of Behavioral Nutrition and Physical Activity

RESEARCH

Open Access

Impulsivity is longitudinally associated with healthy and unhealthy dietary patterns in individuals with overweight or obesity and metabolic syndrome within the framework of the PREDIMED-Plus trial

Carlos Gómez-Martínez[1,2,3], Nancy Babio[1,2,3*], Jordi Júlvez[4], Stephanie K. Nishi[1,2,3,5,6], Fernando Fernández-Aranda[3,7], Miguel Ángel Martínez-González[3,8], Aida Cuenca-Royo[3,9], Rebeca Fernández[3,10], Susana Jiménez-Murcia[3,7], Rafael de la Torre[3,9,11], Xavier Pintó[3,12,13], Mirjam Bloemendaal[14,15], Montse Fitó[3,9], Dolores Corella[3,10], Alejandro Arias[14,15] and Jordi Salas-Salvadó[1,2,3*]

Abstract

Background: Few studies have analyzed the associations between impulsivity and dietary patterns. Some of them have shown a cross-sectional inverse relationship between impulsivity and healthy diet scores, whereas others reported a positive association with unhealthy dietary assessments. We aimed to examine longitudinal associations of impulsivity trait with adherence to healthy and unhealthy dietary patterns in older participants at high risk of cardiovascular disease over 3 years of follow-up.

Methods: A 3-year prospective cohort analysis within the PREDIMED-Plus-Cognition study conducted in 4 PREDIMED-Plus study centers was performed. The PREDIMED-Plus study aimed to test the beneficial effect of a lifestyle intervention on the primary prevention of cardiovascular disease. The participants with overweight or obesity and metabolic syndrome included in the present study ($n=462$; mean age of 65.3 years; 51.5% female) completed both the UPPS-P Impulsive Behavior Scale (range: 0–236 points) and the 143-item Food Frequency Questionnaire at baseline, 1-year and 3-years of follow-up. Ten diet scores assessing healthy and unhealthy dietary patterns were evaluated. Linear mixed models were performed adjusting by several confounders to study the longitudinal associations between impulsivity trait and adherence to dietary pattern scores over 3 years of follow-up (also assessing interactions by sex, age, and intervention group).

*Correspondence: nancy.babio@urv.cat; jordi.salas@urv.cat

[1] Universitat Rovira i Virgili, Departament de Bioquímica i Biotecnologia, Unitat de Nutrició Humana, Reus, Spain
Full list of author information is available at the end of the article

Results: Impulsivity were negatively associated with adherence to the Healthy Plant-Based [β = -0.92 (95%CI -1.67, -0.16)], Mediterranean [β = -0.43 (95%CI -0.79, -0.07)], Energy-Restricted Mediterranean [β = -0.76 (95%CI -1.16, -0.37)], Alternative Healthy Eating Index [β = -0.88 (95%CI -1.52, -0.23)], Portfolio [β = -0.57 (95%CI -0.91, -0.22)], and DASH [β = -0.50 (95%CI -0.79, -0.22)] diet scores over 3 years of follow-up, whereas impulsivity was positively related with adherence to the unhealthy Western diet [β = 1.59 (95%CI 0.59, 2.58)] over time. An interaction by intervention group was found, with those participants in the intervention group with high impulsivity levels having lower adherence to several healthy dietary patterns.

Conclusions: Heightened impulsivity was longitudinally associated with lower adherence to healthy dietary patterns and higher adherence to the Western diet over 3 years of follow-up. Furthermore, nutritional intervention programs should consider impulsivity as a relevant factor for the intervention success.

Trial registration: Name of registry: Effect of an energy-restricted Mediterranean diet, physical activity and behavioral intervention on the primary prevention of cardiovascular disease. Trial registration number: ISRCTN 89,898,870. Date of registration: 05/28/2014.

Keywords: Alternative Healthy Eating Index, DASH diet, Dietary patterns, Mediterranean diet, MIND diet, Planetary Health Diet, Plant-based diet, Portfolio diet, Impulsivity

Introduction

Excessive food consumption and weight gain are recognized public health problems, with obesity prevalence being a global epidemic which has tripled since 1975 [1]. Psychological characteristics, such as psychological traits, are considered relevant factors in regard to food choice and dietary intake throughout the lifespan [2–4]. Impulsivity is one psychological trait that has been proposed as being an important factor conditioning eating behaviors, and therefore weight gain or weight loss, and the risk of obesity [5–8].

Personality traits are relatively stable characteristics of individuals, yet can present as a spectrum of possible behaviors given they may be affected by situational cues, specific environmental and social pressures can induce some extreme behaviors across the spectrum of psychological traits [9]. These psychological traits have been recognized as important predictors for health related-outcomes [10]. For example, the impulsivity trait has been proposed as a key factor in successful weight loss in people with extreme obesity who are candidates for bariatric surgery [11]. Impulsivity is defined as "a predisposition toward rapid unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions to the impulsive individuals or to others" [12]. Impulsivity can affect different aspects of a persons' life and may be determined by both the genetic background and an individuals' development [13, 14]. Impulsivity predisposes individuals to respond to their emotional urges, to lack premeditation and planning, and have sensation seeking [15].

Impulsivity has also been related to difficulties delaying immediate rewards [16–18]. In relation to dietary assessments, few cross-sectional studies have suggested that low impulsivity levels are associated with higher adherence to healthy dietary assessments [3, 5]. Specifically, lower impulsivity has also been related with greater control of food intake and body weight [3], and less emotional eating. Furthermore, in comparison to restrained and non-restrained dieters, impulsivity has been postulated to play a role in modifying the participants' capacity to adhere to an specific diet, which could lead to overeating [6, 7]. Greater impulsivity has also been found to be positively associated with total energy intake, as well as an increased consumption of saturated fats, sugars, appetizers and snacks [5, 19]. Recently, a French study reported that participants with higher levels of impulsivity exhibited a reduced capacity to follow the French nutritional guidelines, assessed by an a priori healthy dietary pattern quality score [5].

To date, limited research has been conducted evaluating the association between impulsivity and dietary assessments, with only cross-sectional evidence being available [3, 5–7]. Additionally, to our knowledge, only one of these aforementioned studies involved analysis of a dietary pattern score [5]. The PREDIMED-Plus-Cognition study presents an opportunity to fill this knowledge gap enabling a longitudinal assessment of impulsivity trait and dietary patterns using repeated measures of impulsivity and diet consumption for a follow-up period of 3 years.

Therefore, the aim of our study was to evaluate longitudinal associations between impulsivity levels and adherence to different dietary pattern scores in an older senior population at high cardiovascular risk. We hypothesized that higher impulsivity trait would be associated with lower adherence to healthy dietary patterns and higher with unhealthy dietary patterns.

Methods

Study design

The present work provides an observational prospective cohort design using baseline, 1-year and 3-year follow-up data of the PREDIMED-Plus-Cognition population, a sub-study conducted within the PREDIMED-plus (in Spanish: PREvención con DIeta MEDiterránea) framework. The PREDIMED-Plus study is an ongoing 6-year multicenter, randomized, parallel-group clinical trial conducted in Spain for the primary prevention of cardiovascular disease. Participants were recruited between September 2013 and December 2016 and randomly allocated in a 1:1 ratio to either the intervention or control group, using a centrally controlled, computer-generated random-number internet-based system with stratification by center, sex, and age (< 65, 65–70, and > 70 years). Couples sharing the same household were randomized as pairs, using the couple as a randomization unit. Participants in the intervention group received intensive training to adhere to an energy-reduced Mediterranean diet together with physical activity promotion and behavioral support aimed to achieve and maintain weight loss. Participants in the intervention group were followed 3 times/month (an individual motivational interview, a telephone call, and a group session). Participants in the control group received nutritional educational sessions every 6 months (an individual visit and a group session) to follow a non-caloric reduced Mediterranean diet using the same PREDIMED study approach [20]. No specific advice for increasing physical activity or weight loss was provided to the control group. All participants received free extra virgin olive oil (1 L/month) to reinforce their adherence to the Mediterranean diet. The study protocol has been comprehensively described elsewhere [21, 22], and can be found at http://www.predimedplus.com. The trial was registered at the International Standard Randomized Controlled Trial registry (http://www.isrctn.com/ISRCTN89898870).

Study population

Eligible participants were aged between 55 and 75 years old with overweight or obesity ($27 \leq BMI < 40$ kg/m^2) meeting at least 3 criteria for metabolic syndrome [23]. From the original PREDIMED-Plus population ($n = 6{,}874$), the present investigation refers to the PREDIMED-Plus-Cognition study subset of participants ($n = 487$) randomized in the following recruitment centers: Universitat Rovira i Virgili, Universidad de Valencia, Institut Hospital del Mar d'Investigacions Mèdiques-IMIM and Bellvitge University Hospital-IDIBELL. Exclusion criteria are reported elsewhere [21]. For the present analysis, we excluded 25 participants with implausible energy intake values (≤ 800 or ≥ 4000 kcal/d for males; ≤ 500 or ≥ 3500 kcal/d for females) [24], resulting in a total population of 462 participants for the analysis. The flow-chart of the studied participants is shown in Supplemental Fig. 1 [see Additional file 1].

All participants provided written informed consent, and the ethical committees of all participating institutions approved the study protocol and procedures.

Impulsivity

Impulsivity was assessed at baseline, 1-year and 3-years of follow-up with the Impulsive Behavior Scale (UPPS-P) [15], validated for Spanish populations [25]. The UPPS-P is a 59-item self-reported questionnaire using a 4-point Likert scale (from 1 = "agree" to 4 = "disagree strongly"), which measures impulsivity traits by assessing 5 factors of impulsivity-related pathways: negative urgency, (lack of) perseverance, (lack of) premeditation, sensation seeking, and positive urgency. These 5-related impulsivity factors were obtained by combining their respective items, and the total UPPS-P score was obtained by summing all the unweighted UPPS-P items. Higher UPPS-P scores indicate higher levels of impulsivity. The α Cronbach values for the total score were 0.91 at baseline, 0.93 at 1-year of follow-up and 0.94 at 3-year of follow-up.

Although impulsivity trait is relatively stable over time, in our study it was preferred to assess impulsivity trait as a time-varying variable rather than solely at baseline in order to account for possible minimal variability, as for example impulsivity has been seen to change with increasing age and other factors [14], as well as to give more robustness to the analyses assessing impulsivity trait in more than one time-point.

Covariates

Sex, age, level of education, civil status and smoking status were obtained at baseline from self-reported questionnaires administered by trained staff in face-to-face interviews. Physical activity, BMI, alcohol intake and energy intake were obtained at baseline, 1-year and 3-years of follow-up. Physical activity was evaluated using the short validated version of the Minnesota Leisure-Time Physical Activity Questionnaire [26]. Weight and height were measured by duplicate by trained staff using calibrated scales and wall-mounted stadiometers, respectively. BMI was calculated using the mean values of total body weight and height. Dietary intake was assessed via face-to-face interviews using the validated, semi-quantitative 143-item Food-Frequency Questionnaire

(FFQ) [27, 28], and total energy and alcohol intake were obtained from the FFQs [27].

Dietary pattern scores

The FFQ collected information on portion sizes and nine consumption frequencies (from "never or almost never" to "≥6 times/day") for each assessed food item consumed over the previous year. Energy and nutrient intakes were obtained using data from the Spanish food composition database and by multiplying the frequency by the portion size, accounting for the duration of the period considered [29].

A total of 10 dietary pattern adherence scores were calculated. Eight dietary scores (Healthy Plant-Based diet, Unhealthy Plant-Based diet, Alternative Healthy Eating Index, Portfolio diet, Dietary Approaches to Stop Hypertension [DASH], Mediterranean-DASH diet Intervention for Neurodegenerative Delay [MIND], Planetary Health Diet, and Western diet) were determined based on data obtained from the 143-FFQ. Another score (the Energy-Restricted Mediterranean diet) was obtained from a 17-item Mediterranean diet questionnaire, which was assessed via face-to-face interviews by trained staff. The remaining diet score (the Mediterranean diet, without energy restriction specified) was obtained using data from the 143-FFQ as well as from equivalent items in the 17-point Mediterranean diet questionnaire.

Plant-based diets, characterized by higher plant food consumption than animal foods, are associated with a favorable cardiovascular disease risk [30]. In the present report, both the Healthy and Unhealthy Plant-Based dietary patterns were determined using the respective diet scores, with adherence scores ranging from 18 to 90 points [31]. Mediterranean diets have been associated with multiple health benefits, in particular cardiovascular health [32]. Adherence to an energy-restricted Mediterranean diet was evaluated by the 17-item Mediterranean diet questionnaire, with a score ranging from 0 to 17 points [33]. Adherence to the Mediterranean diet, without energy restriction, was determined based on the validated 14-item Mediterranean diet questionnaire (also called MEDAS), with the possible score ranging from 0 to 14 points [34, 35]. The 2010- Alternative Healthy Eating Index is a dietary pattern which follows the Dietary Guidelines for Americans and includes dietary factors involved in the development of chronic disease, with a possible score ranging from 0 to 110 points [36]. The Portfolio diet is a plant-based dietary pattern that combines recognized cholesterol-lowering foods, with an adherence score ranging from 6 to 30 points [37]. The DASH diet is a dietary pattern that was developed to reduce hypertension, and possible scores could range from 0 to 40 points [38]. The MIND diet is a diet tailored to protect against cognitive decline, and adherence scores could range from 0 to 15 points [39]. The Planetary Healthy Diet score defined by the EAT-Lancet commission is an ecological dietary pattern based on sustainable food choices, with possible adherence scores ranging from 0 to 14 points [40]. A Western diet presents high consumption of red meat and fast or fried food and low food intake of fruits, vegetables and fish [41, 42], being this dietary pattern associated with different health issues [42]. Adherence of these 10 dietary scores were evaluated in order to broadly assess possible differences between impulsivity and several dietary patterns, and for the sake of testing robustness (i.e., to determine if all healthy dietary scores or patterns tend to be negatively associated and all unhealthy dietary patterns are positively related). Supplemental Table 1 provides a description of the method performed to obtain the Western diet score, with a possible score ranging from 12 to 60 points [see Additional file 1]. For all aforementioned dietary patterns evaluated, higher scores indicate higher adherence to their respective dietary pattern.

Statistical analysis

For the current analyses, the PREDIMED-Plus-Cognition study database updated in September 2021 was used.

Baseline participant characteristics are presented as numbers and percentages for categorical variables and mean ± standard deviation for quantitative variables. Linear mixed models were performed to assess longitudinal associations between the impulsivity trait as the exposure variable and dietary pattern scores as the outcomes, both measured as continuum time-varying variables. Associations between UPPS-P subscales and dietary patterns were also assessed using linear mixed models. Random effects were hierarchically established by center and by members sharing the same household unit ($n=418$), respectively. The random intercept was performed for each participant and the random slope was performed considering baseline, 1-year and 3-years of follow-up data. Linear mixed models handle missing data accounting for the fact that repeated measures for each participant are intracorrelated, in the present study this meant including participants and using data when information from at least one of the three time-points was available. Two models were fitted to adjust linear mixed models. Model 1 was adjusted by sex, age (years) and intervention group. Model 2 was further adjusted by education level (primary school or less; high school or college), civil status (single, divorced, separated or widower; married) and smoking status (never smoked; former or current smoker) at baseline, whereas physical activity (MET min/week), BMI (kg/m^2), alcohol intake (g/d, adding the

quadratic term) and energy intake (kcal/d) were adjusted including data at each time-point.

Interaction analyses between impulsivity and sex, age and intervention group were performed by comparing the model with and without the interaction product using the likelihood ratio test. A sensitivity analysis was conducted to test the longitudinal associations between impulsivity and dietary patterns by intervention group. We also analyzed longitudinal associations between baseline UPPS-P score and 3-year adherence to healthy and unhealthy dietary patterns.

As the range of UPPS-P is large (0–236 points), all beta coefficients were multiplied by 100 hundred and robust variance estimators were used in all models to account for intracluster correlations. The data was analyzed using the Stata-14 software program (StataCorp). Statistical significance was set using the Benjamini–Hochberg false discovery rate correction procedure [43] at a Q-value < 0.05.

Results

Descriptive results

Table 1 shows baseline characteristics of the studied population ($n = 462$). The mean age was 65.3 ± 4.7 years and 51.5% were female. Approximately, a half of the participants had at least the primary school educational level, three quarters were married, and a half had never smoked. A total of 28.1% of the participants presented overweight (BMI < 30 kg/m^2), with the rest having obesity (BMI ≥ 30 kg/m^2). At baseline, the mean ± SD, minimum and maximum score for UPPS-P were 108.2 ± 22.7, 71 and 196 points, respectively. In regard to the UPPS-P scores at the 1- and 3-year follow-up the mean ± SD, minimum and maximum were 109.2 ± 24.5, 71 and 207, and 106.8 ± 24.1, 68 and 199, respectively. Baseline energy intake, food group consumption, and the 10 dietary pattern scores evaluated as mean ± SD are shown in Table 1.

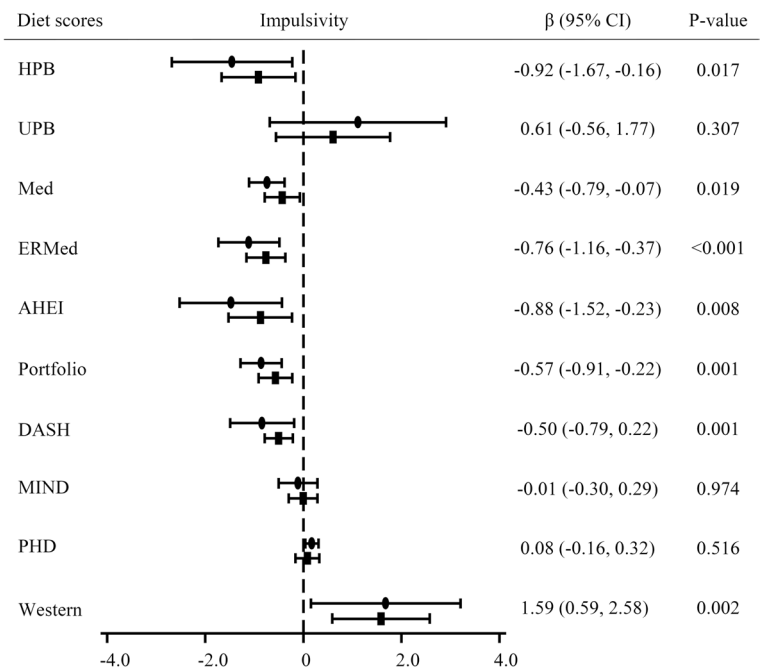


Fig. 1 Longitudinal associations between impulsivity and dietary pattern scores ($n = 438$). Abbreviations: HPB, Healthy Plant-Based diet; UPB, Unhealthy Plant-Based diet; Med, Mediterranean diet; ERMed, Energy-Restricted Mediterranean diet, AHEI, Alternative Healthy Eating Index; Portfolio, Portfolio diet; DASH, Dietary Approaches to Stop Hypertension; MIND, Mediterranean-DASH Diet Intervention for Neurodegenerative Delay; PHD, Planetary Health Diet; Western, Western diet. Impulsivity was assessed using the UPPS-P Impulsive Behaviour Scale. Linear mixed models were used to assess associations and Beta coefficients were multiplied by 100, with robust variance estimators to account for intracluster correlations. Only model 2 beta coefficients and *p*-values were shown at the right of the figure. Circle dots referred model 1: associations were adjusted by sex, age (years) and intervention group at baseline. Square dots referred model 2: associations were further adjusted by education level (primary school or less; higher school or college), civil status (single, divorced, separated or widower; married) and smoking status (never smoked; former or current smoker) at baseline, whereas physical activity (MET min/week), body mass index (kg/m.^{2}), alcohol intake (g/d, adding the quadratic term), and energy intake (kcal/d) at each time-point. All significant associations remained significant after Benjamini–Hochberg correction in both model 1 and model 2

Table 1 Baseline participant characteristics ($n=462$)

General characteristics	Values
Age (years)	65.3 ± 4.7
Sex (women)	238 (51.5)
Intervention group	228 (49.3)
Education level	
Primary school or less	251 (54.3)
High school or college	211 (45.7)
Civil status	
Single, divorced, separated or widower	98 (21.2)
Married	364 (78.8)
Smoking status	
Never smoked	231 (50.0)
Former or current smoker	231 (50.0)
Physical activity (MET min/week)	2343 ± 2004
Body Mass Index (kg/m^2)	32.5 ± 3.4
Psychological assessment (Range)	
UPPS-P Impulsive Behavior Scale (0–236 points)	108.1 ± 22.6
Energy intake and food groups consumption	
Energy intake (kcal/d)	2329 ± 475
Fruit (g/d)	340.2 ± 174.0
Vegetables (g/d)	344.2 ± 136.0
Legumes (g/d)	19.0 ± 9.82
Nuts (g/d)	13.5 ± 13.7
Extra virgin olive oil (g/d)	32.7 ± 19.9
Grains (g/d)	145.4 ± 69.0
Fish (g/d)	109.8 ± 43.1
Meat (g/d)	156.2 ± 56.3
Dairy products (g/d)	323.7 ± 179.7
Alcohol (g/d)	8.7 ± 11.3
Dietary pattern scores (Range)	
Healthy Plant-Based diet (18–90 points)	56.6 ± 7.6
Unhealthy Plant-Based diet (18–90 points)	57.3 ± 6.5
Mediterranean diet (0–14 points)	8.0 ± 1.8
Energy-restricted Mediterranean diet (0–17 points)	7.9 ± 2.5
Alternative Healthy Eating Index (0–110 points)	65.3 ± 8.6
Portfolio diet (6–30 points)	16.7 ± 4.0
DASH diet (0–40 points)	23.8 ± 5.2
MIND diet (0–15 points)	9.2 ± 1.2
Planetary Health Diet (0–14 points)	9.2 ± 1.5
Western diet (12–60 points)	28.9 ± 5.6

Abbreviations: *DASH* Dietary Approaches to Stop Hypertension, *MIND* Mediterranean-DASH Diet Intervention for Neurodegenerative Delay

Data are expressed as n (%) for categorical variables and mean ± SD for quantitative variables

The UPPS-P was measured only in 349 participants

For longitudinal analyses, UPPS-P measurement was conducted in 438 participants in which dietary assessments were conducted in all the study population.

Impulsivity and dietary pattern scores

Figure 1 shows the longitudinal associations between impulsivity and adherence to diet scores over the 3 years of follow-up. Higher impulsivity values were associated with less adherence to the Healthy Plant-Based diet (β = -1.46; CI 95% [-2.68, -0.23]), Mediterranean diet (β = -0.74; CI 95% [-1.11, -0.38]), Energy-Restricted Mediterranean diet (β = -1.11; CI 95% [-1.73, -0.49]), Alternative Healthy Eating Index (β = -1.48; CI 95% [-2.52, -0.44]), Portfolio diet (β = -0.86; CI 95% [-1.28, -0.44]), and DASH diet (β = -0.84; CI 95% [-1.50, -0.19]) scores over 3 years of follow-up, and contrary, with higher adherence to the Western diet score (β = 1.68; CI 95% [0.15, 3.21]) over time, in model 1. These associations remained significant in the fully adjusted model. No significant associations were found in the case of the Unhealthy Plant-Based diets, MIND diet, and Planetary Health Diet. Supplemental Fig. 2 shows longitudinal associations between UPPS-P subscales and adherence to dietary pattern scores over time [see Additional file 1].

There were no significant interactions by sex and age between impulsivity and dietary pattern scores (data not shown). Significant interactions by intervention or control group were found between impulsivity and adherence to the Mediterranean diet, Energy-Restricted Mediterranean diet, Portfolio diet, and MIND diet adherence scores over time (Fig. 2).

A sensitivity analysis was performed due to several significant interactions being displayed by the PREDIMED-Plus-Cognition trial intervention or control group between impulsivity and adherence to the assessed dietary patterns over 3 years of follow-up. This sensitivity analysis indicated a positive association between impulsivity and the Western diet score for the control group, whereas impulsivity was associated with lower adherence to the Mediterranean diet, Energy-Restricted Mediterranean diet, Alternative Healthy Eating Index, Portfolio diet, and DASH diet scores over time for the intervention group (Supplemental Table 2) [see Additional file 1]. We further analyzed longitudinal associations between baseline UPPS-P score and adherence to dietary patterns over 3 years of follow-up (data not shown), and the results followed similar trends although only the adherence to the Western diet remained statistically significant (β = 2.45; CI 95% [0.94, 3.96]).

Discussion

To the best of our knowledge, the present study is the first to investigate longitudinal associations between impulsivity and adherence to various dietary patterns over 3 years of follow-up, while also accounting for several confounders. Our main finding showed that impulsivity was negatively associated with several healthy

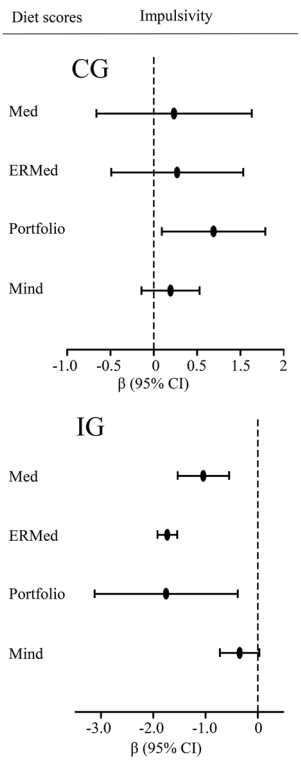


Fig. 2 Interactions in longitudinal associations between impulsivity and dietary pattern scores by intervention group ($n=438$). Abbreviations: CG, Control group; IG, Intervention group; Med, Mediterranean diet, ERMed, Energy-Restricted Mediterranean diet; Portfolio, Portfolio diet; MIND, Mediterranean-DASH Diet Intervention for Neurodegenerative Delay. Impulsivity was assessed using the UPPS-P Impulsive Behaviour Scale. Linear mixed models were used to assess associations and Beta coefficients were multiplied by 100, with robust variance estimators to account for intracluster correlations. Only significant interactions by intervention group were shown. Associations were adjusted by sex, age (years), intervention group, education level (primary school or less; higher school or college), civil status (single, divorced, separated or widower; married) and smoking status (never smoked; former or current smoker) at baseline, whereas physical activity (MET min/week), body mass index (kg/m.^{2}), alcohol intake (g/d, adding the quadratic term), and energy intake (kcal/d) were considered using data at each time-point. Unless in the control group for Portfolio diet, all significant associations remained significant after Benjamini–Hochberg correction. CG, $n=219$; IG, $n=219$

diet scores and positively related with adherence to an unhealthy dietary pattern in a Mediterranean population with overweight or obesity and metabolic syndrome participating in a lifestyle intervention program with a Mediterranean diet.

Limited research has been conducted studying relationships between impulsivity and dietary patterns. The NutriNet-Santé cohort has assessed cross-sectional associations between impulsivity and the representative score of the French Nutrition Guideline in an adult population, finding an inverse relationship [5]. In line with this study, our work also found in an older population that higher impulsivity levels were related with less adherence over 3 years of follow-up to most of the dietary scores assessed that have been associated with multiple health benefits [44]. Furthermore, impulsivity trait were positively associated with greater increases in the adherence to a Western diet style over time, a typical food pattern linked with an increased risk of chronic diseases [42]. However, a relationship between impulsivity trait and adherence to the MIND diet was not found. A possible explanation could be that the MIND diet is more permissive with red meat consumption, includes cheese consumption as a component of the score, and does not consider the consumption of fruits, aside from berries, in contrast to other healthy diet scores reflecting significant negative associations. In addition, impulsivity and adherence to the Planetary Healthy Index over time did not show a relationship either. In comparison with the diet scores displaying significant inverse associations, the Planetary Healthy Index allows for low-moderate but sustainable consumption of foods often considered to be more palatable, such as starchy vegetables, dairy foods, several kinds of protein sources (e.g., red meat or eggs), saturated oils, and added sugars, similar to the MIND diet. This leniency in food quantities and consumption of often more palatable food groups may explain why a non-significant relationship was observed between impulsivity and the MIND diet and the Planetary Healthy Diet, instead of a significant inverse association.

In our study, relationships between impulsivity and adherence to unhealthy dietary patterns over 3 years of follow-up showed discrepancies in their findings depending on the food group components of the diet scores assessed. Some evidence was found indicating positive cross-sectional relationships between impulsivity trait and the Western pattern style [19], but it is unknown for other non-healthy dietary patterns as those based in plant foods. In the present study, impulsivity showed a non-significant positive association with adherence to the Unhealthy Plant-Based diet over 3 years of follow-up, whereas a positive relationship was observed with the Western diet. This latter association demonstrated that participants with heightened impulsivity tend to easily follow a diet including a lower adherence to the consumption of healthy food groups (such as whole grains, fruits, vegetables, fish, nuts and legumes) and a higher adherence to the consumption of unhealthy food groups (such as refined grains, fast foods, red and processed meats, butters, sugar drinks, sweets and desserts) over time. Nevertheless, when impulsivity were assessed in relation to adherence to a food pattern representing a non-healthy plant-based diet, no association was

shown. The Unhealthy Plant-Based diet considers animal food sources as a negative component, and this may be an explanation for the non-significance seen with impulsivity levels compared to adherence to the Western style diet over 3 years of follow-up.

Impulsivity is characterized by a tendency to act rashly under extreme positive or negative emotions, a lack of perseverance and premeditation, and the search for experiences and feelings [12, 15]. These attributes may predispose an individual to have greater difficulties in following a healthy dietary pattern that could be perceived as being less palatable or presents with restrictions to food groups which are socially commonly consumed. Furthermore, impulsivity is closely related to the reward system and food addiction [16, 18], and palatable foods have been suggested to affect the reward system in the same way as other kind of addictions such as alcoholism or drug abuse [45]. In addition, situational cues could induce more extreme behaviors in the spectrum of trait impulsivity [9]. For example, the power of heavy marketing has been observed to have an effect on prime automatic eating behaviors based on food advertisements, incrementing unhealthy food choices and the urge to eat [17, 46].

Consequently, our results demonstrated that higher impulsivity levels were more likely to be associated with a greater difficulty in adhering over 3 years of follow-up to healthy dietary patterns that have been shown to be useful in the prevention of cardiovascular-related problems or cancer [30, 32, 36, 37, 39, 44]. At the same time, people with high impulsivity levels tend to easily adhere to the unhealthy Western diet over time, a food pattern largely associated with different chronic diseases and health related conditions [42]. Therefore, food choices which may be driven by this psychological trait of impulsivity may play a role in increasing or reducing the risk of nutrition-related non-communicative diseases.

Our results showed few significant associations between negative urgency, positive urgency, sensation seeking, and perseverance UPPS-P subscales with adherence to some dietary patterns over 3 years of follow-up. This fact could be explained due to impulsivity being a multidimensional construct [15], suggesting that this psychological trait, as a composite, presents stronger associations with dietary patterns than specific impulsivity-related pathways.

Additionally, when impulsivity trait was only assessed at baseline, similar trends were shown for all dietary patterns as when we take into account impulsivity trait as time-varying variable, but only a significant positive association was found between impulsivity trait and adherence to the Western diet over time. These differences could be explained by using impulsivity as time-varying variable gives more robustness to our analyses. Moreover, these results could also manifest that little variations in impulsivity trait may occur over time leading to modifications in behaviors as it relates to adherence to dietary patterns.

In individuals not following an intervention program, we hypothesize that the same results would be found, as some research has shown cross-sectional positive associations between impulsivity trait and adherence to the healthy dietary French score in a total population of 51,043 participants.

Interestingly, interactions by PREDIMED-Plus intervention group were seen between impulsivity and adherence to some of the diet scores assessed over time. In comparison with participants in the control group, those in the intervention group showed significant negative associations between impulsivity and adherence to the Mediterranean diets and the Portfolio diet over 3 years of follow-up. Personality traits, including the psychological trait of impulsivity, might influence decisions as to whether an immediate over delayed reward is chosen. This could lead to overconsumption influenced by motivations and subsequently the selection of available highly palatable and more convenient foods instead of other more healthful options [8, 16, 47, 48]. As such, participants with higher impulsivity could present with difficulties delaying unhealthy food choices instead of waiting to choose a healthier option promoted by the active intervention program, derived by a lack of perseverance and forethought, and possibly driven by an overactivation of their reward system [16–18]. The key point is that this relationship was not observed in the control group. This may be because these participants were not required to follow the more restrictive intervention program focused on weight reduction and promotion of physical activity with behavioral support. Hence, participants in the control group did not have these added potential stressors and psychological conditions with which participants with higher impulsivity may not be able to manage additional general nutritional recommendations. Thus, higher impulsivity in the context of an active intervention program might result in less adherence to general healthy dietary recommendations.

Impulsivity has been observed to be modified in mindfulness intervention programs in individuals with drug abuse disorders [49, 50]. Therefore, mindfulness interventions could help participants to better follow dietary recommendations made by dietitians in those participants with high impulsivity due to improved emotion regulation and reduction of their impulsivity traits lack of premeditation and positive urgency.

One of the most important strengths of our study is the assessment of impulsivity and multiple dietary patterns at different time-point (3 times during a 3-year

period), enabling a relatively robust longitudinal analysis. In addition, our study evaluated the associations between impulsivity and adherence to several dietary patterns over 3 years of follow-up, including healthy and unhealthy dietary patterns, but also other dietary patterns considering nutritional as well as ecological and environmental considerations. Another strength is that our analyses were adjusted for several relevant confounders. Furthermore, the impulsivity construct indicated a strong internal consistency showed by the Cronbach's alpha values in each time point assessed. And finally, this analysis was performed in a relatively large study population compared with other studies assessing relationships between impulsivity and dietary assessments. However, different study limitations deserve to be recognized. The first and more important limitation is the observational study design, limiting the ability to establish causal relationships. Moreover, our study was conducted in an older Mediterranean population with overweight or obesity and at high risk of cardiovascular disease, and therefore the results may not be able to be extrapolated to other populations. Finally, FFQs present with some limitations of reliability, however in our study a validated FFQ was utilized, reducing the possibility of these reliability issues.

Conclusions

Results showed that higher impulsivity trait values were associated with lower adherence to healthy dietary patterns over 3 years of follow-up in a population at high cardiovascular risk following a lifestyle intervention. Moreover, no associations between impulsivity and adherence to both the unhealthy plant-based dietary pattern and the Planetary Healthy Diet were found over time, possibly due to their less restrictive nature with regard to animal-based food consumption in its conception. Furthermore, impulsivity was positively related with greater adherence to a typical unhealthy Western style diet over time. Therefore, the impulsivity trait may be a risk factor of health diseases via participants' decision-making related to food consumption. In addition, our results suggest that impulsivity should be considered in case of lifestyle intervention programs aimed at modifying dietary patterns as impulsivity is an important behavioral trait that potentially influence the participants' capacity to adhere to the intervention.

Abbreviations

95%CI: 95% Confidence interval; AHEI: Alternative Healthy Eating Index; BMI: Body Mass Index; DASH: Dietary Approaches to Stop Hypertension; ERMed: Energy-Restricted Mediterranean diet; MIND: Mediterranean-DASH Diet Intervention for Neurodegenerative Delay; Med: Mediterranean diet; PHD: Planetary Health Diet; Portfolio: Portfolio diet; UPB: Unhealthy Plant-Based diet; UPPS-P: Urgency, Premeditation (lack of), Perseverance (lack of), Sensation Seeking, Positive Urgency, Impulsive Behavior Scale; Western: Western diet.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12966-022-01335-8.

Additional file 1: Supplemental Table 1. Western diet score. **Supplemental Table 2.** Longitudinal associations between impulsivity and dietary pattern scores by intervention group (*n*=438).

Additional file 2.

Additional file 3.

Acknowledgements

The authors wish to thank the PREDIMED-Plus participants and all staff members for their engagement, as well as to the primary care centers taking part in the study. We also thank the CIBEROBN, CIBERESP and CIBERDEM initiatives of Instituto de Salud Carlos III in Spain, and the CERCA Program of the Generalitat de Catalunya.

Authors' contributions

The principal PREDIMED-Plus-Cognition investigators RT, FF-A, DC, MF, JS-S contributed to study concept and design and to data extraction from the participants, as well as NB and JJ. CG-M. CG-M, SKN performed the statistical analyses, and the interpretation of the results. CG-M, NB, JJ, SKN drafted the manuscript. All authors reviewed the manuscript for important intellectual content and approved the final version to be published.

Funding

This work was supported by the official Spanish Institutions for funding scientific biomedical research, CIBER Fisiopatología de la Obesidad y Nutrición (CIBEROBN) and Instituto de Salud Carlos III (ISCIII), through the Fondo de Investigación para la Salud (FIS), which is co-funded by the European Regional Development Fund (six coordinated FIS projects leaded by JS-S, including the following projects: PI13/00673, PI13/00492, PI13/00272, PI13/01123, PI13/00462, PI13/00233, PI13/02184, PI13/00728, PI13/01090, PI13/01056, PI14/01722, PI14/00636, PI14/00618, PI14/00696, PI14/01206, PI14/01919, PI14/00853, PI14/01374, PI14/00972, PI14/00728, PI14/01471, PI16/00473, PI16/00662, PI16/01873, PI16/01094, PI16/00501, PI16/00533, PI16/00381, PI16/00366, PI16/01522, PI16/01120, PI17/00764, PI17/01183, PI17/00855, PI17/01347, PI17/00525, PI17/01827, PI17/00532, PI17/00215, PI17/01441, PI17/00508, PI17/01732, PI17/00926, PI19/00957, PI19/00386, PI19/00309, PI19/01032, PI19/00576, PI19/00017, PI19/01226, PI19/00781, PI19/01560, PI19/01332, PI20/01802, PI20/00138, PI20/01532, PI20/00456, PI20/00339, PI20/00557, PI20/00886, PI20/01158); the Especial Action Project entitled: Implementación y evaluación de una intervención intensiva sobre la actividad física Cohorte PREDIMED-Plus grant to JS-S; the Recercaixa (number 2013ACUP00194) grant to JS-S; grants from the Consejería de Salud de la Junta de Andalucía (PI0458/2013, PS0358/2016, PI0137/2018); the PROMETEO/2017/017 and PROMETEO 21/2021 grants from the Generalitat Valenciana, and the grant PID2019-108858RB-I00 funded by AEI 10.13039/501100011033 and by "ERDF A way of making Europe" to DC; the SEMERGEN grant; None of the funding sources took part in the design, collection, analysis, interpretation of the data, or writing the report, or in the decision to submit the manuscript for publication. We thank CERCA Programme/Generalitat de Catalunya for institutional support and partial support was also provided by SLT006/17/00246, funded by the Department of Health of the Generalitat de Catalunya by the calls "Acció instrumental de programes de recerca orientats en l'àmbit de la recerca i la innovació en salut" and "Pla estratègic de recerca i innovació en salut (PERIS)". This research was also partially funded by EU-H2020 Grants (Eat2beNICE/ H2020-SFS-2016–2, Ref 728018; and PRIME/ H2020-SC1-BHC-2018–2020, Ref: 847879). CG-M receives a predoctoral grant from the University of Rovira i Virgili (2020PMF-PIPF-37); JS-S, senior author of this paper, is partially supported by ICREA under the ICREA Academia program. SKN is supported by a postdoctoral fellowship from the Canadian Institutes of Health Research (CIHR, MFE-171207). JJ holds the Miguel Servet-II contract (CPII19/00015) awarded by the Instituto de Salud Carlos III (co-funded by the European Social Fund "Investing in your future").

Availability of data and materials
There are restrictions on the availability of data for the PREDIMED-Plus trial, due to the signed consent agreements around data sharing, which only allow access to external researchers for studies following the project purposes. Requestors wishing to access the PREDIMED-Plus trial data used in this study can make a request to the PREDIMED-Plus trial Steering Committee chair: predimed_plus_scommitte@googlegroups.com. The request will then be passed to members of the PREDIMED-Plus Steering Committee for deliberation.

Declarations

Ethics approval and consent to participate
All participants provided written informed consent. According to the ethical standards of the Declaration of Helsinki by the Research Ethics Committees, all the participating institutions approved the study protocol and procedures (PR240/13; PI13/120; 2011–005398-22; 13–07-25/7proj2). All participants signed an informed consent and this manuscript did not publish personal data of participants.

Consent for publication
NA

Competing interests
JS-S reported receiving research support from the Instituto de Salud Carlos III, Ministerio de Educación y Ciencia, Departament de Salut Pública de la Generalitat de Catalunya, the European Commission, the USA National Institutes of Health; receiving consulting fees or travel expenses from Instituto Danone, and Mundipharma, receiving nonfinancial support from Hojiblanca, Patrimonio Comunal Olivarero, the Almond Board of California, Pistachio Growers and Borges S.A; serving on the board of and receiving grant support through his institution from the International Nut and Dried Foundation and the Eroski Foundation; and personal fees from Instituto Danone Spain; Serving in the Scientific Board of Danone Institute International (non-payed member). SKN is a volunteer member of the not-for profit group Plant Based Canada. DC reported receiving grants from Instituto de Salud Carlos III. FF-A received consultancy honoraria from Novo Nordisk and editorial honoraria as EIC from Wiley. All other authors declare no commercial or financial relationships that could be construed as a potential conflict of interest. None of the sponsors had a role in any aspect of the present study, including design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, approval of the manuscript, and decision to submit the manuscript for publication.

Author details
[1]Universitat Rovira i Virgili, Departament de Bioquímica i Biotecnologia, Unitat de Nutrició Humana, Reus, Spain. [2]Institut d'Investigació Sanitària Pere Virgili (IISPV), Hospital Universitari Sant Joan de Reus, Reus, Spain. [3]Centro de Investigación Biomédica en Red de Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III (ISCIII), Madrid, Spain. [4]Institut d'Investigació Sanitària Pere Virgili (IISPV), Clinical and Epidemiological Neuroscience Group (NeuroÈpia), Reus, Spain. [5]Toronto 3D (Diet, Digestive Tract and Disease) Knowledge Synthesis and Clinical Trials Unit, Toronto, ON, Canada. [6]Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital, Unity Health Toronto, Toronto, ON, Canada. [7]Department of Psychiatry, School of Medicine and Health Sciences, University Hospital Bellvitge-IDIBELL and Department of Clinical Sciences, University of Barcelona, Barcelona, Spain. [8]Department of Preventive Medicine and Public Health. IdISNA, University of Navarra, Pamplona, Spain. [9]Integrative Pharmacology and Systems Neurosciences Research Group, Neurosciences Research Program, Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain. [10]Department of Preventive Medicine, University of Valencia, Valencia, Spain. [11]Faculty of Experimental and Health Sciences, Universitat Pompeu Fabra (UPF), Barcelona, Spain. [12]Lipids and Vascular Risk Unit, Internal Medicine, Hospital Universitario de Bellvitge-IBIDELL, Hospitalet de Llobregat, Barcelona, Spain. [13]Universitat de Barcelona, Barcelona, Spain. [14]Department of Human Genetics, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, The Netherlands. [15]Department of Psychiatry, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, The Netherlands.

Received: 27 January 2022 Accepted: 10 July 2022
Published: 8 August 2022

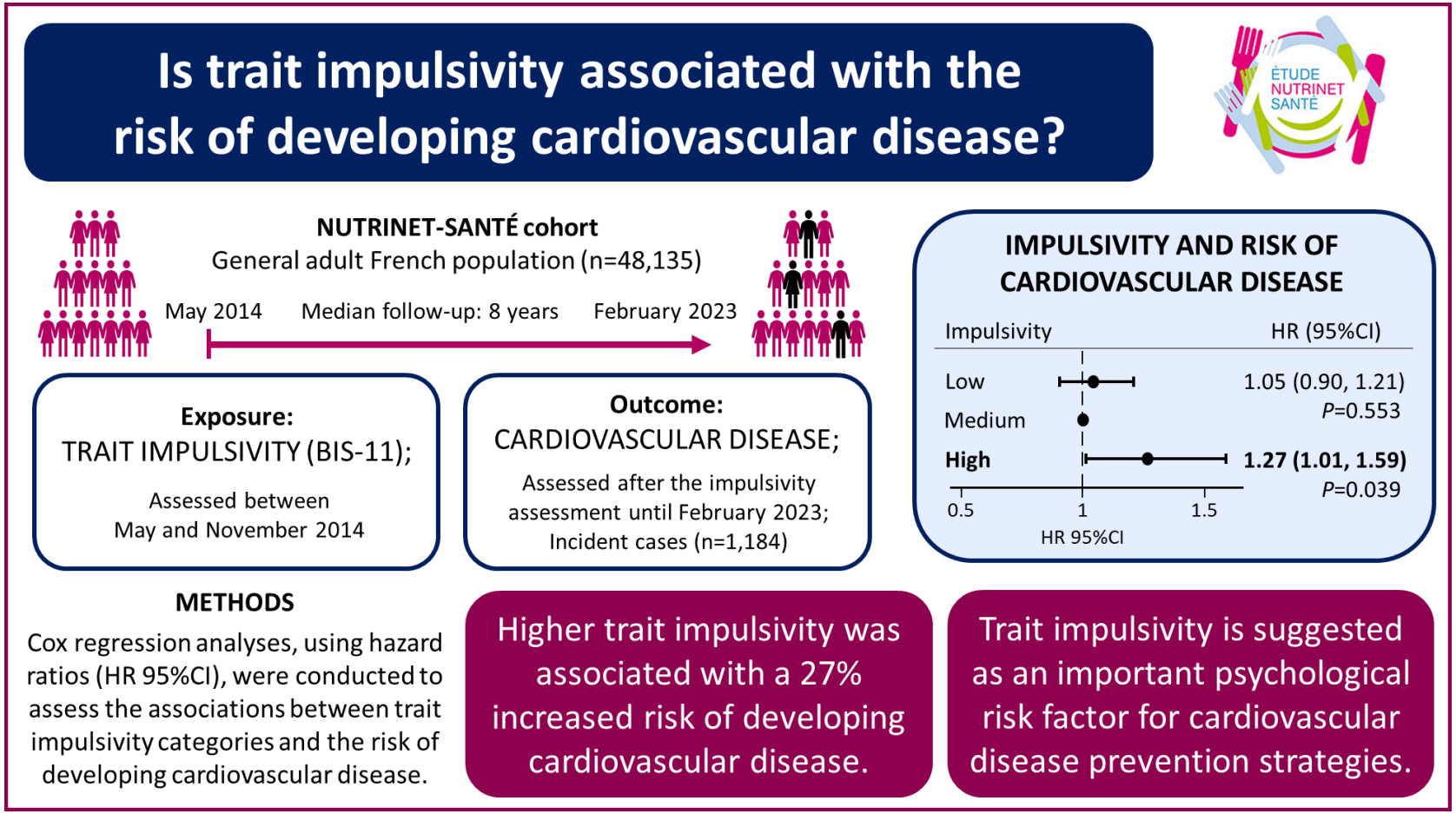
References
1. World Health Organization. A report about overweight and obesity. Geneva: World Health Organization; 2021. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. Accessed 18 Jan 2021.
2. Gacek M, Kosiba G, Wojtowicz A. Personality determinants of diet quality among polish and spanish physical education students. Int J Environ Res Public Health. 2021;18:466.
3. van den Bree MBM, Przybeck TR, Robert CC. Diet and personality: associations in a population-based sample. Appetite. 2006;46:177–88.
4. Mõttus R, McNeill G, Jia X, Craig LCA, Starr JM, Deary IJ. The associations between personality, diet and body mass index in older people. Health Psychol. 2013;32:353–60.
5. Bénard M, Bellisle F, Kesse-Guyot E, Julia C, Andreeva VA, Etilé F, Reach G, Dechelotte P, Tavolacci M-P, Hercberg S, et al. Impulsivity is associated with food intake, snacking, and eating disorders in a general population. Am J Clin Nutr. 2019;109:117–26.
6. Leitch MA, Morgan MJ, Yeomans MR. Different subtypes of impulsivity differentiate uncontrolled eating and dietary restraint. Appetite. 2013;69:54–63.
7. Guerrieri R, Nederkoorn C, Schrooten M, Martijn C, Jansen A. Inducing impulsivity leads high and low restrained eaters into overeating, whereas current dieters stick to their diet. Appetite. 2009;53:93–100.
8. Mallorquí-Bagué N, Lozano-Madrid M, Vintró-Alcaraz C, Forcano L, Díaz-López A, Galera A, Fernández-Carrión R, Granero R, Jiménez-Murcia S, Corella D, et al. Effects of a psychosocial intervention at one-year follow-up in a PREDIMED-plus sample with obesity and metabolic syndrome. Sci Rep. 2021;11:9144.
9. Svrakic DM, Przybeck TR, Cloninger CR. Mood states and personality traits. J Affect Disord. 1992;24:217–26.
10. Harper RG. Personality-guided therapy in behavioral medicine. 1 ed. Washington DC: American Psychological Association; 2004.
11. Sarwer DB, Allison KC, Wadden TA, Ashare R, Spitzer JC, McCuen-Wurst C, LaGrotte C, Williams NN, Edwards M, Tewksbury C, et al. Psychopathology, disordered eating, and impulsivity as predictors of outcomes of bariatric surgery. Surg Obes Relat Dis. 2019;5:650–5.
12. Moeller FG, Barratt ES, Dougherty DM, Schmitz JM, Swann AC. Psychiatric aspects of impulsivity. Am J Psychiatry. 2001;158:1783–93.
13. Hollander E, Rosen J. Impulsivity. J Psychopharmacol. 2000;14:S39-44.
14 Liu M, Argyriou E, Cyders MA. Developmental considerations for assessment and treatment of impulsivity in older adults. Curr Top Behav Neurosci. 2020;47:165–77.
15. Lynam DR, Smith GT, Whiteside SP, Cyders MA. The UPPS–P: Assessing five personality pathways to impulsive behavior (Technical Report). West Lafayette: Purdue University; 2006.
16. Maxwell AL, Gardiner E, Loxton NJ. Investigating the relationship between reward sensitivity, impulsivity, and food addiction: a systematic review. Eur Eat Disord Rev. 2020;28:368–84.
17. Kidd C, Loxton NJ. Junk food advertising moderates the indirect effect of reward sensitivity and food consumption via the urge to eat. Physiol Behav. 2018;188:276–82.
18. Loxton NJ. The role of reward sensitivity and impulsivity in overeating and food addiction. Curr Addict Reports. 2018;5(2):212–22.
19. Lumley J, Stevenson RJ, Oaten MJ, Mahmut M, Yeomans MR. Individual differences in impulsivity and their relationship to a Western-style diet. Pers Individ Dif. 2016;97:178–85.
20. Estruch R, Ros E, Salas-Salvadó J, Covas M-I, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Fiol M, Lapetra J, et al. Primary prevention of cardiovascular disease with a mediterranean diet supplemented with extra-virgin olive oil or nuts. N Engl J Med. 2018;378:e34.
21. Martínez-González MA, Buil-Cosiales P, Corella D, Bulló M, Fitó M, Vioque J, Romaguera D, Martínez JA, Wärnberg J, López-Miranda J, et al. Cohort profile: design and methods of the PREDIMED-plus randomized trial. Int J Epidemiol. 2019;48:387–388o.
22. Salas-Salvadó J, Díaz-López A, Ruiz-Canela M, Basora J, Fitó M, Corella D, Serra-Majem L, Wärnberg J, Romaguera D, Estruch R, et al. Effect of a Lifestyle Intervention Program With Energy-Restricted Mediterranean

Diet and Exercise on Weight Loss and Cardiovascular Risk Factors: One-Year Results of the PREDIMED-Plus Trial. Diabetes Care. 2018;42:dc180836.
23. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart J-C, James WPT, Loria CM, Smith SC. Harmonizing the Metabolic Syndrome. Circulation. 2009;120:1640–5.
24. Willett W. Nutritional Epidemiology. 3rd. ed. New York: Oxford University Press; 2012.
25. Verdejo-García A, Lozano Ó, Moya M, Alcázar MÁ, Pérez-García M. Psychometric properties of a Spanish version of the UPPS–P impulsive behavior scale: reliability, validity and association with trait and cognitive impulsivity. J Pers Assess. 2010;92:70–7.
26. Molina L, Sarmiento M, Peñafiel J, Donaire D, Garcia-Aymerich J, Gomez M, Ble M, Ruiz S, Frances A, Schröder H, et al. Validation of the regicor short physical activity questionnaire for the adult population. PLoS One. 2017;12:e0168148.
27. Martin-Moreno JM, Boyle P, Gorgojo L, Maisonneuve P, Fernandez-Rodriguez JC, Salvini S, Willett WC. Development and validation of a food frequency questionnaire in Spain. Int J Epidemiol. 1993;22:512–9.
28. Fernández-Ballart JD, Piñol JL, Zazpe I, Corella D, Carrasco P, Toledo E, Perez-Bauer M, Martínez-González MÁ, Salas-Salvadó J, Martín-Moreno JM. Relative validity of a semi-quantitative food-frequency questionnaire in an elderly Mediterranean population of Spain. Br J Nutr. 2010;103:1808–16.
29. Moreiras O, Carbajal Á, Cabrera L, Cuadrado C. Tablas de composición de alimentos: Guía de prácticas. 19 ed. Madrid: Pirámide; 2018.
30. Gan ZH, Cheong HC, Tu Y-K, Kuo P-H. Association between plant-based dietary patterns and risk of cardiovascular disease: a systematic review and meta-analysis of prospective cohort studies. Nutrients. 2021;13:3952.
31. Satija A, Bhupathiraju SN, Rimm EB, Spiegelman D, Chiuve SE, Borgi L, Willett WC, Manson JE, Sun Q, Hu FB. Plant-based dietary patterns and incidence of Type 2 diabetes in US men and women: results from three prospective cohort studies. PLOS Med. 2016;13:e1002039.
32. Becerra-Tomás N, Blanco Mejía S, Viguiliouk E, Khan T, Kendall CWC, Kahleova H, Rahelić D, Sievenpiper JL, Salas-Salvadó J. Mediterranean diet, cardiovascular disease and mortality in diabetes: a systematic review and meta-analysis of prospective cohort studies and randomized clinical trials. Crit Rev Food Sci Nutr. 2020;60:1207–27.
33. Schröder H, Zomeño MD, Martínez-González MA, Salas-Salvadó J, Corella D, Vioque J, Romaguera D, Martínez JA, Tinahones FJ, Miranda JL, et al. Validity of the energy-restricted mediterranean diet adherence screener. Clin Nutr. 2021;40:4971–9.
34. García-Conesa M-T, Philippou E, Pafilas C, Massaro M, Quarta S, Andrade V, Jorge R, Chervenkov M, Ivanova T, Dimitrova D, et al. Exploring the validity of the 14-Item Mediterranean Diet Adherence Screener (MEDAS): a cross-national study in seven European countries around the mediterranean region. Nutrients. 2020;12:2960.
35. Schröder H, Fitó M, Estruch R, Martínez-González MA, Corella D, Salas-Salvadó J, Lamuela-Raventós R, Ros E, Salaverría I, Fiol M, et al. A short screener is valid for assessing mediterranean diet adherence among older Spanish men and women. J Nutr. 2011;141:1140–5.
36. Chiuve SE, Fung TT, Rimm EB, Hu FB, McCullough ML, Wang M, Stampfer MJ, Willett WC. Alternative dietary indices both strongly predict risk of chronic disease. J Nutr. 2012;142:1009–18.
37. Chiavaroli L, Nishi SK, Khan TA, Braunstein CR, Glenn AJ, Mejia SB, Rahelić D, Kahleová H, Salas-Salvadó J, Jenkins DJA, et al. Portfolio dietary pattern and cardiovascular disease: a systematic review and meta-analysis of controlled trials. Prog Cardiovasc Dis. 2018;61:43–53.
38. Fung TT. Adherence to a DASH-style diet and risk of coronary heart disease and stroke in women. Arch Intern Med. 2008;168:713.
39. Morris MC, Tangney CC, Wang Y, Sacks FM, Barnes LL, Bennett DA, Aggarwal NT. MIND diet slows cognitive decline with aging. Alzheimer's Dement. 2015;11:1015–22.
40. EAT-Lancet Commission. Healthy Diets. In: EAT-Lancet Commission Summary Report about Food Planet Health: Healthy Diets From Sustainable Food Systems. EAT-Lancet Commission; 2019. https://eatforum.org/eat-lancet-commission/eat-lancet-commission-summary-report. Accessed 8 Oct 2021.
41. Cordain L, Eaton SB, Sebastian A, Mann N, Lindeberg S, Watkins BA, O'Keefe JH, Brand-Miller J. Origins and evolution of the Western diet: health implications for the 21st century. Am J Clin Nutr. 2005;81:341–54.
42. Uribarri J, Woodruff S, Goodman S, Cai W, Chen X, Pyzik R, Yong A, Striker GE, Vlassara H. Advanced glycation end products in foods and a practical guide to their reduction in the diet. J Am Diet Assoc. 2010;110:911–6.
43. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Ser B. 1995;57:289–300.
44. Cena H, Calder PC. Defining a healthy diet: evidence for the role of contemporary dietary patterns in health and disease. Nutrients. 2020;12:334.
45. Fletcher PC, Kenny PJ. Food addiction: a valid concept? Neuropsychopharmacol. 2018;43:2506–13.
46. Harris JL, Bargh JA, Brownell KD. Priming effects of television food advertising on eating behavior. Health Psychol. 2009;28:404–13.
47. Keller C, Siegrist M. Successful and unsuccessful restrained eating. does dispositional self-control matter? Appetite. 2014;74:101–6.
48. Sarmugam R, Worsley A. Dietary behaviours, impulsivity and food involvement: identification of three consumer segments. Nutrients. 2015;7:8036–57.
49. Gallo GG, Curado DF, Opaleye ES, Donate APG, Scattone VV, Noto AR. Impulsivity and mindfulness among inpatients with alcohol use disorder. Subst Use Misuse. 2021;56:25–32.
50. Tang Y-Y, Tang R, Posner MI. Mindfulness meditation improves emotion regulation and reduces drug abuse. Drug Alcohol Depend. 2016;163:S13–8.

Publisher's Note

CHAPTER 2:
TRAIT IMPULSIVITY AND INCIDENCE OF CARDIOVASCULAR DISEASE

Figure 7. Graphical abstract of Chapter 2. Trait impulsivity and incidence of cardiovascular disease over 8 years of follow-up.



Trait impulsivity is associated with an increased risk of cardiovascular disease incidence over 8 years of follow-up: Results from the NutriNet-Santé cohort

Carlos Gómez-Martínez[1,2,3], Pauline Paolassini-Guesnier[4], Léopold Fezeu[4], Bernard Srour[4], Serge Hercberg[4], Mathilde Touvier[4], Nancy Babio[1,2,3], Jordi Salas-Salvadó[1,2,3], Sandrine Péneau[4]

[1] Universitat Rovira i Virgili, Departament de Bioquímica i Biotecnologia. Grup d'Alimentació, Nutrició, Desenvolupament i Salut Mental (ANUT-DSM). Unitat de Nutrició Humana, Reus, Spain.

[2] Institut d'Investigació Sanitària Pere Virgili (IISPV), Reus, Spain.

[3] Centro de Investigación Biomédica en Red de Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III (ISCIII), Madrid, Spain.

[4] Université Sorbonne Paris Nord and Université Paris Cité, INSERM, INRAE, CNAM, Center of Research in Epidemiology and StatisticS (CRESS), Nutritional Epidemiology Research Team (EREN), F-93017 Bobigny, France.

Corresponding Author:

Dr. Sandrine Péneau; s.peneau@eren.smbh.univ-paris13.fr; EREN - UFR SMBH 74, rue Marcel Cachin, 93017 Bobigny Cedex France.

ABSTRACT

Introduction: Cardiovascular disease (CVD), though preventable, remains the leading cause of mortality among noncommunicable diseases. Psychological factors, such as trait impulsivity, have emerged as potential determinants in the onset of medical conditions. However, research investigating the potential relationships with CVD remains limited. Therefore, our objective was to assess the prospective associations between trait impulsivity and the incidence of CVD.

Methods: A prospective observational study was conducted between May 2014 and February 2023 within the NutriNet-Santé cohort. Trait impulsivity (low, medium [reference], high) was assessed using the Barratt Impulsiveness Scale 11. Incident CVD events, including coronary heart and cerebrovascular diseases, were identified through follow-up assessments and confirmed by NutriNet-Santé experts using medical records and ICD-10 codes. Cox regression models, using hazard ratios and 95% confidence intervals (HR [95%CI]), were conducted to examine associations between impulsivity and CVD risk. Potential interactions were assessed.

Results: Of the 48,135 participants studied (women=78.1%; baseline age=50.5±14.5y), 1,184 developed CVD over nearly 8 years of follow-up (median:7.84; IQR:4.04-8.50). Individuals with high impulsivity had higher CVD risk (HR=1.27 [1.01, 1.59], *P*=0.039). In participants with type 2 diabetes (T2D) specifically, low impulsivity was associated with lower CVD risk (HR=0.42 [0.20, 0.88], *P*=0.022), while no association was observed in individuals without T2D.

Conclusion: Participants with high impulsivity showed an increased CVD risk overall. Additionally, among those with T2D, low impulsivity was associated with a reduced risk. If these findings are replicated across diverse populations and settings, trait impulsivity could emerge as a significant psychological risk factor in CVD prevention.

KEYWORDS: cardiovascular disease, cerebrovascular disease, coronary heart disease, impulsivity, personality, prospective cohort study, psychological traits.

INTRODUCTION

Cardiovascular disease (CVD) is a group of disorders of the heart and blood vessels which claimed 17.9 million lives in 2019 worldwide, accounting for 32% of all deaths (1). Several risk factors are known to increase the incidence of CVD, including genetics, poor dietary habits, and diabetes (2).

Personality traits define the patterns of thoughts, feelings, and behaviors and have been proposed as important factors in the development of chronic diseases, including CVD (3). Personality traits are often developed throughout life and are considered to remain consistent across many situations and circumstances (4). Impulsivity as a personality trait is defined by a tendency to act quickly, without thorough consideration, often driven by emotional impulses, and with limited attentional focus (5), and has been associated with deficient inhibitory processes and high reward system reactivity (6). This personality trait has been shown to be more modifiable than other personality traits (7,8), and predisposes individuals to act within a spectrum of behaviors that can lead to impulsive actions (9).

Trait impulsivity has been associated with several noncommunicable diseases including type 2 diabetes or obesity (10–12). However, evidence on its relationship with CVD incidence is still lacking. Only one cross-sectional study has investigated associations between facets of impulsivity and a composite measure of cardiometabolic risk (13). This study found that both trait and behavioral impulsivity were associated with higher cardiometabolic risk through diverse lifestyle behavioral pathways (13). In addition, trait impulsivity has been associated with increased CVD risk factors such as higher cigarette smoking, greater food addiction, and lower adherence to healthy dietary patterns (14–16). These findings suggest that high trait impulsivity may potentially increase the risk of developing CVD.

Therefore, the aim of the present study was to assess the associations between trait impulsivity and the risk of developing CVD over 8 years of follow-up within the NutriNet-Santé cohort. Additionally, we sought to determine whether these associations varied across different population subgroups.

METHODS

Study design and population

A prospective study design was performed within the NutriNet-Santé cohort, a web-based observational study that aims to assess the associations between diet and its determinants and health status. Recruitment for the NutriNet-Santé study started in May 2009 and is currently ongoing with open enrolment. Volunteers are being recruited through multimedia campaigns targeting the general French population. Inclusion criteria are individuals aged 18 years or older, fluent in French and with access to the Internet. Participants are followed using a personal account on the study website (https://etude-nutrinet-sante.fr/), where they provided detailed information by completing several questionnaires.

At enrolment, participants are asked to complete several self-administered web-based questionnaires assessing their socioeconomic conditions, health status, and lifestyle characteristics such as diet, physical activity and anthropometric measures. Thereafter, participants complete this set of questionnaires annually, and an additional set of optional questionnaires is sent to participants monthly. Further details of the study protocol can be found on the following website: https://info.etude-nutrinet-sante.fr/siteinfo/, where comprehensive information on the rationale, design and methodology of the study is available (17). The study protocol was registered at https://www.clinicaltrials.gov/ (NCT03335644).

All participants are required to provide electronic informed consent prior to their involvement in the study. The study procedures have received approval from the Institutional Review Board of the French Institute for Health and Medical Research (IRB INSERM no: 0000388FWA00005831) as well as from the Commission Nationale de l'Informatique et des Libertés (CNIL no: 908450 and 909216). The study accomplishes the Declaration of Helsinki standards.

Impulsivity

Trait impulsivity was assessed using the 11th version of the Barrat Impulsiveness Scale (BIS-11) (18), adapted from the validated French version of the BIS-10 (19). The BIS-11 is the most widely used questionnaire for assessing trait impulsivity in both clinical practice and research (5). The administration of this questionnaire was performed between May and

November 2014. The BIS-11 is a 30-item self-reported questionnaire scored on a 4-point Likert scale ranging from "rarely/never" (1 point) to "almost always/always" (4 points). The BIS-11 total score ranges from 30 to 120 points and is obtained by summing its items, with higher scores indicating greater trait impulsivity. The α Cronbach coefficient for the total score was 0.77, indicating an acceptable internal consistency. In addition, impulsivity categories derived from the BIS-11 were obtained. The cut-off points for defining low (<52), medium (≥52 and ≤71), and high (>71) trait impulsivity categories were based on the recommendations of the BIS-11 scale (5).

Ascertainment of cardiovascular disease events

Participants were asked to report any major health events, such as CVD, through the annual health status questionnaire, a special health check-up questionnaire sent every six months, or at any time on the NutriNet-Santé intranet. Participants are also asked to send their medical records, such as diagnoses, examinations, or hospitalizations. The medical records and diagnoses were validated by the study physician experts and, if necessary, additional medical information was obtained from the participants' physicians or medical institutions. When participant updates were missing for more than a year in the NutriNet-Santé intranet, the physician expert committee contacted the participants' families or physicians to be aware about their health status. Additionally, CVD events were integrated with the Système National d'Information Inter-Régimes de l'Assurance Maladie (SNIIRAM) database, administered by the Caisse Nationale de l'Assurance Maladie of the French national insurance system (CNAM), as well as to the French national mortality registry (CépiDC) to identify mortality due to a CVD event. This linkage limitates the potential bias from those who had not reported a CVD event.

The CVD events were classified using the International Classification of Diseases 10th Revision (ICD-10) (20) in order to obtain overall cardiovascular disease, coronary heart disease, and cerebrovascular disease. Coronary heart disease includes: myocardial infarction (I21), acute coronary syndrome (I20.0 and I21.4), angina pectoris (I20.1, I20.8, I20.9), and angioplasty (Z95.8). Cerebrovascular disease includes: stroke (I64) and transient ischemic attack (G45.8 and G45.9). Overall cardiovascular disease includes both coronary heart and cerebrovascular diseases events.

Covariates

Confounders potentially modifying the association between trait impulsivity and CVD were collected. Selected confounders were: sociodemographics including sex, age (years), and educational level (less than high school degree, <2 years after high school degree, ≥2 years after high school degree); lifestyle including smoking intensity (pack/day), physical activity (low, medium, high) using the International Physical Activity Questionnaire (IPAQ) (21), energy intake without alcohol (kcal/day), alcohol intake (g/day) and diet quality (simplified Programme National Nutrition Santé - Guidelines Score 2 (sPNNS-GS2) (22) using 24h-dietary records; anthropometrics including BMI (kg/m2); personal history of disease including hypertension prevalence or medication (no, yes), hypercholesterolemia prevalence or medication (no, yes), hypertriglyceridemia prevalence or medication (no, yes), T2D prevalence or medication (no, yes), and depressive symptomatology (no, yes) using the self-reported Center for Epidemiologic Studies Depression Scale questionnaire (CES-D) (23); and family history of disease including family history of CVD (no, yes).

Statistical analysis

For the present study, only participants from the NutriNet-Santé cohort who completed the impulsivity questionnaire and did not have a prevalent CVD event at the moment of the impulsivity assessment were included. Covariates with missing values were handled with Multiple Imputation by Chained Equations (MICE) and fully conditional specification (Supplementary Method 1).

Baseline population characteristics were compared using t-test or chi-square, as appropriate, between included and excluded participants (Supplementary Table 1). The participant's baseline characteristics are presented as numbers and percentages for qualitative variables, and as mean ± standard deviation (SD) for quantitative variables. Comparisons between categories of trait impulsivity (low, medium, high) were based on chi-square for categorical variables and ANOVA for quantitative variables.

Cox regression models, using hazard ratio and 95% confidence interval (HR 95%CI), were conducted to study the associations between trait impulsivity and the risk of CVD (overall, coronary heart, and cerebrovascular) incidence over 8 years of follow-up. Incidence rates per

1,000 person-year were also estimated. Trait impulsivity was assessed categorically (low, medium as the reference, and high). P for trend was obtained by using the median impulsivity in each category. Participants contributed person-time from the impulsivity assessment until the date of the CVD event, date of last follow-up, date of death, or 8th February 2023, whichever occurred first. The main model was adjusted at baseline by age (as time-scale), sex, educational level, smoking intensity, physical activity (with a logarithmic time interaction for overall cardiovascular and cerebrovascular diseases), energy intake (with a logarithmic time interaction for overall CVD), alcohol intake, diet quality (with a logarithmic time interaction for overall CVD), BMI, hypertension prevalence or medication, hypercholesterolemia prevalence or medication, hypertriglyceridemia prevalence or medication, and T2D prevalence or medication. The rationale for the selection of covariates is described in Supplemental Table 2.

Linearity assumptions were assessed using Restricted Cubic Spline functions between trait impulsivity and overall, coronary heart, and cerebrovascular diseases (Supplementary Figure 1; Supplementary Figure 2; Supplementary Figure 3). Cumulative hazard risks between impulsivity categories and the incidence of CVD were estimated (Supplementary Figure 4). Pearson correlation coefficients were examined to confirm the absence of collinearity among continuous covariates (Supplementary Table 3). Schoenfeld residuals were evaluated to validate proportional hazard risk assumptions (Supplementary Table 4). The covariates violating the non-proportional hazard assumptions were corrected by adding a logarithmic time interaction term (physical activity, energy intake excluding alcohol, and diet quality for overall CVD; and physical activity for cerebrovascular disease). In addition, Schoenfeld residuals were reevaluated correcting covariates showing non-proportional hazard risk (Supplementary Table 4).

Sensitivity analyses were conducted to evaluate the robustness of the results. The association between impulsivity and the risk of developing overall CVD was analyzed using stratified estimates for non-proportional hazard covariates (Supplementary Table 5) and without a correction for non-proportional hazard risk covariates (Supplementary Table 6). A total of seven additional models were assessed to investigate potential confounding effects (Supplementary Table 7). Associations between trait impulsivity and hard CVD events were

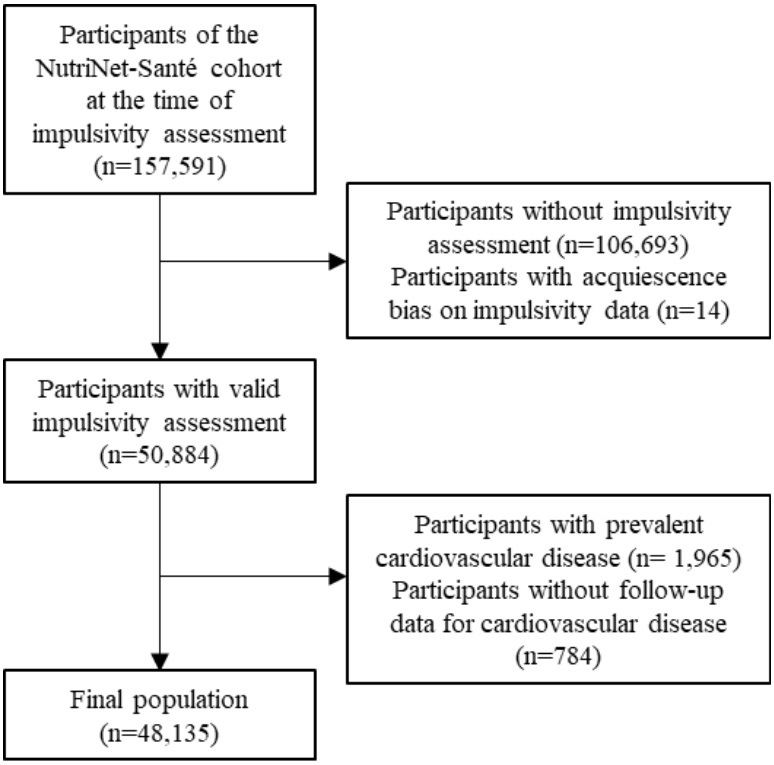
also evaluated. Hard coronary heart disease included myocardial infarction, acute coronary syndrome, and angioplasty, and excluded angina pectoris. Hard cerebrovascular disease included stroke and excluded transient ischemic attack (Supplementary Table 8). An additional analysis was also performed to assess the impact of excluding incident cases of CVD within the initial 2 years of follow-up (to challenge the potential reverse causality bias) (Supplementary Table 9). Finally, interactions by sex, age (<60y, ≥60y), overweight (BMI: <25, ≥25 kg/m2), diet quality (sPNNS-GS2: median to determine low and high diet quality), and prevalence of T2D (no, yes) were conducted using the likelihood ratio test. The only statically significant interaction observed was with T2D. Consequently, analyses were stratified by T2D status for overall CVD (Figure 3), but associations with coronary heart disease and cerebrovascular disease are only detailed in Supplementary Table 10 and Supplementary Table 11, respectively, due to low incident cases that may limit interpretability. Analyses were conducted using STATA 14 and statistical significance was considered as P-value<0.05.

RESULTS

Description of the study population

Of the 157,591 participants enrolled in the NutriNet-Santé study at the time of the impulsivity assessment, a total of 109,456 were excluded due to lack of a valid impulsivity assessment (n=106,707) or CVD assessment (n=784), or due to prevalent CVD (n=1,965) (Figure 1). Among the 48,135 included participants, a total of 1,184 developed CVD, of which 632 were classified as coronary heart disease and 554 as cerebrovascular disease (two participants had on the same day a coronary heart and cerebrovascular disease). The median follow-up was nearly 8 years (median: 7.84; interquartile range: 4.04-8.50) (person-years: 292,769). The incidence rate (95%CI) per 1,000 person-years were 4.04 (3.82, 4.28) for overall CVD, 2.14 (1.98, 2.32) for coronary heart disease, and 1.88 (1.73, 2.04) for cerebrovascular disease.

Figure 1. Flowchart of the studied population.



Baseline characteristics of the population are shown in Table 1. The mean age of the population was 50.5 years (SD: 14.5), with females comprising approximately three-quarters of the population. Individuals with higher impulsivity levels were more likely to be younger and females, to have lower educational level, reduced physical activity and poorer diet quality. They also exhibited higher smoking intensity, increased alcohol consumption, higher BMI and a greater prevalence or medication use for hypertension, hypertriglyceridemia and T2D, and a greater prevalence of depressive symptomatology.

Table 1. Baseline characteristics of the study population, NutriNet-Santé cohort, France, 2014-2023 (n=48,135).

Characteristics	All participants	Trait impulsivity			*P*-value*
		Low (n=8,582)	Medium (n=36,577)	High (n=2,976)	
Age (years)	50.47 ± 14.49†	50.93 ± 14.02	50.43 ± 14.53	49.68 ± 15.27	<0.001
Sex (female)	37,580 (78.07)‡	6,233 (72.63)	28,881 (78.96)	2,466 (82.86)	<0.001
Educational level (n=47,985)					<0.001
Less than high school degree	1,056 (2.20)	119 (1.39)	803 (2.20)	134 (4.51)	
<2 years after high school degree	14,054 (29.29)	2,152 (25.14)	10,713 (29.39)	1,189 (40.03)	
≥2 years after high school degree	32,875 (68.51)	6,289 (73.47)	24,939 (68.41)	1,647 (55.45)	
Smoking intensity (pack/day) (n=45,871)	0.30 ± 0.49	0.25 ± 0.45	0.30 ± 0.49	0.42 ± 0.56	<0.001
Physical activity (IPAQ) (n=48,037)					<0.001
Low	11,084 (23.07)	1,865 (21.77)	8,453 (23.15)	766 (25.88)	
Moderate	20,143 (41.93)	3,541 (41.34)	15,420 (42.23)	1,182 (39.93)	
High	16,810 (34.99)	3,160 (36.89)	12,638 (34.61)	1,012 (34.19)	
Energy intake excluding alcohol (kcal/day) (n=44,819)	1,787.03 ± 473.75	1,785.70 ± 472.55	1,786.44 ± 471.77	1,789.41 ± 501.82	0.44
Alcohol intake (g/day) (n=44,819)	7.85 ± 12.00	7.05 ± 11.12	7.98 ± 12.07	8.63 ± 13.45	<0.001
Diet quality (sPNNS-GS2; range: −17 to 13.5) (n= 44,044)	1.27 ± 3.56	1.41 ± 3.55	1.26 ± 3.51	0.95 ± 3.78	<0.001
BMI (kg/m^2) (n=47,962)	23.96 ± 4.50	23.71 ± 4.26	23.98 ± 4.49	24.55 ± 5.16	<0.001
Hypertension prevalence and/or medication	6,412 (13.32)	1,117 (13.02)	4,840 (13.23)	455 (15.29)	0.004
Hypercholesterolemia prevalence and/or medication	8,601 (17.87)	1,498 (17.46)	6,549 (17.90)	554 (18.62)	0.34
Hypertriglyceridemia prevalence and/or medication	1,827 (3.80)	310 (3.61)	1,366 (3.73)	151 (5.07)	0.001
T2D prevalence and/or medication	1,301 (2.70)	206 (2.40)	982 (2.68)	113 (3.80)	<0.001
Family history of cardiovascular disease (CVD) (n=47,850)	17,529 (36.63)	3,090 (36.19)	13,355 (36.72)	1,084 (36.90)	0.63
Depressive symptomatology (n=19,393)	2,358 (12.16)	263 (7.79)	1,799 (12.11)	296 (25.45)	<0.001

Abbreviations: IPAQ, International Physical Activity Questionnaire; sPNNS-GS2, simplified Programme National Nutrition Santé - Guidelines Score 2; BMI, body mass index; T2D, type 2 diabetes; CVD, cardiovascular disease. Trait impulsivity categories were determined using the following cut-offs: low (<52), medium (≥52 and ≤71) and high (>71), based on the Barratt Impulsiveness Scale 11 questionnaire.

* P-value showing comparisons between categories of trait impulsivity (low, medium, high) based on chi-square for categorical variables and ANOVA for quantitative variables. † mean ± SD (all such values). ‡ n (%) (all such values).

Associations between trait impulsivity and CVD

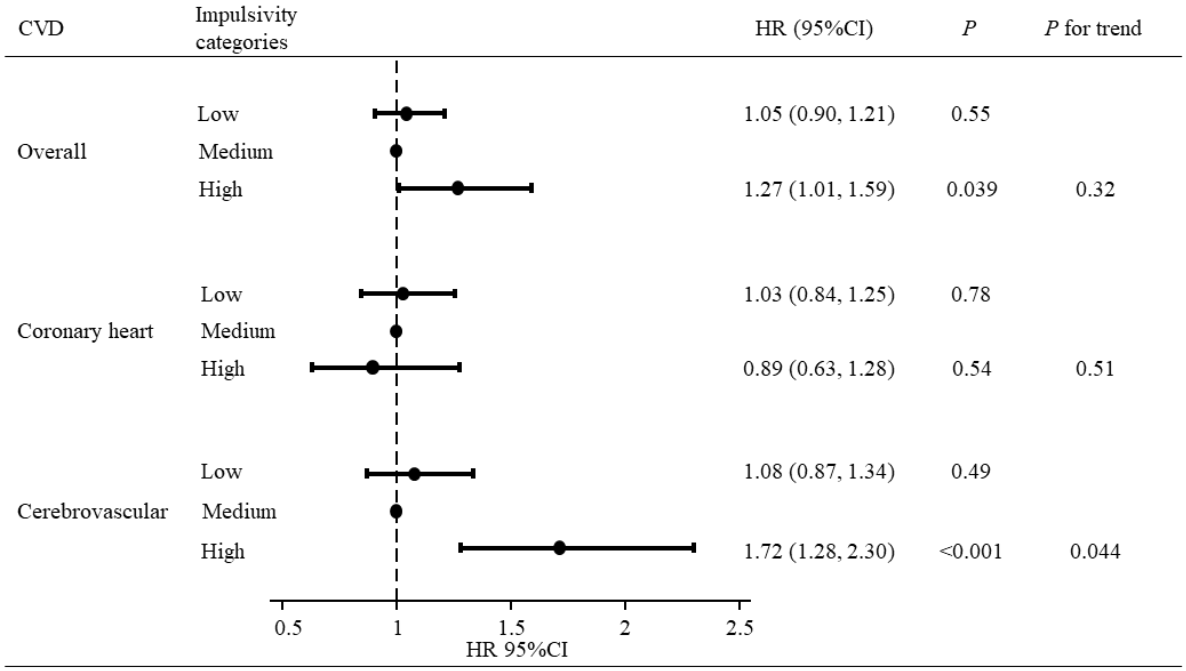
Compared with the medium impulsivity category, participants with high impulsivity presented a higher risk of developing overall CVD (P=0.039) and cerebrovascular disease (P<0.001) (Figure 2). No significant associations were found between impulsivity categories and coronary heart disease. Additionally, a significant trend was observed between impulsivity categories and cerebrovascular disease (P=0.044), but not in the case of overall (P=0.32) and coronary heart diseases (P=0.51) (Figure 2).

Analyses were stratified by T2D due to the significant interaction observed (P=0.014) (Figure 3). Among participants without T2D at baseline, those with high impulsivity had a borderline higher risk of developing overall CVD (P=0.055) compared with participants with medium impulsivity levels. Additionally, among participants with T2D, those with low impulsivity had a lower risk of developing overall CVD (P=0.022). A significant trend was observed between impulsivity categories and overall CVD in individuals with T2D only (P=0.020).

Additional analyses were performed on coronary heart disease and cerebrovascular diseases in individual without (Supplementary Table 10) and with T2D (Supplementary Table 11). Among participants without T2D at baseline, those with high impulsivity had a higher risk of developing cerebrovascular disease only (P<0.001). Among participants with T2D at baseline, those with low impulsivity had a lower risk of developing coronary heart disease only (P=0.043).

Sensitivity analyses consistently showed the same directionality and significance in the associations between impulsivity and overall CVD risk when evaluating non-proportional hazard risk covariates with correction using stratified estimates (Supplementary Table 4) and without correction (Supplementary Table 5). Furthermore, the directions and significances of the associations between impulsivity and overall, coronary heart, and cerebrovascular diseases remained unchanged in seven additional models, with various adjustments (Supplementary Table 6). However, when examining associations of impulsivity with hard CVD events (Supplementary Table 7) or when excluding CVD events during the first 2 years of follow-up (Supplementary Table 8), the associations were attenuated and did not reach statistical significance.

Figure 2. Associations between trait impulsivity and cardiovascular disease risk. NutriNet-Santé cohort, France, 2014-2023 (n=48,135).

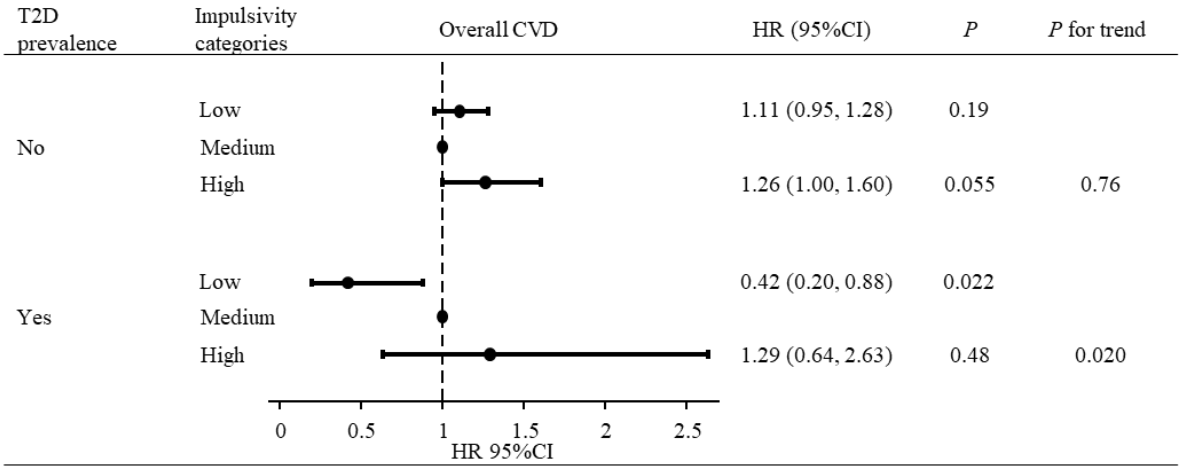


Abbreviations: CVD, cardiovascular disease; HR (95%CI), hazard ratio and 95% confidence interval; Per 1SD, per 1 standard deviation increment; rate, incidence rate per 1,000 person-years; BMI, body mass index. Cut-off points for low (<52), medium (≥52 and ≤71), and high (>71) impulsivity categories using the Barratt Impulsiveness Scale 11 questionnaire.

Coronary heart disease includes: myocardial infarction, acute coronary syndrome, angioplasty, and angina pectoris. Cerebrovascular disease includes: stroke and transient ischemic attack. Overall CVD includes coronary heart and cerebrovascular diseases. Incident cases of overall CVD (n=1,184/48,135) had a rate of 4.04 per 1,000 person-years. Incident cases of coronary heart disease (n=632/48,112) had a rate of 1.98 per 1,000 person-years. Incident cases of cerebrovascular disease (n=554/48,123) had a rate of 1.88 per 1,000 person-years. Two participants had a coronary heart and cerebrovascular disease event on the same day, and these participants were included in both analyses.

Cox regression analyses were performed using hazard ratios and 95% CI to assess associations of impulsivity categories (medium as reference) with the risk of developing overall CVD over a median follow-up of 8 years in the NutriNet-Santé cohort. The *P* for trend was obtained by averaging the median score of each impulsivity category. Main model was adjusted for baseline age (time-scale), sex, educational level (less than high school degree, <2 years after high school degree, ≥2 years after high school degree), smoking intensity (pack/day), physical activity (International Physical Activity Questionnaire: low, moderate, high), energy intake excluding alcohol (kcal/day), alcohol intake (g/day), diet quality (simplified Programme National Nutrition Santé - Guidelines Score 2), BMI (kg/m^2), hypertension prevalence or medication (no, yes), hypercholesterolemia prevalence or medication (no, yes), hypertriglyceridemia prevalence or medication (no, yes), and T2D prevalence or medication (no, yes). Non-proportional hazard risk covariates were corrected by including a logarithmic time interaction term for physical activity, energy intake excluding alcohol, and diet quality in the analysis of overall CVD, and for physical activity in the analysis of cerebrovascular disease.

Figure 3. Associations between trait impulsivity and cardiovascular disease risk by type 2 diabetes prevalence. NutriNet-Santé cohort, France, 2014-2023 (n=48,135).



Abbreviations: T2D, type 2 diabetes prevalence; CVD, cardiovascular disease; HR (95%CI), hazard ratio and 95% confidence interval; HR per 1SD, hazard ratio and 95%CI per 1 standard deviation increment; rate, incidence rate per 1,000 person-years; BMI, body mass index. Cut-off points for low (<52), medium (≥52 and ≤71), and high (>71) impulsivity categories using the Barratt Impulsiveness Scale 11 questionnaire.

Overall CVD includes myocardial infarction, acute coronary syndrome, angioplasty, angina pectoris, stroke, and transient ischemic attack. Participants without prevalent T2D: incident cases of overall CVD (n=1,096/46,834) had a rate of 3.84 per 1,000 person-years. Participants with prevalent T2D: incident cases of overall CVD (n=88/1,301) had a rate of 11.91 per 1,000 person-years.

Cox regression analyses were performed using hazard ratios and 95% CI to assess associations of impulsivity categories (medium as reference) with the risk of developing overall CVD over a median follow-up of 8 years in the NutriNet-Santé cohort. Analyses were stratified by the T2D prevalence due to a significant interaction (*P*=0.014). The *P* for trend was obtained by averaging the median impulsivity score of each impulsivity category. Main model was adjusted for baseline age (time-scale), sex, educational level (less than high school degree, <2 years after high school degree, ≥2 years after high school degree), smoking intensity (pack/day), physical activity (International Physical Activity Questionnaire: low, moderate, high), energy intake excluding alcohol (kcal/day), alcohol intake (g/day), diet quality (simplified Programme National Nutrition Santé - Guidelines Score 2), BMI (kg/m2), hypertension prevalence or medication (no, yes), hypercholesterolemia prevalence or medication (no, yes), hypertriglyceridemia prevalence or medication (no, yes), and T2D prevalence or medication (no, yes). Non-proportional hazard risk covariates were corrected by including a logarithmic time interaction term for physical activity, energy intake excluding alcohol, and diet quality in the analysis of overall CVD.

DISCUSSION

This study is the first, to our knowledge, to investigate associations between trait impulsivity and the incidence of CVD. Our findings indicate that individuals with higher levels of impulsivity had an increased risk of developing CVD overall, particularly cerebrovascular events, compared to those with medium impulsivity levels. Additionally, among individuals with prevalent T2D, lower impulsivity was associated with a reduced risk of developing CVD overall, whereas no significant association was observed in individuals without T2D.

Although no prior studies have specifically examined the link between trait impulsivity and CVD incidence, our data align with a previous cross-sectional study showing that both trait and behavioral impulsivity are positively associated with a composite score of cardiovascular disease risk (13). Several mechanisms may explain the observed associations. First, impulsive unhealthy behaviors may lead to unhealthy lifestyle choices. Trait impulsivity has been associated with lower adherence to healthy dietary patterns and higher BMI (11,16), may be driven by food addiction (15), which are established risk factors for CVD and therefore may indirectly contribute to its incidence (1). Another potential mechanism is based on the mind-heart-body framework (22), which suggests that psychological factors, such as stress, interact with the heart's reactivity and the release of hormones in the body (24). The pathways connecting stress and cardiovascular risk involve neural regions associated with stress, such as the limbic and prefrontal areas (24), which are also involved in impulsivity (6,25,26). This overlap may partly explain the association between trait impulsivity and CVD. Lastly, the serotonin and dopamine networks, which play a key role in impulsivity (27), have also been linked to the cardiovascular system and may have an impact on the development and prevention of CVD (28,29).

In our study, we found an association between trait impulsivity and cerebrovascular disease, but not with incident coronary heart disease. This finding is consistent with a previous pooled analysis of 6 U.S. cohorts including 58,105 participants, which showed that the personality traits of conscientiousness and neuroticism, as measured by the Big Five questionnaire, were inversely and positively associated with incident stroke, respectively (31) Notably, this analysis did not assess coronary heart disease (30). Trait impulsivity has been proposed as an antagonist to conscientiousness, which is characterized by self-control, responsibility, and

organization, and it related to neuroticism due to the regular experience of negative emotions (31). Finally, a low internal locus of control, a concept related to impulsivity as both show difficulties with self-regulation (32), has been associated with a higher risk of myocardial infarction but showed no link in the case of stroke (33).

The mechanisms explaining the association observed in our study between trait impulsivity and incident cerebrovascular disease, but not coronary heart disease, may involve differential impacts of impulsivity on risk factors and physiological mechanisms related to cardiovascular risk. For example, impulsivity has been associated with elevated blood pressure (34), which has been more strongly associated with cerebrovascular disease than with coronary heart disease (35). This disparity may be due to the unique vulnerabilities of cerebral arteries, which have thinner walls and less elastic tissue compared to coronary arteries (36). Moreover, impulsivity has been associated with increased use of alcohol, cigarettes, or amphetamines (14), behaviors that are also more strongly associated with cerebrovascular disease than with coronary heart disease (37–39).

T2D is a well-known risk factor for incident CVD (1). Our results confirmed the association between high impulsivity and CVD in individuals without T2D, though this association was only borderline significant. In contrast, no such association was observed in participants with T2D, possibly due to a smaller sample size. Notably, within the T2D group, low impulsivity was linked to a lower risk of CVD, suggesting a potential protective effect of lower impulsivity. Previous research within the same cohort has shown positive associations between trait impulsivity and a higher risk of incident T2D (12). Additionally, in individuals with T2D, facets of trait impulsivity have been cross-sectionally associated with poorer self-care behaviors, such as weight gain, reduced physical activity, poor diet quality, and medication non-adherence (40–42), as well as with worse diabetes control, as indicated by glycated hemoglobin levels (43). These findings underscore trait impulsivity as a significant psychological factor to consider for mitigating the risk of incident CVD in individuals with T2D particularly.

Strengths of the present analyses include the exploration of novel associations, a large sample size, a relatively long follow-up period, comprehensive assessment of CVD events, and extensive sensitivity analyses. The sensitivity analyses, which included adjustments for

multiple confounders and interaction assessments, confirmed the robustness of the findings. Additional adjustments for several confounders did not alter the significance of the associations between trait impulsivity and incident CVD. However, there are some limitations to note. Firstly, the observational design of the study precludes causal inferences. Additionally, excluding incident cases within the first 2 years of follow-up led to a loss of significance in these associations, which may be due to a reduction in CVD events by nearly half. Excluding early incident cases aimed to mitigate potential reverse causation. Since personality traits are stable from adulthood and likely precede chronic diseases (3,44), reverse causation is less probable but cannot be entirely ruled out. Secondly, sensitivity analyses focusing solely on hard CVD events also yielded non-significant results, potentially due to reduced statistical power. For example, the incidence of cerebrovascular events decreased from 1.1% to 0.3% when shifting from all events to hard events. Thirdly, trait impulsivity was assessed via self-report using a widely accepted questionnaire. Despite its validity, self-reported measures may introduce bias. Lastly, caution should be exercised when generalizing these findings to other populations. The NutriNet-Santé cohort had a higher proportion of female participants, and impulsivity tends to be greater in men than in women (45). Moreover, voluntary enrollment is typically associated with higher education levels and better health (46). In this line of thinking, a study conducted in France in 2013 involving about 3.5 million people reported similar CVD prevalence compared with in our study, but incidence rates were clearly higher in men than in women (47). Therefore, the observed associations of the current work may be slightly conservative.

The clinical relevance of this study warrants emphasis. First, while impulsivity traits are viewed as adaptive responses in various contexts (48), high levels of impulsivity have been consistently associated with risky behaviors (11,16,49), poor health outcomes (13,14,16,40,41), and psychiatric conditions (11,48), with a significant public health burden. The current study highlights that a higher impulsivity is linked to an increased risk of incident CVD, which is the leading cause of mortality among non-communicable diseases (1). By decreasing impulsivity, a beneficial feedback loop between positive psychological states and cardiovascular health could occur under the mind-heart-body framework (50). Thus, trait impulsivity emerges as an important factor to consider for the prevention of cardiometabolic

health. Future clinical trials with large populations are needed to further explore the novel relationships between impulsivity and chronic diseases such as CVD.

CONCLUSIONS

In conclusion, this study found that participants with high trait impulsivity had a significantly increased risk of developing CVD over a median follow-up of 8 years within a large French cohort. Additionally, among individuals with prevalent T2D, low impulsivity was associated with a significantly reduced risk of developing CVD. While these findings are notable, replication in diverse populations and settings is necessary to validate their generalizability. Nonetheless, trait impulsivity emerges as a promising psychological risk factor worthy of consideration in CVD prevention strategies.

DECLARATIONS

Acknowledgements

The authors thank Cédric Agaesse (dietary data manager) and Alexandre De-Sa (dietitian); Selim Aloui (IT manager), Thi Hong Van Duong, Régis Gatibelza, Jagatjit Mohinder and Aladi Timera (computer scientists); Julien Allegre, Nathalie Arnault, Laurent Bourhis, Nicolas Dechamp (biostatisticians), and Fabien Szabo de Edelenyi, Ph.D. (biostatistics team manager); Maria Gomes and Mirette Foham (NutriNet-Santé participant support) and Paola Yvroud, M.D. (health event validator) (all affiliated with CRESS-EREN) for their technical contribution to the NutriNet-Santé study. The authors sincerely thank all the volunteers of the NutriNet-Santé cohort.

Ethics approval and consent to participate

Electronic informed consent is provided by each person included in the NutriNet-Santé cohort. The study is registered at https://clinicaltrials.gov/ct2/show/NCT03335644, conducted according to the Declaration of Helsinki guidelines and approved by the Institutional Review Board of the French Institute for Health and Medical Research (IRB-Inserm) and the Commission Nationale de l'Informatique et des Libertés (CNIL No 908450/909216).

Competing interests

The authors declare no competing interests.

Funding

The NutriNet-Santé study was supported by the following public institutions: the Ministry of Health, Public Health France, the National Institute of Health and Medical Research (INSERM), the National Institute of Agricultural, Food and Environmental Research (INRAE), the National Conservatory of Arts and Crafts (CNAM) and Université Sorbonne Paris Nord. CG-M receives a predoctoral scholarship (2020PMF-PIPF-37) from URV. Researchers were independent from funders. The funders had no role in considering the study design or in the collection, analysis, interpretation of data, writing of the report, or decision to submit the article for publication.

Authors' Contributions

SH, LF, MT and SP contributed to the NutriNet-Santé study conceptualization and coordination. SP coordinated the project. CG-M, PG, BS, LF, SP contributed to the methodology and formal analysis. CG-M wrote the original draft and revised the manuscript based on comments from SP. All authors reviewed and approved the manuscript for submission. All authors had the final responsibility for the decision to submit for publication.

Availability of data and materials

Researchers from public institutions can submit a collaboration request to Dr. Mathilde Touvier via collaboration@etude-nutrinet-sante.fr, including information on the institution and a brief description of the project. All requests will be reviewed by the steering committee of the NutriNet-Santé study. If the collaboration is accepted, a data access agreement will be necessary, and appropriate authorizations from competent administrative authorities may be needed. In accordance with existing regulations, no personal data will be accessible. The analysis code can be requested from the authors.

REFERENCES

1. World Health Organization. A report about cardiovascular diseases. World Health Organization. June 11, 2021. Accessed June 27, 2022. https://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)
2. Mozaffarian D, Wilson PWF, Kannel WB. Beyond Established and Novel Risk Factors. *Circulation*. 2008;117(23):3031-3038. doi:10.1161/CIRCULATIONAHA.107.738732
3. Harper RG. *Personality-Guided Therapy in Behavioral Medicine.* 1st ed. American Psychological Association; 2004. doi:10.1037/10650-000
4. Roberts BW, DelVecchio WF. The rank-order consistency of personality traits from childhood to old age: A quantitative review of longitudinal studies. *Psychol Bull*. 2000;126(1):3-25. doi:10.1037/0033-2909.126.1.3
5. Stanford MS, Mathias CW, Dougherty DM, Lake SL, Anderson NE, Patton JH. Fifty years of the Barratt Impulsiveness Scale: An update and review. *Pers Individ Dif*. 2009;47(5):385-395. doi:10.1016/j.paid.2009.04.008
6. Bari A, Robbins TW. Inhibition and impulsivity: Behavioral and neural basis of response control. *Prog Neurobiol*. 2013;108:44-79. doi:10.1016/j.pneurobio.2013.06.005

7. DeYoung C, Reuter A. Impulsivity as a personality trait. In: Vohs K, Baumeister R, eds. *Handbook of Self-Regulation: Research, Theory, and Applications*. Third edition. Guilford Press; 2016:345-363. https://www.researchgate.net/publication/284080443

8. Rababah JA, Al-Hammouri MM, Tawalbeh L, Alhawatmeh H, Hasan M. Self-care among persons with heart failure: Examining the impact of mindfulness and impulsivity using conditional process analysis. *Nurs Forum (Auckl)*. 2022;57(4):558-567. doi:10.1111/nuf.12719

9. Mischel W, Shoda Y. A Cognitive-Affective System Theory of Personality: Reconceptualizing Situations, Dispositions, Dynamics, and Invariance in Personality Structure. *Psychol Rev*. 1995;102(2):246-268. doi:10.1037/0033-295X.102.2.246

10. Bénard M, Camilleri GM, Etilé F, et al. Association between Impulsivity and Weight Status in a General Population. *Nutrients*. 2017;9(3):217. doi:10.3390/NU9030217

11. Emery RL, Levine MD. Questionnaire and behavioral task measures of impulsivity are differentially associated with body mass index: A comprehensive meta-analysis. *Psychol Bull*. 2017;143(8):868-902. doi:10.1037/bul0000105

12. Gómez-Martínez C, Paolassini-Guesnier P, Fezeu L, et al. Trait impulsivity is associated with an increased risk of type 2 diabetes incidence in adults over 8 years of follow-up: results from the NutriNet-Santé cohort. *BMC Med*. 2024;22(1):332. doi:10.1186/s12916-024-03540-7

13. Emery RL, Levine MD, Creswell KG, et al. Impulsivity and midlife cardiometabolic risk: The role of maladaptive health behaviors. *Health Psychology*. 2020;39(8):642-654. doi:10.1037/hea0000884

14. Lee RSC, Hoppenbrouwers S, Franken I. A Systematic Meta-Review of Impulsivity and Compulsivity in Addictive Behaviors. *Neuropsychol Rev*. 2019;29(1):14-26. doi:10.1007/s11065-019-09402-x

15. VanderBroek-Stice L, Stojek MK, Beach SRH, vanDellen MR, MacKillop J. Multidimensional assessment of impulsivity in relation to obesity and food addiction. *Appetite*. 2017;112:59-68. doi:10.1016/j.appet.2017.01.009

16. Gómez-Martínez C, Babio N, Júlvez J, et al. Impulsivity is longitudinally associated with healthy and unhealthy dietary patterns in individuals with overweight or obesity and metabolic syndrome within the framework of the PREDIMED-Plus trial. *International Journal of Behavioral Nutrition and Physical Activity*. 2022;19(1):101. doi:10.1186/s12966-022-01335-8

17. Hercberg S, Castetbon K, Czernichow S, et al. The Nutrinet-Santé Study: a web-based prospective study on the relationship between nutrition and health and determinants of dietary patterns and nutritional status. *BMC Public Health*. 2010;10(1):242. doi:10.1186/1471-2458-10-242

18. Patton JH, Stanford MS, Barratt ES. Factor structure of the Barratt Impulsiveness Scale. *J Clin Psychol*. 1995;51(6):768-774. doi:10.1002/1097-4679(199511)51:6<768::AID-JCLP2270510607>3.0.CO;2-1

19. Baylé FJ, Bourdel MC, Caci H, et al. [Factor analysis of french translation of the Barratt impulsivity scale (BIS-10)]. *Can J Psychiatry*. 2000;45(2):156-165. doi:10.1177/070674370004500206

20. World Health Organization. *International Statistical Classification of Diseases and Related Health Problems, 10th Revision, 5th Ed.* Vol 1. World Heal. World Health Organization; 2016. http://www.who.int/classifications/icd/icdonlineversions/en/

21. Mõttus R, McNeill G, Jia X, Craig LCA, Starr JM, Deary IJ. The associations between personality, diet and body mass index in older people. *Health Psychology*. 2013;32(4):353-360. doi:10.1037/a0025537

22. Chaltiel D, Adjibade M, Deschamps V, et al. Programme National Nutrition Santé – guidelines score 2 (PNNS-GS2): development and validation of a diet quality score reflecting the 2017 French dietary guidelines. *British Journal of Nutrition*. 2019;122(03):331-342. doi:10.1017/S0007114519001181

23. Fuhrer R., Rouillon F. La version française de l'échelle CES-D (Center for Epidemiologic Studies-Depression Scale). Description et traduction de l'échelle d'autoévaluation. *Psychiatry and Psychobiology*. 1989;4(3):163-166. doi:10.1017/S0767399X00001590

24. Ginty AT, Kraynak TE, Fisher JP, Gianaros PJ. Cardiovascular and autonomic reactivity to psychological stress: Neurophysiological substrates and links to cardiovascular disease. *Autonomic Neuroscience*. 2017;207:2-9. doi:10.1016/j.autneu.2017.03.003

25. Dalley JW, Everitt BJ, Robbins TW. Impulsivity, Compulsivity, and Top-Down Cognitive Control. *Neuron*. 2011;69(4):680-694. doi:10.1016/J.NEURON.2011.01.020

26. Brewster BM, Pasqualini MS, Martin LE. Functional Brain Connectivity and Inhibitory Control in Older Adults: A Preliminary Study. *Front Aging Neurosci*. 2022;14:125. doi:10.3389/fnagi.2022.763494

27. Dalley JW, Roiser JP. Dopamine, serotonin and impulsivity. *Neuroscience*. 2012;215:42-58. doi:10.1016/j.neuroscience.2012.03.065

28. Neumann J, Hofmann B, Dhein S, Gergs U. Role of Dopamine in the Heart in Health and Disease. *Int J Mol Sci*. 2023;24(5):5042. doi:10.3390/ijms24055042

29. Maurer-Spurej E. Serotonin reuptake inhibitors and cardiovascular diseases: a platelet connection. *CMLS Cellular and Molecular Life Sciences*. 2005;62(2):159-170. doi:10.1007/s00018-004-4262-1

30. Stephan Y, Sutin AR, Luchetti M, Aschwanden D, Terracciano A. Personality and Risk of Incident Stroke in 6 Prospective Studies. *Stroke*. 2023;54(8):2069-2076. doi:10.1161/STROKEAHA.123.042617

31. Roberts BW, Lejuez C, Krueger RF, Richards JM, Hill PL. What is conscientiousness and how can it be assessed? *Dev Psychol*. 2014;50(5):1315-1330. doi:10.1037/a0031109

32. Kalenscher T, Ohmann T, Güntürkün O. The neuroscience of impulsive and self-controlled decisions. *International Journal of Psychophysiology*. 2006;62(2):203-211. doi:10.1016/j.ijpsycho.2006.05.010

33. Stürmer T, Hasselbach P, Amelang M. Personality, lifestyle, and risk of cardiovascular disease and cancer: follow-up of population based cohort. *BMJ*. 2006;332(7554):1359. doi:10.1136/bmj.38833.479560.80

34. Fuemmeler BF, Østbye T, Yang C, McClernon FJ, Kollins SH. Association between attention-deficit/hyperactivity disorder symptoms and obesity and hypertension in early adulthood: a population-based study. *International Journal of Obesity 2011 35:6*. 2010;35(6):852-862. doi:10.1038/ijo.2010.214

35. Stevens SL, Wood S, Koshiaris C, et al. Blood pressure variability and cardiovascular disease: systematic review and meta-analysis. *BMJ*. 2016;354:i4098. doi:10.1136/bmj.i4098

36. Salehi Omran S, Gutierrez J, Mohr JP, Elkind MSV. Structural and Functional Characteristics of Cerebral Arteries as an Explanation for Clinical Syndromes Limited to the Brain. *Cerebrovascular Diseases*. 2023;52(1):52-60. doi:10.1159/000524724

37. Millwood IY, Walters RG, Mei XW, et al. Conventional and genetic evidence on alcohol and vascular disease aetiology: a prospective study of 500 000 men and women in China. *The Lancet*. 2019;393(10183):1831-1842. doi:10.1016/S0140-6736(18)31772-0

38. O'Keefe EL, Dhore-patil A, Lavie CJ. Early-Onset Cardiovascular Disease From Cocaine, Amphetamines, Alcohol, and Marijuana. *Canadian Journal of Cardiology*. 2022;38(9):1342-1351. doi:10.1016/j.cjca.2022.06.027

39. Banks E, Joshy G, Korda RJ, et al. Tobacco smoking and risk of 36 cardiovascular disease subtypes: fatal and non-fatal outcomes in a large prospective Australian study. *BMC Med*. 2019;17(1):128. doi:10.1186/s12916-019-1351-4

40. Hadj-Abo A, Enge S, Rose J, Kunte H, Fleischhauer M. Individual differences in impulsivity and need for cognition as potential risk or resilience factors of diabetes self-management and glycemic control. Suksomboon N, ed. *PLoS One*. 2020;15(1):e0227995. doi:10.1371/journal.pone.0227995

41. Wainwright K, Romanowich P, Crabtree MA. Associations between impulsivity and self-care adherence in individuals diagnosed with Type 2 or prediabetes. Gullo MJ, ed. *PLoS One*. 2022;17(3):e0263961. doi:10.1371/journal.pone.0263961

42. Testa G, Camacho-Barcia L, Gómez-Martínez C, et al. Impulsive Personality Traits Predicted Weight Loss in Individuals with Type 2 Diabetes after 3 Years of Lifestyle Interventions. *J Clin Med*. 2022;11(12):3476. doi:10.3390/jcm11123476

43. Gómez-Martínez C, Babio N, Camacho-Barcia L, et al. Glycated hemoglobin, type 2 diabetes, and poor diabetes control are positively associated with impulsivity changes in aged individuals with overweight or obesity and metabolic syndrome. *Ann N Y Acad Sci*. Published online August 16, 2024. doi:10.1111/nyas.15205

44. Svrakic DM, Przybeck TR, Cloninger CR. Mood states and personality traits. *J Affect Disord*. 1992;24(4):217-226. doi:10.1016/0165-0327(92)90106-G

45. Cross CP, Copping LT, Campbell A. Sex differences in impulsivity: A meta-analysis. *Psychol Bull*. 2011;137(1):97-130. doi:10.1037/a0021591

46. Andreeva VA, Salanave B, Castetbon K, et al. Comparison of the sociodemographic characteristics of the large NutriNet-Santé e-cohort with French Census data: the issue of volunteer bias revisited. *J Epidemiol Community Health (1978)*. 2015;69(9):893-898. doi:10.1136/jech-2014-205263

47. Tuppin P, Rivière S, Rigault A, et al. Prevalence and economic burden of cardiovascular diseases in France in 2013 according to the national health insurance scheme database. *Arch Cardiovasc Dis*. 2016;109(6-7):399-411. doi:10.1016/j.acvd.2016.01.011

48. Dalley JW, Robbins TW. Fractionating impulsivity: neuropsychiatric implications. *Nat Rev Neurosci*. 2017;18(3):158-171. doi:10.1038/nrn.2017.8

49. Kale D, Stautz K, Cooper A. Impulsivity related personality traits and cigarette smoking in adults: A meta-analysis using the UPPS-P model of impulsivity and reward sensitivity. *Drug Alcohol Depend*. 2018;185:149-167. doi:10.1016/j.drugalcdep.2018.01.003

50. Levine GN, Cohen BE, Commodore-Mensah Y, et al. Psychological Health, Well-Being, and the Mind-Heart-Body Connection: A Scientific Statement From the American Heart Association. *Circulation*. 2021;143(10):E763-E783. doi:10.1161/CIR.0000000000000947

SUPPLEMENTARY MATERIAL

Supplementary Method 1. Multiple Imputation by Chained Equations.

Supplementary Figure 1. Restricted cubic splines between trait impulsivity and risk of developing overall CVD.

Supplementary Figure 2. Restricted cubic splines between trait impulsivity and risk of developing coronary heart disease.

Supplementary Figure 3. Restricted cubic splines between trait impulsivity and risk of developing cerebrovascular disease.

Supplementary Figure 4. Cumulative hazard ratio between categories of trait impulsivity and the risk of developing overall CVD.

Supplementary Table 1. Baseline characteristics of included and excluded population.

Supplementary Table 2. Rationale for selected confounders.

Supplementary Table 3. Pearson correlations between continuous variables included in the main model.

Supplementary Table 4. Assessment of proportional hazard risk assumptions between trait impulsivity and CVD incidence, with and without correction for non-proportional hazard risks covariates.

Supplementary Table 5. Associations between trait impulsivity and risk of developing CVD over 8 years using stratified estimates to account for non-proportional hazard risk covariates.

Supplementary Table 6. Associations between trait impulsivity and risk of developing CVD over 8 years without correction for non-proportional hazard risk covariates.

Supplementary Table 7. All models of associations between trait impulsivity and risk of developing CVD over 8 years.

Supplementary Table 8. Associations between trait impulsivity and risk of developing hard CVD over 8 years.

Supplementary Table 9. Associations between trait impulsivity and risk of developing CVD over 8 years excluding cardiovascular disease events in the first 2 years of follow-up.

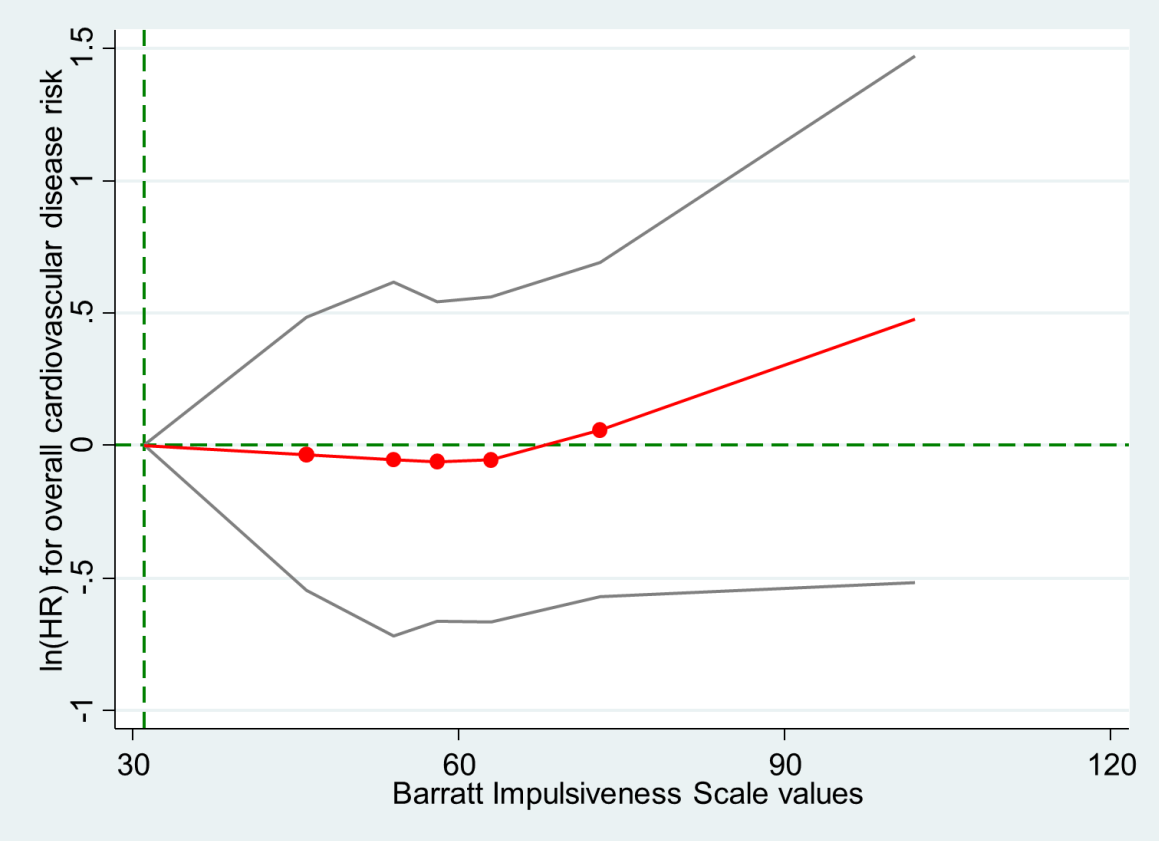
Supplementary Table 10. Associations between trait impulsivity and risk of developing CVD over 8 years in participants without prevalence of type 2 diabetes.

Supplementary Table 11. Associations between trait impulsivity and risk of developing CVD over 8 years in participants presenting prevalence of type 2 diabetes.

Supplementary Method 1. Multiple Imputation by Chained Equations.

Within the sample (n=48,135), missing values for covariates were handled using the Multiple Imputation by Chained Equations method using fully conditional specification (imputed datasets= 20; seed= 1234) for the following covariates: educational level (n=150 of missing data; 0.3% of missing data), smoking intensity pack-day (n=2,264; 4.7%), physical activity (n=98; 0.2%), energy intake excluding alcohol (n=3,316; 6.9%), alcohol intake (n=3,316; 6.9%), diet quality (n=4,091; 8.5%), BMI (n=173; 0.4%), family history of cardiovascular disease (CVD) (n=285; 0.6%), and depressive symptomatology (n=28,742; 59.7%).

Supplementary Figure 1. Restricted cubic splines between trait impulsivity and risk of developing overall CVD.

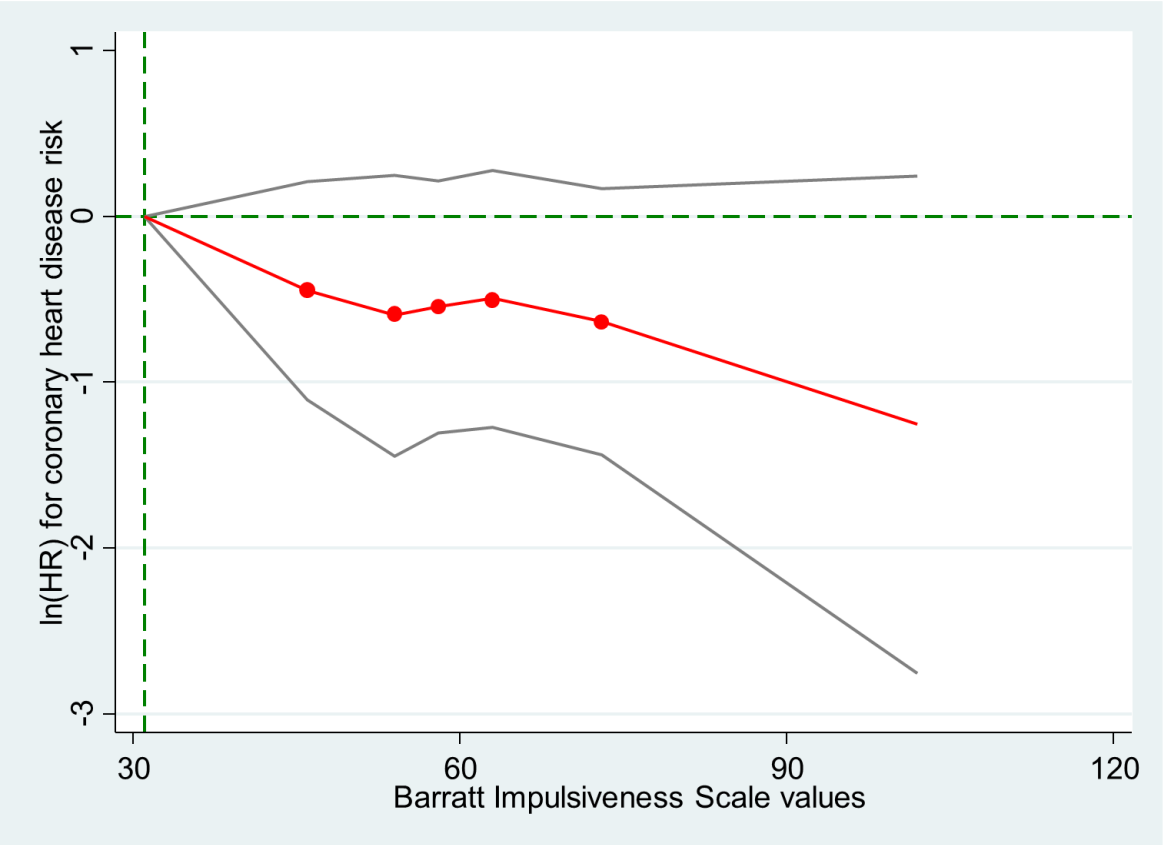


Cox regression analyses were performed using hazard ratios and 95% CI to assess associations between trait impulsivity values and the risk of developing overall CVD over a median follow-up of 8 years in the NutriNet-Santé cohort.

Spline plot modeling the association between total trait impulsivity and CVD risk was obtained using restricted cubic spline and piecewise cubic polynomials across 5 adjacent knots of trait impulsivity. Knots are represented with a red dot for total impulsivity: 46, 54, 58, 63, 73.

Main model was adjusted for baseline age (time-scale), sex, educational level (less than high school degree, <2 years after high school degree, ≥2 years after high school degree), smoking intensity (pack/day), physical activity (International Physical Activity Questionnaire: low, moderate, high), energy intake excluding alcohol (kcal/day), alcohol intake (g/day), diet quality (simplified Programme National Nutrition Santé - Guidelines Score 2), BMI (kg/m^2), hypertension prevalence or medication (no, yes), hypercholesterolemia prevalence or medication (no, yes), hypertriglyceridemia prevalence or medication (no, yes), and T2D prevalence or medication (no, yes). *P*-value for potential non-linear association (*P*=0.65).

Supplementary Figure 2. Restricted cubic splines between trait impulsivity and risk of developing coronary heart disease.

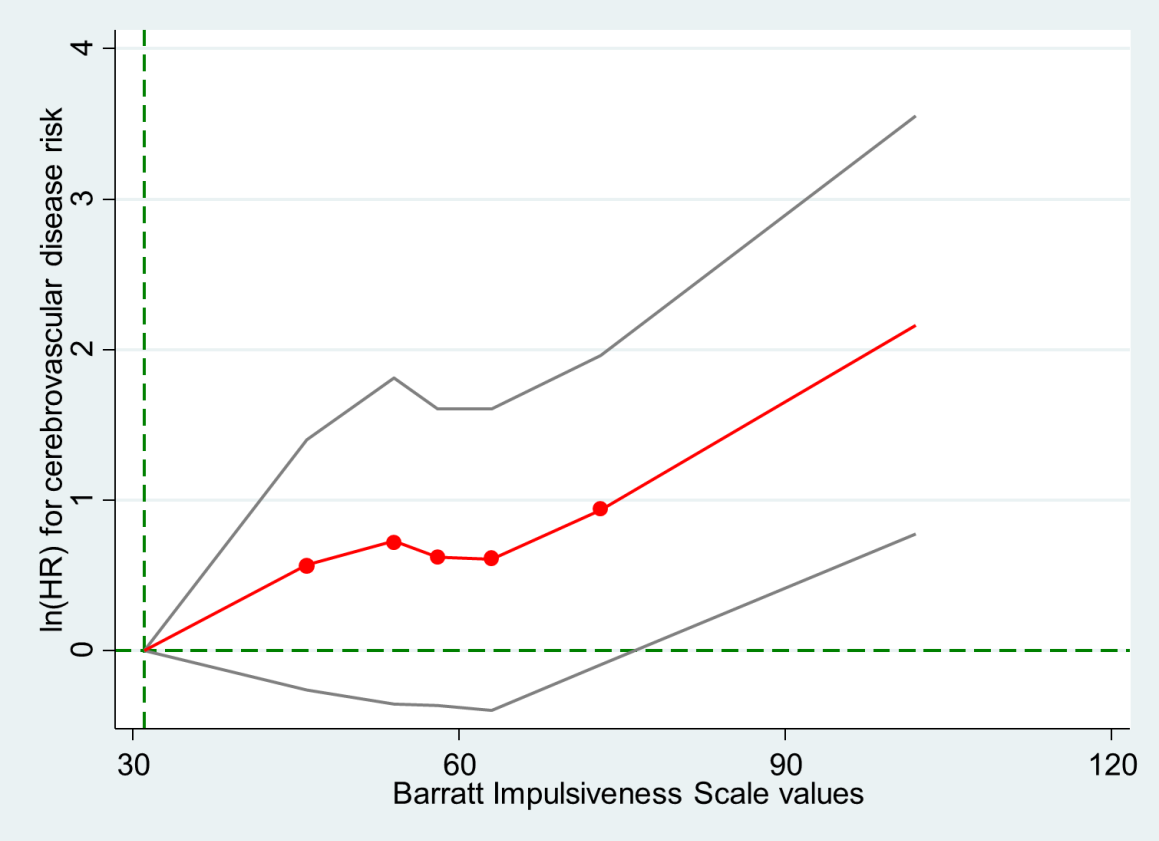


Cox regression analyses were performed using hazard ratios and 95% CI to assess associations between trait impulsivity values and the risk of developing coronary heart disease over a median follow-up of 8 years in the NutriNet-Santé cohort.

Spline plot modeling the association between total trait impulsivity and coronary heart disease risk was obtained using restricted cubic spline and piecewise cubic polynomials across 5 adjacent knots of trait impulsivity. Knots are represented with a red dot for total impulsivity: 46, 54, 58, 63, 73.

Main model was adjusted for baseline age (time-scale), sex, educational level (less than high school degree, <2 years after high school degree, ≥2 years after high school degree), smoking intensity (pack/day), physical activity (International Physical Activity Questionnaire: low, moderate, high), energy intake excluding alcohol (kcal/day), alcohol intake (g/day), diet quality (simplified Programme National Nutrition Santé - Guidelines Score 2), BMI (kg/m^2), hypertension prevalence or medication (no, yes), hypercholesterolemia prevalence or medication (no, yes), hypertriglyceridemia prevalence or medication (no, yes), and T2D prevalence or medication (no, yes). *P*-value for potential non-linear association (*P*=0.49).

Supplementary Figure 3. Restricted cubic splines between trait impulsivity and risk of developing cerebrovascular disease.

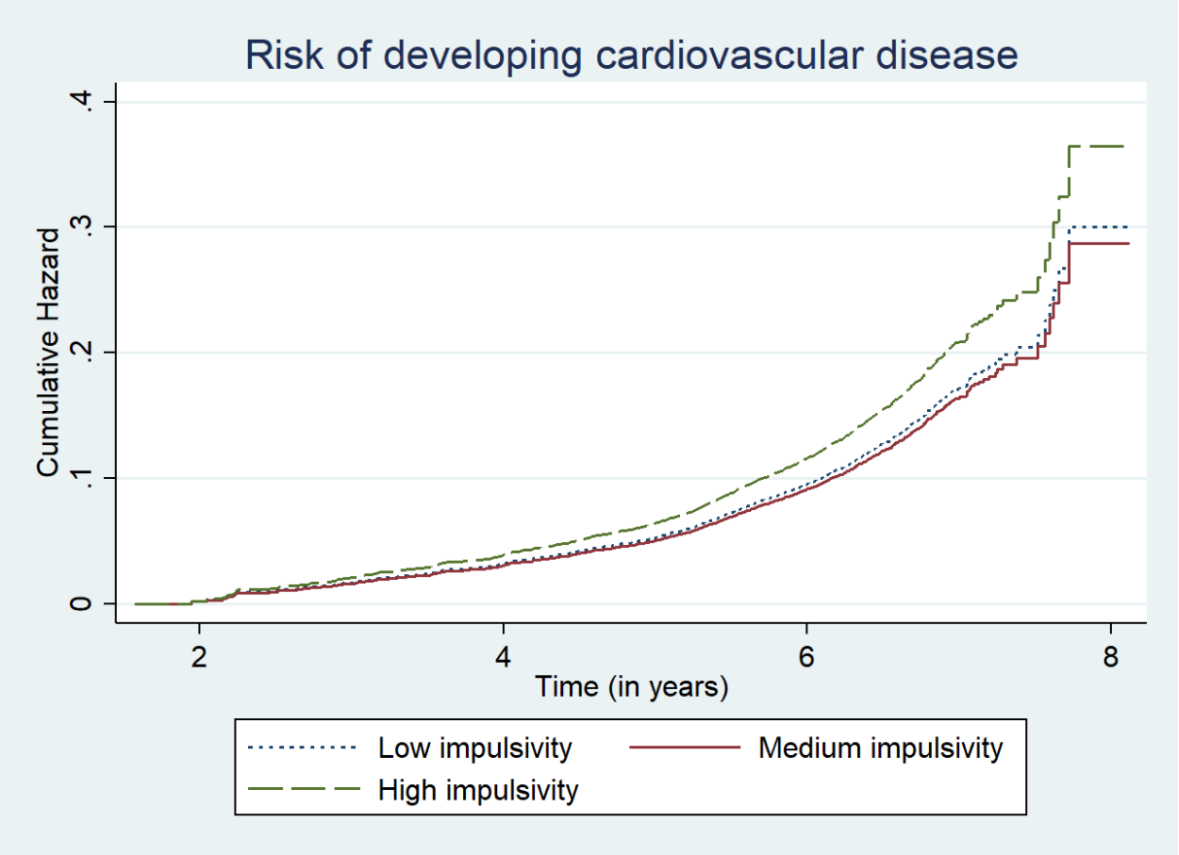


Cox regression analyses were performed using hazard ratios and 95% CI to assess associations between trait impulsivity values and the risk of developing cerebrovascular disease over a median follow-up of 8 years in the NutriNet-Santé cohort.

Spline plot modeling the association between total trait impulsivity and cerebrovascular disease risk was obtained using restricted cubic spline and piecewise cubic polynomials across 5 adjacent knots of trait impulsivity. Knots are represented with a red dot for total impulsivity: 46, 54, 58, 63, 73.

Main model was adjusted for baseline age (time-scale), sex, educational level (less than high school degree, <2 years after high school degree, ≥2 years after high school degree), smoking intensity (pack/day), physical activity (International Physical Activity Questionnaire: low, moderate, high), energy intake excluding alcohol (kcal/day), alcohol intake (g/day), diet quality (simplified Programme National Nutrition Santé - Guidelines Score 2), BMI (kg/m^2), hypertension prevalence or medication (no, yes), hypercholesterolemia prevalence or medication (no, yes), hypertriglyceridemia prevalence or medication (no, yes), and T2D prevalence or medication (no, yes). *P*-value for potential non-linear association (*P*=0.030).

Supplementary Figure 4. Cumulative hazard ratio between categories of trait impulsivity and the risk of developing overall CVD.



Cox regression analyses were performed using hazard ratios and 95% CI to assess associations across trait impulsivity categories and the risk of developing overall CVD over a median follow-up of 8 years in the NutriNet-Santé cohort.

Cumulative hazards were estimated for low (<52), medium (≥52 and ≤71) and high (>71) impulsivity categories using the Barratt Impulsiveness Scale 11 questionnaire.

Main model was adjusted for baseline age (time-scale), sex, educational level (less than high school degree, <2 years after high school degree, ≥2 years after high school degree), smoking intensity (pack/day), physical activity (International Physical Activity Questionnaire: low, moderate, high), energy intake excluding alcohol (kcal/day), alcohol intake (g/day), diet quality (simplified Programme National Nutrition Santé - Guidelines Score 2), BMI (kg/m^2), hypertension prevalence or medication (no, yes), hypercholesterolemia prevalence or medication (no, yes), hypertriglyceridemia prevalence or medication (no, yes), and T2D prevalence or medication (no, yes).

Supplementary Table 1. Baseline characteristics of included and excluded population.

Characteristics	Included population (n=48,135)		Excluded population (n=109,456)		*P*-value*
	n	Values	n	Values	
Age (years)	48,135	50.47 ± 14.49[†]	109,384	44.28 ± 14.42	<0.001
Sex (female)	48,135	37,580 (78.07)[‡]	109,384	84,913 (77.63)	0.051
Educational level	47,985		103,734		<0.001
Less than high school degree		1,056 (2.20)		4,063 (3.92)	
<2 years after high school degree		14,054 (29.29)		38,807 (37.41)	
≥2 years after high school degree		32,875 (68.51)		60,864 (58.67)	
Smoking intensity (pack/day)	45,871	0.30 ± 0.49	105,911	0.33 ± 0.49	<0.001
Physical activity (IPAQ)	48,037		93,757		<0.001
Low		11,084 (23.07)		25,643 (27,35)	
Moderate		20,143 (41.93)		38,005 (40.54)	
High		16,810 (34.99)		30,109 (32.11)	
Energy intake excluding alcohol (kcal/day)	44,819	1,787.03 ± 473.75	69,379	1,799.98 ± 493.58	0.030
Alcohol intake (g/day)	44,819	7.85 ± 12.00	69,379	7.39 ± 12.53	<0.001
Diet quality (sPNNS-GS2; range: −17 to 13.5)	44,044	1.27 ± 3.56	59,793	1.02 ± 3.55	<0.001
BMI (kg/m^2)	47,962	23.96 ± 4.50	104,729	24.38 ± 5.07	<0.001
Hypertension prevalence and/or medication	48,135	6,412 (13.32)	107,939	10,630 (9.85)	<0.001
Hypercholesterolemia prevalence and/or medication	48,135	8,601 (17.87)	107,940	10,221 (9.47)	<0.001
Hypertriglyceridemia prevalence and/or medication	48,135	1,827 (3.80)	107,393	2,395 (2.22)	<0.001
T2D prevalence and/or medication	48,135	1,301 (2.70)	107,939	2,508 (2.32)	<0.001
Family history of CVD	47,850	17,529 (36.63)	105,878	28,908 (27.30)	<0.001
Depressive symptomatology	19,393	2,358 (12.16)	18,294	2,997 (16.38)	<0.001

Abbreviations: IPAQ, International Physical Activity Questionnaire; sPNNS-GS2, simplified Programme National Nutrition Santé - Guidelines Score 2; BMI, body mass index; T2D, type 2 diabetes; CVD, cardiovascular disease.

Trait impulsivity categories were determined using the following cut-offs: low (<52), medium (≥52 and ≤71) and high (>71), based on the Barratt Impulsiveness Scale 11 questionnaire.

* *P*-value showing comparisons between included and excluded population based on chi-square for categorical variables and t-test for quantitative variables.

[†] mean ± SD (all such values).

[‡] n (%) (all such values).

Supplementary Table 2. Rationale for selected confounders.

Covariate	Coding of the variable	Relationship with impulsivity	Relationship with CVD	Method for collection / measurement
Age	Used as time-scale in Cox models	Impulsivity decreases with aging (1,2)	Aging is associated with higher CVD risk (3)	Self-reported socio-demographic and lifestyle questionnaires
Sex	Categorical: male, female	There are different patterns of impulsivity between men and women (4)	Sex-related factors interact to produce differences in CVD outcomes (5)	Self-reported socio-demographic and lifestyle questionnaires
Educational level	Categorical: less than high school degree, <2 years after high school degree, ≥2 years after high school degree	Higher impulsivity is associated with lower educational level (6)	Higher educational level is associated with reduced CVD risk (7)	Self-reported socio-demographic and lifestyle questionnaires
Smoking intensity	Continuous (pack/day). A pack is defined as 20 cigarettes consumed in one day (8)	Higher impulsivity is associated with higher cigarette consumption (9,10)	Smoking pack/day is a better predictor than smoking status and smoking pack/years to assess the risk of CVD outcomes. Higher smoking intensity is associated with higher CVD risk (8)	Self-reported socio-demographic and lifestyle questionnaires
Physical activity	Categorical: low, moderate, high	Impulsivity is associated with patterns of physical activity (11)	Physical inactivity is associated with higher CVD risk (3)	Validated International Physical Activity Questionnaire (12)
Energy intake excluding alcohol intake	Continuous (kcal/day)	Higher impulsivity is associated with higher energy intake (13)	Higher energy intake is associated with higher CVD risk (14)	24h-dietary records linked with the NutriNet-Santé food composition database
Alcohol intake	Continuous adding a quadratic term (g/day)	Higher impulsivity is associated with higher alcohol intake (13)	Light to moderate alcohol consumption is associated with reduced CVD risk, but heavy alcohol consumption is associated with higher CVD risk (15,16)	24h-dietary records linked with the NutriNet-Santé food composition database
Diet quality	Continuous: simplified Programme National Nutrition Santé - Guidelines Score 2 (range: −17 to 13.5)	Higher impulsivity is associated with lower adherence to healthy dietary patterns and with higher adherence to unhealthy dietary patterns (13,17)	Poor diet quality is associated with higher CVD risk (3,18)	24h-dietary records linked with the NutriNet-Santé food composition database. sPNNS-GS2, simplified Programme National Nutrition Santé - Guidelines Score 2 (19)

BMI	Continuous (kg/m^2)	Higher impulsivity is associated with higher BMI (20)	Obesity is associated with higher CVD risk (21)	Self-reported socio-demographic and lifestyle questionnaires
Hypertension prevalence or medication	Categorical: yes, no	Higher impulsivity is associated with higher hypertension risk (22)	Hypertension is associated with higher CVD risk (3)	Self-reported socio-demographic and lifestyle questionnaires
Hypercholesterolemia prevalence or medication	Categorical: yes, no	Higher impulsivity is associated with lower HDL-cholesterol levels (23)	Hypercholesterolemia is associated with higher CVD risk (3)	Self-reported socio-demographic and lifestyle questionnaires
Hypertriglyceridemia prevalence or medication	Categorical: yes, no	Higher impulsivity is associated with higher triglyceride levels (23)	Hypertriglyceridemia is associated with higher CVD risk (3)	Self-reported socio-demographic and lifestyle questionnaires
T2D or medication (no, yes)	Categorical: yes, no	Impulsivity is higher in participants with T2D (24)	T2D is associated with higher CVD risk (3)	Self-reported socio-demographic and lifestyle questionnaires. Type 2 diabetes events were validated by the NutriNet-Santé physicians and further merged with French health institution data (SNIIRAM and CNAM)
		SENSITIVITY ANALYSES		
Family history of CVD	Categorical: yes, no	Impulsivity is associated with CVD risk (25). However, to our knowledge, no evidence exists regarding family history of CVD	Family history of CVD is associated with higher risk of CVD (26)	Self-reported socio-demographic and lifestyle questionnaires
Depressive symptomatology (in sensitivity analyses due to the high number of missing data)	Categorical: yes, no	Higher impulsivity is associated with higher depressive symptomatology (27)	Depression is associated with higher CVD risk (28)	Self-reported Center for Epidemiologic Studies Depression Scale questionnaire (29)

Abbreviations: CVD, cardiovascular disease; BMI, body mass index; T2D, type 2 diabetes; SNIIRAM, Système National d'Informations Inter-Régimes de l'Assurance Maladie; CNAM, Caisse nationale de l'Assurance Maladie.

Supplementary Table 3. Pearson correlations between continuous variables included in the main model.

Covariables	Age	Smoking intensity	Energy intake without alcohol	Alcohol intake	Diet quality	BMI
Age	-					
Smoking intensity	0.22[§]*	-				
Energy intake without alcohol	-0.030*	0.0043*	-			
Alcohol intake	0.14*	0.19*	0.15*	-		
Diet quality	0.040*	-0.090*	-0.38*	-0.42*	-	
BMI	0.21*	0.16*	0.063*	0.080*	-0.14*	-

Abbreviations: BMI, body mass index.

[§] Pearson correlation coefficients (all such values).

* $P < 0.001$

Supplementary Table 4. Assessment of proportional hazard risk assumptions between trait impulsivity and CVD incidence, with and without correction for non-proportional hazard risks covariates.

	Overall CVD		Coronary heart	Cerebrovascular	
	P-value		*P*-value	*P*-value	
Characteristic	Without correction	With correction	Without correction	Without correction	With correction
Impulsivity					
Low	0.79	0.71	0.99	0.64	0.62
Medium	Ref.	Ref.	Ref.	Ref.	Ref.
High	0.12	0.12	0.64	0.17	0.15
Sex (female)	0.13	0.087	0.052	0.97	0.97
Educational level					
Less than high school degree	0.65	0.67	0.87	0.67	0.66
<2 years after high school degree	Ref.	Ref.	Ref.	Ref.	Ref.
≥2 years after high school degree	0.96	0.78	0.57	0.51	0.50
Smoking intensity	0.24	0.28	0.064	0.93	0.91
Physical activity					
Low	Ref.	-	Ref.	Ref.	-
Moderate	0.049	-	0.47	0.0021	-
High	0.71	-	0.15	0.11	-
Energy intake without alcohol	0.039	-	0.072	0.32	0.26
Alcohol intake	0.63	0.73	0.90	0.41	0.43
Diet quality	0.018	-	0.064	0.14	0.14
BMI	0.54	0.72	0.33	0.98	0.88
Hypertension prevalence or medication	0.29	0.19	0.92	0.11	0.13
Hypercholesterolemia prevalence or medication	0.35	0.33	0.68	0.33	0.35
Hypertriglyceridemia prevalence or medication	0.86	0.88	0.87	0.90	0.90
T2D prevalence or medication	0.17	0.17	0.20	0.45	0.43
Global test	0.055	0.40	0.36	0.14	0.52

Abbreviations: CVD, cardiovascular disease; BMI, body mass index; T2D, type 2 diabetes.

The assessment of proportional hazard risk was tested using the Schoenfeld residuals test in the main model.

The correction of non-proportional hazard risk was performed using stratified estimates for significant covariates showing a non-proportional hazard risk assumption at baseline (physical activity, energy intake excluding alcohol, and diet quality for overall CVD; physical activity for cerebrovascular disease).

Supplementary Table 5. Associations between trait impulsivity and risk of developing CVD over 8 years using stratified estimates to account for non-proportional hazard risk covariates.

	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	*P* for trend
Overall CVD	Low impulsivity (n=107/8,580) (rate=1.97)		Medium impulsivity (n=396/36,567) (rate=1.77)		High impulsivity (n=51/2,976) (rate=3.03)		
	1.05 (0.90, 1.21)	0.55	-	-	1.27 (1.01, 1.60)	0.037	0.32
Cerebrovascular disease	Low (n=107/8,580) (rate=1.97)		Medium (n=396/36,567) (rate=1.77)		High (n=51/2,976) (rate=3.03)		
	1.08 (0.87, 1.34)	0.48	-	-	1.71 (1.27, 2.30)	<0.001	0.047

Abbreviations: CVD, cardiovascular disease; HR (95%CI), hazard ratio and 95% confidence interval; Per 1SD, per 1 standard deviation increment; rate, incidence rate per 1,000 person-years; T2D, type 2 diabetes.

Cut-off points for low (<52), medium (≥52 and ≤71), and high (>71) impulsivity categories using the Barratt Impulsiveness Scale 11 questionnaire.

Overall CVD includes: myocardial infarction, acute coronary syndrome, angioplasty, angina pectoris, stroke, and transient ischemic attack. The total number of participants and the incident cases and incidence rates of CVDs are described in the trait impulsivity line section of the table.

Cox regression analyses were performed using hazard ratios and 95% CI to assess associations of impulsivity categories (medium as reference) and per 1SD increase with the risk of developing overall CVD over a median follow-up of 8 years in the NutriNet-Santé cohort. The P for trend was obtained by averaging the median impulsivity score of each impulsivity category. Main model was adjusted for baseline age (time-scale), sex, educational level (less than high school degree, <2 years after high school degree, ≥2 years after high school degree), smoking intensity (pack/day), physical activity (International Physical Activity Questionnaire: low, moderate, high), energy intake excluding alcohol (kcal/day), alcohol intake (g/day), diet quality (simplified Programme National Nutrition Santé - Guidelines Score 2), BMI (kg/m2), hypertension prevalence or medication (no, yes), hypercholesterolemia prevalence or medication (no, yes), hypertriglyceridemia prevalence or medication (no, yes), and T2D prevalence or medication (no, yes). Non-proportional hazard risk covariates were corrected by stratified estimates for physical activity, energy intake excluding alcohol, and diet quality in the analysis of overall CVD.

Supplementary Table 6. Associations between trait impulsivity and risk of developing CVD over 8 years without correction for non-proportional hazard risk covariates.

	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	*P* for trend
Overall CVD	Low impulsivity (n=231/8,582) (rate=4.29)		Medium impulsivity (n=869/36,577) (rate=3.91)		High impulsivity (n=84/2,976) (rate=5.03)		
	1.05 (0.90, 1.21)	0.55	-	-	1.27 (1.01, 1.59)	0.039	0.32
Cerebrovascular disease	Low impulsivity (n=107/8,580) (rate=1.97)		Medium impulsivity (n=396/36,567) (rate=1.77)		High impulsivity (n=51/2,976) (rate=3.03)		
	1.08 (0.87, 1.34)	0.49	-	-	1.72 (1.28, 2.30)	<0.001	0.044

Abbreviations: CVD, cardiovascular disease; HR (95%CI), hazard ratio and 95% confidence interval; Per 1SD, per 1 standard deviation increment; rate, incidence rate per 1,000 person-years; T2D, type 2 diabetes.

Cut-off points for low (<52), medium (≥52 and ≤71), and high (>71) impulsivity categories using the Barratt Impulsiveness Scale 11 questionnaire.

Overall CVD includes: myocardial infarction, acute coronary syndrome, angioplasty, angina pectoris, stroke, and transient ischemic attack. The total number of participants and the incident cases and incidence rates of CVD are described in the trait impulsivity line section of the table.

Cox regression analyses were performed using hazard ratios and 95% CI to assess associations of impulsivity categories (medium as reference) and per 1SD increase with the risk of developing overall CVD over a median follow-up of 8 years in the NutriNet-Santé cohort. The P for trend was obtained by averaging the median impulsivity score of each impulsivity category. Main model was adjusted for baseline age (time-scale), sex, educational level (less than high school degree, <2 years after high school degree, ≥2 years after high school degree), smoking intensity (pack/day), physical activity (International Physical Activity Questionnaire: low, moderate, high), energy intake excluding alcohol (kcal/day), alcohol intake (g/day), diet quality (simplified Programme National Nutrition Santé - Guidelines Score 2), BMI (kg/m2), hypertension prevalence or medication (no, yes), hypercholesterolemia prevalence or medication (no, yes), hypertriglyceridemia prevalence or medication (no, yes), and T2D prevalence or medication (no, yes).

Supplementary Table 7. All models of associations between trait impulsivity and risk of developing CVD over 8 years.

		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	*P* for trend
		Low impulsivity (n=231/8,582) (rate=4.29)		Medium impulsivity (n=869/36,577) (rate=3.91)		High impulsivity (n=84/2,976) (rate=5.03)		
Overall CVD	Model 1	1.02 (0.88, 1.18)	0.80	-	-	1.34 (1.07, 1.67)	0.011	0.12
	Model 2	1.03 (0.89, 1.19)	0.70	-	-	1.29 (1.03, 1.62)	0.025	0.21
	Model 3	1.03 (0.89, 1.19)	0.73	-	-	1.29 (1.03, 1.61)	0.029	0.21
	Model 4	1.03 (0.89, 1.19)	0.73	-	-	1.28 (1.03, 1.61)	0.029	0.21
	Model 5	1.03 (0.89, 1.19)	0.67	-	-	1.27 (1.01, 1.59)	0.038	0.26
	Model 6	1.05 (0.90, 1.21)	0.55	-	-	1.27 (1.01, 1.59)	0.038	0.33
	Model 7	1.05 (0.90, 1.21)	0.53	-	-	1.27 (1.01, 1.59)	0.042	0.35
		Low impulsivity (n=125/8,578) (rate=2.30)		Medium impulsivity (n=474/36,558) (rate=2.12)		High impulsivity (n=33/2,976) (rate=1.95)		
Coronary heart disease	Model 1	0.99 (0.81, 1.21)	0.92	-	-	0.97 (0.68, 1.38)	0.87	0.97
	Model 2	1.00 (0.82, 1.22)	0.99	-	-	0.93 (0.65, 1.33)	0.70	0.78
	Model 3	1.00 (0.82, 1.22)	0.98	-	-	0.92 (0.65, 1.31)	0.64	0.73
	Model 4	1.00 (0.82, 1.22)	0.97	-	-	0.92 (0.64, 1.31)	0.64	0.72
	Model 5	1.01 (0.83, 1.23)	0.92	-	-	0.91 (0.64, 1.29)	0.59	0.66
	Model 6	1.03 (0.84, 1.26)	0.78	-	-	0.90 (0.63, 1.28)	0.55	0.52
	Model 7	1.03 (0.85, 1.26)	0.76	-	-	0.89 (0.63, 1.28)	0.54	0.50
		Low impulsivity (n=107/8,580) (rate=1.97)		Medium impulsivity (n=396/36,567) (rate=1.77)		High impulsivity (n=51/2,976) (rate=3.03)		
Cerebrovascular disease	Model 1	1.07 (0.86, 1.32)	0.56	-	-	1.75 (1.31, 2.35)	<0.001	0.026
	Model 2	1.07 (0.87, 1.33)	0.51	-	-	1.72 (1.28, 2.30)	<0.001	0.039
	Model 3	1.06 (0.86, 1.32)	0.58	-	-	1.72 (1.28, 2.31)	<0.001	0.032
	Model 4	1.06 (0.86, 1.32)	0.58	-	-	1.72 (1.28, 2.31)	<0.001	0.032
	Model 5	1.07 (0.86, 1.32)	0.55	-	-	1.71 (1.27, 2.29)	<0.001	0.038
	Model 6	1.08 (0.87, 1.34)	0.52	-	-	1.72 (1.28, 2.30)	<0.001	0.044
	Model 7	1.08 (0.87, 1.34)	0.48	-	-	1.72 (1.28, 2.31)	<0.001	0.048

Abbreviations: CVD, cardiovascular disease; HR (95%CI), hazard ratio and 95% confidence interval; Per 1SD, per 1 standard deviation increment; rate, incidence rate per 1,000 person-years.

Cut-off points for low (<52), medium (≥52 and ≤71), and high (>71) impulsivity categories using the Barratt Impulsiveness Scale 11 questionnaire; T2D, type 2 diabetes.

Coronary heart disease includes: myocardial infarction, acute coronary syndrome, angioplasty, and angina pectoris. Cerebrovascular disease includes: stroke and transient ischemic attack. Overall CVD includes coronary heart and cerebrovascular diseases. The total number of participants and the incident cases and incidence rates of CVD are described in the trait impulsivity line section of the table. Two participants had a coronary heart and cerebrovascular disease event on the same day, and these participants were included in both analyses.

Cox regression analyses were performed using hazard ratios and 95% CI to assess associations of impulsivity categories (medium as reference) and per 1SD increase with the risk of developing overall CVD, coronary heart disease, and cerebrovascular disease over a median follow-up of 8 years in the NutriNet-Santé cohort. The *P* for trend was obtained by averaging the median impulsivity score of each impulsivity category. Trait impulsivity was log base 10 transformed for associations between linear trait impulsivity and cerebrovascular disease. All confounding factors were adjusted at baseline in the following models.

Model 1: adjusted for sex and age (time-scale).

Model 2 (sociodemographics): Model 1 + educational level (less than high school degree, <2 years after high school degree, ≥2 years after high school degree).

Model 3 (lifestyle): Model 2 + smoking intensity (pack/day), physical activity (International Physical Activity Questionnaire: low, moderate, high), energy intake excluding alcohol (kcal/day), and alcohol intake (g/day).

Model 4 (diet quality): Model 3 + baseline diet quality (simplified Programme National Nutrition Santé - Guidelines Score 2).

Model 5 (anthropometrics): Model 4 + baseline body mass index (kg/m^2).

Main model (personal history of disease): Model 5 + baseline hypertension prevalence or medication (no, yes), hypercholesterolemia prevalence or medication (no, yes), hypertriglyceridemia prevalence or medication (no, yes), and T2D prevalence or medication (no, yes). See Figure 2.

Model 6 (family history of disease): Main model + baseline family history of CVD (no, yes).

Model 7 (depressive symptomatology): Model 6 + baseline depressive symptomatology (Center for Epidemiologic Studies Depression Scale: no, yes).

Non-proportional hazard risk covariates were corrected by including a logarithmic time interaction term for physical activity, energy intake excluding alcohol, and diet quality in the analysis of overall CVD, and for physical activity in the analysis of cerebrovascular disease.

Supplementary Table 8. Associations between trait impulsivity and risk of developing hard CVD over 8 years.

	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	*P* for trend
Hard overall CVD	Low impulsivity (n=141/4,492) (rate=2.63)		Medium impulsivity (n=561/36,269) (rate=2.53)		High impulsivity (n=39/2,931) (rate=2.35)		
	0.97 (0.81, 1.17)	0.78	-	-	0.92 (0.66, 1.27)	0.60	0.89
Hard coronary heart disease	Low impulsivity (n=113/8,491) (rate=2.10)		Medium impulsivity (n=419/36,264) (rate=1.89)		High impulsivity (n=28/2,931) (rate=1.68)		
	1.03 (0.84, 1.28)	0.75	-	-	0.87 (0.59, 1.28)	0.47	0.45
Hard cerebrovascular disease	Low impulsivity (n=28/8,486) (rate=0.52)		Medium impulsivity (n=142/36,250) (rate=0.64)		High impulsivity (n=11/2,931) (rate=0.66)		
	0.79 (0.52, 1.18)	0.25	-	-	1.04 (0.56, 1.93)	0.90	0.32

Abbreviations: CVD, cardiovascular disease; HR (95%CI), hazard ratio and 95% confidence interval; Per 1SD, per 1 standard deviation increment; rate, incidence rate per 1,000 person-years; T2D, type 2 diabetes.

Cut-off points for low (<52), medium (≥52 and ≤71), and high (>71) impulsivity categories using the Barratt Impulsiveness Scale 11 questionnaire.

Hard coronary heart disease includes: myocardial infarction, acute coronary syndrome, and angioplasty (exclude angina pectoris). Hard cerebrovascular disease includes: stroke (exclude transient ischemic attack). Hard overall CVD includes both hard coronary heart and hard cerebrovascular diseases. The total number of participants and the incident cases and incidence rates of hard CVDs are described in the trait impulsivity line section of the table.

Cox regression analyses were performed using hazard ratios and 95% CI to assess associations of impulsivity categories (medium as reference) and per 1SD increase with the risk of developing hard overall CVD, hard coronary heart disease, and hard cerebrovascular disease over a median follow-up of 8 years in the NutriNet-Santé cohort. The *P* for trend was obtained by averaging the median impulsivity score of each impulsivity category. Trait impulsivity was log base 10 transformed for associations between linear trait impulsivity and cerebrovascular disease. Main model was adjusted for baseline age (time-scale), sex, educational level (less than high school degree, <2 years after high school degree, ≥2 years after high school degree), smoking intensity (pack/day), physical activity (International Physical Activity Questionnaire: low, moderate, high), energy intake excluding alcohol (kcal/day), alcohol intake (g/day), diet quality (simplified Programme National Nutrition Santé - Guidelines Score 2), BMI (kg/m2), hypertension prevalence or medication (no, yes), hypercholesterolemia prevalence or medication (no, yes), hypertriglyceridemia prevalence or medication (no, yes), and T2D prevalence or medication (no, yes). Non-proportional hazard risk covariates were corrected by including a logarithmic time interaction term for physical activity, energy intake excluding alcohol, and diet quality in the analysis of hard overall CVD, and for physical activity in the analysis of hard cerebrovascular disease.

Supplementary Table 9. Associations between trait impulsivity and risk of developing CVD over 8 years excluding cardiovascular disease events in the first 2 years of follow-up.

	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	*P* for trend
Overall CVD	Low impulsivity (n=155/7,421) (rate=2.94)		Medium impulsivity (n=571/31,125) (rate=2.63)		High impulsivity (n=48/2,407) (rate=2.95)		
	1.07 (0.90, 1.28)	0.45	-	-	1.14 (0.85, 1.53)	0.39	0.99
Coronary heart disease	Low impulsivity (n=89/7,355) (rate=1.69)		Medium impulsivity (n=321/30,875) (rate=1.48)		High impulsivity (n=22/2,381) (rate=1.36)		
	1.09 (0.86, 1.38)	0.49	-	-	0.92 (0.59, 1.42)	0.70	0.42
Cerebrovascular disease	Low impulsivity (n=66/7,332) (rate=1.26)		Medium impulsivity (n=250/30,804) (rate=1.16)		High impulsivity (n=26/2,385) (rate=1.61)		
	1.06 (0.81, 1.39)	0.68	-	-	1.41 (0.94, 2.12)	0.095	0.40

Abbreviations: CVD, cardiovascular disease; HR (95%CI), hazard ratio and 95% confidence interval; Per 1SD, per 1 standard deviation increment; rate, incidence rate per 1,000 person-years; T2D, type 2 diabetes.

Cut-off points for low (<52), medium (≥52 and ≤71), and high (>71) impulsivity categories using the Barratt Impulsiveness Scale 11 questionnaire.

Coronary heart disease includes: myocardial infarction, acute coronary syndrome, angioplasty, and angina pectoris. Cerebrovascular disease includes: stroke and transient ischemic attack. Overall CVD includes both coronary heart and cerebrovascular diseases. The total number of participants and the incident cases and incidence rates of CVD are described in the trait impulsivity line section of the table.

Cox regression analyses were performed using hazard ratios and 95% CI to assess associations of impulsivity categories (medium as reference) and per 1SD increase with the risk of developing overall CVD, coronary heart disease, and cerebrovascular disease over a median follow-up of 8.19 (interquartile range: 5.85-8.54) years in the NutriNet-Santé cohort. Participants with a CVD event in the first 2 years of follow-up were excluded. The *P* for trend was obtained by averaging the median impulsivity score of each impulsivity category. Trait impulsivity was log base 10 transformed for associations between linear trait impulsivity and cerebrovascular disease. Main model was adjusted for baseline age (time-scale), sex, educational level (less than high school degree, <2 years after high school degree, ≥2 years after high school degree), smoking intensity (pack/day), physical activity (International Physical Activity Questionnaire: low, moderate, high), energy intake excluding alcohol (kcal/day), alcohol intake (g/day), diet quality (simplified Programme National Nutrition Santé - Guidelines Score 2), BMI (kg/m2), hypertension prevalence or medication (no, yes), hypercholesterolemia prevalence or medication (no, yes), hypertriglyceridemia prevalence or medication (no, yes), and T2D prevalence or medication (no, yes). Non-proportional hazard risk covariates were corrected by including a logarithmic time interaction term for physical activity, energy intake excluding alcohol, and diet quality in the analysis of overall CVD, and for physical activity in the analysis of cerebrovascular disease.

Supplementary Table 10. Associations between trait impulsivity and risk of developing CVD over 8 years in participants without prevalence of type 2 diabetes.

	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	*P* for trend
Coronary heart disease	Low impulsivity (n=118/8,271) (rate=2.25)		Medium impulsivity (n=422/35,219) (rate=1.94)		High impulsivity (n=28/2,816) (rate=1.71)		
	1.11 (0.91, 1.37)	0.30	-	-	0.87 (0.59, 1.28)	0.48	0.19
Cerebrovascular disease	Low impulsivity (n=104/8,257) (rate=1.98)		Medium impulsivity (n=375/35,172) (rate=1.72)		High impulsivity (n=47/2,835) (rate=2.89)		
	1.11 (0.89, 1.38)	0.35	-	-	1.71 (1.26, 2.32)	0.001	0.093

Abbreviations: CVD, cardiovascular disease; HR (95%CI), hazard ratio and 95% confidence interval; Per 1SD, per 1 standard deviation increment; rate, incidence rate per 1,000 person-years; T2D, type 2 diabetes.

Cut-off points for low (<52), medium (≥52 and ≤71), and high (>71) impulsivity categories using the Barratt Impulsiveness Scale 11 questionnaire.

Coronary heart disease includes: myocardial infarction, acute coronary syndrome, angioplasty, and angina pectoris. Cerebrovascular disease includes: stroke and transient ischemic attack. Overall CVD includes both coronary heart and cerebrovascular diseases. The total number of participants and the incident cases and incidence rates of CVD are described in the trait impulsivity line section of the table.

Cox regression analyses were performed using hazard ratios and 95% CI to assess associations of impulsivity categories (medium as reference) and per 1SD increase with the risk of developing overall CVD (see Figure 2), coronary heart disease, and cerebrovascular disease over a median follow-up of 8 years in the NutriNet-Santé cohort. The *P* for trend was obtained by averaging the median impulsivity score of each impulsivity category. Main model was adjusted for baseline age (time-scale), sex, educational level (less than high school degree, <2 years after high school degree, ≥2 years after high school degree), smoking intensity (pack/day), physical activity (International Physical Activity Questionnaire: low, moderate, high), energy intake excluding alcohol (kcal/day), alcohol intake (g/day), diet quality (simplified Programme National Nutrition Santé - Guidelines Score 2), BMI (kg/m2), hypertension prevalence or medication (no, yes), hypercholesterolemia prevalence or medication (no, yes), hypertriglyceridemia prevalence or medication (no, yes), and T2D prevalence or medication (no, yes). Non-proportional hazard risk covariates were corrected by including a logarithmic time interaction term for physical activity in the analysis of cerebrovascular disease.

Supplementary Table 11. Associations between trait impulsivity and risk of developing CVD over 8 years in participants presenting prevalence of type 2 diabetes.

	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	*P* for trend
Coronary heart disease	Low (n=6/204) (rate=4.66)		Medium (n=51/962) (rate=9.04)		High (n=5/109) (rate=8.57)		
	0.41 (0.17, 1.97)	0.043	-	-	0.96 (0.38, 2.45)	0.93	0.13
Cerebrovascular disease	Low (n=2/200) (rate=1.55)		Medium (n=20/931) (rate=3.46)		High (n=4/108) (rate=6.88)		
	0.51 (0.12, 2.21)	0.37	-	-	2.27 (0.73, 7.05)	0.16	0.072

Abbreviations: CVD, cardiovascular disease; HR (95%CI), hazard ratio and 95% confidence interval; Per 1SD, per 1 standard deviation increment; rate, incidence rate per 1,000 person-years; T2D, type 2 diabetes.

Cut-off points for low (<52), medium (≥52 and ≤71), and high (>71) impulsivity categories using the Barratt Impulsiveness Scale 11 questionnaire.

Coronary heart disease includes: myocardial infarction, acute coronary syndrome, angioplasty, and angina pectoris. Cerebrovascular disease includes: stroke and transient ischemic attack. Overall CVD includes both coronary heart and cerebrovascular diseases. The total number of participants and the incident cases and incidence rates of CVD are described in the trait impulsivity line section of the table.

Cox regression analyses were performed using hazard ratios and 95% CI to assess associations of impulsivity categories (medium as reference) and per 1SD increase with the risk of developing Overall CVD (see Figure 2), coronary heart disease, and cerebrovascular disease over a median follow-up of 8 years in the NutriNet-Santé cohort. Participants with a cardiovascular disease event in the first 2 years of follow-up were excluded. The *P* for trend was obtained by averaging the median impulsivity score of each impulsivity category. Main model was adjusted for baseline age (time-scale), sex, educational level (less than high school degree, <2 years after high school degree, ≥2 years after high school degree), smoking intensity (pack/day), physical activity (International Physical Activity Questionnaire: low, moderate, high), energy intake excluding alcohol (kcal/day), alcohol intake (g/day), diet quality (simplified Programme National Nutrition Santé - Guidelines Score 2), BMI (kg/m2), hypertension prevalence or medication (no, yes), hypercholesterolemia prevalence or medication (no, yes), hypertriglyceridemia prevalence or medication (no, yes), and T2D prevalence or medication (no, yes). Non-proportional hazard risk covariates were corrected by including a logarithmic time interaction term for physical activity in the analysis of cerebrovascular disease.

REFERENCES

1. Steinberg L, Albert D, Cauffman E, Banich M, Graham S, Woolard J. Age differences in sensation seeking and impulsivity as indexed by behavior and self-report: Evidence for a dual systems model. *Dev Psychol*. 2008;44(6):1764-1778. doi:10.1037/a0012955

2. Moustafa AA, Tindle R, Frydecka D, Misiak B. Impulsivity and its relationship with anxiety, depression and stress. *Compr Psychiatry*. 2017;74:173-179. doi:10.1016/j.comppsych.2017.01.013

3. Mozaffarian D, Wilson PWF, Kannel WB. Beyond Established and Novel Risk Factors. *Circulation*. 2008;117(23):3031-3038. doi:10.1161/CIRCULATIONAHA.107.738732

4. Cross CP, Copping LT, Campbell A. Sex differences in impulsivity: A meta-analysis. *Psychol Bull*. 2011;137(1):97-130. doi:10.1037/a0021591

5. Regitz-Zagrosek V, Gebhard C. Gender medicine: effects of sex and gender on cardiovascular disease manifestation and outcomes. *Nat Rev Cardiol*. 2023;20(4):236-247. doi:10.1038/s41569-022-00797-4

6. Schwartz JA, Connolly EJ, Alsolami A. Within-Individual Changes in Impulsivity and Sensation Seeking from Childhood to Early Adulthood and Educational Attainment. *J Youth Adolesc*. 2022;51(11):2190-2204. doi:10.1007/S10964-022-01663-9/TABLES/3

7. Winkleby MA, Jatulis DE, Frank E, Fortmann SP. Socioeconomic status and health: how education, income, and occupation contribute to risk factors for cardiovascular disease. *Am J Public Health*. 1992;82(6):816-820. doi:10.2105/AJPH.82.6.816

8. Nance R, Delaney J, McEvoy JW, et al. Smoking intensity (pack/day) is a better measure than pack-years or smoking status for modeling cardiovascular disease outcomes. *J Clin Epidemiol*. 2017;81:111-119. doi:10.1016/j.jclinepi.2016.09.010

9. Kale D, Stautz K, Cooper A. Impulsivity related personality traits and cigarette smoking in adults: A meta-analysis using the UPPS-P model of impulsivity and reward sensitivity. *Drug Alcohol Depend*. 2018;185:149-167. doi:10.1016/j.drugalcdep.2018.01.003

10. Bos J, Hayden MJ, Lum JAG, Staiger PK. UPPS-P impulsive personality traits and adolescent cigarette smoking: A meta-analysis. *Drug Alcohol Depend*. 2019;197:335-343. doi:10.1016/j.drugalcdep.2019.01.018

11. Castañer M, Aiello S, Prat Q, Andueza J, Crescimanno G, Camerino O. Impulsivity and physical activity: A T-Pattern detection of motor behavior profiles. *Physiol Behav*. 2020;219:112849. doi:10.1016/j.physbeh.2020.112849

12. Mõttus R, McNeill G, Jia X, Craig LCA, Starr JM, Deary IJ. The associations between personality, diet and body mass index in older people. *Health Psychology*. 2013;32(4):353-360. doi:10.1037/a0025537

13. Bénard M, Bellisle F, Kesse-Guyot E, et al. Impulsivity is associated with food intake, snacking, and eating disorders in a general population. *Am J Clin Nutr*. 2019;109(1):117-126. doi:10.1093/ajcn/nqy255

14. Franco M, Ordunez P, Caballero B, et al. Impact of Energy Intake, Physical Activity, and Population-wide Weight Loss on Cardiovascular Disease and Diabetes Mortality in Cuba, 1980 2005. *Am J Epidemiol*. 2007;166(12):1374-1380. doi:10.1093/aje/kwm226

15. Klatsky AL. Alcohol and cardiovascular diseases: A historical overview. *Ann N Y Acad Sci*. 2002;957:7-15. doi:10.1111/J.1749-6632.2002.TB02901.X

16. Ronksley PE, Brien SE, Turner BJ, Mukamal KJ, Ghali WA. Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis. *BMJ*. 2011;342(feb22 1):d671-d671. doi:10.1136/bmj.d671

17. Gómez-Martínez C, Babio N, Júlvez J, et al. Impulsivity is longitudinally associated with healthy and unhealthy dietary patterns in individuals with overweight or obesity and metabolic syndrome within the

framework of the PREDIMED-Plus trial. *International Journal of Behavioral Nutrition and Physical Activity*. 2022;19(1):101. doi:10.1186/s12966-022-01335-8

18. Pan A, Lin X, Hemler E, Hu FB. Diet and Cardiovascular Disease: Advances and Challenges in Population-Based Studies. *Cell Metab*. 2018;27(3):489-496. doi:10.1016/J.CMET.2018.02.017

19. Chaltiel D, Adjibade M, Deschamps V, et al. Programme National Nutrition Santé – guidelines score 2 (PNNS-GS2): development and validation of a diet quality score reflecting the 2017 French dietary guidelines. *British Journal of Nutrition*. 2019;122(03):331-342. doi:10.1017/S0007114519001181

20. Emery RL, Levine MD. Questionnaire and behavioral task measures of impulsivity are differentially associated with body mass index: A comprehensive meta-analysis. *Psychol Bull*. 2017;143(8):868-902. doi:10.1037/bul0000105

21. Van Gaal LF, Mertens IL, De Block CE. Mechanisms linking obesity with cardiovascular disease. *Nature*. 2006;444(7121):875-880. doi:10.1038/nature05487

22. Fuemmeler BF, Østbye T, Yang C, McClernon FJ, Kollins SH. Association between attention-deficit/hyperactivity disorder symptoms and obesity and hypertension in early adulthood: a population-based study. *International Journal of Obesity 2011 35:6*. 2010;35(6):852-862. doi:10.1038/ijo.2010.214

23. Sutin AR, Terracciano A, Deiana B, et al. Cholesterol, triglycerides, and the Five-Factor Model of personality. *Biol Psychol*. 2010;84(2):186-191. doi:10.1016/j.biopsycho.2010.01.012

24. Testa G, Mora-Maltas B, Camacho-Barcia L, et al. Transdiagnostic Perspective of Impulsivity and Compulsivity in Obesity: From Cognitive Profile to Self-Reported Dimensions in Clinical Samples with and without Diabetes. *Nutrients*. 2021;13(12):4426. doi:10.3390/nu13124426

25. Emery RL, Levine MD, Creswell KG, et al. Impulsivity and midlife cardiometabolic risk: The role of maladaptive health behaviors. *Health Psychology*. 2020;39(8):642-654. doi:10.1037/hea0000884

26. Lloyd-Jones DM, Nam BH, D'Agostino, Sr RB, et al. Parental Cardiovascular Disease as a Risk Factor for Cardiovascular Disease in Middle-aged Adults. *JAMA*. 2004;291(18):2204. doi:10.1001/jama.291.18.2204

27. Fields SA, Schueler J, Arthur KM, Harris B. The Role of Impulsivity in Major Depression: A Systematic Review. *Curr Behav Neurosci Rep*. 2021;8(2):38-50. doi:10.1007/s40473-021-00231-y

28. Hare DL, Toukhsati SR, Johansson P, Jaarsma T. Depression and cardiovascular disease: a clinical review. *Eur Heart J*. 2014;35(21):1365-1372. doi:10.1093/eurheartj/eht462

29. Fuhrer R., Rouillon F. La version française de l'échelle CES-D (Center for Epidemiologic Studies-Depression Scale). Description et traduction de l'échelle d'autoévaluation. *Psychiatry and Psychobiology*. 1989;4(3):163-166. doi:10.1017/S0767399X00001590

UNIVERSITAT ROVIRA I VIRGILI
Psychology and Disease: Unveiling Emerging Perspectives on Their Interplay
Carlos Gómez Martínez

CHAPTER 3:
TRAIT IMPULSIVITY AND INCIDENCE OF TYPE 2 DIABETES

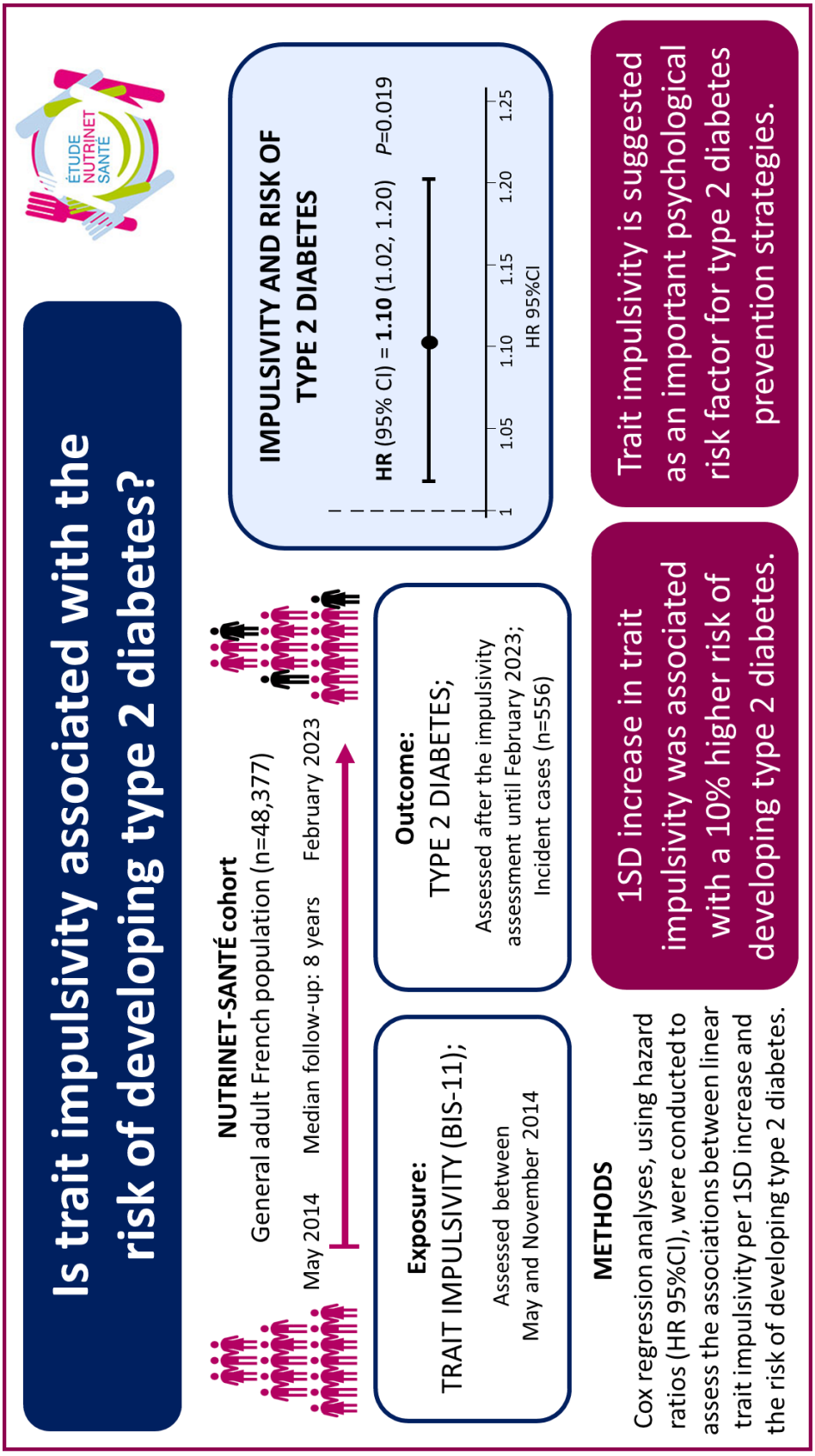


Figure 8. Graphical abstract of Chapter 3. Trait impulsivity and incidence of type 2 diabetes.

BMC Medicine

RESEARCH ARTICLE

Open Access

Trait impulsivity is associated with an increased risk of type 2 diabetes incidence in adults over 8 years of follow-up: results from the NutriNet-Santé cohort

Carlos Gómez-Martínez[1,2,3], Pauline Paolassini-Guesnier[4], Léopold Fezeu[4], Bernard Srour[4], Serge Hercberg[4], Mathilde Touvier[4], Nancy Babio[1,2,3], Jordi Salas-Salvadó[1,2,3†] and Sandrine Péneau[4*†]

Abstract

Background Type 2 diabetes is one of the most prevalent and preventable diseases worldwide and impulsivity, a psychological trait characterized by making quick decisions without forethought, has been suggested as a key feature for health-related conditions. However, there have been no studies examining the relationships between impulsivity and the incidence of type 2 diabetes and our aim was to assess the prospective association between trait impulsivity and the risk of developing type 2 diabetes.

Methods A prospective observational study design was conducted between May 2014 and February 2023 within the NutriNet-Santé cohort. A web-based platform was used to collect data from the French adult population, with voluntary enrollment and participation. Of the 157,591 adults (≥ 18 years old) participating in the NutriNet-Santé study when impulsivity was assessed, 109,214 participants were excluded due to prevalent type 1 or 2 diabetes or missing data for impulsivity or follow-up data for type 2 diabetes. Trait impulsivity, and the attention, motor, and non-planning subfactors, were assessed at baseline using the Barratt Impulsiveness Scale 11. Incident type 2 diabetes was ascertained through follow-up. Medical information was reviewed by NutriNet-Santé physician experts to ascertain incident diabetes cases based on the ICD-10. Cox regression models, using hazard ratios and 95% confidence intervals (HR [95% CI]), were performed to evaluate associations between impulsivity per 1 standard deviation increment and type 2 diabetes risk, adjusting by recognized confounders.

Results Of the 48,377 individuals studied (women 77.6%; age at baseline = 50.6 year ± 14.5 years), 556 individuals developed type 2 diabetes over a median follow-up of 7.78 (IQR: 3.97–8.49) years. Baseline impulsivity was associated with an increased risk of type 2 diabetes incidence (HR = 1.10 [1.02, 1.20]). The motor impulsivity subfactor was positively associated with type 2 diabetes risk (HR = 1.14 [1.04, 1.24]), whereas no associations were found for attention and non-planning impulsivity subfactors.

†Jordi Salas-Salvadó and Sandrine Péneau contributed equally to this work.

*Correspondence:
Sandrine Péneau
s.peneau@eren.smbh.univ-paris13.fr
Full list of author information is available at the end of the article

Conclusions Trait impulsivity was associated with an increased type 2 diabetes risk, mainly driven by the motor impulsivity subfactor. If these results are replicated in other populations and settings, trait impulsivity may become an important psychological risk factor to be considered in the prevention of type 2 diabetes.

Cohort registration Name of registry: The NutriNet-Santé Study. A Web-based Prospective Cohort Study of the Relationship Between Nutrition and Health and of Dietary Patterns and Nutritional Status Predictors.

Cohort registration number: NCT03335644.

Date of registration: October 11, 2017.

URL: https://clinicaltrials.gov/ct2/show/NCT03335644

Keywords Impulsivity, Prospective cohort study, Motor, Attention, Planning, Personality, Psychological traits, Type 2 diabetes

Background

Type 2 diabetes is a chronic metabolic disease characterized by insulin resistance and elevated levels of blood glucose, with a worldwide prevalence of 422 million people and around 1.6 million deaths attributable to this medical condition yearly [1].

Genetic predisposition and different lifestyle behaviors have been recognized as risk factors for diabetes [2]. Personality traits predispose individuals to act within a range of behaviors [3] and have also been suggested as risk factors for different health outcomes, including diabetes [4]. Personality traits are relatively stable characteristics across the lifespan but can also be modified through psychological-based interventions [5, 6].

Trait impulsivity, in particular, is a personality trait characterized by difficulties with sustained attention, rapid motor reactions, and lack of planning [7], and has been linked to impaired inhibitory processes and higher reward sensitivity [8]. Some studies have found associations between trait impulsivity, poor diet quality [9], higher body mass index (BMI) [10], and cardiometabolic risk [11]. Therefore, impulsivity could be expected to increase the risk of type 2 diabetes incidence. However, to the best of our knowledge, there has not been any prospective exploration of associations between impulsivity and the risk of developing type 2 diabetes. A few cross-sectional studies have been performed and produced promising results [12, 13]. In one study, higher glucose levels were associated with lower inhibitory control (i.e., higher behavioral impulsivity), especially in participants with prediabetes [12]. Participants with prediabetes also exhibited a greater impulsive reward sensitivity compared to healthy control individuals [13]. Similar associations were observed in individuals with type 2 diabetes, where higher HOMA-insulin resistance and glycated hemoglobin levels were associated with poorer performance on behavioral cognitive control and decision-making, respectively [14, 15]. Finally, both higher trait and behavioral impulsivity were found to be associated with poor diabetes management [16, 17].

As impulsivity has been suggested to play a role in diabetes status and control, we hypothesize that those individuals with high trait impulsivity will have an increased risk of developing type 2 diabetes. Therefore, the main aim of this work was to assess the associations between baseline trait impulsivity and the risk of type 2 diabetes incidence over 8 years of follow-up in the NutriNet-Santé cohort.

Methods

Study design and population

A prospective study design was performed in the context of the NutriNet-Santé study cohort, a web-based observational study with the objective to study relationships between nutrition and health, as well as the determinants of eating behavior and health status. The NutriNet-Santé recruitment started in May 2009 and currently has an open ongoing enrolment. Volunteers are recruited via multimedia campaigns from the general French population and are included if they are ≥ 18 years old, speak French fluently, and have internet access. They are followed using a personal account on the study website (https://etude-nutrinet-sante.fr/), through which they provide detailed information by answering multiple questionnaires.

At inclusion, participants complete several self-report web-based questionnaires to assess their diet, physical activity, anthropometric measures, lifestyle characteristics, socioeconomic conditions, and health status. Participants then complete this same set of questionnaires every year after inclusion. Another set of optional questionnaires related to determinants of eating behaviors, nutritional status, and specific health-related aspects is sent to every participant each month. More information on the study protocol can be found on the following website: https://info.etude-nutrinet-sante.fr/siteinfo/, where

the detailed study rationale, design, and methods are provided [18]. The study protocol was registered at https://www.clinicaltrials.gov/ (NCT03335644).

All participants report an electronic informed consent. Procedures were approved by the Institutional Research Board of the French Institute for Health and Medical Research (IRB INSERM no: 0000388FWA00005831) and the Commission Nationale de l'Informatique et des Libertés (CNIL no: 908450 and 909,216). The study accomplishes the Declaration of Helsinki standards.

Impulsivity

Trait impulsivity was assessed using the validated French version of the Barratt Impulsiveness Scale (BIS-11) [19], derived from the BIS-10 [20]. The BIS-11 is the most used questionnaire to assess trait impulsivity in both research and clinical practice [7]. This questionnaire was administered between May and November 2014. The BIS-11 is a 30-item self-reported questionnaire with a 4-point Likert scale scoring, ranging from "rarely/never" (1 point) to "almost always/always" (4 points). The total BIS-11 score, as well as their impulsivity subfactors (attentional, motor, and non-planning), were obtained by adding their respective items. The range of impulsivity scores was as follows: BIS-11 total score (range 30–120), attentional subfactor (range 8–32), motor subfactor (range 11–44), and non-planning subfactor (range 11–44). Higher values in the scores reflect higher impulsivity. The α Cronbach value for the total score was 0.77, indicating an acceptable internal consistency.

Type 2 diabetes

Type 2 diabetes status was assessed using a multisource approach (Additional file 1: Supplementary Method 1). Incident cases of type 2 diabetes and medication for this disease were recorded through yearly health questionnaires, a specific health check-up questionnaire every 6 months, or at any time spontaneously through the NutriNet-Santé platform. Medical information was reviewed by NutriNet-Santé physician experts to ascertain incident diabetes cases. Furthermore, this medical record data was linked to the Système National d'Information Inter-Régimes de l'Assurance Maladie (SNIIRAM) from the Caisse Nationale de l'Assurance Maladie of the French national insurance system where participants medication and medical consultation history was available. The SNIIRAM uses the International Chronic Diseases Classification Clinical Modification 10th Revision (ICD-10) [21] to ascertain type 2 diabetes incident cases. The first incident type 2 diabetes case was considered between the impulsivity assessment and 8th February 2023.

Covariates

Potential confounders of the relation between trait impulsivity and type 2 diabetes were collected. We used the data closest to the date of completion of the BIS-11. Selected confounders were sociodemographics: sex (male, female), age (years), and educational level (less than high school degree, < 2 years after high school degree, ≥ 2 years after high school degree); lifestyle: smoking status (never, former, current), physical activity (low, medium, high) using the International Physical Activity Questionnaire (IPAQ) [22], energy intake without alcohol (kcal/day), alcohol intake (g/day) using 24 h-dietary records, and diet quality using the simplified Programme National Nutrition Santé—Guidelines Score 2 (sPNNS-GS2) [23]; personal history of disease: prevalence or medication use for hypertension (no, yes), hypercholesterolemia (no, yes), and hypertriglyceridemia (no, yes); family history of diabetes disease (no, yes); depressive symptomatology (no, yes) using the self-reported Center for Epidemiologic Studies Depression Scale questionnaire (CES-D) [24]; and anthropometrics: BMI (kg/m^2).

Statistical analysis

For this study, we included participants from the NutriNet-Santé cohort who completed the BIS-11 and did not have prevalent type 1 or 2 diabetes diagnosed at baseline. Covariates with missing values were handled using Multiple Imputation by Chained Equations (MICE) by fully condition specification (Additional file 1: Supplementary Method 2).

Differences in trait impulsivity scores between the excluded participants with prevalent type 2 diabetes and those included in the final population were assessed using a *t*-test. A comparison of baseline population characteristics between included and excluded participants was performed, using *t*-test or chi-square, as appropriate. Baseline participant characteristics are presented as numbers and percentages for qualitative variables and as mean ± standard deviation (SD) for quantitative variables. Comparisons across trait impulsivity categories (low, medium, and high) were based on chi-square for categorical variables and one-way ANOVA for quantitative variables.

Cox regression models, using hazard ratios and 95% confidence interval (HR 95% CI), were performed to evaluate the linear associations between 1 SD increment of trait impulsivity (and attention, motor, and non-planning subfactors) and the incidence of type 2 diabetes, over 8 years of follow-up. Participants contributed person-time from their impulsivity assessment until the date of type 2 diabetes event, date of last follow-up, date of death,

or 8th February 2023, whichever occurred first, and incidence rates were estimated. A parsimonious model was run and adjusted at baseline for age (as timescale) and sex. The main model was further adjusted at baseline for educational level (with a logarithmic time interaction), smoking status, physical activity, energy intake without alcohol, alcohol intake, and diet quality. The rationale for covariates selection is described in Additional file 2: Table S1 [9, 23, 25–40] and Additional file 2: Table S2 [10, 24, 41–46].

Linearity assumptions between total impulsivity, and its subfactors, with type 2 diabetes incidence were verified using restricted cubic spline functions. If the associations were non-linear (motor subfactor only), a correction was applied using a logarithmic base 10 transformation. Impulsivity categories were used to estimate cumulative hazard risks (Additional file 3: Fig. S1). Impulsivity categories were determined by using specified cut-offs [7]: low (<52), medium (≥ 52 and ≤ 71), and high (>71). An exploratory analysis was conducted studying the associations between trait impulsivity categories and the incidence of type 2 diabetes, using Cox regression models. Pearson correlation coefficients were assessed to confirm the absence of collinearity between the continuous variables included in the main model (Additional file 2: Table S3). Schoenfeld residuals were computed to confirm the risk of proportionality hazard assumptions. Covariates with non-proportional hazard risk were corrected in the main analyses by establishing an interaction by logarithmic time (education level only). Furthermore, Schoenfeld residuals were tested again correcting for non-proportional hazard covariates.

Sensitivity analyses were performed to verify the robustness of the findings. Associations between impulsivity and type 2 diabetes risk were analyzed using stratified estimates for non-proportional hazard covariates and without a correction for these non-proportional covariates. A total of six additional models were evaluated with the aim of studying various confounding factors. The exclusion of incident cases of type 2 diabetes during the first 2 years of follow-up was also assessed. Interactions were tested using the likelihood ratio test for sex, age (<60 years, ≥ 60 years), overweight (BMI: <25, ≥ 25 kg/m^2), and diet quality (sPNNS-GS2: median to determine low and high diet quality, by sex). A post hoc mediation analysis was conducted to assess the role of baseline BMI in the association between a 1 SD increase in total trait impulsivity and the risk of developing type 2 diabetes. Linear regressions were used to determine the association between impulsivity (exposure) and BMI (mediator), and Cox regressions were used to determine the association of impulsivity and BMI with incident type 2 diabetes (outcome). BMI was fixed as its mean. The model was adjusted for the same covariates as the main model, and confounders were fixed either at the mode (sex, education, smoking status, and physical activity) or at the mean (energy intake, alcohol intake, and diet quality). Analyses were performed using the bootstrapping decomposition method (seed: 4500; replicates: 1000).

Analyses were performed with STATA 14. The STATA med4way package [47] was used for mediation analyses. Statistically significant results were considered when P value was <0.05.

Results

Description of the study population

Among the 157,591 individuals included in the NutriNet-Santé study at the time of impulsivity assessment, a total of 48,377 participants were included in the present analyses and of these, 556 developed type 2 diabetes (Fig. 1).

Comparison of baseline population characteristics between included and excluded participants can be found in Additional file 2: Table S4. Baseline characteristics of the studied population were shown in Table 1. Mean age was 50.4 (SD: 14.6) years, and around three-quarters of the population were women. Compared with individuals presenting lower impulsivity, those with higher impulsivity were more likely to be younger, female, and former or current smokers; to have a lower level of education, physical activity, and diet quality; and to have a higher alcohol consumption, BMI, and prevalence or medication use of hypertension, hypertriglyceridemia, and depressive symptomatology. The median follow-up was approximately 8 (median: 7.78; interquartile range: 3.97–8.49) years (person-years: 297,027), and the incidence rate (95% CI) was 1.87 (1.72, 2.03) for 1000 person-years.

Participants excluded due to prevalent type 2 diabetes at baseline exhibited higher trait impulsivity scores (mean: 59.83; SD: 8.48) compared to the final population (mean: 58.70; SD: 7.98) analyzed ($P<0.001$). No statistically significant difference was observed in the total impulsivity score between participants with prevalent (mean: 59.83; SD: 8.48) and incident (mean: 59.35; SD: 8.06) type 2 diabetes ($P=0.15$).

Associations between trait impulsivity and type 2 diabetes

Restricted cubic splines suggested a linear relationship between total impulsivity and type 2 incident diabetes ($P=0.51$) (Additional file 3: Fig. S2).

In both the parsimonious and main model, a positive linear significant association was found between a 1 SD increment of impulsivity and incidence of type 2 diabetes (main model; HR [95% CI] = 1.10 [1.02, 1.20]; $P=0.019$) (Fig. 2). The associations between trait impulsivity categories and the incidence of type 2 diabetes were not significant (Additional file 2: Table S5).

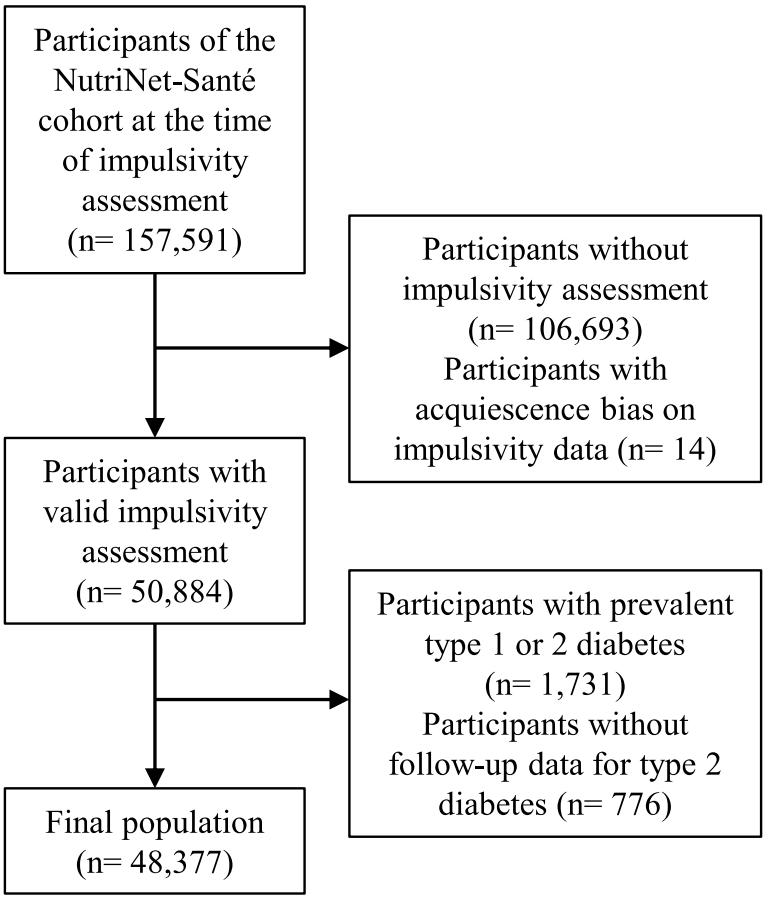


Fig. 1 Flowchart of the studied population

In the parsimonious model, all impulsivity subfactors (attention, motor, and non-planning) were associated with an increased risk of type 2 diabetes incidence, although only motor impulsivity remained significantly related in the main model (HR [95% CI] = 1.14 [1.04, 1.24]; $P = 0.003$) (Fig. 3).

Given the non-proportional hazard estimates observed for educational level (Additional file 2: Table S6; Additional file 2: Table S7), sensitivity analyses were performed with a stratification on educational level and without correction for this covariate. In both analyses, the directionality and significance of the associations between total impulsivity, its subfactors, and type 2 diabetes were maintained (Additional file 2: Table S8; Additional file 2: Table S9). The associations between total trait impulsivity and type 2 diabetes were also maintained after the adjustment of sociodemographic and lifestyle confounders (Additional file 2: Table S10). However, the additional adjustment for personal and familiar history of disease, as well as for depressive symptomatology, attenuated the relationships showing borderline non-significant results (all $P \leq 0.075$). More specifically, after the inclusion of BMI in the models, the association was largely attenuated becoming non-significant ($P = 0.53$). When excluding participants with early incident type 2 diabetes (first 2 years of follow-up), the associations were also attenuated ($P = 0.11$) (Additional file 2: Table S11). Assessed interactions for sex, age, overweight, and diet quality showed no significant results (all $P > 0.20$). The results of the mediation analysis by BMI in the association between trait impulsivity and the risk of developing type 2 diabetes showed a significant total effect (HR [95% CI] = 1.10 [1.00, 1.19]; $P = 0.048$), a borderline significant controlled direct effect when BMI was fixed at its mean (HR = 1.09 [0.99, 1.18]; $P = 0.070$), and a significant pure indirect effect (HR [95% CI] = 1.02 [1.01, 1.03]; $P < 0.001$) indicating a strong mediation effect of BMI (Additional file 3: Fig. S3).

Discussion

To the best of our knowledge, this is the first study investigating long-term relationships between impulsivity and type 2 diabetes incidence. In the present study, conducted in the context of a large population, baseline trait

Table 1 Baseline characteristics of the study population by trait impulsivity categories, NutriNet-Santé cohort, France, 2014–2023 ($n = 48,377$)

Characteristics	All participants	Trait impulsivity			*P* value*
		Low ($n = 8659$)	Medium ($n = 36,743$)	High ($n = 2975$)	
Age (years)	50.63 ± 14.56†	51.11 ± 14.06	50.59 ± 14.60	49.78 ± 15.37	< 0.001
Sex (female)	37,568 (77.66)‡	6244 (72.11)	28,863 (78.55)	2461 (82.72)	< 0.001
Educational level ($n = 48,278$)					< 0.001
Less than high school degree	1032 (2.14)	120 (1.39)	779 (2.13)	133 (4.48)	
< 2 years after high school degree	14,108 (31.39)	2167 (25.09)	10,753 (29.36)	1188 (40.01)	
≥ 2 years after high school degree	33,091 (68.61)	6351 (73.52)	25,092 (68.51)	1648 (55.51)	
Smoking status ($n = 48,376$)					< 0.001
Never	22,333 (46.17)	4625 (53.41)	16,687 (45.42)	1021 (34.32)	
Former	20,899 (43.20)	3423 (39.53)	16,051 (43.69)	1425 (47.90)	
Current	5144 (10.63)	611 (7.06)	4004 (10.90)	529 (17.78)	
Physical activity (IPAQ) ($n = 48,314$)					< 0.001
Low	11,025 (22.83)	8408 (22.92)	84,088 (22.92)	751 (25.37)	
Medium	20,248 (41.94)	3561 (41.20)	15,501 (42.26)	1186 (40.07)	
High	17,009 (35.23)	3217 (37.22)	12,769 (34.81)	1023 (34.56)	
Energy intake without alcohol (kcal/day) ($n = 45,080$)	1787.29 ± 474.28	1789.09 ± 474.73	1786.23 ± 471.91	1795.35 ± 502.41	0.59
Alcohol intake (g/day) ($n = 45,080$)	7.92 ± 12.01	7.21 ± 11.12	8.05 ± 12.10	8.66 ± 13.22	< 0.001
Diet quality (sPNNS-GS2; range: − 17 to 13.5) ($n = 44,318$)	1.28 ± 3.56	1.41 ± 3.55	1.27 ± 3.54	0.95 ± 3.80	< 0.001
Body mass index (kg/m^2) ($n = 48,212$)	23.86 ± 4.34	23.65 ± 4.16	23.87 ± 4.36	24.41 ± 5.00	< 0.001
Hypertension prevalence and/or medication	6400 (13.23)	1131 (13.06)	4818 (13.11)	451 (15.16)	0.006
Hypercholesterolemia prevalence and/or medication	8719 (18.02)	1545 (17.84)	6618 (18.01)	556 (18.69)	0.58
Hypertriglyceridemia prevalence and/or medication	1657 (3.43)	285 (3.29)	1243 (3.38)	129 (4.34)	0.017
Family history of diabetes ($n = 47,996$)	9689 (20.19)	1717 (19.97)	7370 (20.21)	602 (20.53)	0.78
Depressive symptomatology ($n = 19,464$)	2359 (12.12)	263 (7.71)	14,887 (12.14)	288 (24.68)	< 0.001

Abbreviations: *IPAQ*, International Physical Activity Questionnaire; *sPNNS-GS2*, simplified Programme National Nutrition Santé—Guidelines Score 2

Trait impulsivity categories were determined using the following cut-offs: low (< 52), medium (≥ 52 and ≤ 71), and high (> 71), based on the Barratt Impulsiveness Scale 11 questionnaire

* *P* value showing comparisons between categories of trait impulsivity (low, medium, high) based on chi-square for categorical variables and ANOVA for quantitative variables

† Mean ± SD (all such values)

‡ *n* (%) (all such values)

impulsivity was significantly associated with an increased risk of type 2 diabetes, independently of several recognized confounding factors.

Psychological aspects have been highlighted as major characteristics for the establishment of diseases [4]. Psychological traits predispose human behavior based on established patterns of emotions and cognitive processes that interact with genetic, biological, cultural, and social spheres [3]. Therefore, it seems reasonable that psychological traits, such as an impulsive proneness which has been associated with unhealthy behaviors and glycemic dysregulations [11, 16, 17], may play a role in the development of glucose-related diseases such as type 2 diabetes.

Unfortunately, there is a lack of studies analyzing the associations between personality traits and the incidence of type 2 diabetes, and none of the studies has examined these associations evaluating trait impulsivity. Remarkably, the present work shows an association between trait impulsivity and the risk of developing type 2 diabetes. Our data support previous cross-sectional studies in populations with or at risk of developing type 2 diabetes where an inverse relationship between behavioral impulsivity levels and glycemic status [12–15], and poor diabetes control [16, 17] have been reported.

The present results are also in line with those of a pooled project including 5 prospective cohorts and 34,914 adults from the USA and the UK where higher trait conscientiousness was linearly associated with lower type 2 diabetes incidence and its caused-related mortality [48]. Trait impulsivity has been proposed as an antagonist of conscientiousness, which is described as the propensity to be self-controlled, responsible, and well-organized [49]. The associations shown in the present work between impulsivity and type 2 diabetes could

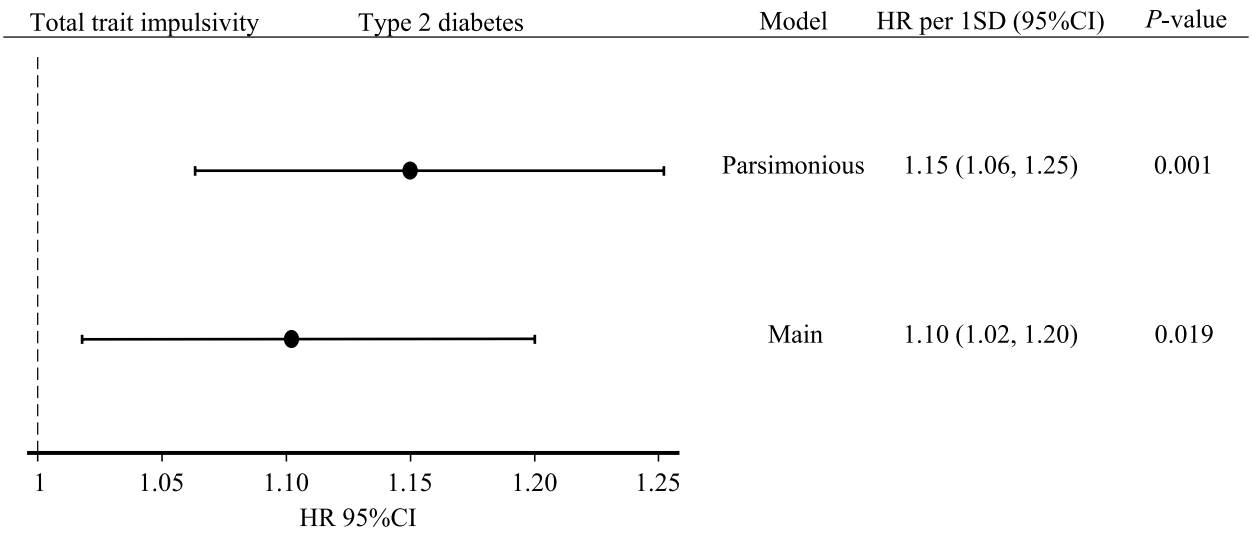


Fig. 2 Associations between trait impulsivity and type 2 diabetes risk, NutriNet-Santé cohort, France, 2014–2023 ($n = 48,377$). Abbreviations: HR per 1 SD (95% CI), hazard ratio per 1 standard deviation increment and 95% confidence interval. Cox regression analyses were performed using hazard ratios and 95% CI to assess associations between 1 SD increment of total trait impulsivity and the risk of type 2 diabetes incidence over a median follow-up of 8 years in the NutriNet-Santé cohort. Total population ($n = 48,377$) and type 2 diabetes incident cases ($n = 556$). Person-years = 297,027 and incidence rate = 1.87 (95% CI: 1.72, 2.03) per 1000 person-years. Parsimonious model: adjusted for baseline sex and age (time scale). Main model: parsimonious model + baseline education level (less than high school degree, < 2 years after high school degree, ≥ 2 years after high school degree), smoking status (never, former, current smoker), physical activity (International Physical Activity Questionnaire: high, moderate, low), energy intake without alcohol (kcal/day), alcohol intake (g/day), and diet quality (simplified Programme National Nutrition Santé—Guidelines Score 2). Non-proportional hazard risk covariates were corrected by adding a logarithmic time interaction (educational level only)

be explained by the idiosyncratic neurological impulsivity network, which may lead to impulsive behaviors guided by the trait impulsivity proneness. The characteristic impulsive neural pathway involves the prefrontal cortex (high-order cognitive system), ventral striatum and nucleus accumbens (reward-dopaminergic system), and amygdala (emotional-limbic system) regions [50]. The interaction between this network and impulsivity traits drives individuals to have a great urgency to respond to their positive and negative emotional states and a high sensitivity to immediate rewards, combined with a lack of prefrontal cortex capacity to restrain the need for immediate gratification or to avoid negative emotions [51, 52]. Consequently, this interplay between trait and neurological impulsivity predisposes individuals to externalize impulsive behaviors characterized by acting without considering the consequences of their behavior [51, 52]. These mechanisms may also explain the positive associations found between impulsivity measures and major risk factors for type 2 diabetes such as diet quality [9], BMI [10], insulin resistance [14], and hyperglycemia [12].

Some lifestyle behaviors, such as poor diet quality, have been shown to increase cytokines production in adipose tissue and liver, promoting insulin resistance [53]. Results from the Nurses' Health Studies, which followed more than 200,000 participants, indicated that the consumption of unhealthy food was associated with an increased incidence of type 2 diabetes [54]. Trait impulsivity has also been shown to be inversely associated with the adherence to healthy dietary patterns [9]. In our analyses, the adjustment for different food-related variables did not change the directionality and significance of the associations between impulsivity and type 2 diabetes incidence, but we cannot completely discard some residual confounding effects. When BMI was included as a covariate in the models, the association was largely attenuated and became non-significant. Mediation analyses confirmed a substantial mediating effect of BMI on the association between trait impulsivity and type 2 diabetes incidence. While the indirect effect through BMI was significant, the direct effect did not reach statistical significance, shedding light on the observed attenuation. Impulsivity has previously been associated with higher odds of obesity in the NutriNet-Santé study and with increasing BMI levels as shown by a meta-analysis [10, 55]. Adiposity has a recognized central role in the development of type 2 diabetes as higher BMI has been shown to induce low-grade inflammation and decrease insulin sensitivity, increasing the risk of hyperglycemia [56]. In addition, longitudinal studies show that negative psychological factors generally precede and predict faster rate of weight gain rather than the opposite [57], suggesting a unidirectional association between impulsivity and BMI on the risk of type 2 diabetes incidence.

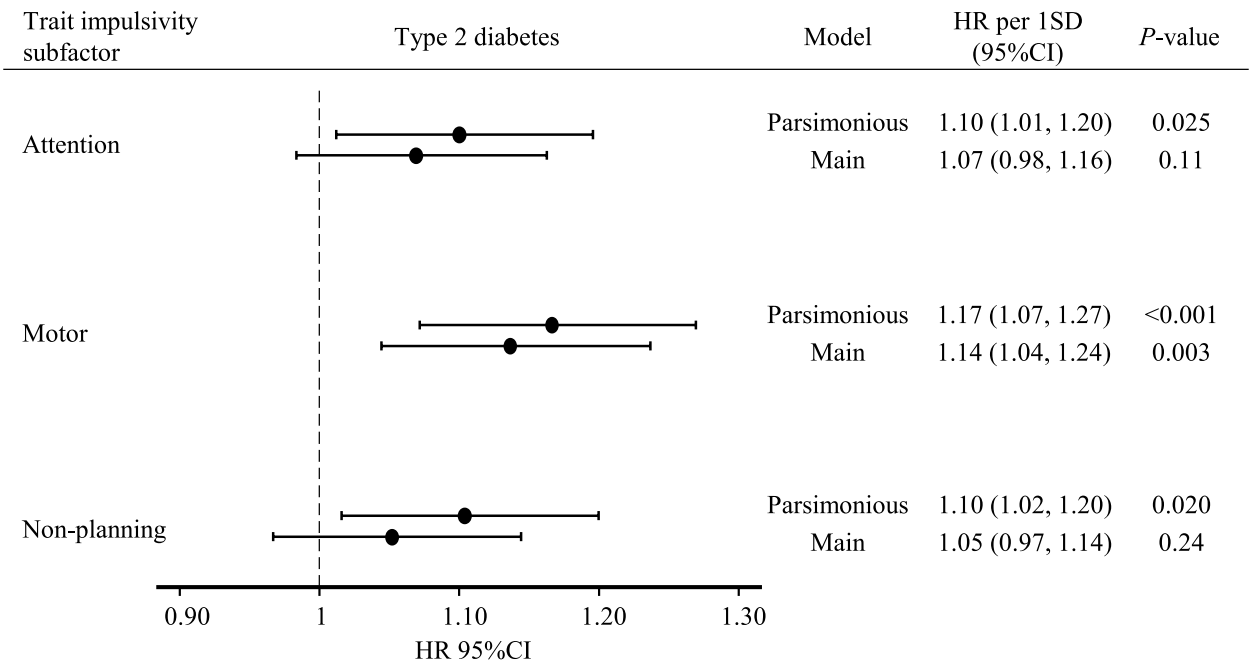


Fig. 3 Associations between trait impulsivity subfactors and type 2 diabetes risk, NutriNet-Santé cohort, France, 2014–2023 ($n = 48,377$). Abbreviations: HR per 1 SD (95% CI), hazard ratio per 1 standard deviation increment and 95% confidence interval. Cox regression analyses were performed using hazard ratios and 95% CI to assess associations between 1 SD increment of attention, motor, and non-planning trait impulsivity subfactors and the risk of type 2 diabetes incidence over a median follow-up of 8 years in the NutriNet-Santé cohort. The attention impulsivity subfactor was log10 transformed due to potential non-linear association ($P = 0.03$). Total population ($n = 48,377$) and type 2 diabetes incident cases ($n = 556$). Person-years = 297,027 and incidence rate = 1.87 (95% CI: 1.72, 2.03) per 1000 person-years. Parsimonious model: adjusted for baseline sex and age (time scale). Main model: parsimonious model + baseline education level (less than high school degree, < 2 years after high school degree, ≥ 2 years after high school degree), smoking status (never, former, current smoker), physical activity (International Physical Activity Questionnaire: high, moderate, low), energy intake without alcohol (kcal/day), alcohol intake (g/day), and diet quality (simplified Programme National Nutrition Santé—Guidelines Score 2). Non-proportional hazard risk covariates were corrected by adding a logarithmic time interaction (educational level only)

When considering subtraits of impulsivity, we observed that motor personality was the only subfactor consistently associated with type 2 diabetes incidence in the main models, whereas attention and non-planning impulsivity subfactors did not show significant associations. Impulsivity subtraits are attributable to different cognitive control subsystems [58]. In particular, the motor impulsivity subfactor, which involves acting without thinking [7], has been found to be more strongly associated with the activation of neural networks related to cognitive control compared with the attention and non-planning subfactors [58]. These neural networks have been proposed to be key neural bases for behavioral impulsivity [8]. Therefore, and in consideration of the fact that personality traits are precursors of behaviors [3], the results of the present study, which demonstrated a consistent association between motor trait impulsivity and the incidence of type 2 diabetes, could suggest that this subfactor may be the precursor of the deleterious relationships found between behavioral impulsivity and glucose-related measurements [12–15]. When participants with incident cases of type 2 diabetes within the first 2 years of follow-up were removed, only the motor subfactor remained associated with type 2 diabetes in the main model, suggesting a strong association for this personality subfactor. It is important to consider that this sensitivity analysis excluded around 7000 participants and almost 50% of incident cases, which considerably reduced the statistical power. Given that half of the cases occurred during the first 2 years of follow-up, it is possible that reverse causation may have occurred between impulsivity and type 2 diabetes. However, the impulsivity trait is theoretically established early in life [52] which reduces the likelihood of such reverse causation.

The main strengths of the present analyses were the novelty of the assessed relationships, the large population studied, and the long period of follow-up, but some limitations deserve to be mentioned. First, the observational design did not allow to establish causal relationships. Second, some additional residual confounding bias could exist, although models were adjusted by several and recognized confounders and multiple sensitivity analyses

were performed to check the robustness of the findings. Third, trait impulsivity was a self-reported measure, but the questionnaire employed was the most widely used assessment of trait impulsivity and was validated for the French population. Addressing impulsive eating more specifically could be of great interest given that disinhibited eating behavior has been positively associated with insulin resistance [59]. Fourth, the type 2 diabetes incidence rate per 1000 person-years observed in our study (1.87) was low compared to the incidence rate (between 7.74 and 8.97 for the period 2012–2020) found in a recent study involving more than 20 million French individuals [60]. The rate observed in our study may be partly explained by the voluntary enrollment of the participants in the NutriNet-Santé study where more women and more participants with higher education, higher income, and professional status are found than in the general French population [61]. These participants may be more likely to have high health awareness and a stronger interest in nutrition which in turn is associated with a lower risk of developing metabolic diseases. The selection bias indicates that caution should be exercised when extrapolating the results to the general population. For example, higher impulsivity values are usually reported in men and our population was predominantly women. However, a sex interaction was tested and not found.

The clinical relevance of this study should be noted. Higher levels of impulsivity have been associated with an increase in the risk of highly prevalent disorders with substantial public health burden such as overeating and obesity [10], eating disorders [62], substance-related disorders [50], and psychiatric conditions [51]. The present work further extends these findings by highlighting the increased risk of developing type 2 diabetes associated with higher impulsivity. Emphasizing positive psychological characteristics could be potential strategies for the primary and secondary prevention of type 2 diabetes. In particular, mindfulness which has showed an inverse association with impulsivity could be beneficial [6, 63]. Additionally, the need for cognition (NFC) has been identified as a protective psychological factor for diabetes self-management and glycemic control [64]. Reducing the intensity of negative emotions in patients with type 2 diabetes is another potential factor of interest given its mediating effect on the relationship between trait impulsivity and executive function [65]. It is also important to acknowledge that impulsive behaviors can sometimes be strategic responses based on individual needs or motivations and therefore may serve adaptive purposes in certain contexts [66]. Therefore, further research is needed to explore the complex associations between impulsivity and chronic diseases, considering both potential benefits and risks.

Conclusions

To conclude, trait impulsivity was associated with an increased risk of type 2 diabetes incidence over 8 years of follow-up in a large French cohort. Specifically, the personality subfactor of motor impulsivity was found to be an important feature to consider for the onset of type 2 diabetes. If these results are confirmed in other populations and settings, trait impulsivity could be a promising psychological risk factor to consider for the prevention of type 2 diabetes.

Abbreviations

BIS-11	Barratt Impulsiveness Scale
BMI	Body mass index
CES-D	Center for Epidemiologic Studies Depression Scale questionnaire
ICD-10	International Chronic Diseases Classification Clinical Modification 10th Revision
IPAQ	International Physical Activity Questionnaire
MICE	Multiple Imputation by Chained Equations
NFC	Need for cognition
SD	Standard deviation
SNIIRAM	Système National d'Information Inter-Régimes de l'Assurance Maladie
sPNNS-GS2	Simplified Programme National Nutrition Santé—Guidelines Score 2

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-024-03540-7.

Additional file 1: Supplementary Method 1 Incident type 2 diabetes ascertainment in NutriNet-Santé and biological data assessment. Supplementary Method 2 Multiple Imputation by Chained Equations

Additional file 2: Table S1 Rationale for selected confounders in the main model. Table S2 Rationale for selected confounders in sensitivity analyses. Table S3 Pearson correlations between continuous variables included in the main model. Table S4 Baseline characteristics of the study population comparing included and excluded participants. Table S5 Associations between categories of trait impulsivity and the risk of developing type 2 diabetes. Table S6 Assessment of proportional hazard risk assumptions between total trait impulsivity and risk of developing type 2 diabetes, with and without correction for non-proportional hazard risks covariates. Table S7 Assessment of proportional hazard risk assumptions between impulsivity subfactors and risk of developing type 2 diabetes, with and without correction for proportional hazard risks covariates. Table S8 Associations between total and subfactors of trait impulsivity and risk of developing type 2 diabetes over 8 years using stratified estimates for non-proportional hazard risk covariates. Table S9 Associations between total and subfactors of trait impulsivity and risk of developing type 2 diabetes over 8 years without proportional hazard risk correction. Table S10 All models of associations between total and subfactors of trait impulsivity and risk of developing type 2 diabetes over 8 years. Table S11 Associations between total and subfactors of trait impulsivity and risk of developing type 2 diabetes over 8 years excluding incident cases in the first 2 years of follow-up

Additional file 3: Fig. S1 Cumulative hazards between categories of total trait impulsivity and risk of developing type 2 diabetes. Fig. S2 Restricted cubic splines between trait impulsivity and risk of developing type 2 diabetes. Fig. S3 Mediation analysis of body mass indexlevels in the associations between total trait impulsivity and the risk of developing type 2 diabetes

Acknowledgements
The authors thank Cédric Agaesse (dietary data manager) and Alexandre De-Sa (dietitian); Selim Aloui (IT manager), Thi Hong Van Duong, Régis Gatibelza, Jagatjit Mohinder, and Aladi Timera (computer scientists); Julien Allegre, Nathalie Arnault, Laurent Bourhis, Nicolas Dechamp (biostatisticians), and Fabien Szabo de Edelenyi, Ph.D. (biostatistics team manager); Maria Gomes and Mirette Foham (NutriNet-Santé participant support); and Paola Yvroud, M.D. (health event validator) (all affiliated with CRESS-EREN) for their technical contribution to the NutriNet-Santé study. The authors sincerely thank all the volunteers of the NutriNet-Santé cohort.

Authors' contributions
SH, LF, MT, and SP contributed to the NutriNet-Santé study conceptualization and coordination. JS and SP coordinated the project. CG-M, BS, LF, and SP contributed to the methodology and formal analysis. CG-M wrote the original draft and revised the manuscript based on comments from JS and SP. CG-M, PP-G, LF, BS, SH, MT, NB, JS-S, and SP reviewed and approved the manuscript for submission. CG-M, PP-G, LF, BS, SH, MT, NB, JS-S, and SP had the final responsibility for the decision to submit for publication.

Funding
The NutriNet-Santé study was supported by the following public institutions: the Ministry of Health, Public Health France, the National Institute of Health and Medical Research (INSERM), the National Institute of Agricultural, Food and Environmental Research (INRAE), the National Conservatory of Arts and Crafts (CNAM), and Université Sorbonne Paris Nord. CG-M receives a predoctoral (2020PMF-PIPF-37) from URV. Researchers were independent from funders. The funders had no role in considering the study design or in the collection, analysis, interpretation of data, writing of the report, or decision to submit the article for publication.

Availability of data and materials
Researchers from public institutions can submit a collaboration request to Dr. Mathilde Touvier via collaboration@etude-nutrinet-sante.fr, including information on the institution and a brief description of the project. All requests will be reviewed by the steering committee of the NutriNet-Santé study. If the collaboration is accepted, a data access agreement will be necessary, and appropriate authorizations from competent administrative authorities may be needed. In accordance with existing regulations, no personal data will be accessible. The analysis code can be requested from the authors.

Declarations

Ethics approval and consent to participate
Electronic informed consent is provided by each person included in the NutriNet-Santé cohort. The study is registered at https://clinicaltrials.gov/ct2/show/NCT03335644, conducted according to the Declaration of Helsinki guidelines and approved by the Institutional Review Board of the French Institute for Health and Medical Research (IRB-Inserm) and the Commission Nationale de l'Informatique et des Libertés (CNIL No 908450/909216).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Universitat Rovira i Virgili, Departament de Bioquímica i Biotecnologia, Alimentació, Nutrició, Desenvolupament i Salut Mental (ANUT-DSM), Reus, Spain. [2]Institut d'Investigació Sanitària Pere Virgili (IISPV), Reus, Spain. [3]Centro de Investigación Biomédica en Red de Fisiopatología de La Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III (ISCIII), Madrid, Spain. [4]Center of Research in Epidemiology and StatisticS (CRESS), Nutritional Epidemiology Research Team (EREN), Université Sorbonne Paris Nord and Université Paris Cité, INSERM, INRAE, CNAM, 93017 Bobigny, France.

Received: 9 January 2024 Accepted: 24 July 2024
Published online: 15 August 2024

References

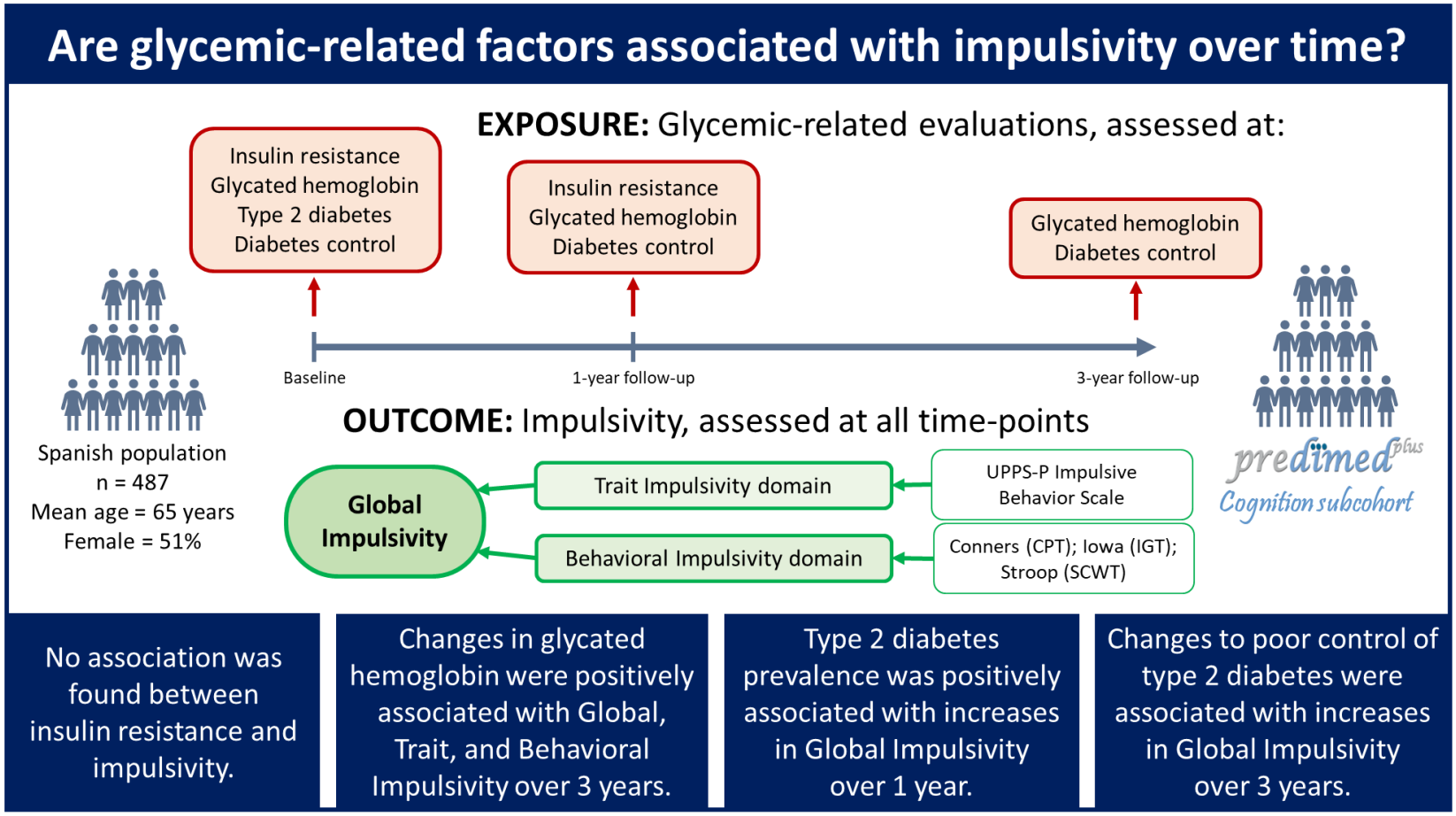
1. World Health Organization. A report about diabetes. June 8, 2020. https://www.who.int/health-topics/diabetes. Accessed 27 Nov 2020.
2. Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes. Lancet. 2017;389(10085):2239–51.
3. Mischel W, Shoda Y. A cognitive-affective system theory of personality: reconceptualizing situations, dispositions, dynamics, and invariance in personality structure. Psychol Rev. 1995;102(2):246–68.
4. Harper RG. Personality-guided therapy in behavioral medicine. 1st ed. Washington DC: American Psychological Association; 2004.
5. Liu M, Argyriou E, Cyders MA. Developmental considerations for assessment and treatment of impulsivity in older adults. In: de Wit H, Jentsch JD. Current topics in behavioral neurosciences. Berlin/Heidelberg, Germany: Springer, Cham; 2020. p. 165–77.
6. Rababah JA, Al-Hammouri MM, Tawalbeh L, Alhawatmeh H, Hasan M. Self-care among persons with heart failure: examining the impact of mindfulness and impulsivity using conditional process analysis. Nurs Forum (Auckl). 2022;57(4):558–67.
7. Stanford MS, Mathias CW, Dougherty DM, Lake SL, Anderson NE, Patton JH. Fifty years of the Barratt Impulsiveness Scale: an update and review. Pers Individ Dif. 2009;47(5):385–95.
8. Bari A, Robbins TW. Inhibition and impulsivity: Behavioral and neural basis of response control. Prog Neurobiol. 2013;108(1):44–79.
9. Gómez-Martínez C, Babio N, Júlvez J, Nishi SK, Fernández-Aranda F, Martínez-González MÁ, et al. Impulsivity is longitudinally associated with healthy and unhealthy dietary patterns in individuals with overweight or obesity and metabolic syndrome within the framework of the PREDIMED-Plus trial. Int J Behav Nutr Phys Act. 2022;19(1):101.
10. Emery RL, Levine MD. Questionnaire and behavioral task measures of impulsivity are differentially associated with body mass index: a comprehensive meta-analysis. Psychol Bull. 2017;143(8):868–902.
11. Emery RL, Levine MD, Creswell KG, Wright AGC, Marsland AL, Matthews KA, et al. Impulsivity and midlife cardiometabolic risk: the role of maladaptive health behaviors. Health Psychol. 2020;39(8):642–54.
12. Hawkins MAW, Gunstad J, Calvo D, Spitznagel MB. Higher fasting glucose is associated with poorer cognition among healthy young adults. Health Psychol. 2016;35(2):199–202.
13. Epstein LH, Paluch RA, Stein JS, Quattrin T, Mastrandrea LD, Bree KA, et al. Delay discounting, glycemic regulation and health behaviors in adults with prediabetes. Behav Med. 2021;47(3):194–204.
14. Eckstrand KL, Mummareddy N, Kang H, Cowan R, Zhou M, Zald D, et al. An insulin resistance associated neural correlate of impulsivity in type 2 diabetes mellitus. PLoS ONE. 2017;12(12):e0189113.
15. Sun DM, Ma Y, Sun ZB, Xie L, Huang JZ, Chen WS, et al. Decision-making in primary onset middle-age type 2 diabetes mellitus: a BOLD-fMRI study. Sci Rep. 2017;1(7):10246.
16. Reach G, Michault A, Bihan H, Paulino C, Cohen R, Le Clésiau H. Patients' impatience is an independent determinant of poor diabetes control. Diabetes Metab. 2011;37(6):497–504.
17. Wainwright K, Romanowich P, Crabtree MA. Associations between impulsivity and self-care adherence in individuals diagnosed with type 2 or prediabetes. PLoS ONE. 2022;17(3):e0263961.
18. Hercberg S, Castetbon K, Czernichow S, Malon A, Mejean C, Kesse E, et al. The Nutrinet-Santé Study: a web-based prospective study on the relationship between nutrition and health and determinants of dietary patterns and nutritional status. BMC Public Health. 2010;10(1):242.
19. Patton JH, Stanford MS, Barratt ES. Factor structure of the Barratt Impulsiveness Scale. J Clin Psychol. 1995;51(6):768–74.
20. Baylé FJ, Bourdel MC, Caci H, Gorwood P, Chignon JM, Adés J, et al. Factor analysis of French translation of the Barratt impulsivity scale (BIS-10). Can J Psychiatry. 2000;45(2):156–65.
21. World Health Organization. International statistical classification of diseases and related health problems, 10th revision. 5th ed. France: World Health Organization; 2016.
22. Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc. 2003;35(8):1381–95.
23. Chaltiel D, Adjibade M, Deschamps V, Touvier M, Hercberg S, Julia C, et al. Programme National Nutrition Santé – guidelines score 2 (PNNS-GS2): development and validation of a diet quality score reflecting the 2017 French dietary guidelines. Br J Nutr. 2019;122(2):331–42.

24. Fuhrer R, Rouillon F. La version française de l'échelle CES-D (Center for Epidemiologic Studies-Depression Scale). Description et traduction de l'échelle d'autoévaluation. Psychiatry and Psychobiology. 1989;4(3):163–6.
25. Steinberg L, Albert D, Cauffman E, Banich M, Graham S, Woolard J. Age differences in sensation seeking and impulsivity as indexed by behavior and self-report: evidence for a dual systems model. Dev Psychol. 2008;44(6):1764–78.
26. Moustafa AA, Tindle R, Frydecka D, Misiak B. Impulsivity and its relationship with anxiety, depression and stress. Compr Psychiatry. 2017;74(1):173–9.
27. Haffner SM. Epidemiology of type 2 diabetes: risk factors. Diabetes Care. 1998;21(Supplement_3):C3-6.
28. Cross CP, Copping LT, Campbell A. Sex differences in impulsivity: a meta-analysis. Psychol Bull. 2011;137(1):97–130.
29. Kautzky-Willer A, Leutner M, Harreiter J. Sex differences in type 2 diabetes. Diabetologia. 2023;66(6):986–1002.
30. Schwartz JA, Connolly EJ, Alsolami A. Within-individual changes in impulsivity and sensation seeking from childhood to early adulthood and educational attainment. J Youth Adolesc. 2022;51(11):2190–204.
31. Bellou V, Belbasis L, Tzoulaki I, Evangelou E. Risk factors for type 2 diabetes mellitus: an exposure-wide umbrella review of meta-analyses. PLoS ONE. 2018;13(3):e0194127.
32. Kale D, Stautz K, Cooper A. Impulsivity related personality traits and cigarette smoking in adults: a meta-analysis using the UPPS-P model of impulsivity and reward sensitivity. Drug Alcohol Depend. 2018;185(1):149–67.
33. Bos J, Hayden MJ, Lum JAG, Staiger PK. UPPS-P impulsive personality traits and adolescent cigarette smoking: a meta-analysis. Drug Alcohol Depend. 2019;197(1):335–43.
34. Dendup T, Feng X, Clingan S, Astell-Burt T. Environmental risk factors for developing type 2 diabetes mellitus: a systematic review. Int J Environ Res Public Health. 2018;15(1):78.
35. Castañer M, Aiello S, Prat Q, Andueza J, Crescimanno G, Camerino O. Impulsivity and physical activity: a T-pattern detection of motor behavior profiles. Physiol Behav. 2020;219:112849.
36. Booth FW, Roberts CK, Laye MJ. Lack of exercise is a major cause of chronic diseases. Compr Physiol. 2012;2(2):1143–211.
37. Mõttus R, McNeill G, Jia X, Craig LCA, Starr JM, Deary IJ. The associations between personality, diet and body mass index in older people. Health Psychol. 2013;32(4):353–60.
38. Bénard M, Bellisle F, Kesse-Guyot E, Julia C, Andreeva VA, Etilé F, et al. Impulsivity is associated with food intake, snacking, and eating disorders in a general population. Am J Clin Nutr. 2019;109(1):117–26.
39. Villegas R, Shu XO, Yang G, Matthews CE, Li H, Cai H, et al. Energy balance and type 2 diabetes: a report from the Shanghai Women's Health Study. Nutr Metab Cardiovasc Dis. 2009;19(3):190–7.
40. van de Wiel A. Diabetes mellitus and alcohol. Diabetes Metab Res Rev. 2004;20(4):263–7.
41. Fuemmeler BF, Østbye T, Yang C, McClernon FJ, Kollins SH. Association between attention-deficit/hyperactivity disorder symptoms and obesity and hypertension in early adulthood: a population-based study. Int J Obes (Lond). 2011;35(6):852–62.
42. Sutin AR, Terracciano A, Deiana B, Uda M, Schlessinger D, Lakatta EG, et al. Cholesterol, triglycerides, and the five-factor model of personality. Biol Psychol. 2010;84(2):186–91.
43. Eriksson A-K, Gustavsson JP, Hilding A, Granath F, Ekbom A, Östenson C-G. Personality traits and abnormal glucose regulation in middle-aged Swedish men and women. Diabetes Res Clin Pract. 2012;95(1):145–52.
44. Scott RA, Langenberg C, Sharp SJ, Franks PW, Rolandsson O, Drogan D, et al. The link between family history and risk of type 2 diabetes is not explained by anthropometric, lifestyle or genetic risk factors: the EPIC-InterAct study. Diabetologia. 2013;56(1):60–9.
45. Fields SA, Schueler J, Arthur KM, Harris B. The role of impulsivity in major depression: a systematic review. Curr Behav Neurosci Rep. 2021;8(1):38–50.
46. Graham EA, Deschênes SS, Khalil MN, Danna S, Filion KB, Schmitz N. Measures of depression and risk of type 2 diabetes: a systematic review and meta-analysis. J Affect Disord. 2020;265(1):224–32.
47. Discacciati A, Bellavia A, Lee JJ, Mazumdar M, Valeri L. Med4way: a Stata command to investigate mediating and interactive mechanisms using the four-way effect decomposition. Int J Epidemiol. 2019;48(1):15–20.
48. Jokela M, Elovainio M, Nyberg ST, Tabák AG, Hintsa T, Batty GD, et al. Personality and risk of diabetes in adults: pooled analysis of 5 cohort studies. Health Psychol. 2014;33(12):1618–21.
49. Roberts BW, Lejuez C, Krueger RF, Richards JM, Hill PL. What is conscientiousness and how can it be assessed? Dev Psychol. 2014;50(5):1315–30.
50. Kozak K, Lucatch AM, Lowe DJE, Balodis IM, MacKillop J, George TP. The neurobiology of impulsivity and substance use disorders: implications for treatment. Ann N Y Acad Sci. 2019;1451(1):71–91.
51. Moeller FG, Barratt ES, Dougherty DM, Schmitz JM, Swann AC. Psychiatric aspects of impulsivity. Am J Psychiatry. 2001;158(11):1783–93.
52. DeYoung C, Reuter A. Impulsivity as a personality trait. In: Vohs K, Baumeister R, editors. Handbook of self-regulation: research, theory, and applications. 3rd ed. New York: Guilford Press; 2016. p. 345–63.
53. Shoelson SE. Inflammation and insulin resistance. J Clin Invest. 2006;116(7):1793–801.
54. Ley SH, Ardisson Korat AV, Sun Q, Tobias DK, Zhang C, Qi L, et al. Contribution of the nurses' health studies to uncovering risk factors for type 2 diabetes: diet, lifestyle, biomarkers, and genetics. Am J Public Health. 2016;106(9):1624–30.
55. Bénard M, Camilleri GM, Etilé F, Méjean C, Bellisle F, Reach G, et al. Association between impulsivity and weight status in a general population. Nutrients. 2017;9(3):217.
56. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature. 2006;444(7121):840–6.
57. Levine GN, Cohen BE, Commodore-Mensah Y, Fleury J, Huffman JC, Khalid U, et al. Psychological health, well-being, and the mind-heart-body connection: a scientific statement from the American Heart Association. Circulation. 2021;143(10):E763–83.
58. Huang S, Zhu Z, Zhang W, Chen Y, Zhen S. Trait impulsivity components correlate differently with proactive and reactive control. PLoS ONE. 2017;12(4):e0176102.
59. Schwab S, Xu T, Ryan K, Steinle N. Eating behavior disinhibition predicts insulin resistance in the Old Order Amish. J Hum Nutr Food Sci. 2017;5(2):1109.
60. Guion M, Mandereau-Bruno L, Goria S, Cosson E, Fosse-Edorh S. Eleven-year trends in socioeconomic inequalities in the prevalence and incidence of pharmacologically treated type 2 diabetes in France, 2010–2020. Diabetes Metab. 2024;50(2):101509.
61. Andreeva VA, Salanave B, Castetbon K, Deschamps V, Vernay M, Kesse-Guyot E, et al. Comparison of the sociodemographic characteristics of the large NutriNet-Santé e-cohort with French census data: the issue of volunteer bias revisited. J Epidemiol Community Health (1978). 2015;69(9):893–8.
62. Boswell RG, Grilo CM. General impulsivity in binge-eating disorder. CNS Spectr. 2021;26(5):538–44.
63. Royuela-Colomer E, Fernández-González L, Orue I. Longitudinal associations between internalizing symptoms, dispositional mindfulness, rumination and impulsivity in adolescents. J Youth Adolesc. 2021;50(10):2067–78.
64. Hadj-Abo A, Enge S, Rose J, Kunte H, Fleischhauer M. Individual differences in impulsivity and need for cognition as potential risk or resilience factors of diabetes self-management and glycemic control. PLoS ONE. 2020;15(1):e0227995.
65. Liu N, Heng C-N, Cui Y, Li L, Guo Y-X, Liu Q, et al. The relationship between trait impulsivity and everyday executive functions among patients with type 2 diabetes mellitus: the mediating effect of negative emotions. J Diabetes Res. 2023;2023(1):5224654.
66. Kopetz CE, Woerner JI, Briskin JL. Another look at impulsivity: could impulsive behavior be strategic? Soc Personal Psychol Compass. 2018;12(5):e12385.

Publisher's Note

CHAPTER 4:
GLYCEMIC STATUS AND IMPULSIVITY

Figure 9. Graphical abstract of Chapter 4. Glycemic status and impulsivity.



DOI: 10.1111/nyas.15205

ORIGINAL ARTICLE

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES

Glycated hemoglobin, type 2 diabetes, and poor diabetes control are positively associated with impulsivity changes in aged individuals with overweight or obesity and metabolic syndrome

Carlos Gómez-Martínez[1,2,3] | Nancy Babio[1,2,3,#] | Lucía Camacho-Barcia[3,4,5] | Jordi Júlvez[6] | Stephanie K. Nishi[1,2,3,7,8] | Zenaida Vázquez[3,9] | Laura Forcano[10] | Andrea Álvarez-Sala[3,11] | Aida Cuenca-Royo[10] | Rafael de la Torre[3,10,12] | Marta Fanlo-Maresma[3,13] | Susanna Tello[10] | Dolores Corella[3,11] | Alejandro Arias Vásquez[14,15] | Søren Dalsgaard[16,17] | Barbara Franke[14,15] | Fernando Fernández-Aranda[3,4,18] | Jordi Salas-Salvadó[1,2,3,#]

[1]Universitat Rovira i Virgili, Departament de Bioquímica i Biotecnologia. Grup d'Alimentació, Nutrició, Desenvolupament i Salut Mental (ANUT-DSM), Unitat de Nutrició Humana, Reus, Spain

[2]Institut d'Investigació Sanitària Pere Virgili (IISPV), Hospital Universitari Sant Joan de Reus, Reus, Spain

[3]Centro de Investigación Biomédica en Red de Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III (ISCIII), Madrid, Spain

[4]Department of Clinical Psychology, Bellvitge University Hospital, Barcelona, Spain

[5]Psychoneurobiology of Eating and Addictive Behaviors Group, Neurosciences Programme, Bellvitge Biomedical Research Institute (IDIBELL), Barcelona, Spain

[6]Institut d'Investigació Sanitària Pere Virgili (IISPV), Clinical and Epidemiological Neuroscience Group (NeuroÈpia), Reus, Spain

[7]Toronto 3D (Diet, Digestive Tract and Disease) Knowledge Synthesis and Clinical Trials Unit, Toronto, Ontario, Canada

[8]Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital, Unity Health Toronto, Toronto, Ontario, Canada

[9]Department of Preventive Medicine and Public Health, Instituto de Investigación Sanitaria de Navarra (IdISNA), University of Navarra, Pamplona, Spain

[10]Integrative Pharmacology and Systems Neurosciences Research Group, Neurosciences Research Program, Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain

[11]Department of Preventive Medicine, University of Valencia, Valencia, Spain

[12]Faculty of Experimental and Health Sciences, Universitat Pompeu Fabra (UPF), Barcelona, Spain

[13]Lipids and Vascular Risk Unit, Internal Medicine, Hospital Universitario de Bellvitge-IBIDELL, Hospitalet de Llobregat, Barcelona, Spain

[14]Department of Human Genetics, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, The Netherlands

[15]Department of Cognitive Neuroscience, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, The Netherlands

[16]Child and Adolescent Mental Health Center, Copenhagen University Hospital – Mental Health Services CPH, Copenhagen, Denmark

[17]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

[18]Department of Clinical Sciences, School of Medicine and Health Sciences, University of Barcelona, Barcelona, Spain

Correspondence
Jordi Salas-Salvadó and Nancy Babio, Human Nutrition Unit, Faculty of Medicine and Health Sciences, Universitat Rovira i Virgili, C/Sant Llorenç 21, 43201 Reus, Spain. Email: jordi.salas@urv.cat; nancy.babio@urv.cat

Abstract

Impulsivity has been proposed to have an impact on glycemic dysregulation. However, it remains uncertain whether an unfavorable glycemic status could also contribute to

#Both authors are corresponding authors.

Funding information
Instituto de Salud Carlos III, Grant/Award Numbers: PI20/00886, CD22/00171, CPII19/00015, PI13/00233, PI13/00272, PI13/00462, PI13/00492, PI13/00673, PI13/00728, PI13/01056, PI13/01090, PI13/01123, PI13/02184, PI14/00618, PI14/00636, PI14/00696, PI14/00728, PI14/00853, PI14/00972, PI14/01206, PI14/01374, PI14/01471, PI14/01722, PI14/01919, PI16/00366, PI16/00381, PI16/00473, PI16/00501, PI16/00533, PI16/00662, PI16/01094, PI16/01120, PI16/01522, PI16/01873, PI17/00215, PI17/00508, PI17/00525, PI17/00532, PI17/00764, PI17/00855, PI17/00926, PI17/01183, PI17/01347, PI17/01441, PI17/01732, PI17/01827, PI19/00017, PI19/00309, PI19/00386, PI19/00576, PI19/00781, PI19/00957, PI19/01032, PI19/01226, PI19/01332, PI19/01560, PI20/00138, PI20/00339, PI20/00456, PI20/00557, PI20/01158, PI20/01532, PI20/01802, FORT23/00032, PI20/132; Universitat Rovira i Virgili, Grant/Award Number: 2020PMF-PIPF-37; Horizon 2020 Framework Programme, Grant/Award Numbers: Eat2beNICE/ H2020-SFS-2016-2, Ref 728018, PRIME/ H2020-SC1-BHC-2018-2020, Ref: 847879; Consejería de Salud y Bienestar Social, Junta de Andalucía, Grant/Award Numbers: PI0137/2018, PI0458/2013, PS0358/2016; Generalitat de Catalunya, Grant/Award Numbers: SLT006/17/00246, 2021 SGR 00824; 'la Caixa' Foundation, Grant/Award Number: 2013ACUP00194; Generalitat de Valenciana, Grant/Award Numbers: APOSTD2020-164, PROMETEO/2017/017, PROMETEO/21/2021; Ministerio de Ciencia e Innovacion, Madrid, Spain, Grant/Award Number: PID2019-108858RB-I00; Canadian Institutes of Health Research (CIHR), Grant/Award Number: MFE-171207

an increase in impulsivity levels. This study aims to analyze associations of baseline and time-varying glycemic status with 3-year time-varying impulsivity in older adults at high risk of cardiovascular disease. A 3-year prospective cohort design was conducted within the PREDIMED-Plus-Cognition substudy. The total population includes 487 participants (mean age = 65.2 years; female = 50.5%) with overweight or obesity and metabolic syndrome. Insulin resistance (HOMA-IR), glycated hemoglobin (HbA1c), presence of type 2 diabetes mellitus, and type 2 diabetes control were evaluated. Impulsivity was measured using the Impulsive Behavior Scale questionnaire and various cognitive measurements. Impulsivity z-scores were generated to obtain Global, Trait, and Behavioral Impulsivity domains. Linear mixed models were used to study the longitudinal associations across baseline, 1-year, and 3-year follow-up visits. HOMA-IR was not significantly related to impulsivity. Participants with higher HbA1c levels, type 2 diabetes, and poor control of diabetes showed positive associations with the Global Impulsivity domain over time, and those with higher HbA1c levels were further related to increases in the Trait and Behavioral Impulsivity domains over the follow-up visits. These results suggest a potential positive feedback loop between impulsivity and glycemic-related dysregulation.

KEYWORDS
glycated hemoglobin (HbA1c), impulsivity, insulin resistance (HOMA-IR), type 2 diabetes control, type 2 diabetes mellitus

INTRODUCTION

Personality traits have been identified as stable characteristics that modulate individual responses to various types of environmental stressors.[1] They play a crucial role in enabling individuals to show a spectrum of potential behaviors,[2] and have been recognized as relevant predictors of various health outcomes.[3] Impulsivity is defined as "a predisposition toward rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions to the impulsive individual or to others."[4] Impulsivity is a personality trait which has been shown to be more modifiable across the lifespan than other personality traits.[5] The development of impulsivity can be influenced by genetic background and ontogenetic processes,[5,6] and impulsive behaviors are manifested when individuals ultimately engage in unplanned and rash actions.

This personality predisposition is associated with maladaptive impulsive behaviors that increase the risk for highly prevalent disorders and diseases with significant public health burdens, such as overeating and obesity,[7,8] cardiovascular disease,[9,10] eating disorders,[11,12] and substance-related disorders,[13,14] among others. With regard to glycemic dysregulation, high glucose levels in healthy participants have been shown to be positively associated with inattention, poor inhibitory control, and risky decision-making.[15,16] Along this line, it has been reported that participants with prediabetes or type 2 diabetes mellitus have higher levels of trait impulsivity compared to healthy individuals.[17,18] These findings suggest that both high trait and behavioral impulsivity may drive the establishment of glycemic impairment and may lead to a poor glycemic prognosis. Indeed, behavioral impulsivity, as assessed by higher reward sensitivity, has been associated with poor adherence to diabetes medications and

uncontrolled levels of glycated hemoglobin (HbA1c) levels in studies of adolescents with type 1 diabetes and adults with type 2 diabetes.[19,20] Moreover, trait impulsivity has been positively associated with poor management of type 2 diabetes and self-care in adults.[21,22]

Conversely, it has been suggested that glycemic dysregulation, such as higher glucose levels, may modulate impulsivity.[23] For example, in individuals with type 1 diabetes, the neural reward system—which is related to impulsivity[14]—was found to play a key role in the observed associations between metabolic trajectories and cognitive impulsivity.[24] Along this line, the association between higher insulin resistance and poor performance on behavioral impulsivity tasks is mediated by the activation of impulsivity-related neural areas in individuals with type 2 diabetes and obesity.[25] However, no associations have been found between trait impulsivity and fluctuations in glucose levels[26,27] or changes in HbA1c levels,[28] or between behavioral impulsivity and blood glucose levels.[27]

Therefore, the directionality of these potential associations is controversial, and new research in this field is needed using prospective studies and clinical trials that simultaneously assess both trait and behavioral measures of impulsivity.

The aim of the present study was to assess the associations between insulin resistance, glycated hemoglobin, presence of type 2 diabetes mellitus, and type 2 diabetes control with several assessments of impulsivity across 3 years of follow-up in an older Mediterranean population at high risk of cardiovascular disease. A positive longitudinal association between poorer glycemic status and impulsivity was hypothesized.

MATERIALS AND METHODS

Study design

An observational prospective study was conducted with the PREDIMED-Plus-Cognition cohort, a substudy conducted within the PREDIMED-plus cohort. The baseline visit of the PREDIMED-Plus study is the same as for the PREDIMED-Plus-Cognition study. PREDIMED-Plus is a 6-year multicenter, randomized, parallel-group clinical trial conducted in Spain with the primary aim of evaluating the effect of lifestyle intervention on the primary prevention of cardiovascular disease and mortality. Participants in the intervention group received recommendations to increase their adherence to an energy-reduced Mediterranean diet and physical activity promotion. In contrast, participants in the control group only received general usual care recommendations to follow an energy-unrestricted Mediterranean diet. Participants were recruited between September 2013 and December 2016. The study protocol has been described elsewhere[29,30] and is available at http://www.predimedplus.com. The trial was registered in the International Standard Randomized Controlled Trial registry, and details can be found at http://www.isrctn.com/ISRCTN89898870.

Study population

Eligible participants were men aged 55–75 years and women aged 60–75 years with overweight or obesity (27 kg/m^2 ≥ body mass index [BMI] < 40 kg/m^2) and meeting at least three criteria for metabolic syndrome[31] at baseline. Exclusion criteria have been reported elsewhere.[30] As part of the initial PREDIMED-Plus population (n = 6874), the current study included participants from the PREDIMED-Plus-Cognition substudy (n = 487) recruited in four Spanish centers: Institut Hospital del Mar d'Investigacions Mèdiques, Bellvitge University Hospital, Universitat Rovira i Virgili, and Universidad de Valencia. As the latter center did not perform the computerized cognitive tests, only 417 participants were analyzed for cognitive assessments. The participants' flowchart and data availability are shown in Figure S1.

Ethical standards

All participants provided written informed consent. According to the ethical standards of the Declaration of Helsinki by the Research Ethics Committees, all the participating institutions approved the study protocol and procedures (CEIC del Hospital de Bellvitge—University Hospital Bellvitge-IDIBELL: PR240/13; CEIC Parc de Salut Mar y IDIAP Jordi Gol—IMIM: PI13/130; CEIC Corporativo de Atención Primaria de la Comunitat Valenciana—University of Valencia: CEIC del Hospital Universitari Sant Joan de Reus y IDIAB Jordi Gol—Universitat Rovira i Virgili: 2011-005398-22; 13-07-25/7proj2).

Glycemic status

Exposures were assessed at baseline or as a time-varying variable across the 3 years of follow-up, depending on their availability. Blood samples were collected at baseline, 1-year, and 3-year follow-up under fasting conditions, and biochemical analyses were performed to determine glycated hemoglobin (HbA1c) using standard laboratory methods at baseline and across follow-up. Insulin was measured by an electrochemiluminescence immunoassay using an Elecsys immunoanalyzer (Roche Diagnostics), and the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) index was calculated[32] at baseline and at 1-year follow-up. Participants with a previous diagnosis of diabetes or use of antidiabetic medication were identified as positive cases of type 2 diabetes mellitus at baseline, as well as according to the American Diabetes Association criteria: HbA1c ≥6.5% (48 mmol/mol) or having fasting plasma glucose ≥136 mg/dL at both the screening and baseline visits. Type 2 diabetes control was assessed at baseline and as time-varying exposure across the follow-up by categorizing participants into those having good glycemic control (HbA1c <7% or <53 mmol/mol) and poor glycemic control (HbA1c ≥7% or ≥53 mmol/mol).[33]

Covariates

Sex, age, intervention group, educational level, marital status, smoking status, and presence of hypertension and hypercholesterolemia were obtained from self-reported questionnaires administered by trained PREDIMED-Plus personnel and were assessed at baseline. Physical activity, Mediterranean diet adherence, alcohol consumption, and presence of obesity and depressive symptomatology were assessed as time-varying variables across time points. Weight and height were measured to determine BMI, and the presence of obesity was defined as BMI >30 kg/m^2. Physical activity was estimated using the validated Regicor Short Physical Activity Questionnaire.[34] Adherence to the Mediterranean diet was assessed using the validated 17-point Mediterranean diet adherence screener questionnaire.[35] Risk for depressive symptomatology was assessed using the Beck Depression Inventory-II questionnaire.[36]

Impulsivity

Trait and behavioral impulsivity were assessed at the baseline, 1-year, and 3-year follow-up visits.

Trait impulsivity was evaluated using the Impulsive Behavior Scale (UPPS-P),[37] validated for the Spanish population.[38] The UPPS-P assesses five personality subfactors related to impulsivity pathways: negative urgency, (lack of) perseverance, (lack of) premeditation, sensation seeking, and positive urgency. Scores for each dimension and a total score of the UPPS-P were calculated by adding the unweighted respective items, with higher scores indicating higher levels of impulsivity. Cronbach's α values for the total score were 0.92, 0.93, and 0.93 at baseline, 1-year, and 3-year of follow-up, respectively.

Behavioral impulsivity was evaluated using the commissions and perseverations scores of the Conners' Continuous Performance Test (CPT) third edition,[39] the Iowa Gambling Task (IGT),[40] and the Stroop Color and Word Test (SWCT).[41] Further description of behavioral impulsivity assessments can be found in the Supplementary Material.

Statistical analysis

The PREDIMED-Plus-Cognition database, updated in September 2021, was used for the present analyses.

To facilitate comparisons across impulsivity assessments, z-scores were generated for each impulsivity measurement, and z-score domains of Global, Trait, and Behavioral Impulsivity were further obtained following specified methods.[42,43] More detailed information about impulsivity z-scores can be found in the Supplementary Methods.

Baseline participant characteristics are presented as numbers and percentages and mean ± standard deviation (SD) for qualitative and quantitative variables, respectively. Linear mixed models were performed to assess longitudinal relationships between glycemic-related measures and impulsivity z-scores. Linear mixed models address missing data by assuming that repeated measures for each participant are intracorrelated. These models maximize the use of all available data, even if the data were collected at a single point in time during the follow-up visits. Specifically, analyses were performed to assess the associations of: (a) baseline levels of HOMA-IR and HbA1c, presence of type 2 diabetes (no/yes), and diabetes control in participants having type 2 diabetes (no/yes) with impulsivity z-scores as time-varying outcomes; and (b) time-varying HOMA-IR, HbA1c, and type 2 diabetes control with time-varying impulsivity z-scores. The time variable was introduced as a categorical variable in the models with an interaction with the respective glycemic status exposure, along with the respective glycemic exposure and the time variables. The results were interpreted using the baseline visit as the reference. Additionally, a *p*-value for trend was estimated by conducting the same models using the time variable as a continuous variable. Three models were fitted, and covariates were specified in figure and table footnotes and in the Supplementary Methods. Random effects were hierarchically established by center, members sharing the same household unit, and each participant's response. The random slope was defined considering follow-up periods.

We tested interactions for sex, age (<65 or ≥65 years; based on the median of the population), intervention group, and presence of obesity (no/yes) and depressive symptomatology (no/yes) in the associations between glycemic status and the Global Impulsivity z-score by comparing the model with and without the interaction product using the likelihood ratio test.

The Stata-18 software program (StataCorp) was used to perform the statistical analyses, and significance was defined as $p < 0.05$.

RESULTS

Descriptive results

Table 1 shows the sociodemographic, lifestyle, and medical history of disease characteristics of the study population at baseline (n = 487). The mean age was 65.2 ± 4.7 years, and 49.5% of participants were men. Approximately half of the population had completed primary school level education, three-quarters were married, and half had never smoked. Almost 75% of the study population had obesity or hypercholesterolemia, while 84.4% had hypertension and 19.9% had depressive symptomatology. Baseline scores for trait and behavioral measures of impulsivity are shown in Table 1. The mean and SD for the total UPPS-P score at baseline and 1- and 3-year follow-up visits were 108.7 ± 22.7, 109.1 ± 24.1, and 106.9 ± 23.9, respectively. Table S1 shows the baseline population characteristics by intervention and control group, with no statistical differences between groups for any assessed variable.

TABLE 1 Baseline participant characteristics ($n = 487$).

Characteristics	Values
General characteristics	
Age (years)	65.2 ± 4.71
Sex (female)	246 (50.5)
Intervention group	240 (49.3)
Education level	
Primary school or less	260 (53.4)
High school	142 (29.2)
College	85 (17.4)
Marital status	
Single, divorced, separated	54 (11.1)
Married	382 (78.4)
Widowed	51 (10.5)
Smoking status	
Never smoked	239 (49.1)
Former smoker	189 (38.8)
Current smoker	59 (12.1)
Physical activity (MET min/week)	2361 ± 2036
Alcohol intake (g/day)	8.98 (11.8)
Adherence to Mediterranean diet (0–17 points)	7.77 (2.47)
Body mass index (kg/m^2)	32.5 ± 3.41
Obesity (BMI ≥ 30 kg/m^2)	354 (72.7)
Hypercholesterolemia	357 (73.3)
Hypertension	411 (84.4)
Medication for diabetes[a]	121 (24.85)
Depressive symptomatology (BDI-II score)	8.52 ± 6.91
Depressive symptomatology	97 (19.9)
Glycemic assessments[b]	
HOMA-IR	5.59 ± 4.01
HbA1c (%)	6.14 ± 0.84
HbA1c (mmol/mol)	43.6 ± 9.15
Type 2 diabetes prevalence	148 (30.4)
Good type 2 diabetes control[c]	78 (52.7)
HbA1c (%)	6.29 ± 0.36
HbA1c (mmol/mol)	45.3 ± 3.94
Poor type 2 diabetes control[d]	70 (47.3)
HbA1c (%)	7.84 ± 0.96
HbA1c (mmol/mol)	62.1 ± 10.4
Impulsivity assessments[b]	
UPPS-P total score (0–236 points)	108.7 ± 22.7
UPPS-P Negative Urgency (0–48 points)	24.5 ± 7.38
UPPS-P Premeditation (0–44 points)	19.8 ± 5.60
UPPS-P Perseverance (0–40 points)	18.9 ± 4.96
UPPS-P Sensation Seeking (0–48 points)	22.3 ± 6.05
UPPS-P Positive Urgency (0–56 points)	23.0 ± 8.24
CPT Commissions	19.5 ± 11.9
CPT Perseverations	0.48 ± 0.98
Iowa Gambling Test	1.25 ± 16.2
Stroop Color Word Test	−1.25 ± 8.12

Note: Data are expressed as *n* (%) for categorical variables and mean ± SD for quantitative variables.
Abbreviations: BDI-II, Beck's Depression Inventory-II; BMI, body mass index; CPT, Conner's Performance Test; HbA1c, glycated hemoglobin; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; UPPS-P, Impulsive Behavior Scale.
[a]Medication for diabetes included participants taking insulin, insulin secretagogues, other noninsulin hypoglycemics, thiazolidinediones, metformin, other biguanides, sulfonylureas, alpha-glucosidase inhibitors, GLP-1 analogues, DPP-4 inhibitors, or SGLT2 inhibitors.
[b]See Figure S1 for data availability over time.
[c]Good type 2 diabetes control defined as HbA1c <7% or <53 mmol/mol.
[d]Poor type 2 diabetes control defined as HbA1c ≥7% or ≥53 mmol/mol.

Glycemic-related assessments and impulsivity

As shown in Table 2, no associations of baseline and 1-year time-varying HOMA-IR with 3-year time-varying impulsivity domains were found.

Table 3 displays the relationships of baseline and 3-year time-varying HbA1c with impulsivity domains across the 3 years of follow-up. In the fully adjusted model, baseline HbA1c levels were associated with increases in Global Impulsivity and Trait Impulsivity at 1-year follow-up, and with increases in Behavioral Impulsivity at the 3-year follow-up. When HbA1c was assessed as a time-varying exposure, positive associations were observed at all the follow-up time points for Global Impulsivity (1-year follow-up: $\beta = 0.23$; 95% CI [0.05, 0.42]; 3-year follow-up: $\beta = 0.25$; 95% CI [0.07, 0.43]) and Trait Impulsivity (1-year follow-up: $\beta = 0.23$, 95% CI [0.08, 0.38]; 3-year follow-up: $\beta = 0.20$, 95% CI [0.06, 0.38]). For the Behavioral Impulsivity domain, the association was shown only at the 3-year follow-up ($\beta = 0.20$; 95% CI [0.02, 0.38]), although a significant positive trend across visits was found for all impulsivity domains.

Table 4 presents the associations between type 2 diabetes at baseline and impulsivity domains across 3 years of follow-up, with participants without diabetes as the reference. In all models, the presence of type 2 diabetes was only significantly associated with high Global Impulsivity at 1-year follow-up (fully adjusted model: $\beta = 0.36$; 95% CI [0.05, 0.67]). No relationships were found for the Trait and Behavioral Impulsivity domains, nor were significant trends observed over time.

Table 5 shows the relationships of baseline and time-varying type 2 diabetes control with time-varying impulsivity domains over 3 years, considering participants with good type 2 diabetes control as the reference. In all models, poor type 2 diabetes control at baseline was positively associated with Global Impulsivity at 1-year follow-up. In the fully adjusted model when type 2 diabetes control was assessed considering the three time points, poor diabetes control was associ-

TABLE 2 Associations of baseline and time-varying HOMA-IR with time-varying impulsivity domains.

HOMA-IR	Model	Time point	Baseline			Time-varying		
Impulsivity		Time point	*n*	β (95% CI)	*p*	*n*	β (95% CI)	*p*
Global Impulsivity	1	Year 1		0.012 (−0.025, 0.049)	0.531	267	0.012 (−0.025, 0.049)	0.517
	1	Year 3	287	0.008 (−0.031, 0.048)	0.681	–	–	–
Trait Impulsivity	1	Year 1		0.018 (−0.012, 0.048)	0.234	379	0.019 (−0.011, 0.049)	0.205
	1	Year 3	390	−0.008 (−0.040, 0.024)	0.630	–	–	–
Behavioral Impulsivity	1	Year 1		−0.008 (−0.042, 0.026)	0.659	309	−0.006 (−0.040, 0.028)	0.734
	1	Year 3	321	0.014 (−0.027, 0.054)	0.505	–	–	–
Global Impulsivity	2	Year 1		0.008 (−0.028, 0.045)	0.650	267	0.010 (−0.026, 0.046)	0.588
	2	Year 3	287	0.015 (−0.024, 0.054)	0.456	–	–	–
Trait Impulsivity	2	Year 1		0.014 (−0.015, 0.044)	0.343	379	0.015 (−0.015, 0.045)	0.337
	2	Year 3	390	−0.010 (−0.042, 0.022)	0.553	–	–	–
Behavioral Impulsivity	2	Year 1		−0.011 (−0.044, 0.023)	0.539	309	−0.009 (−0.042, 0.025)	0.611
	2	Year 3	321	0.018 (−0.023, 0.058)	0.386	–	–	–
Global Impulsivity	3	Year 1		0.001 (−0.038, 0.041)	0.945	263	0.007 (−0.033, 0.046)	0.744
	3	Year 3	284	0.011 (−0.029, 0.050)	0.590	–	–	–
Trait Impulsivity	3	Year 1		0.011 (−0.020, 0.043)	0.477	374	0.013 (−0.019, 0.044)	0.437
	3	Year 3	386	−0.012 (−0.044, 0.020)	0.450	–	–	–
Behavioral Impulsivity	3	Year 1		−0.020 (−0.057, 0.016)	0.274	308	−0.017 (−0.052, 0.019)	0.368
	3	Year 3	320	0.017 (−0.024, 0.058)	0.407	–	–	–

Note: Linear mixed models were performed using beta coefficients and 95% CI to assess the associations of baseline and time-varying linear HOMA-IR levels with time-varying linear impulsivity domains. Time-varying assessments only include data between baseline and 1-year follow-up due to HOMA-IR data not being available at the 3-year follow-up. Model 1: adjusted by sex, age (years), and intervention group at baseline. Model 2: further adjusted by educational level (primary school; secondary school; college), marital status (single, divorced, or separated; married; widowed), smoking status (smoker; former smoker; never smoked), hypertension (no/yes) and hypercholesterolemia (no/yes) at baseline, and physical activity (MET min/week), 17-point Mediterranean diet (score), alcohol intake (g/day), obesity (no/yes), and use of diabetes medication (no, yes) as time-varying variables. Model 3: further adjusted by depressive symptomatology (no/yes) as time-varying variable. Random effects were hierarchically established by center, members sharing the same household unit, and participants' responses. The random slope was determined at baseline and 1-year follow-up. The *p* for trend was estimated using the time variable as a linear variable instead of a categorical variable. Participants taking an insulin treatment were excluded for HOMA-IR analysis ($n = 10$).

ated with higher Global Impulsivity levels at each time point (1-year follow-up: $\beta = 0.95$, 95% CI [0.27, 1.62]; 3-year follow-up: $\beta = 0.61$, 95% CI [0.05, 1.17]) and higher Trait Impulsivity at the third year of follow-up ($\beta = 0.49$; 95% CI [0.01, 0.97]), and a positive trend was also observed for the Trait Impulsivity domain ($p = 0.041$). No other associations were found between type 2 diabetes control and impulsivity domains.

Figure 1 shows graphically the association of baseline HOMA-IR, baseline presence of type 2 diabetes mellitus, 3-year time-varying HbA1c, and 3-year time-varying diabetes control with Global Impulsivity across the 3-year follow-up period.

Specific relationships of HOMA-IR, HbA1c, presence of type 2 diabetes, and control of type 2 diabetes with trait impulsivity subfactors and each impulsivity-related behavioral assessment are shown in Table S2, Table S3, Table S4, and Table S5, respectively.

No interactions with age, sex, intervention group, and presence of obesity or depressive symptomatology were found in the analyses performed for HOMA-IR, HbA1c, and type 2 diabetes with the Global Impulsivity z-score in any of the models evaluated.

DISCUSSION

To the best of our knowledge, this is the first study examining the associations of HOMA-IR, HbA1c, type 2 diabetes mellitus, and diabetes control with impulsivity over 3 years of follow-up, further assessing glucose-related exposures at baseline and as time-varying variables and also controlling for several potential confounding factors. The main findings of the present study indicated that a worse glycemic status at baseline (assessed by HbA1c levels, presence of type 2 diabetes, and poor type 2 diabetes control) was associated with increases in the Global Impulsivity domain at 1-year follow-up. In addition, when considering exposures as time-varying factors across the 3 years of follow-up, the progression to a worse glycemic status (assessed by HbA1c and poor type 2 diabetes control) was associated with higher Global Impulsivity at each time point, compared to the baseline visit. Insulin resistance, as measured by HOMA-IR, showed no relationships with impulsivity z-scores.

Impulsivity is considered a personality trait characterized by a predisposition to act quickly and without forethought. It is established

TABLE 3 Associations of baseline and time-varying HbA1c with time-varying impulsivity domains.

HbA1c	Model	Time point	Baseline			Time-varying		
Impulsivity		Time point	*n*	β (95% CI)	*p*	*n*	β (95% CI)	*p*
Global Impulsivity	1	Year 1		0.275 (0.120, 0.129)	0.001		0.262 (0.075, 0.449)	0.004
	1	Year 3	342	0.082 (−0.087, 0.252)	0.341	344	0.134 (−0.036, 0.303)	0.123
Trait Impulsivity	1	Year 1		0.228 (0.102, 0.354)	<0.001		0.237 (0.092, 0.382)	0.001
	1	Year 3	445	0.054 (−0.082, 0.189)	0.438	461	0.152 (0.013, 0.291)	0.032
Behavioral Impulsivity	1	Year 1		0.028 (−0.111, 0.166)	0.697		0.025 (−0.138, 0.188)	0.761
	1	Year 3	380	0.120 (−0.042, 0.282)	0.146	382	0.104 (−0.062, 0.271)	0.218
Global Impulsivity	2	Year 1		0.272 (0.117, 0.427)	0.001		0.236 (0.050, 0.423)	0.013
	2	Year 3	342	0.089 (−0.079, 0.257)	0.298	344	0.157 (−0.015, 0.238)	0.073
Trait Impulsivity	2	Year 1		0.226 (0.100, 0.352)	<0.001		0.220 (0.074, 0.366)	0.003
	2	Year 3	445	0.054 (−0.081, 0.188)	0.435	461	0.163 (0.023, 0.302)	0.022 *
Behavioral Impulsivity	2	Year 1		0.041 (−0.098, 0.180)	0.563		0.043 (−0.121, 0.207)	0.607
	2	Year 3	380	0.139 (−0.022, 0.300)	0.090	382	0.137 (−0.031, 0.304)	0.110
Global Impulsivity	3	Year 1		0.270 (0.115, 0.425)	0.001		0.231 (0.045, 0.418)	0.015
	3	Year 3	339	0.133 (−0.039, 0.305)	0.131	341	0.253 (0.072, 0.434)	0.006 **
Trait Impulsivity	3	Year 1		0.238 (0.112, 0.365)	<0.001		0.230 (0.082, 0.378)	0.002
	3	Year 3	441	0.073 (−0.062, 0.207)	0.288	457	0.197 (0.056, 0.338)	0.006 **
Behavioral Impulsivity	3	Year 1		0.049 (−0.093, 0.191)	0.496		0.052 (−0.115, 0.218)	0.543
	3	Year 3	379	0.167 (0.003, 0.332)	0.046	381	0.198 (0.021, 0.375)	0.028 *

Note: Linear mixed models were performed using beta coefficients and 95% CI to assess the associations of baseline and time-varying linear HbA1c levels with time-varying linear impulsivity domains. Model 1: adjusted by sex, age (years), and intervention group at baseline. Model 2: further adjusted by educational level (primary school; secondary school; college), marital status (single, divorced, or separated; married; widowed), smoking status (smoker; former smoker; never smoked), hypertension (no/yes) and hypercholesterolemia (no/yes) at baseline, and physical activity (MET min/week), 17-point Mediterranean diet (score), alcohol intake (g/day), obesity (no/yes), and use of diabetes medication (no, yes) as time-varying variables. Model 3: further adjusted by depressive symptomatology (no/yes) as time-varying variable. Random effects were hierarchically established by center, members sharing the same household unit, and participants' responses. The random slope was determined at baseline, 1-year follow-up, and 3-year follow-up. The *p* for trend was estimated using the time variable as a linear variable instead of a categorical variable.
*p for trend <0.05; **p for trend <0.01.

before adulthood, and remains relatively stable over time, though showing more variability compared to other personality traits. Behavioral impulsivity is observed if this predisposition results in actions with a lack of premeditation and is guided by emotional urges.[5,37,44] Therefore, an impulsive predisposition to interact with the environment can result in impulsive behaviors that may lead to the establishment of a worse glycemic status. Indeed, some studies have shown that impulsivity promotes hyperglycemia and poor diabetes control[17–22] as well as increases cardiometabolic risk.[9,10] However, a key aspect that needs to be further explored is whether these metabolic impairments might subsequently also lead to an increase in impulsivity levels, potentially inducing a positive feedback loop between impulsivity and poorer glycemic status.

Impulsivity covers many psychological and cognitive characteristics.[44,45] Therefore, assessing several specific trait and behavioral impulsivity features in order to obtain Global, Trait, and Behavioral Impulsivity domains that average directionalities in composite z-scores provides a new and more comprehensive approach for assessing the extensive nature of impulsivity. In fact, in the meta-analysis of Sharma and colleagues, it was hypothesized that trait and behavioral impulsivity composites would predict important life outcomes much more strongly than either type of measure alone.[44] As no previous studies have reported relationships between glycemic parameters and impulsivity composites, our study addresses this gap in the literature by exploring these associations.

Insulin receptors are widespread throughout the brain.[46] They have been shown to be present in neural regions such as the hypothalamus, the mesolimbic pathway that regulates dopamine release to prefrontal areas, and the ventromedial prefrontal, insular, and orbitofrontal cortices, which are regions that have been identified as having impulsivity-related functions regulating the interpretation of emotions, perceptual integration, decision-making, and motor control.[47–49] Therefore, insulin sensitivity appears to be associated with neural pathways related to impulsivity, but limited research evaluating these associations using questionnaires or cognitive tasks assessing impulsivity in adult or older individuals was found. In our study, both baseline and time-varying HOMA-IR at 1-year follow-up showed no association with Global, Trait, or Behavioral Impulsivity domains over time, neither with specific impulsivity traits nor with behavioral assessments. This

TABLE 4 Associations of baseline type 2 diabetes prevalence with time-varying impulsivity domains.

Presence of type 2 diabetes	Model	Time point	Baseline		
Impulsivity		Time point	*n*	β (95% CI)	*p*
Global Impulsivity	1	Year 1		0.373 (0.064, 0.682)	0.018
	1	Year 3	344	0.243 (−0.088, 0.574)	0.150
Trait Impulsivity	1	Year 1		0.220 (−0.019, 0.459)	0.072
	1	Year 3	462	−0.025 (−0.276, 0.226)	0.845
Behavioral Impulsivity	1	Year 1		0.183 (−0.086, 0.453)	0.183
	1	Year 3	382	0.264 (−0.054, 0.582)	0.104
Global Impulsivity	2	Year 1		0.384 (0.074, 0.696)	0.015
	2	Year 3	344	0.232 (−0.093, 0.558)	0.162
Trait Impulsivity	2	Year 1		0.213 (−0.028, 0.455)	0.084
	2	Year 3	462	−0.030 (−0.279, 0.219)	0.811
Behavioral Impulsivity	2	Year 1		0.202 (−0.068, 0.473)	0.202
	2	Year 3	382	0.268 (−0.047, 0.583)	0.096
Global Impulsivity	3	Year 1		0.361 (0.051, 0.670)	0.022
	3	Year 3	341	0.260 (−0.070, 0.591)	0.122
Trait Impulsivity	3	Year 1		0.229 (−0.017, 0.174)	0.068
	3	Year 3	458	−0.010 (−0.256, 0.237)	0.940
Behavioral Impulsivity	3	Year 1		0.211 (−0.065, 0.487)	0.136
	3	Year 3	381	0.281 (−0.041, 0.604)	0.087

Note: Linear mixed models were performed using beta coefficients and 95% CI to assess the associations of baseline type 2 diabetes prevalence ("no prevalence" as the reference category) with time-varying linear impulsivity domains. Model 1: adjusted by sex, age (years), and intervention group at baseline. Model 2: further adjusted by educational level (primary school; secondary school; college), marital status (single, divorced, or separated; married; widowed), smoking status (smoker; former smoker; never smoked), hypertension (no/yes) and hypercholesterolemia (no/yes) at baseline, and physical activity (MET min/week), 17-point Mediterranean diet (score), alcohol intake (g/day), obesity (no/yes), and use of diabetes medication (no, yes) as time-varying variables. Model 3: further adjusted by depressive symptomatology (no/yes) as time-varying variable. Random effects were hierarchically established by center, members sharing the same household unit, and participants' responses. The random slope was determined at baseline, 1-year follow-up, and 3-year follow-up. The *p* for trend was estimated using the time variable as a linear variable instead of a categorical variable.

apparent discrepancy in our results relative to previous studies may be explained by the duration of the study and the assessment of impulsivity: in our study, we used a long observational follow-up period to assess specific trait and behavioral measures of impulsivity, whereas previous work had assessed impulsivity using neuroimaging techniques or intranasal insulin administration over immediate or short periods of time.[25,47–49]

In the present study, it was shown that baseline and changes of HbA1c levels were positively associated with changes in the Global Impulsivity domain, suggesting an overall effect of HbA1c on impulsivity. Regarding trait impulsivity, baseline and changes of HbA1c levels were also associated with increases in the Trait Impulsivity domain. Moreover, positive relationships were found between HbA1c levels and all impulsivity-related personality subfactors as assessed by a lack of premeditation and perseveration, sensation seeking, and positive and negative emotional urgency. Glucose impairments may influence trait impulsivity through hypothalamic brain areas. Hypothalamic regions have been identified as a major neural integration center of personality traits, as both are involved in hormonal regulation that affects mental function, shapes the individual's perception and integration of environmental stimuli, and ultimately determines how the individual will behave.[50–52] Specifically, impulsivity has been linked to the ventromedial hypothalamic–melatonin circuit, as upregulation or downregulation of melatonin increases impulsivity in rats,[53,54] and fluctuations in blood glucose levels have been linked to the ventromedial hypothalamic region.[55] Therefore, we hypothesize that high glucose levels may increase trait impulsivity through this hypothalamic–melatonin pathway. However, other potential unknown mechanisms cannot be disregarded. Regarding behavioral impulsivity, higher HbA1c levels were associated with CPT-Commissions and IGT z-scores over time, indicating attention deficits and risky decision-making, respectively. Nevertheless, when attention, decision-making, impulse control (CPT-Perseverance), and cognitive inhibition (SCWT) functions were estimated as a composite of behavioral impulsivity, a convergence of directionalities and magnitudes resulted in a positive association between baseline and changes of HbA1c levels and changes in the Behavioral Impulsivity domain over 3 years of follow-up. Our findings may be explained by previous results showing that increases in HbA1c were associated with poorer cognitive performance over short and long periods of time,[42,56] which may promote higher levels of behavioral impulsivity[16] via deleterious endothelial function and oxidative stress in brain cells.[57,58]

TABLE 5 Associations of baseline and time-varying type 2 diabetes control with time-varying impulsivity domains.

Poor type 2 diabetes control	Model	Time point	Baseline			Time-varying		
Impulsivity		Time point	*n*	β (95% CI)	*p*	*n*	β (95% CI)	*p*
Global Impulsivity	1	Year 1		0.601 (0.059, 1.143)	0.030		0.850 (0.179, 1.521)	0.013
	1	Year 3	84	−0.329 (−0.904, 0.247)	0.263	85	0.228 (−0.425, 0.881)	0.494
Trait Impulsivity	1	Year 1		0.418 (−0.070, 0.907)	0.093		0.064 (−0.490, 0.617)	0.822
	1	Year 3	129	0.088 (−0.328, 0.503)	0.679	139	0.287 (−0.192, 0.766)	0.240
Behavioral Impulsivity	1	Year 1		0.127 (−0.335, 0.590)	0.589		0.250 (−0.298, 0.798)	0.371
	1	Year 3	97	0.103 (−0.480, 0.687)	0.728	98	0.122 (−0.496, 0.740)	0.699
Global Impulsivity	2	Year 1		0.776 (0.241, 1.310)	0.004		1.029 (0.353, 1.705)	0.003
	2	Year 3	84	−0.014 (−0.252, 0.496)	0.956	85	0.436 (−0.154, 1.026)	0.148
Trait Impulsivity	2	Year 1		0.475 (−0.001, 0.952)	0.051		0.218 (−0.327, 0.763)	0.433
	2	Year 3	129	0.134 (−0.280, 0.548)	0.525	139	0.398 (−0.083, 0.880)	0.105
Behavioral Impulsivity	2	Year 1		0.211 (−0.252, 0.675)	0.352		0.369 (−0.191, 0.928)	0.183
	2	Year 3	97	0.186 (−0.355, 0.727)	0.501	98	0.207 (−0.374, 0.788)	0.484
Global Impulsivity	3	Year 1		0.754 (0.229, 1.278)	0.010		0.947 (0.274, 1.620)	0.011
	3	Year 3	84	0.089 (−0.409, 0.587)	0.727	85	0.611 (0.047, 1.174)	0.034
Trait Impulsivity	3	Year 1		0.464 (−0.011, 0.940)	0.056		0.190 (−0.360, 0.740)	0.679
	3	Year 3	129	0.178 (−0.239, 0.596)	0.403	139	0.488 (0.009, 0.966)	0.046 *
Behavioral Impulsivity	3	Year 1		0.200 (−0.265, 0.665)	0.399		0.356 (−0.208, 0.919)	0.216
	3	Year 3	97	0.257 (−0.308, 0.822)	0.373	98	0.298 (−0.302, 0.899)	0.330

Note: Linear mixed models were performed using beta coefficients and 95% CI to assess the associations of baseline and time-varying type 2 diabetes control ("good control" as the reference category and defined as HbA1c <7% and "poor control" defined as HbA1c ≥7%) with time-varying linear impulsivity domains. Model 1: adjusted by sex, age (years), and intervention group at baseline. Model 2: further adjusted by educational level (primary school; secondary school; college), marital status (single, divorced, or separated; married; widowed), smoking status (smoker; former smoker; never smoked), hypertension (no/yes) and hypercholesterolemia (no/yes) at baseline, and physical activity (MET min/week), 17-point Mediterranean diet (score), alcohol intake (g/day), obesity (no/yes), and use of diabetes medication (no, yes) as time-varying variables. Model 3: further adjusted by depressive symptomatology (no/yes) as time-varying variable. Random effects were hierarchically established by center, members sharing the same household unit, and participants' responses. The random slope was determined at baseline, 1-year follow-up, and 3-year follow-up. The *p* for trend was estimated using the time variable as a linear variable instead of a categorical variable.
*p for trend <0.05.

In the current study, participants with type 2 diabetes or with a poor control of this chronic disease at baseline presented with higher Global Impulsivity levels at 1-year follow-up. When type 2 diabetes control was assessed using information across visits, participants with poor control had significant increases in Global Impulsivity at all time points, and in Trait Impulsivity at the third year of follow-up as well as a positive trend in this domain over the 3 years of follow-up. In an earlier cross-sectional study, 18 participants with type 2 diabetes showed poorer decision-making and decreased activation in the prefrontal areas related to this cognitive impulsivity function compared to healthy controls.[59] Other cross-sectional studies found elevated trait and behavioral impulsivity-related features in individuals with type 2 diabetes,[28] as well as inverse cross-sectional associations between trait impulsivity and diabetes self-care behaviors[21] and diabetes control (as assessed by HbA1c levels).[22] In line with this, relationships between poor diabetes control and higher behavioral impulsivity have also been reported.[18,19] Nevertheless, a lack of studies evaluating associations between type 2 diabetes (compared to healthy controls) and impulsivity exists, and to the best of our understanding, the current work is the first in evaluating longitudinal associations between type 2 diabetes or its control with impulsivity assessments. In addition, our results showed that the unique impulsivity domain associated with both conditions, the presence of type 2 diabetes and a poor control of this disease, was the Global Impulsivity domain. These results suggest that type 2 diabetes and a poor control of this metabolic condition are associated with a broader construct of impulsivity-related functions, also extending the scientific evidence in this field from cross-sectional to longitudinal findings in a Mediterranean population at high risk of cardiovascular disease.

The present study also showed that when glycemic status was assessed using baseline data only, there were more significant results for impulsivity at the 1-year follow-up compared with the 3-year follow-up. This may be partially explained by the active interventions in both arms of the PREDIMED-Plus clinical trial, which attempted to improve the health status of participants with the assistance of healthcare professionals. The effect of the interventions is usually greater in the early stages of clinical trials than in the subsequent years,[60] as was also found for body composition in the

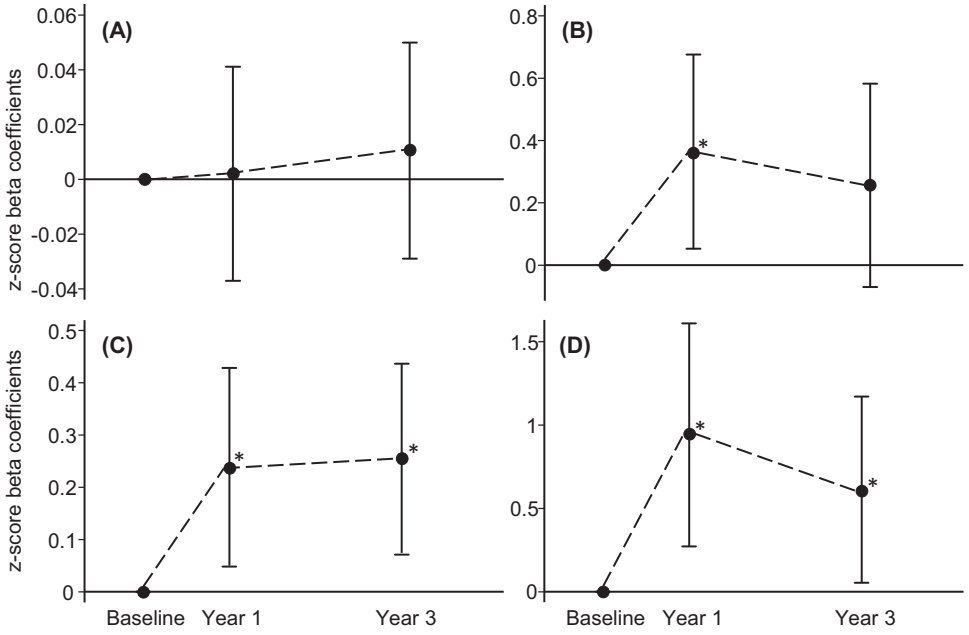


FIGURE 1 Longitudinal associations of baseline HOMA-IR, baseline type 2 diabetes, time-varying HbA1c, and time-varying diabetes control with Global Impulsivity. (A) Insulin resistance measured by HOMA-IR levels. (B) Presence of type 2 diabetes mellitus (no/yes). (C) Glycated hemoglobin (HbA1c) levels. (D) Type 2 diabetes control (good [as the reference category and defined as HbA1c <7%]/poor [defined as HbA1c ≥7%]). Linear mixed models were performed using beta coefficients and 95% CI to assess the longitudinal associations between glycemic-related factors and the Global Impulsivity domain over the 3 years of follow-up. The model was adjusted by sex, age (years), intervention group, educational level (primary school; secondary school; college), marital status (single, divorced, or separated; married; widowed), smoking status (smoker; former smoker; never smoked), hypertension (no/yes), and hypercholesterolemia (no/yes) at baseline, while physical activity (MET min/week), 17-point Mediterranean diet (score), alcohol intake (g/day), obesity (no/yes), diabetes medications (no/yes), and depressive symptomatology (no/yes) as time-varying variables. Random effects were hierarchically established by center, members sharing the same household unit, and participants' responses. The random slope was determined at baseline, 1-year follow-up, and 3-year follow-up.

PREDIMED-Plus study,[61] suggesting that important psychosocial and motivational characteristics associated with the interventions may play a crucial role. For these reasons, the present analyses were conducted assessing exposures, outcomes, and relevant intervention-related components (Mediterranean diet adherence, physical activity, and obesity) and psychological (depressive symptomatology) covariates as time-varying variables. This approach attempted to mitigate these potential confounding effects of the intervention in the studied associations and strengthen the validity of the results examined. It is important to highlight that compared to the first linear mixed model that included only minimally adjusted confounders, the model with the addition of depressive symptomatology had a greater impact on the coefficients in many of the associations examined than the model that included a greater number of covariates such as sociodemographics, lifestyle, and history of disease. This finding may highlight the importance of assessing psychological status as a possible bias factor in future research investigating the relationship between glycemic status and impulsivity, as has been noted in previous studies without an intervention.[21,22]

Our study has some limitations and strengths. First, the observational design of our study does not allow to establish cause–effect relationships. Nevertheless, the present study discusses possible mechanisms for a potential positive feedback loop between impulsivity and a worse glycemic status, also based on the bidirectional mind–heart–body framework.[62] Second, as our study was conducted in a senior Mediterranean population with metabolic syndrome, our results cannot directly be extrapolated to other populations. As strengths, the current study was conducted in a relatively large cohort and presents the first longitudinal results assessing the relationships between glycemic status (assessed by biomarkers) and impulsivity. Finally, we broadly measured the various facets of impulsivity, covering its comprehensive nature.

CONCLUSION

In conclusion, participants with higher HbA1c levels, presence of type 2 diabetes, and with poor type 2 diabetes control were longitudinally associated with increases in overall impulsivity, as assessed by a composite of trait and behavioral impulsivity-related measures. Furthermore, this study contributes to the existing literature on the relationship between impulsivity and glycemic status by suggesting a novel perspective: the existence of a positive feedback loop between impulsivity and glycemic dysregulation. This new perspective allows for a better understanding of the aforementioned relationships and not only emphasizes the need to assess impulsivity for type 2 diabetes prevention, but also highlights that the onset of metabolic dysregulation

promotes new problems driven by additional increases in impulsivity. Nevertheless, additional longitudinal prospective cohort studies and clinical trials are warranted in the future to better understand cause–effect relationships and to explore whether interventions aimed at improving glycemic status could reduce impulsivity levels, thereby further promoting positive health benefits.

AUTHOR CONTRIBUTIONS

The principal PREDIMED-Plus-Cognition investigators R.T., F.F.-A., D.C., and J.S.-S. contributed to study concept and design and to data extraction from the participants. C.G.-M. performed the statistical analyses and C.G.-M., N.B., and J.S.-S. the interpretation of the results. C.G.-M., N.B., S.K.N., and J.S.-S. drafted the manuscript. All authors reviewed the manuscript for important intellectual content and approved the final version to be published.

ACKNOWLEDGMENTS

We thank the PREDIMED-Plus participants and staff members for their participation, as well as the primary care centers that took part in the study. Furthermore, we thank the CERCA Program of the Generalitat de Catalunya and the CIBEROBN, CIBERESP, and CIBERDEM initiatives of Instituto de Salud Carlos III in Spain. This work was supported by the official Spanish Institutions for funding scientific biomedical research, CIBER Fisiopatología de la Obesidad y Nutrición (CIBEROBN) and Instituto de Salud Carlos III (ISCIII), through the Fondo de Investigación para la Salud (FIS), which is cofunded by the European Regional Development Fund (six coordinated FIS projects leaded by J.S.-S., including the following projects: PI13/00673, PI13/00492, PI13/00272, PI13/01133, PI13/00462, PI13/00233, PI13/02184, PI13/00728, PI13/01090, PI13/01056, PI14/01722, PI14/00636, PI14/00618, PI14/00696, PI14/01306, PI14/01919, PI14/00853, PI14/01374, PI14/00972, PI14/00728, PI14/01471, PI16/00473, PI16/00662, PI16/01873, PI16/01094, PI16/00501, PI16/00533, PI16/00381, PI16/00366, PI16/01522, PI16/01130, PI17/00764, PI17/01183, PI17/00855, PI17/01347, PI17/00525, PI17/01827, PI17/00532, PI17/00215, PI17/01441, PI17/00508, PI17/01732, PI17/00926, PI19/00957, PI19/00386, PI19/00309, PI19/01032, PI19/00576, PI19/00017, PI19/01326, PI19/00781, PI19/01560, PI19/01332, PI20/01802, PI20/00138, PI20/01532, PI20/00456, PI20/00339, PI20/00557, PI20/00886, PI20/01158; the Especial Action Project entitled: Implementación y evaluación de una intervención intensiva sobre la actividad física Cohorte PREDIMED-Plus grant to J.S.-S.; the Recercaixa (number 2013ACUP00194) grant to J.S.-S.; grants from the Consejería de Salud de la Junta de Andalucía (PI0458/2013, PS0358/2016, PI0137/2018); the PROMETEO/2017/017 and PROMETEO/21/2021 grants from the Generalitat Valenciana, and the grant PID2019-108858RB-I00 funded by AEI 10.13039/501100011033 and by "ERDF A way of making Europe" to D.C.; the APOSTD2020-164 from the Generalitat Valenciana to A.A.-S.; the SEMERGEN grant; C.G.-M. receives a predoctoral grant from the University of Rovira i Virgili (2020PMF-PIPF-37); J.S.-S., senior author of this paper, is partially supported by ICREA under the ICREA Academia program; L.C.-B. was supported by Sara Borrell fellowship CD22/00171 funded by the Instituto de Salud Carlos III (ISCIII) and cofounded by the European Union; J.J. holds the Miguel Servet-II contract (CPII19/00015) awarded by the Instituto de Salud Carlos III (cofunded by the European Social Fund "Investing in your future"). S.K.N. was supported by a postdoctoral fellowship from the Canadian Institutes of Health Research (CIHR, MFE-171207). F.F.-A. obtained from Generalitat de Catalunya the 2021 SGR 00824 grant, and from Instituto de Salud Carlos II the FORT23/00032 and the PI20/132 grants. None of the funding sources took part in the design, collection, analysis, interpretation of the data, or writing the report, or in the decision to submit the manuscript for publication. We thank CERCA Programme/Generalitat de Catalunya for institutional support and partial support was also provided by SLT006/17/00246, funded by the Department of Health of the Generalitat de Catalunya by the calls "Acció instrumental de programes de recerca orientats en l'àmbit de la recerca i la innovació en salut" and "Pla estratègic de recerca i innovació en salut (PERIS)." This research was also partially funded by EU-H2020 Grants (Eat2beNICE/ H2020-SFS-2016-2, Ref 728018; and PRIME/ H2020-SC1-BHC-2018-2020, Ref: 847879).

COMPETING INTERESTS

J.S.-S. reported receiving research support from the Instituto de Salud Carlos III, Ministerio de Educación y Ciencia, Departament de Salut Pública de la Generalitat de Catalunya, the European Commission, and the USA National Institutes of Health; receiving consulting fees or travel expenses from Instituto Danone; receiving nonfinancial support from Hojiblanca, Patrimonio Comunal Olivarero, the Almond Board of California, Pistachio Growers and Borges S.A; serving on the board of and receiving grant support through his institution from the International Nut and Dried Foundation; serving in the Scientific Board of Danone Institute International (nonpayed member); and personal fees from Instituto Danone Spain. D.C. reported receiving grants from Instituto de Salud Carlos III. F.F.-A. received consultancy honoraria from Novo Nordisk. B.F. received educational speaking fees and travel support from Medice. All other authors declare no commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

There are restrictions on the availability of data for the PREDIMED-Plus trial, due to the signed consent agreements around data sharing, which only allow access to external researchers for studies following the project purposes. Requestors wishing to access the PREDIMED-Plus trial data used in this study can make a request to the PREDIMED-Plus trial Steering Committee chair: predimed_plus_scommitte@googlegroups.com. The request will then be passed to members of the PREDIMED-Plus Steering Committee for deliberation.

ORCID

Jordi Salas-Salvadó https://orcid.org/0000-0003-2700-7459

PEER REVIEW

The peer review history for this article is available at: https://publons.com/publon/10.1111/nyas.15205

REFERENCES

1. Mischel, W., & Shoda, Y. (1995). A cognitive-affective system theory of personality: Reconceptualizing situations, dispositions, dynamics, and invariance in personality structure. *Psychological Review*, *102*(2), 246–268. https://doi.org/10.1037/0033-295X.102.2.246
2. Svrakic, D. M., Przybeck, T. R., & Cloninger, C. R. (1992). Mood states and personality traits. *Journal of Affective Disorders*, *24*(4), 217–226. https://doi.org/10.1016/0165-0327(92)90106-G
3. Harper, R. G. (2004). *Personality-guided therapy in behavioral medicine*. American Psychological Association.
4. Moeller, F. G., Barratt, E. S., Dougherty, D. M., Schmitz, J. M., & Swann, A. C. (2001). Psychiatric aspects of impulsivity. *American Journal of Psychiatry*, *158*(11), 1783–1793. https://doi.org/10.1176/appi.ajp.158.11.1783
5. Liu, M., Argyriou, E., & Cyders, M. A. (2020). Developmental considerations for assessment and treatment of impulsivity in older adults. *Current Topics in Behavioral Neurosciences*, *47*, 165–177. https://doi.org/10.1007/7854_2019_1246
6. Hollander, E., & Rosen, J. (2000). Impulsivity. *Journal of Psychopharmacology*, *14*(2_suppl1), S39–S44. https://doi.org/10.1177/026988110001420S106
7. Emery, R. L., & Levine, M. D. (2017). Questionnaire and behavioral task measures of impulsivity are differentially associated with body mass index: A comprehensive meta-analysis. *Psychological Bulletin*, *143*(8), 868–902. https://doi.org/10.1037/bul0000105
8. Garcia-Garcia, I., Neseliler, S., Morys, F., Dadar, M., Yau, Y. H., Scala, S. G., Zeighami, Y., Sun, N., Collins, D. L., Vainik, U., & Dagher, A. (2022). Relationship between impulsivity, uncontrolled eating and body mass index: A hierarchical model. *International Journal of Obesity*, *46*(1), 129–136.
9. van den, B., & Clark, C. (2021). The role of impulsivity on health behavior related to cardiovascular disease among young adults. *Psychological Trauma: Theory, Research, Practice, and Policy*, *13*(3), 271–276. https://doi.org/10.1037/tra0000910
10. Emery, R. L., Levine, M. D., Creswell, K. G., Wright, A. G., Marsland, A. L., Matthews, K. A., Flory, J. D., & Manuck, S. B. (2020). Impulsivity and midlife cardiometabolic risk: The role of maladaptive health behaviors. *Health Psychology*, *39*(8), 642–654. https://doi.org/10.1037/hea0000884
11. Boswell, R. G., & Grilo, C. M. (2021). General impulsivity in binge-eating disorder. *CNS Spectrums*, *26*(5), 538–544. https://doi.org/10.1017/S1092852920001674
12. Carr, M. M., Wiedemann, A. A., Macdonald-Gagnon, G., & Potenza, M. N. (2021). Impulsivity and compulsivity in binge eating disorder: A systematic review of behavioral studies. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *110*, 110318. https://doi.org/10.1016/j.pnpbp.2021.11031813
13. Herman, A. M., & Duka, T. (2019). Facets of impulsivity and alcohol use: What role do emotions play? *Neuroscience & Biobehavioral Reviews*, *106*, 202–216. https://doi.org/10.1016/j.neubiorev.2018.08.011
14. Kozak, K., Lucatch, A. M., Lowe, D. J., Balodis, I. M., MacKillop, J., & George, T. P. (2019). The neurobiology of impulsivity and substance use disorders: Implications for treatment. *Annals of the New York Academy of Sciences*, *1451*(1), 71–91. https://doi.org/10.1111/nyas.13977
15. Riby, L. M., Lai Teik Ong, D., Azmie, N. B. M., Ooi, E. L., Regina, C., Yeo, E. K. W., Massa, J., & Aquili, L. (2017). Impulsiveness, postprandial blood glucose, and glucoregulation affect measures of behavioral flexibility. *Nutrition Research*, *48*, 65–75. https://doi.org/10.1016/j.nutres.2017.10.011
16. Hawkins, M. A., Gunstad, J., Calvo, D., & Spitznagel, M. B. (2016). Higher fasting glucose is associated with poorer cognition among healthy young adults. *Health Psychology*, *35*(2), 199–202. https://doi.org/10.1037/hea0000248
17. Epstein, L. H., Paluch, R. A., Stein, J. S., Quattrin, T., Mastrandrea, L. D., Bree, K. A., Sze, Y. Y., Greenawald, M. H., Biondolillo, M. J., & Bickel, W. K. (2021). Delay discounting, glycemic regulation and health behaviors in adults with prediabetes. *Behavioral Medicine*, *47*(3), 194–204. https://doi.org/10.1080/08964289.2020.1712581
18. Lebeau, G., Consoli, S. M., Le Bouc, R., Sola-Gazagnes, A., Hartemann, A., Simon, D., Reach, G., Altman, J. J., Pessiglione, M., Limosin, F., & Lemogne, C. (2016). Delay discounting of gains and losses, glycemic control and therapeutic adherence in type 2 diabetes. *Behavioural Processes*, *132*, 42–48. https://doi.org/10.1016/j.beproc.2016.09.006
19. Reach, G., Michault, A., Bihan, H., Paulino, C., Cohen, R., & Le Clésiau, H. (2011). Patients' impatience is an independent determinant of poor diabetes control. *Diabetes & Metabolism*, *37*(6), 497–504. https://doi.org/10.1016/j.diabet.2011.03.004
20. Lansing, A. H., Stanger, C., Crochiere, R., Carracher, A., & Budney, A. (2017). Delay discounting and parental monitoring in adolescents with poorly controlled type 1 diabetes. *Journal of Behavioral Medicine*, *40*(6), 864–874. https://doi.org/10.1007/s10865-017-9856-9
21. Wainwright, K., Romanowich, P., & Crabtree, M. A. (2022). Associations between impulsivity and self-care adherence in individuals diagnosed with Type 2 or prediabetes. *PLoS ONE*, *17*(3), e0263961. https://doi.org/10.1371/journal.pone.0263961
22. Hadj-Abo, A., Enge, S., Rose, J., Kunte, H., & Fleischhauer, M. (2020). Individual differences in impulsivity and need for cognition as potential risk or resilience factors of diabetes self-management and glycemic control. *PLoS ONE*, *15*(1), e0227995. https://doi.org/10.1371/journal.pone.0227995
23. Gailliot, M. T., & Baumeister, R. F. (2007). The physiology of willpower: Linking blood glucose to self-control. *Personality and Social Psychology Review*, *11*(4), 303–327. https://doi.org/10.1177/1088868307303030
24. Jorge, H., Duarte, I. C., Paiva, S., Relvas, A. P., & Castelo-Branco, M. (2022). Abnormal responses in cognitive impulsivity circuits are associated with glycosylated hemoglobin trajectories in type 1 diabetes mellitus and impaired metabolic control. *Diabetes & Metabolism*, *46*(6), 866–878. https://doi.org/10.4093/dmj.2021.0307
25. Eckstrand, K. L., Mummareddy, N., Kang, H., Cowan, R., Zhou, M., Zald, D., Silver, H. J., Niswender, K. D., & Avison, M. J. (2017). An insulin resistance associated neural correlate of impulsivity in type 2 diabetes mellitus. *PLoS ONE*, *12*(12), e0189113. https://doi.org/10.1371/journal.pone.0189113
26. Eriksson, A. K., Gustavsson, J. P., Hilding, A., Granath, F., Ekbom, A., & Ostenson, C. G. (2012). Personality traits and abnormal glucose regulation in middle-aged Swedish men and women. *Diabetes Research and Clinical Practice*, *95*(1), 145–152. https://doi.org/10.1016/j.diabres.2011.10.003
27. Klement, J., Kubera, B., Eggeling, J., Rädel, C., Wagner, C., Park, S. Q., & Peters, A. (2018). Effects of blood glucose on delay discounting, food intake and counterregulation in lean and obese men. *Psychoneuroendocrinology*, *89*, 177–184. https://doi.org/10.1016/j.psyneuen.2018.01.014
28. Testa, G., Camacho-Barcia, L., Gómez-Martínez, C., Mora-Maltas, B., de la Torre, R., Pintó, X., Corella, D., Granero, R., Cuenca-Royo, A., Jiménez-Murcia, S., Babio, N., Fernández-Carrión, R., Esteve-Luque, V., Forcano, L., Ni, J., Malcampo, M., De Las Heras-Delgado, S., Fitó, M., Salas-Salvadó, J., & Fernández-Aranda, F. (2022). Impulsive personality traits predicted weight loss in individuals with type 2 diabetes after 3 years of lifestyle interventions. *Journal of Clinical Medicine*, *11*(12), 3476. https://doi.org/10.3390/jcm11123476
29. Salas-Salvadó, J., Díaz-López, A., Ruiz-Canela, M., Basora, J., Fitó, M., Corella, D., Serra-Majem, L., Wärnberg, J., Romaguera, D., Estruch,

R., Vidal, J., Martínez, J. A., Arós, F., Vázquez, C., Ros, E., Vioque, J., López-Miranda, J., Bueno-Cavanillas, A., Tur, J. A., … PREDIMED-Plus investigators. (2019). Effect of a lifestyle intervention program with energy-restricted Mediterranean diet and exercise on weight loss and cardiovascular risk factors: One-year results of the PREDIMED-Plus Trial. *Diabetes Care*, *42*(5), 777–788. https://doi.org/10.2337/dc18-0836

30. Martínez-González, M. A., Buil-Cosiales, P., Corella, D., Bulló, M., Fitó, M., Vioque, J., Romaguera, D., Martínez, J. A., Wärnberg, J., López-Miranda, J., Estruch, R., Bueno-Cavanillas, A., Arós, F., Tur, J. A., Tinahones, F., Serra-Majem, L., Martín, V., Lapetra, J., Vázquez, C., … Salas-Salvadó, J. (2019). Cohort Profile: Design and methods of the PREDIMED-Plus randomized trial. *International Journal of Epidemiology*, *48*(2), 387–388. https://doi.org/10.1093/ije/dyy225
31. Alberti, K. G., Eckel, R. H., Grundy, S. M., Zimmet, P. Z., Cleeman, J. I., Donato, K. A., Fruchart, J. C., James, W. P., Loria, C. M., & Smith, S. C., jr. (2009). Harmonizing the metabolic syndrome: A joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*, *120*(16), 1640–1645. https://doi.org/10.1161/CIRCULATIONAHA.109.192644
32. Matthews, D. R., Hosker, J. P., Rudenski, A. S., Naylor, B. A., Treacher, D. F., & Turner, R. C. (1985). Homeostasis model assessment: Insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*, *28*(7), 412–419. https://doi.org/10.1007/BF00280883
33. American Diabetes Association Professional Practice Committee. (2022). 6. Glycemic Targets: Standards of Medical Care in Diabetes-2022. *Diabetes Care*, *45*(Suppl 1), S83–S96. https://doi.org/10.2337/dc22-S006
34. Molina, L., Sarmiento, M., Peñafiel, J., Donaire, D., Garcia-Aymerich, J., Gomez, M., Ble, M., Ruiz, S., Frances, A., Schröder, H., Marrugat, J., & Elosua, R. (2017). Validation of the Regicor Short Physical Activity Questionnaire for the adult population. *PLoS ONE*, *12*(1), e0168148. https://doi.org/10.1371/journal.pone.0168148
35. Schröder, H., Zomeño, M. D., Martínez-González, M. A., Salas-Salvadó, J., Corella, D., Vioque, J., Romaguera, D., Martínez, J. A., Tinahones, F. J., Miranda, J. L., Estruch, R., Bueno-Cavanillas, A., Alonso Gómez, A. M., Tur, J. A., Warnberg, J., Serra-Majem, L., Martín, V., Vázquez, C., Lapetra, J., … Castañer, O. (2021). Validity of the energy-restricted Mediterranean Diet Adherence Screener. *Clinical Nutrition*, *40*(8), 4971–4979. https://doi.org/10.1016/j.clnu.2021.06.030
36. Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry*, *4*, 561–571. https://doi.org/10.1001/archpsyc.1961.01710120031004
37. Lynam, D. R., Smith, G. T., Whiteside, S. P., & Cyders, M. A. (2006). *The UPPS-P: Assessing five personality pathways to impulsive behavior*. Purdue University.
38. Verdejo-García, A., Lozano, O., Moya, M., Alcázar, M. A., & Pérez-García, M. (2010). Psychometric properties of a Spanish version of the UPPS-P impulsive behavior scale: Reliability, validity and association with trait and cognitive impulsivity. *Journal of Personality Assessment*, *92*(1), 70–77. https://doi.org/10.1080/00223890903382369
39. Conners, C. K., Sitarenios, G., & Ayearst, L. E. (2018). Conners' Continuous Performance Test Third Edition. In J. S. Kreutzer, J. DeLuca, & B. Caplan (Eds.), *Encyclopedia of Clinical Neuropsychology* (pp. 929–933). Springer. https://doi.org/10.1007/978-3-319-57111-9_1535
40. Bechara, A., Damasio, H., Tranel, D., & Damasio, A. R. (1997). Deciding advantageously before knowing the advantageous strategy. *Science*, *275*(5304), 1293–1295. https://doi.org/10.1126/science.275.5304.1293
41. Golden, C. (2001). *Manual STROOP-Test de Colores y Palabras* (3rd ed.). TEA Ediciones.
42. Rawlings, A. M., Sharrett, A. R., Schneider, A. L., Coresh, J., Albert, M., Couper, D., Griswold, M., Gottesman, R. F., Wagenknecht, L. E., Windham, B. G., & Selvin, E. (2014). Diabetes in midlife and cognitive change over 20 years: A cohort study. *Annals of Internal Medicine*, *161*(11), 785–793. https://doi.org/10.7326/M14-0737
43. Tuligenga, R. H., Dugravot, A., Tabák, A. G., Elbaz, A., Brunner, E. J., Kivimäki, M., & Singh-Manoux, A. (2014). Midlife type 2 diabetes and poor glycaemic control as risk factors for cognitive decline in early old age: A post-hoc analysis of the Whitehall II cohort study. *Lancet Diabetes & Endocrinology*, *2*(3), 228–235. https://doi.org/10.1016/S2213-8587(13)70192-X
44. Sharma, L., Markon, K. E., & Clark, L. A. (2014). Toward a theory of distinct types of "impulsive" behaviors: A meta-analysis of self-report and behavioral measures. *Psychological Bulletin*, *140*(2), 374–408. https://doi.org/10.1037/a0034418
45. Creswell, K. G., Wright, A. G. C., Flory, J. D., Skrzynski, C. J., & Manuck, S. B. (2019). Multidimensional assessment of impulsivity-related measures in relation to externalizing behaviors. *Psychological Medicine*, *49*(10), 1678–1690. https://doi.org/10.1017/S0033291718002295
46. Laron, Z. (2009). Insulin and the brain. *Archives of Physiology and Biochemistry*, *115*(2), 112–116. https://doi.org/10.1080/13813450902949012
47. Edwin Thanarajah, S., Iglesias, S., Kuzmanovic, B., Rigoux, L., Stephan, K. E., Brüning, J. C., & Tittgemeyer, M. (2019). Modulation of midbrain neurocircuitry by intranasal insulin. *Neuroimage*, *194*, 120–127. https://doi.org/10.1016/j.neuroimage.2019.03.050
48. Heni, M., Kullmann, S., Ketterer, C., Guthoff, M., Linder, K., Wagner, R., Stingl, K. T., Veit, R., Staiger, H., Häring, H. U., Preissl, H., & Fritsche, A. (2012). Nasal insulin changes peripheral insulin sensitivity simultaneously with altered activity in homeostatic and reward-related human brain regions. *Diabetologia*, *55*(6), 1773–1782. https://doi.org/10.1007/s00125-012-2528-y
49. Scherer, T., Sakamoto, K., & Buettner, C. (2021). Brain insulin signalling in metabolic homeostasis and disease. *Nature Reviews Endocrinology*, *17*(8), 468–483. https://doi.org/10.1038/s41574-021-00498-x
50. Levine, J. E. (2000). The hypothalamus as a major integrating center. In P. M. Conn, & M. E. Freeman (Eds.), *Neuroendocrinology in physiology and medicine* (pp. 75–93). Humana Press. https://doi.org/10.1007/978-1-59259-707-9_5
51. Eisenlohr-Moul, T. A., & Owens, S. A. (2020). Hormones and personality. In V. Zeigler-Hill, & T. K. Shackelford (Eds.), *Encyclopedia of personality and individual differences* (pp. 2010–2032). Springer. https://doi.org/10.1007/978-3-319-24612-3_762
52. Erlanger, D. M., Kutner, K. C., & Jacobs, A. R. (1999). Hormones and cognition: Current concepts and issues in neuropsychology. *Neuropsychology Review*, *9*(4), 175–207. https://doi.org/10.1023/a:1021634622577
53. Noble, E. E., Wang, Z., Liu, C. M., Davis, E. A., Suarez, A. N., Stein, L. M., Tsan, L., Terrill, S. J., Hsu, T. M., Jung, A. H., Raycraft, L. M., Hahn, J. D., Darvas, M., Cortella, A. M., Schier, L. A., Johnson, A. W., Hayes, M. R., Holschneider, D. P., & Kanoski, S. E. (2019). Hypothalamus-hippocampus circuitry regulates impulsivity via melanin-concentrating hormone. *Nature Communications*, *10*(1), 4923. https://doi.org/10.1038/s41467-019-12895-y
54. Pereira-da-Silva, M., De Souza, C. T., Gasparetti, A. L., Saad, M. J., & Velloso, L. A. (2005). Melanin-concentrating hormone induces insulin resistance through a mechanism independent of body weight gain. *Journal of Endocrinology*, *186*(1), 193–201. https://doi.org/10.1677/joe.1.06111
55. Hirschberg, P. R., Sarkar, P., Teegala, S. B., & Routh, V. H. (2020). Ventromedial hypothalamus glucose-inhibited neurones: A role in glucose

and energy homeostasis? *Journal of Neuroendocrinology*, *32*(1), e12773. https://doi.org/10.1111/jne.12773

56. Gómez-Martínez, C., Babio, N., Júlvez, J., Becerra-Tomás, N., Martínez-González, M. Á., Corella, D., Castañer, O., Romaguera, D., Vioque, J., Alonso-Gómez, Á. M., Wärnberg, J., Martínez, J. A., Serra-Majem, L., Estruch, R., Tinahones, F. J., Lapetra, J., Pintó, X., Tur, J. A., López-Miranda, J., … Salas-Salvadó, J. (2021). Glycemic dysregulations are associated with worsening cognitive function in older participants at high risk of cardiovascular disease: Two-year follow-up in the PREDIMED-Plus study. *Frontiers in Endocrinology*, *12*, 754347. https://doi.org/10.3389/fendo.2021.754347
57. Monnier, L., Mas, E., Ginet, C., Michel, F., Villon, L., Cristol, J. P., & Colette, C. (2006). Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *JAMA*, *295*(14), 1681–1687. https://doi.org/10.1001/jama.295.14.1681
58. Ceriello, A., Esposito, K., Piconi, L., Ihnat, M. A., Thorpe, J. E., Testa, R., Boemi, M., & Giugliano, D. (2008). Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. *Diabetes*, *57*(5), 1349–1354. https://doi.org/10.2337/db08-0063
59. Sun, D. M., Ma, Y., Sun, Z. B., Xie, L., Huang, J. Z., Chen, W. S., Duan, S. X., Lin, Z. R., Guo, R. W., Le, H. B., Xu, W. C., & Ma, S. H. (2017). Decision-making in primary onset middle-age type 2 diabetes mellitus: A BOLD-fMRI study. *Scientific Reports*, *7*(1), 10246. https://doi.org/10.1038/s41598-017-10228-x
60. Norrie, J. (2023). The importance of long-term follow-up in clinical trials. *Lancet Global Health*, *11*(7), e995–e996. https://doi.org/10.1016/S2214-109X(23)00244-9
61. Konieczna, J., Ruiz-Canela, M., Galmes-Panades, A. M., Abete, I., Babio, N., Fiol, M., Martín-Sánchez, V., Estruch, R., Vidal, J., Buil-Cosiales, P., García-Gavilán, J. F., Moñino, M., Marcos-Delgado, A., Casas, R., Olbeyra, R., Fitó, M., Hu, F. B., Martínez-Gonzalez, M. Á., Martínez, J. A., … Salas-Salvadó, J. (2023). An energy-reduced Mediterranean diet, physical activity, and body composition: An interim subgroup analysis of the PREDIMED-Plus randomized clinical trial. *JAMA Network Open*, *6*(10), e2337994. https://doi.org/10.1001/jamanetworkopen.2023.37994
62. Levine, G. N., Cohen, B. E., Commodore-Mensah, Y., Fleury, J., Huffman, J. C., Khalid, U., Labarthe, D. R., Lavretsky, H., Michos, E. D., Spatz, E. S., & Kubzansky, L. D. (2021). Psychological health, well-being, and the mind-heart-body connection: A scientific statement from the American Heart Association. *Circulation*, *143*(10), e763–e783. https://doi.org/10.1161/CIR.0000000000000947

SUPPORTING INFORMATION

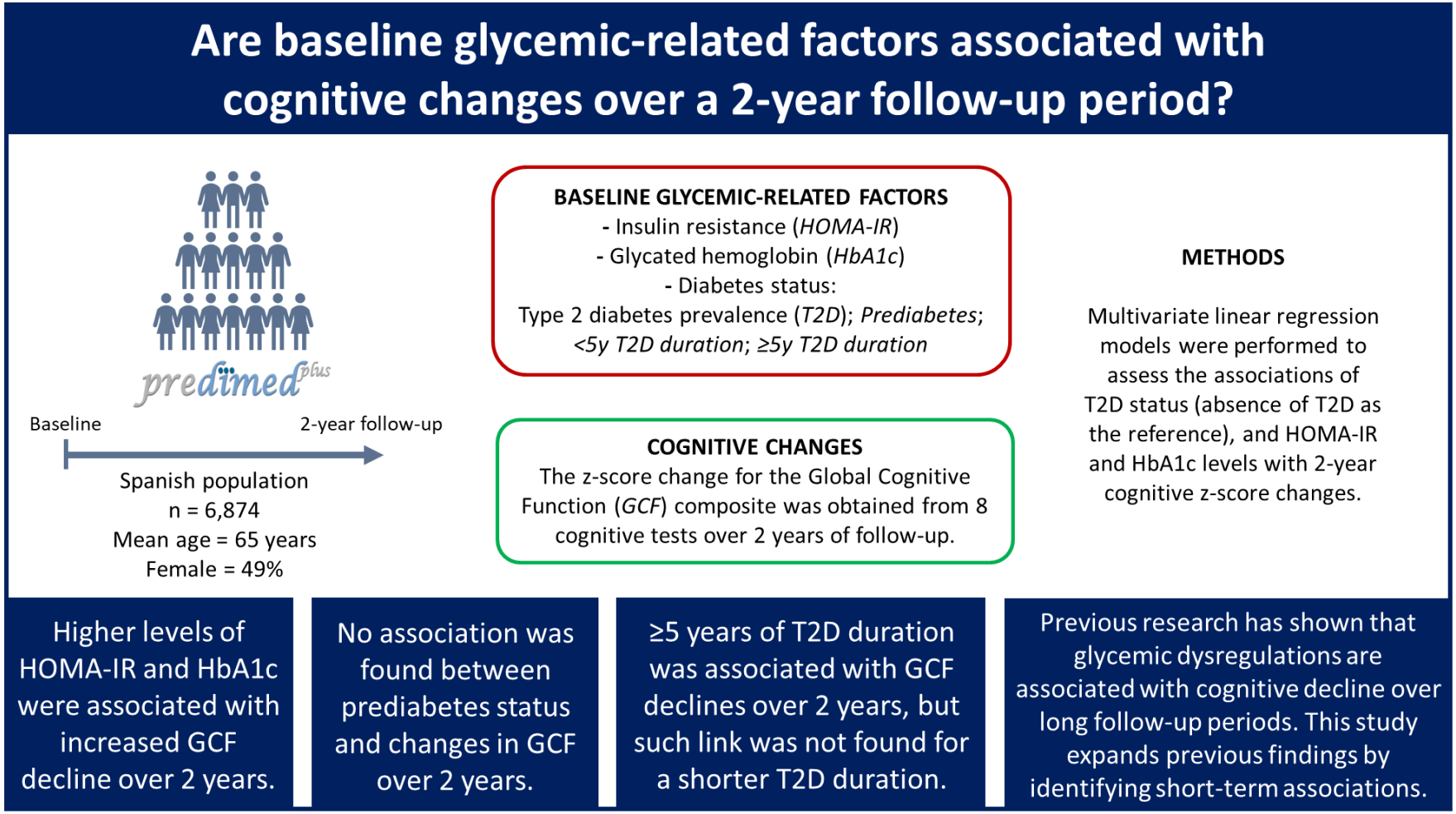
Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Gómez-Martínez, C., Babio, N., Camacho-Barcia, L., Júlvez, J., Nishi, S. K., Vázquez, Z., Forcano, L., Álvarez-Sala, A., Cuenca-Royo, A., de la Torre, R., Fanlo-Maresma, M., Tello, S., Corella, D., Vásquez, A. A., Dalsgaard, S., Franke, B., Fernández-Aranda, F., & Salas-Salvadó, J. (2024). Glycated hemoglobin, type 2 diabetes, and poor diabetes control are positively associated with impulsivity changes in aged individuals with overweight or obesity and metabolic syndrome. *Ann NY Acad Sci.*, 1–14. https://doi.org/10.1111/nyas.15205

UNIVERSITAT ROVIRA I VIRGILI
Psychology and Disease: Unveiling Emerging Perspectives on Their Interplay
Carlos Gómez Martínez

CHAPTER 5: GLYCEMIC STATUS AND COGNITIVE FUNCTION

Figure 10. Graphical abstract of Chapter 5. Glycemic status and cognitive function.



frontiers in Endocrinology

ORIGINAL RESEARCH
published: 29 October 2021
doi: 10.3389/fendo.2021.754347

Glycemic Dysregulations Are Associated With Worsening Cognitive Function in Older Participants at High Risk of Cardiovascular Disease: Two-Year Follow-up in the PREDIMED-Plus Study

Carlos Gómez-Martínez[1,2,3], Nancy Babio[1,2,3,4], Jordi Júlvez[2], Nerea Becerra-Tomás[1,2,3], Miguel Á. Martínez-González[3,5,6], Dolores Corella[3,7], Olga Castañer[3,8], Dora Romaguera[3,9], Jesús Vioque[10,11,12], Ángel M. Alonso-Gómez[3,13], Julia Wärnberg[3,14], José A. Martínez[3,15,16], Luís Serra-Majem[3,17], Ramón Estruch[3,18], Francisco J. Tinahones[3,19], José Lapetra[3,20], Xavier Pintó[3,21,22], Josep A. Tur[3,23], José López-Miranda[3,24], Aurora Bueno-Cavanillas[10,25,26], José J. Gaforio[10,27], Pilar Matía-Martín[28], Lidia Daimiel[29], Vicente Martín-Sánchez[3,30], Josep Vidal[31,32], Clotilde Vázquez[3,33], Emilio Ros[3,34], Søren Dalsgaard[35,36], Carmen Sayón-Orea[5], José V. Sorlí[3,7], Rafael de la Torre[3,37,38], Itziar Abete[3,15], Lucas Tojal-Sierra[3,13], Francisco J. Barón-López[3,14], Noelia Fernández-Brufal[39], Jadwiga Konieczna[3,9], Antonio García-Ríos[3,24], Emilio Sacanella[3,18], M. Rosa Bernal-López[3,40], José M. Santos-Lozano[3,20], Cristina Razquin[3,5], Andrea Alvarez-Sala[3,7], Albert Goday[3,8], M. Angeles Zulet[3,15], Jessica Vaquero-Luna[3,13], Javier Diez-Espino[3,5,41], Aida Cuenca-Royo[3,8], Fernando Fernández-Aranda[3,42,43], Mònica Bulló[1,2,3‡] and Jordi Salas-Salvadó[1,2,3,4*‡] on behalf of the PREDIMED-Plus Investigators[†]*

[1] Universitat Rovira i Virgili, Departament de Bioquímica i Biotecnologia, Unitat de Nutrició Humana, Reus, Spain, [2] Institut d'Investigació Sanitària Pere Virgili (IISPV), Hospital Universitari San Joan de Reus, Reus, Spain, [3] Consorcio CIBER, M.P. Fisiopatología de la Obesidad y Nutrición (CIBERObn), Instituto de Salud Carlos III (ISCIII), Madrid, Spain, [4] Nutrition Unit, University Hospital of Sant Joan de Reus, Reus, Spain, [5] Department of Preventive Medicine and Public Health, Instituto de Investigación Sanitaria de Navarra (IdISNA), University of Navarra, Pamplona, Spain, [6] Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, United States, [7] Department of Preventive Medicine, University of Valencia, Valencia, Spain, [8] Cardiovascular Risk and Nutrition Research Group (CARIN), Hospital del Mar Research Institute (IMIM), Barcelona, Spain, [9] Health Research Institute of the Balearic Islands (IdISBa), University Hospital Son Espases, Palma, Spain, [10] CIBER de Epidemiología y Salud Pública (CIBERESP), ISCIII, Madrid, Spain, [11] Nutritional Epidemiology Unit, Miguel Hernandez University, Alicante, Spain, [12] Instituto de Investigación Sanitaria y Biomédica de Alicante-Universidad Miguel Hernández (ISABIAL-UMH), Alicante, Spain, [13] Bioaraba Health Research Institute, Osakidetza Basque Health Service, Araba University Hospital, University of the Basque Country Universidad del País Vasco / Euskal Herriko Unibertsitatea (UPV/EHU), Vitoria-Gasteiz, Spain, [14] EpiPHAAN Research Group, School of Health Sciences, Instituto de Investigación Biomédica de Málaga (IBIMA), University of Malaga, Malaga, Spain, [15] Department of Nutrition, Food Science and Physiology, Instituto de Investigación Sanitaria de Navarra (IdISNA), University of Navarra, Pamplona, Spain, [16] Cardiometabolic Nutrition Group, Precision Nutrition and Cardiometabolic Health Program, IMDEA Food, Campus de Excelencia Internacional Universidad Autónoma de Madrid + Consejo Superior de Investigaciones Científicas (CEI UAM + CSIC), Madrid, Spain, [17] Research Institute of Biomedical and Health Sciences (IUIBS), Preventive Medicine Service, Centro Hospitalario Universitario Insular Materno Infantil (CHUIMI), Canarian Health Service, University of Las Palmas de Gran Canaria, Las Palmas, Spain, [18] Department of Internal Medicine, Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS), Hospital Clinic, University of Barcelona, Barcelona, Spain, [19] Department of Endocrinology, Instituto de Investigación Biomédica de Málaga (IBIMA), Virgen de la Victoria Hospital, University of Malaga, Malaga, Spain, [20] Research Unit, Department of Family Medicine,

Edited by:
Gaetano Santulli, Columbia University, United States

Reviewed by:
David H. Wagner, University of Colorado Denver, United States
Shamasunder Acharya, Hunter New England Health, Australia

***Correspondence:**
Jordi Salas-Salvadó
jordi.salas@urv.cat
Nancy Babio
nancy.babio@urv.cat

[†]*A list of PREDIMED-Plus investigators is included as appendix*

[‡]*These authors share senior authorship*

Specialty section:
This article was submitted to Clinical Diabetes, a section of the journal Frontiers in Endocrinology

Received: *06 August 2021*
Accepted: *22 September 2021*
Published: *29 October 2021*

Distrito Sanitario Atención Primaria Sevilla, Sevilla, Spain, [21] Lipids and Vascular Risk Unit, Internal Medicine, Hospital Universitario de Bellvitge-IBIDELL, Hospitalet de Llobregat, Barcelona, Spain, [22] Universitat de Barcelona, Barcelona, Spain, [23] Research Group on Community Nutrition & Oxidative Stress, University of Balearic Islands-Instituto Universitario de Investigación en Ciencias de la Salud (IUNICS) & Health Research Institute of the Balearic Islands (IdISBa), Palma de Mallorca, Spain, [24] Department of Internal Medicine, Maimonides Biomedical Research Institute of Cordoba (IMIBIC), Reina Sofia University Hospital, University of Cordoba, Cordoba, Spain, [25] Department of Preventive Medicine, University of Granada, Granada, Spain, [26] Instituto de Investigación Biosanitaria ibs.GRANADA, Granada, Spain, [27] Departamento de Ciencias de la Salud, Instituto Universitario de Investigación en Olivar y Aceites de Oliva, Universidad de Jaén, Jaén, Spain, [28] Department of Endocrinology and Nutrition, Instituto de Investigación Sanitaria Hospital Clínico San Carlos (IdISSC), Madrid, Spain, [29] Nutritional Control of the Epigenome Group, Precision Nutrition and Obesity Program, IMDEA Food, CEI UAM + CSIC, Madrid, Spain, [30] Institute of Biomedicine (IBIOMED), University of León, León, Spain, [31] CIBER Diabetes y Enfermedades Metabólicas (CIBERDEM), ISCIII, Madrid, Spain, [32] Departament of Endocrinology, Instituto de Investigaciones Biomédicas August Pi i Sunyer (IDIBAPS), Hospital Clínic, University of Barcelona, Barcelona, Spain, [33] Department of Endocrinology, Fundación Jiménez-Díaz, Madrid, Spain, [34] Lipid Clinic, Department of Endocrinology and Nutrition, IDIBAPS, Hospital Clínic, Barcelona, Spain, [35] Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH, Aarhus, Denmark, [36] National Centre for Register-Based Research, Aarhus University, Aarhus, Denmark, [37] Integrated Pharmacology and Systems Neurosciences Research Group, Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain, [38] Departamento de Ciencias Experimentales y de la Salud (CEXS), Universitat Pompeu Fabra, Barcelona, Spain, [39] Centro de Salud San Fermín, Elche, Spain, [40] Department of Internal Medicine, Regional University Hospital of Malaga, Instituto de Investigación Biomédica de Málaga (IBIMA), University of Malaga, Malaga, Spain, [41] Gerencia de Atención Primaria Servicio Navarro de Salud-Osasunbidea, Navarra, Spain, [42] Department of Psychiatry, University Hospital of Bellvitge-Instituto de Investigación Biomédica de Bellvitge (IDIBELL), Barcelona, Spain, [43] Department of Clinical Sciences, School of Medicine and Health Sciences, University of Barcelona, Barcelona, Spain

Introduction: Type 2 diabetes has been linked to greater cognitive decline, but other glycemic parameters such as prediabetes, diabetes control and treatment, and HOMA-IR and HbA_{1c} diabetes-related biomarkers have shown inconsistent results. Furthermore, there is limited research assessing these relationships in short-term studies. Thus, we aimed to examine 2-year associations between baseline diabetes/glycemic status and changes in cognitive function in older participants at high risk of cardiovascular disease.

Methods: We conducted a 2-year prospective cohort study (n=6,874) within the framework of the PREDIMED-Plus study. The participants (with overweight/obesity and metabolic syndrome; mean age 64.9 years; 48.5% women) completed a battery of 8 cognitive tests, and a global cognitive function Z-score (GCF) was estimated. At baseline, participants were categorized by diabetes status (no-diabetes, prediabetes, and <5 or ≥5-year diabetes duration), and also by diabetes control. Furthermore, insulin resistance (HOMA-IR) and glycated hemoglobin (HbA_{1c}) levels were measured, and antidiabetic medications were recorded. Linear and logistic regression models, adjusted by potential confounders, were fitted to assess associations between glycemic status and changes in cognitive function.

Results: Prediabetes status was unrelated to cognitive decline. However, compared to participants without diabetes, those with ≥5-year diabetes duration had greater reductions in GCF (β=-0.11 (95%CI -0.16;-0.06)], as well as in processing speed and executive function measurements. Inverse associations were observed between baseline HOMA-IR and changes in GCF [β=-0.0094 (95%CI -0.0164;-0.0023)], but also between HbA_{1c} levels and changes in GCF [β=-0.0085 (95%CI -0.0115, -0.0055)], the Mini-Mental State Examination, and other executive function tests. Poor diabetes control was inversely associated with phonologic fluency. The use of insulin treatment was inversely related to cognitive function as measured by the GCF [β=-0.31 (95%CI -0.44, -0.18)], and other cognitive tests.

Conclusions: Insulin resistance, diabetes status, longer diabetes duration, poor glycemic control, and insulin treatment were associated with worsening cognitive function changes in the short term in a population at high cardiovascular risk.

Clinical Trial Registration: http://www.isrctn.com/ISRCTN89898870, identifier ISRCTN: 89898870.

Keywords: cognitive function, diabetes duration, glycated (glycosylated) hemoglobin, insulin resistance, type 2 diabetes, prediabetes

INTRODUCTION

Type 2 diabetes is an important public health problem worldwide. In 2019, the International Diabetes Federation estimated that ∼463 million people were living with diabetes (and 374 million had prediabetes), of whom one-third were >65 years old, and this figure is expected to rise to 700 million by 2045 (1). Diabetes mellitus is not only among the top 10 causes of death worldwide (2), but is also a risk factor for blindness, renal failure, and lower limb amputation, overall decreasing quality of life (2). As well, over 50 million people worldwide live with dementia, a form of cognitive impairment, and this number is expected to triple by 2050 (3). Cognitive impairment, characterized by loss of memory, concentration and reduced ability to learn new things, affecting everyday life, is relatively common and is a costly condition for the health system (3).

Meta-analyses and longitudinal studies of population-based cohorts have shown an increased risk of cognitive dysfunction in people with metabolic syndrome, prediabetes and diabetes (4–6). Specifically, type 2 diabetes has been related to deficits in different cognitive domains (7) and to accelerated cognitive decline, especially in psychomotor speed, memory and executive functions (8). However, some prospective studies have failed to confirm these associations (9, 10). Also, the relationship between cognitive decline and metabolic syndrome, prediabetes, insulin resistance and glycemic control is less well understood (4, 6, 11). Therefore, more studies are warranted to determine if glycemic dysregulations before diabetes onset may affect cognition in order to establish early strategies of prevention-focused on these populations.

Risk factors for cognitive decline when type 2 diabetes has been already established are also of great interest because consideration of these could help screen individuals with diabetes who may particularly benefit from intensive and suitable treatment strategies. The risk of accelerated cognitive decline in type 2 diabetes has been reported by some studies to be dependent on both disease duration and glycemic control (5, 12). Glucose-lowering treatments have also been related to cognitive function in a few epidemiologic studies with moderate-quality evidence (6, 13). Therefore, more studies are required to increase the strength of the evidence for these associations.

Furthermore, there is a gap in the research relating to shorter follow-up studies assessing the aforementioned relationships. Majority of the research to date has been conducted with medium to long-term duration (from 4 to more years of follow-up) (5, 9). The PREDIMED-Plus study offers an unprecedented opportunity to evaluate cognitive changes, using a battery of cognitive tests, and several measurements of glycemic status in a large population at high cardiovascular disease risk in the shorter term (2 years).

The objectives of the present study were to examine longitudinal associations between glycemic status (diabetes status, control/treatment, and related biomarkers) and cognitive decline and impairment. We hypothesized that glycemic dysregulations would be negatively associated with changes in cognitive function.

Abbreviations: BMI, Body Mass Index; CDT, Clock Drawing Test; DST-b, Digit Span Test backward section; DST-f, Digit Span Test forward section; GCF, Global Cognitive Function; HbA_{1c}, glycated hemoglobin; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; IDDP-4, dipeptidyl peptidase-4 inhibitors; MMSE, Mini-Mental State Examination; TMT-A, Trail Making Test A section; TMT-B, Trail Making Test B section; VFT-a, verbal Fluency Test animals category; VFT-p, Verbal Fluency Test letter p category.

MATERIALS AND METHODS

The present study is based on an observational prospective cohort design conducted within the framework of the PREDIMED-Plus study using 2 years of follow-up data. The PREDIMED-Plus study is a multicenter, randomized, parallel-group clinical trial conducted in Spain for primary cardiovascular disease prevention. Participants were randomized to an intensive weight loss intervention program based on an energy-restricted traditional Mediterranean diet, physical activity promotion and behavioral support (intervention group) or usual care consisting of general recommendations to follow an energy-unrestricted Mediterranean diet (control group). The study protocol has been described extensively elsewhere (14) and can be found at http://www.predimedplus.com. The trial was registered in 2014 at the International Standard Randomized Controlled Trial (http://www.isrctn.com/ISRCTN89898870).

Study Population

Eligible participants were community-dwelling adults (55–75 years) with overweight/obesity (27≤ BMI <40 kg/m^2) who met at least three criteria of metabolic syndrome (15). Exclusion criteria are reported elsewhere (14).

Participant recruitment was conducted between October 2013 and December 2016 in 23 Spanish health centers. A total of 6,874 candidates met eligibility criteria and were randomly allocated in a 1:1 ratio to the intervention or control groups, using a centrally controlled, computer-generated random-number internet-based system with stratification by center, sex, and age. Couples sharing the same household were randomized together, using the couple as unit of randomization. The flow-chart of the studied PREDIMED-Plus population is shown in **Supplementary Figure 1**.

All participants provided written informed consent, and the study protocol and procedures were approved by all the ethical committees of all participating institutions.

Diabetes Status and Glycemic Measurements

At baseline fasting blood samples were collected and biochemical analyses were performed to determine fasting plasma glucose and glycated hemoglobin (HbA_{1c}) by routine laboratory methods. Insulin was centrally measured by an electrochemiluminescence immunoassay using an Elecsys immunoanalyzer (Roche Diagnostics, Meylan, France). Insulin resistance was estimated at baseline using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) index (16).

Prediabetes and diabetes were defined following the American Diabetes Association criteria (17). Diabetes was defined as a previous diagnosis of diabetes, HbA_{1c} ≥48 mmol/mol (6.5%), use of antidiabetic medication, or having fasting plasma glucose >126 mg/dl in both the screening and baseline visits. Self-reported diabetes duration was categorized in <5-year and ≥5-year diabetes duration. Prediabetes status was defined as HbA_{1c} being between 39 mmol/mol (5.7%) and 46 mmol/mol (6.4%), or having fasting plasma glucose between ≥100 mg/dl and ≤125 mg/dl. Participants who did not meet any of these parameters were categorized into the no-diabetes category. Furthermore, we categorized diabetes status in participants with diabetes (participants with <5-year and ≥5-year diabetes duration) and no-diabetes (participants with prediabetes and no-diabetes).

Glycated hemoglobin was used to categorize participants into those having "good" or "poor" diabetic control [HbA_{1c} <57 mmol/mol or ≥57 mmol/mol (7.4%)], respectively (17). Diabetes treatment was assessed at baseline using self-reported data on insulin, sulfonylureas, metformin or dipeptidyl peptidase-4 inhibitors (IDPP-4) use.

Covariates

Covariates were evaluated at baseline by trained staff in a face-to-face interview using self-reported general questionnaires on socio-demographics (sex, age, level of education, and civil status), lifestyle (alcohol intake, smoking habits, physical activity, and Mediterranean diet adherence), and disease history. Baseline anthropometric variables (weight and height) were determined to estimate body mass index (BMI). Adherence to an energy-reduced Mediterranean diet was assessed using a 17-point diet score, adapted from a previously validated one (18). Leisure-time physical activity was estimated using a validated short version of the Minnesota Leisure-Time Physical Activity Questionnaire (19, 20). The depressive status risk was evaluated using the Beck Depression Inventory-II (21).

Neuropsychological Assessment

A battery of 8 cognitive tests was administered at baseline and 2 years of follow-up by trained staff. The tests performed, Mini-Mental State Examination (MMSE), Clock Drawing Test (CDT), Digit Span Test forward (DST-f) and backward (DST-b) section, Verbal Fluency Test animals (VFT-a) and "p" (VFT-p) version, and Trail Making Test part A (TMT-A) and B (TMT-B) are described in **Supplementary Material 1**.

Statistical Analyses

We used the December 2020 PREDIMED-Plus database. Descriptive variables are reported as means and standard deviation (SD) for continuous variables or numbers and percentages (%) for qualitative variables. Differences between diabetes status and baseline characteristics were examined using chi-square and one-way ANOVA, for qualitative and quantitative variables, respectively.

For longitudinal analysis, linear and logistic regression models were used, including only participants with complete cognitive data at baseline and 2 years of follow-up for each cognitive test analyzed. To facilitate comparisons across cognitive tests, Z-scores were generated for each cognitive score at baseline and after 2 years using the mean and SD of baseline data, as previously reported (5, 12). A global cognitive function Z-score (GCF) was obtained averaging all cognitive Z-scores at each time point, standardizing by the mean and SD of cognitive Z-scores at baseline.

Using linear regression analyses we examined the associations between baseline status and 2-year changes in cognitive Z-scores in relation to: a) HOMA-IR levels; b) diabetes status, no diabetes being the reference group; c) HbA_{1c} levels; d) glycemic control measured by HbA_{1c} in participants with diabetes, good glycemic control being the reference group; e) diabetes treatment in participants with diabetes, no treatment being the reference group. Two models were fitted to adjust linear and logistic regression analyses. Model 1 was adjusted for baseline sex, age (years), intervention group, and center size (with <250; 250-300, 300-400; >400 randomized participants). Model 2 was additionally adjusted for baseline education level (primary school; high school; college), civil status (single, divorced or separated; married; widower), physical activity (MET min/week), smoking habits (smoker; former smoker; never smoker), alcohol intake (g/day), 17-point Mediterranean diet score, BMI (kg/m^2), hypertension (yes/no), hypercholesterolemia (yes/no), and depression (yes/no). Furthermore, Model 3 was fitted exclusively for antidiabetic treatments to further adjust for baseline diabetes control (good/poor) and diabetes duration (<5-year diabetes duration/≥5-year diabetes duration).

Logistic regression analyses were used to estimate odds ratios (OR) and 95% confidence intervals (95% CI), examining the 2-year risk for cognitive impairment in participants with normal cognitive performance at baseline by diabetes status, with no diabetes being the reference group. Cognitive function cut-offs were defined by the dichotomization of neuropsychological assessments at the respective visits. Cognitive impairment was defined as GCF ≤10^{th} percentile, MMSE ≤24 punctuation, CDT ≤4 punctuation, and VFT-a, VFT-p, DST-d, DST-b ≤ respective mean - 1.5*SD and TMT-A, TMT-B ≥ respective mean + 1.5*SD (22–25).

Interaction analyses between glycemic status (diabetes status, HOMA-IR, HbA_{1c}, and glycemic control and treatment) and sex, age, hypertension and BMI for the GCF were performed by comparing the model with and without the interaction product using the likelihood ratio test.

Participants with missing data on covariables (always <1% missing) were imputed as either the mean of the group or into the subcategory with the highest frequency (26).

All analyses were conducted with robust estimates of the variance to correct for intracluster correlation. The data were analyzed using the Stata-14 software program (StataCorp). Statistical significance was set using the Benjamini-Hochberg false discovery rate correction procedure (27) at a Q-value <0.05.

RESULTS

Descriptive Results

Table 1 shows the baseline characteristics of the study population (n=6,874) according to diabetes status. A total of 20.9% of participants were classified as having no-diabetes, 48.6% prediabetes, 14.8% with <5-year diabetes duration, and 15.6% with ≥5-year diabetes duration. The mean age of the total population was 64.9 ± 4.9 years and 48.5% were women. Participants with ≥5-year diabetes duration were older, had lower education level and alcohol consumption, greater adherence to the Mediterranean diet and higher HbA_{1c} levels. They were also more likely to have hypertension, hypercholesterolemia and depressive symptoms. Participants with <5-year diabetes duration had greater prevalence of obesity and higher HOMA-IR levels, and were less likely to be a woman. Participants without diabetes were more likely to have a higher education level. All cognitive assessments showed significant differences across diabetes status and participants with ≥5-year diabetes duration with lower scores.

TABLE 1 | Baseline characteristics by diabetes status.

Characteristics	Diabetes status				P-value
	No-Diabetes (n=1440)	Prediabetes (n=3341)	<5y Diabetes (n=1020)	≥5y Diabetes (n=1073)	
Age (years)	64.5 ± 4.92	65.0 ± 4.91	64.7 ± 4.98	65.5 ± 4.81	<0.001
Sex (women)	706 (49.03)	1703 (50.97)	435 (42.65)	491 (45.76)	<0.001
Intervention group	730 (50.69)	1632 (48.85)	503 (49.31)	541 (50.42)	0.623
Education level					<0.001
Primary school or less	653 (45.35)	1627 (48.70)	489 (47.94)	593 (55.27)	
High school	417 (28.96)	976 (29.21)	302 (29.61)	291 (27.12)	
College	370 (25.69)	738 (22.09)	229 (22.45)	189 (17.61)	
Civil status					0.803
Single, divorced or separated	199 (13.82)	440 (13.17)	123 (12.06)	135 (12.58)	
Married	1097 (76.18)	2546 (76.20)	797 (78.14)	821 (76.51)	
Widower	144 (10.00)	355 (10.63)	100 (9.80)	117 (10.90)	
Physical activity (MET min/week)	2508 ± 2433	2493 ± 2264	2344 ± 2140	2420 ± 2378	0.236
Current smoker					0.195
Smoker	170 (11.81)	418 (12.51)	138 (13.53)	131 (12.21)	
Former smoker	602 (41.81)	1434 (42.92)	463 (45.39)	484 (45.11)	
Never smoker	668 (46.39)	1434 (44.57)	419 (41.08)	458 (42.68)	
Alcohol consumption (g/day)	11.0 ± 14.2	11.6 ± 15.9	11.7 ± 15.6	9.8 ± 14.6	0.004
17-point Mediterranean diet score	8.51 ± 2.71	8.37 ± 2.70	8.64 ± 2.60	8.72 ± 2.55	0.001
BMI (kg/m²)	32.2 ± 3.46	32.6 ± 3.41	32.9 ± 3.49	32.6 ± 3.52	<0.001
HOMA-IR	3.91 ± 2.61	5.08 ± 3.14	6.65 ± 4.19	6.30 ± 4.45	<0.001
HbA_{1c} (mmol/mol)	36.4 ± 4.7	40.5 ± 3.5	49.3 ± 10.2	54.7 ± 13.1	<0.001
HbA_{1c} (%)	5.48 ± 0.43	5.86 ± 0.32	6.66 ± 0.93	7.16 ± 1.20	<0.001
Hypertension	1192 (82.78)	2764 (82.73)	855 (83.82)	947 (88.26)	<0.001
Hypercholesterolemia	966 (67.08)	2281 (68.27)	755 (74.02)	811 (75.58)	<0.001
Depressive symptomatology	281 (19.51)	667 (19.96)	226 (22.16)	253 (23.58)	0.029
Cognitive assessments	**Diabetes status**				
	No-Diabetes	**Prediabetes**	**<5y Diabetes**	**≥5y Diabetes**	
MMSE (n=6654)	28.3 ± 1.85	28.3 ± 1.86	28.2 ± 1.95	28 ± 2.10	<0.001
CDT (n=6659)	5.95 ± 1.29	5.96 ± 1.21	6.02 ± 1.12	5.76 ± 1.34	<0.001
DST-f (n=5867)	8.95 ± 2.59	8.78 ± 2.39	8.87 ± 2.48	8.52 ± 2.48	<0.001
DST-b (n= 5864)	5.28 ± 2.36	5.11 ± 2.20	5.19 ± 2.19	4.93 ± 2.15	0.043
VFT-a (n=6816)	16.4 ± 5.00	16.1 ± 4.75	16.1 ± 4.84	15.2 ± 4.65	<0.001
VFT-p (n=6816)	12.6 ± 4.62	12.4 ± 4.53	12 ± 4.35	11.4 ± 4.39	<0.001
TMT-A (n=6802)§	50.9 ± 28.0	52.3 ± 27.5	52.7 ± 30.2	56.2 ± 30.2	<0.001
TMT-B (n=6783)§	121.6 ± 68.6	128.0 ± 70.2	130.1 ± 72.3	144.2 ± 79.6	<0.001

<5y diabetes, less than 5 years diabetes duration; ≥5y diabetes, more than 5 years diabetes duration; GCF, Global Cognitive Function; MMSE, Mini-Mental State Examination; CDT, Clock Drawing Test; DST-f, Digit Span Test forward section; DST-b, Digit Span Test backward section; VFT-a, Verbal Fluency Test animal category; VFT-p, Verbal Fluency Test letter "p"; TMT-A, Trail Making Test part A; TMT-B, Trail Making Test part B.

§ Inverse neuropsychological assessment score.

Data are n (%) or mean ± SD for categorical and quantitative variables, respectively.

Only the participants reported in each neuropsychological assessment are available.

Chi-square is used for categorical variables and One-way ANOVA for quantitative variables.

Diabetes Status and Related Biomarkers

Table 2 shows the associations between baseline diabetes status and 2-year changes in cognitive Z-scores. Compared to participants without diabetes, no significant differences in the associations between prediabetes and cognitive tests were observed. Compared to participants without diabetes, those with <5-year diabetes duration displayed larger decrements in cognitive Z-scores measured by the GCF, VFT-a, VFT-p and TMT-B tests in model 1, but these associations were attenuated in model 2. Compared to participants without diabetes, those with ≥5-year diabetes duration displayed larger reductions in all cognitive assessments in model 1, except in the case of the CDT test (**Table 2**). These associations remained significant for the GCF score, and the VFT-a, VFT-p, TMT-A and TMT-B tests in model 2. Similar results were found when comparing participants with diabetes and no-diabetes, finding a larger 2-year decrease with the presence of type 2 diabetes in the MMSE score (**Supplementary Table 1**).

Supplementary Table 2 shows the odds ratio (95% CI) for cognitive impairment incidence after 2 years of follow-up in participants with normal cognitive performance at baseline. Compared with participants without diabetes, those with diabetes had a borderline significant 34% (95% CI 0.96;1.87) higher risk of cognitive impairment when assessed by the GCF

TABLE 2 | Association between baseline diabetes status and changes in cognitive Z-scores.

Z-scores	Diabetes status	Model 1		Model 2	
		β (95% CI)	P-value	β (95% CI)	P-value
GCF	No-Diabetes (n=1023)	Ref.		Ref.	
	Prediabetes (n=2429)	-0.04 (-0.10, 0.03)	0.277	-0.01 (-0.04, 0.03)	0.756
	<5y Diabetes (n=667)	-0.12 (-0.20, -0.03)	0.008*	-0.04 (-0.09, 0.01)	0.109
	≥5y Diabetes (n=684)	-0.27 (-0.36, -0.18)	<0.001*	-0.11 (-0.16, -0.06)	<0.001*
MMSE	No-Diabetes (n=1187)	Ref.		Ref.	
	Prediabetes (n=2786)	-0.01 (-0.07, 0.05)	0.749	0.01 (-0.05, 0.06)	0.865
	<5y Diabetes (n=847)	-0.08 (-0.16, 0.01)	0.054	-0.05 (-0.13, 0.03)	0.209
	≥5y Diabetes (n=865)	-0.11 (-0.19, -0.02)	0.011*	-0.06 (-0.14, 0.02)	0.134
CDT	No-Diabetes (n=1189)	Ref.		Ref.	
	Prediabetes (n=2788)	0.01 (-0.06, 0.07)	0.874	0.01 (-0.05, 0.07)	0.780
	<5y Diabetes (n=846)	-0.01 (-0.09, 0.08)	0.843	0.01 (-0.08, 0.09)	0.847
	≥5y Diabetes (n=866)	-0.09 (-0.18, -0.01)	0.031	-0.06 (-0.14, 0.03)	0.171
DST-f	No-Diabetes (n=1072)	Ref.		Ref.	
	Prediabetes (n=2526)	-0.03 (-0.10, 0.05)	0.474	-0.01 (-0.08, 0.06)	0.725
	<5y Diabetes (n=702)	-0.08 (-0.17, 0.01)	0.087	-0.06 (-0.15, 0.03)	0.198
	≥5y Diabetes (n=716)	-0.12 (-0.21, -0.03)	0.012*	-0.07 (-0.16, 0.02)	0.126
DST-b	No-Diabetes (n=1072)	Ref.		Ref.	
	Prediabetes (n=2525)	-0.04 (-0.11, 0.03)	0.293	-0.02 (-0.09, 0.04)	0.528
	<5y Diabetes (n=702)	-0.07 (-0.16, 0.02)	0.116	-0.04 (-0.13, 0.04)	0.349
	≥5y Diabetes (n=716)	-0.11 (-0.20, -0.02)	0.014*	-0.05 (-0.14, 0.04)	0.251
VFT-a	No-Diabetes (n=1226)	Ref.		Ref.	
	Prediabetes (n=2866)	-0.07 (-0.13, -0.01)	0.033	-0.05 (-0.11, 0.01)	0.101
	<5y Diabetes (n=870)	-0.14 (-0.22, -0.05)	0.001*	-0.10 (-0.17, -0.02)	0.018
	≥5y Diabetes (n=889)	-0.25 (-0.33, -0.16)	<0.001*	-0.18 (-0.26, -0.10)	<0.001*
VFT-p	No-Diabetes (n=1227)	Ref.		Ref.	
	Prediabetes (n=2865)	-0.05 (-0.12, 0.02)	0.149	-0.03 (-0.09, 0.03)	0.348
	<5y Diabetes (n=870)	-0.13 (-0.21, -0.04)	0.005*	-0.08 (-0.16, 0.01)	0.060
	≥5y Diabetes (n=889)	-0.23 (-0.32, -0.14)	<0.001*	-0.15 (-0.23, -0.07)	<0.001*
TMT-A§	No-Diabetes (n=1226)	Ref.		Ref.	
	Prediabetes (n=2862)	-0.02 (-0.08, 0.04)	0.512	-0.03 (-0.09, 0.03)	0.323
	<5y Diabetes (n=869)	0.08 (0.01, 0.16)	0.037	0.05 (-0.02, 0.13)	0.185
	≥5y Diabetes (n=886)	0.20 (0.11, 0.29)	<0.001*	0.15 (0.06, 0.23)	0.001*
TMT-B§	No-Diabetes (n=1221)	Ref.		Ref.	
	Prediabetes (n=2859)	0.01 (-0.05, 0.07)	0.690	0.01 (-0.06, 0.06)	0.994
	<5y Diabetes (n=866)	0.11 (0.03, 0.20)	0.006*	0.08 (0.01, 0.16)	0.039
	≥5y Diabetes (n=883)	0.24 (0.15, 0.32)	<0.001*	0.17 (0.09, 0.25)	<0.001*

<5y diabetes, less than 5 years diabetes duration; ≥5y diabetes, more than 5 years diabetes duration; GCF, Global Cognitive Function; MMSE, Mini-Mental State Examination; CDT, Clock Drawing Test; DST-f, Digit Span Test forward section; DST-b, Digit Span Test backward section; VFT-a, Verbal Fluency Test animal category; VFT-p, Verbal Fluency Test letter "p"; TMT-A, Trail Making Test part A; TMT-B, Trail Making Test part B.

§ Inverse neuropsychological assessment score.

Model 1: adjusted for sex, age (in years), intervention group, and center size (<250; 250-300, 300-400; ≥400).

Model 2: further adjusted for baseline education level (primary school; secondary school; college), civil status (single, divorced or separated; married; widower), physical activity (MET min/week), smoking habits (smoker; former smoker; never smoker), alcohol intake (g/day, adding the quadratic term), 17-point Mediterranean diet score, BMI (kg/m²), hypertension (yes/no), hypercholesterolemia (yes/no), and depressive symptomatology (yes/no).

Beta coefficients were estimated using linear regression models with robust standard errors to account for intracluster correlations.

**Significant association after Benjamini-Hochberg correction.*

Z-score, and a non-significant 30% (95%CI 1.01;1.68) higher risk of impairment based on the VFT-a test after the false discovery rate correction. No significant associations were found between diabetes status and cognitive impairment incidence in the rest of the cognitive tests.

Table 3 shows the association between baseline HOMA-IR (per one unit increment) and changes in cognitive Z-scores after 2 years of follow-up after excluding those participants with insulin treatment. Significant inverse associations between HOMA-IR and changes in cognitive Z-scores measured by GCF and the DST-f and DST-b tests were found (model 2). No significant associations between insulin resistance and changes in cognitive Z-scores were found for the MMSE, CDT, VFT-a, VFT-p, TMT-A and TMT-B tests. Furthermore, a sensitivity analysis was conducted excluding those participants with insulin or sulfonylurea treatment (n=596). Compared with the results of **Table 3**, no changes in the direction of β coefficients or significances after the Benjamini-Hochberg correction were shown.

Table 4 presents the association between baseline HbA_{1c} levels (per one mmol/mol increment) and 2-year changes in cognitive Z-scores. An inverse association was observed between baseline HbA_{1c} levels and the GCF score, as well as the MMSE, VFT-a, VFT-p, TMT-A and TMT-B tests. No significant associations were found for the CDT, DST-f and DST-b tests.

There were no significant interactions by sex, age, hypertension or BMI between the glycemic status (HOMA-IR, HbA_{1c} and glycemic control/treatment) and changes in the GCF score (all p>0.05). However, an interaction by age was found between diabetes status and changes in the GCF score (P=0.046). Compared to participants without diabetes, a larger decline in the GCF score was shown in those participants aged ≤65 years and presenting with prediabetes and <5-year and ≥5-year of diabetes duration, whereas participants aged >65 years with prediabetes showed increased performance in the GCF score. No associations were found between diabetes duration and the GCF score in participants aged >65 years.

Diabetes Control and Treatment

Supplementary Table 3 shows the association between baseline glycemic control (HbA_{1c} ≥57 mmol/mol or <57 mmol/mol) in participants with diabetes and 2-year changes in cognitive Z-scores. Compared to participants with good diabetes control, those with poor control showed a larger decrement in the VFT-p [β= -0.13 (95%CI -0.22;-0.04)] test (model 2). No associations between glycemic control and the rest of the cognitive tests were observed.

Supplementary Table 4 shows the association between baseline insulin treatment in participants with diabetes and changes in cognitive Z-scores. Compared to participants without insulin treatment, those with insulin treatment showed a significantly greater decrease in cognitive function measured by the GCF score and the DST-f, DST-b, VFT-a, VFT-p, TMT-A and TMT-B tests. No associations were observed for the remaining cognitive tests assessed (MMSE and CDT). Concerning oral glucose medication use, sulfonylurea treatment was not significantly associated with an increase in the TMT-A (β= 0.22 [95%CI 0.07;0.38]) Z-score after the Benjamini-Hockberg correction (**Supplementary Table 5**). No significant associations were shown between the use of metformin or IDDP-4 and changes in cognitive Z-scores (**Supplementary Tables 6**, **7**, respectively). When the associations between diabetes treatment and cognitive function were further adjusted by diabetes duration or glycemic control, the results remained similar (model 3).

No significant interactions by sex, age, hypertension, and BMI were observed between diabetes control or treatment and changes in the GCF score.

TABLE 3 | Association between baseline HOMA-IR levels (per one unit increment) and changes in cognitive Z-scores.

Z-scores	Model 1		Model 2	
	β (95% CI)	P-value	β (95% CI)	P-value
GCF (n=4377)	-0.0140 (-0.0217, -0.0061)	<0.001*	-0.0094 (-0.0164, -0.0023)	0.009*
MMSE (n=5180)	-0.0040 (-0.0120, 0.0039)	0.322	-0.0006 (-0.0087, 0.0075)	0.884
CDT (n=5183)	-0.0006 (-0.0075, 0.0064)	0.868	-0.0006 (-0.0077, 0.0065)	0.862
DST-f (n=4560)	-0.0116 (-0.0195, -0.0037)	0.004*	-0.0091 (-0.0170, -0.0013)	0.023
DST-b (n=4559)	-0.0106 (-0.0184, -0.0028)	0.007*	-0.0082 (-0.0157, -0.0006)	0.035
VFT-a (n=5319)	-0.0072 (-0.0144, 0.0001)	0.051	-0.0050 (-0.0121, 0.0020)	0.163
VFT-p (n=5319)	-0.0065 (-0.0146, 0.0015)	0.111	-0.0042 (-0.0115, 0.0030)	0.249
TMT-A (n=5311)§	0.0070 (-0.0008, 0.0147)	0.077	0.0040 (-0.0037, 0.0117)	0.306
TMT-B (n=5301)§	0.0087 (0.0014, 0.0159)	0.019	0.0060 (-0.0007, 0.0127)	0.079

GCF, Global Cognitive Function; MMSE, Mini-Mental State Examination; CDT, Clock Drawing Test; DST-f, Digit Span Test forward section; DST-b, Digit Span Test backward section; VFT-a, Verbal Fluency Test animal category; VFT-p, Verbal Fluency Test letter "p"; TMT-A, Trail Making Test part A; TMT-B, Trail Making Test part B.

§ Inverse neuropsychological assessment score.

Participants with insulin treatment were excluded (n=320) from the analysis.

Model 1: adjusted for sex, age (in years), intervention group, and center size (<250; 250-300, 300-400; ≥400).

Model 2: further adjusted for baseline education level (primary school; secondary school; college), civil status (single, divorced or separated; married; widower), physical activity (MET min/week), smoking habits (smoker; former smoker; never smoker), alcohol intake (g/day, adding the quadratic term), 17-point Mediterranean diet score, BMI (kg/m²), hypertension (yes/no), hypercholesterolemia (yes/no), and depressive symptomatology (yes/no).

Beta coefficients were estimated using linear regression models with robust standard errors to account for intracluster correlations

**Significant association after Benjamini-Hochberg correction.*

TABLE 4 | Association between baseline HbA_{1c} levels (per one mmol/mol increment) and cognitive Z-scores changes.

Z-scores	Model 1		Model 2	
	β (95% CI)	P-value	β (95% CI)	P-value
GCF (n=4406)	-0.0085 (-0.0115, -0.0055)	<0.001*	-0.0056 (-0.0081, -0.0030)	<0.001*
MMSE (n=5162)	-0.0043 (-0.0071, -0.0015)	0.002*	-0.0029 (-0.0055, -0.0002)	0.035*
CDT (n=5166)	-0.0017 (-0.0043, 0.0009)	0.210	-0.0007 (-0.0032, 0.0019)	0.615
DST-f (n=4601)	-0.0030 (-0.0061, 0.0001)	0.058	-0.0015 (-0.0045, 0.0015)	0.330
DST-b (n=4600)	-0.0042 (-0.0072, -0.0013)	0.005*	-0.0023 (-0.0051, 0.0005)	0.114
VFT-a (n=5316)	-0.0071 (-0.0099, -0.0043)	<0.001*	-0.0051 (-0.0078, -0.0024)	<0.001*
VFT-p (n=5316)	-0.0087 (-0.0118, -0.0056)	<0.001*	-0.0063 (-0.0091, -0.0035)	<0.001*
TMT-A (n=5307)§	0.0074 (0.0045, 0.0103)	<0.001*	0.0053 (0.0025, 0.0081)	<0.001*
TMT-B (n=5296)§	0.0072 (0.0043, 0.0100)	<0.001*	0.0045 (0.0019, 0.0072)	0.001*

GCF, Global Cognitive Function; MMSE, Mini-Mental State Examination; CDT, Clock Drawing Test; DST-f, Digit Span Test forward section; DST-b, Digit Span Test backward section; VFT-a, Verbal Fluency Test animal category; VFT-p, Verbal Fluency Test letter "p"; TMT-A, Trail Making Test part A; TMT-B, Trail Making Test part B.

§ Inverse neuropsychological assessment score.

Missing data on HbA_{1c} (n=633).

Model 1: adjusted for sex, age (in years), intervention group, and center size (<250; 250-300, 300-400; ≥400).

Model 2: further adjusted for baseline education level (primary school; secondary school; college), civil status (single, divorced or separated; married; widower), physical activity (MET min/week), smoking habits (smoker; former smoker; never smoker), alcohol intake (g/day, adding the quadratic term), 17-point Mediterranean diet score, BMI (kg/m²), hypertension (yes/no), hypercholesterolemia (yes/no), and depressive symptomatology (yes/no).

Beta coefficients were estimated using linear regression models with robust standard errors to account for intracluster correlations.

**Significant association after Benjamini-Hochberg correction.*

DISCUSSION

To the best of our knowledge, this is the first prospective study investigating associations between glycemic status (diabetes status/control/treatment, and HOMA-IR and HbA_{1c} biomarkers) and cognitive function in a large cohort of older adults at risk high cardiovascular disease in a short period (2-year). In this community-based population, compared to participants without diabetes, those with diabetes showed a larger decline in several cognitive performance measurements. Additionally, longer duration of diabetes was associated with greater decreases in the scores of tests measuring processing speed and executive functions. Furthermore, poor diabetes control, the use of insulin treatment, and increases in HOMA-IR and HbA_{1c} levels were inversely associated with cognitive functioning.

Our results concur with those of meta-analyses of prospective studies, suggesting larger risk of cognitive decline in type 2 diabetes (6–8). The mechanisms explaining these associations remain largely unknown. Several risk factors for cognitive dysfunction in diabetes have been reported, such as hypertension or depression, but each of them appear to have weak isolated effects (28, 29). In order to control for these potential confounding factors, we have adjusted our statistical models for several recognized confounders.

Our findings are similar to those reported in other studies, suggesting a greater risk of cognitive decline in participants with type 2 diabetes, especially in relation to executive functions (5, 8, 30). Similarly, we found inverse associations in participants with diabetes and all the executive function-related tests, except in the case of the DST-b test, which measures working memory. Concerning memory function, we also assessed immediate verbal memory using the DST-f test, which was borderline inversely associated with the presence of diabetes. These results concur with those reported in a recent meta-analysis in which immediate (measured by the DST-f) and working memory (measured by the DST-b) were not associated in type 2 diabetes, while the other memory and executive function abilities assessed were reduced (8). Regarding visuospatial function, discrepancies in longitudinal studies have been reported in individuals with type 2 diabetes (31, 32). However, a small effect size in this function was reported in a meta-analysis conducted in 2014 (30). In our study, a non-significant inverse association between diabetes and the CDT test was observed, and longer follow-up of our population may be needed to observe a significant decline in this cognitive function.

Our results also showed that, compared to participants without diabetes, those with diabetes had a borderline increased risk of developing cognitive impairment as measured by the GCF score, even when the period of follow-up was only 2 years. Meta-analyses including prospective studies have shown an incidence of cognitive impairment in participants with type 2 diabetes (6, 33). However, the assessment of short-time periods were not commonly reported in regard to the association between type 2 diabetes and cognitive function, and it may be the reason for the discrepancies observed between the aforementioned meta-analyses and our study.

As far as we know, no longitudinal studies have been conducted assessing associations between diabetes status and cognitive decline, while also considering both the prediabetes status and the duration of diabetes. Longitudinal cohort studies have shown contradictory results regarding the association of prediabetes with cognition (5, 12, 31, 34), which can be explained by the different range of ages and sample sizes, the tests and cognitive domains assessed, and the length of follow-up. Concerning diabetes duration, our results are in line with other longitudinal studies in which higher rates of cognitive decline

were described in individuals with longer diabetes duration (5, 12).

The observed interaction of the GCF score with age in prediabetes has not been previously reported in the literature and cannot be explained by a specific mechanism. We cannot rule out that this interaction was a random finding and it is a result that requires further investigation.

Several mechanisms have been suggested to explain the association between diabetes status and control with changes in cognitive functioning. Among them, insulin resistance, hyperglycemic excursions and glycemic control have received much attention. Insulin resistance linked to low-grade inflammation is a factor contributing to the onset of diabetes, that appears to play a key role in the cognitive impairment associated with obesity and diabetes, given the role that insulin has in the brain promoting neuronal survival and synaptic plasticity and inhibiting apoptosis and neuroinflammation (35). In the case of peripheral insulin resistance and type 2 diabetes, a decrease in insulin permeation through the blood-brain barrier was observed, leading to a smaller amount of insulin reaching the brain, thus impairing neuronal activation and inducing changes in synaptic plasticity, neuronal apoptosis and neuroinflammation, all responsible for cognitive deterioration (35).

Longitudinal studies linking insulin resistance, as measured by HOMA-IR, and cognitive decline have shown discrepancies. In an older U.S. population with 8 years of follow-up, baseline HOMA-IR was not associated with changes in global cognitive function (36). However, in surviving patients with coronary heart disease, baseline HOMA-IR was associated with subsequent poorer cognitive performance on the composite cognitive score over 15 years (37). Our results were in line with those of the latter study, as we also observed an inverse association between baseline HOMA-IR and changes in cognitive performance using a global cognitive function score.

Additional mechanisms explaining the deleterious association of diabetes on cognitive functioning include hyperglycemic status and glycemic excursions. Increased HbA_{1c} levels or high levels of repeated glucose measurements over time have been linked to cognitive decline and an increased risk of dementia in people without diabetes (38). In our study, no associations between HbA_{1c} levels and changes in cognitive function were observed in participants without diabetes (data not shown). Nevertheless, when HbA_{1c} was measured as a continuous variable, we found negative associations between high baseline values in HbA_{1c} levels and all the cognitive tests measured, except in the case of the CDT and the DSTs, thus aligning with findings from recent studies (34, 36).

When diabetes is established, increased HbA_{1c} levels have been linked to diabetes-associated cognitive decline and dementia, but the strength of these relationships is weak (11). In our study, compared to participants with good diabetes control, those with poor control showed a larger 2-year decrease in cognitive performance measured by the VFT-p test, but this association was not observed in the case of the GCF score and other cognitive assessments. Unlike other typical diabetic end-organ complications, no clear evidence exists that the increased risk of cognitive impairment can be attributed solely to hyperglycemic excursions and glycemic control (11). For example, the ACCORD MIND trial (39), which compared intensive with standard treatment with the aim to lower HbA_{1c} in people with long-standing type 2 diabetes, found no association between the intervention and cognitive function.

Several other mechanisms have been implicated in diabetes-related cognitive decline and dementia. For example, type 2 diabetes has substantial adverse effects on blood vessels and the heart (40), leading to an increased risk of stroke and small cerebral vessel disease. Indeed, neuropathological studies also report an increased burden of cerebrovascular lesions, especially of lacunar type, in people with diabetes (41).

Observational studies have reported that some glucose-lowering medications may have a potential beneficial or deleterious relationship with cognition (6, 13). In our study, contrary to other results showing improved cognitive function (13), no associations between metformin and cognition were observed, as well this was not observed for IDDP-4 or sulfonylureas use. However, in line with findings of recent meta-analyses, insulin-treated participants showed larger cognitive decline than those not treated with insulin (6, 13). This could be explained by the fact that these individuals tend to have worse glycemic control and larger risk of hypoglycemia, a condition that has been linked to cognitive decline and dementia risk (42, 43).

It is worth mentioning a strength of the present study is the novelty of being one of the largest population-based studies longitudinally and concurrently exploring relationships between glycemic status (diabetes status, markers of glucose metabolism, and diabetes control and treatment) and cognitive function in an older individuals at high cardiovascular risk. Moreover, this study suggests that larger follow-up periods are not required to observe associations between glycemic status and cognitive function. Nevertheless, the present findings should be considered in the context of some limitations. Firstly, although we adjusted the models for many potential confounding factors, there may be residual confounding factors not assessed, such as genetic susceptibility (APOE genotype). Unfortunately, genetic data was not available in all the PREDIMED-Plus population. Secondly, the PREDIMED-Plus study did not contemplate the use of neuroimaging, such as magnetic resonance imaging (MRI). Finally, our study has been conducted in older Mediterranean individuals with overweight/obesity at high risk of cardiovascular disease, and therefore we cannot extrapolate our results to other populations.

In conclusion, several glycemic dysregulations, such as insulin resistance measured by HOMA-IR, diabetes status, longer duration of diabetes, poor glycemic control and higher levels of HbA_{1c}, and insulin treatment were associated with greater cognitive decline in older individuals with overweight/obesity at high cardiovascular disease risk in a short time period. We also reported that participants with type 2 diabetes had a borderline increased risk of developing cognitive impairment as measured by the GCF score, compared to those without diabetes.

Therefore, it is clinically relevant to assess novel effective strategies at the initial stages of diabetes-related alterations in order to reduce the impact of cognitive dysfunction when these glycemic dysregulations are more pronounced.

DATA AVAILABILITY STATEMENT

There are restrictions on the availability of data for the PREDIMED-Plus trial, due to the signed consent agreements around data sharing, which only allow access to external researchers for studies following the project purposes. Requestors wishing to access the PREDIMED-Plus trial data used in this study can make a request to the PREDIMED-Plus trial Steering Committee chair: predimed_plus_scommitte@googlegroups.com. The request will then be passed to members of the PREDIMED-Plus Steering Committee for deliberation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by CEI Provincial de Málaga-Servicio Andaluz de Salud O01_feb_PR2 - Predimedplus nodo 1 CEI de los Hospitales Universitarios Virgen Macarena y Virgen del Rocío-Servicio Andaluz de Salud PI13/00673 CEIC Universidad de Navarra 053/2013 CEI de las Illes Balears - Conselleria de Salut Direcció General de Salut Publica i Consum IB 2242/14 PI CEIC del Hospital Clínic de Barcelona HCB/2016/0287 CEIC Parc de Salut Mar y IDIAP Jordi Gol PI13/120 CEIC del Hospital Universitari Sant Joan de Reus y IDIAB Jordi Gol 13-07-25/7proj2 CEI de la Provincia de Granada- Servicio Andaluz de Salud MAB/BGP/pg CEIC de la Fundacion Jiménez Díaz EC 26-14/IIS-FJD CEIC Universidad de Navarra 053/2013 CEIC Euskadi PI2014044 CEIC Corporativo de Atención Primaria de la Comunitat Valenciana 2011-005398-22 CEI Humana de la Universidad de las Palmas de Gran Canaria CEIH-2013-07 CEIC del Hospital de Bellvitge PR240/13 CEI de Cordoba-Junta de Salud 3078 CEI de la Fundación IMDEA Alimentación PI-012 CEIC Hospital Clínico San Carlos de Madrid-Piloto-CEIC Servicio Madrileño de salud-General 30/15 CEI Provincial de Málaga-Servicio Andaluz de Salud CEI de las Illes Balears - Conselleria de Salut Direcció General de Salut Publica i Consum IB 2251/14 PI CEIC del Hospital Clínic de Barcelona HCB/2017/0351 CEIC del Hospital General Universitario de Alicante CEIC PI2017/02 CEIC de la Investigación Biomédica de Andalucía (CCEIBA) CEI de la Universidad de León ÉTICA-ULE-014-2015. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

The principal PREDIMED-Plus investigators (MM, JS-S, DC, JM, AA, JW, JVio, DR, JL-M, RE, FT, JL, LS-M, AB-C, JT, VM-S, XP, PM-M, JVid, CV, LD, and ER) contributed to study concept and design and to data extraction from the participants. CG, NBT, NB, JJ, and JS-S performed the statistical analyses. CG and JS-S drafted the manuscript. All authors reviewed the manuscript for important intellectual content and approved the final version to be published.

FUNDING

This work was supported by the official Spanish Institutions for funding scientific biomedical research, CIBER Fisiopatología de la Obesidad y Nutrición (CIBEROBN) and Instituto de Salud Carlos III (ISCIII), through the Fondo de Investigación para la Salud (FIS), which is co-funded by the European Regional Development Fund (six coordinated FIS projects leaded by JS-S and JVid, including the following projects: PI13/00673, PI13/00492, PI13/00272, PI13/01123, PI13/00462, PI13/00233, PI13/02184, PI13/00728, PI13/01090, PI13/01056, PI14/01722, PI14/00636, PI14/00618, PI14/00696, PI14/01206, PI14/01919, PI14/00853, PI14/01374, PI14/00972, PI14/00728, PI14/01471, PI16/00473, PI16/00662, PI16/01873, PI16/01094, PI16/00501, PI16/00533, PI16/00381, PI16/00366, PI16/01522, PI16/01120, PI17/00764, PI17/01183, PI17/00855, PI17/01347, PI17/00525, PI17/01827, PI17/00532, PI17/00215, PI17/01441, PI17/00508, PI17/01732, PI17/00926, PI19/00957, PI19/00386, PI19/00309, PI19/01032, PI19/00576, PI19/00017, PI19/01226, PI19/00781, PI19/01560, PI19/01332, PI20/01802, PI20/00138, PI20/01532, PI20/00456, PI20/00339, PI20/00557, PI20/00886, PI20/01158); the Especial Action Project entitled: Implementación y evaluación de una intervención intensiva sobre la actividad física Cohorte PREDIMED-Plus grant to JS-S; the European Research Council (Advanced Research Grant 2014–2019; agreement #340918) granted to MM; the Recercaixa (agreement #2013ACUP00194) grant to JS-S; grants from the Consejería de Salud de la Junta de Andalucía (PI0458/2013, PS0358/2016, PI0137/2018); the PROMETEO/2017/017 grant from the Generalitat Valenciana; the SEMERGEN grant; The Horizon 2020 PRIME study (Prevention and Remediation of Insulin Multimorbidity in Europe; grant agreement #847879); JJ holds the Miguel Servet-II contract (CPII19/00015) awarded by the Instituto de Salud Carlos III (co-funded by the European Social Fund "Investing in your future"); JK was supported by the 'FOLIUM' programme within the FUTURMed project from the Fundación Instituto de Investigación Sanitaria Illes Balears (financed by 2017annual plan of the sustainable tourism tax and at 50% with charge to the ESF Operational Program 2014–2020 of the Balearic Islands); AÁ-S received a post-doctoral grant from the Generalitat Valenciana (APOSTD/2020/164); CG receives a predoctoral grant from the University of Rovira i Virgili (2020PMF-PIPF-37); We thank CERCA Programme/Generalitat de Catalunya for institutional support and partial support was also provided by SLT006/17/00246, funded by the Department of Health of the Generalitat de Catalunya by the calls "Acció instrumental de programes de recerca orientats en l'àmbit de la recerca i la innovació en salut" and "Pla estratègic de recerca i innovació en salut (PERIS)"; JS-S, senior author of this article, is partially supported by ICREA under the ICREA

Academia program; None of the funding sources took part in the design, collection, analysis, interpretation of the data, or writing the report, or in the decision to submit the manuscript for publication.

ACKNOWLEDGMENTS

The authors wish to thank the PREDIMED-Plus participants and staff for their engagement, as well as to the primary care centers involved in the study. We also thank the Cerca Programme of the Generalitat de Catalunya, and the CIBEROBN, CIBERESP and CIBERDEM initiatives of Instituto de Salud Carlos III in Spain, and the collaborators in the PRIME consortium for helpful input. The first version of the present article has been published in the public repository Research Square as a preprint publication of our work (44). We particularly thank Stephanie Nishi for her assistance with manuscript language revision.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2021.754347/full#supplementary-material

REFERENCES

1. International Diabetes Federation. *IDF Diabetes Atlas*. Brussels: International Diabetes Federation (2019).
2. Gregg EW, Sattar N, Ali MK. The Changing Face of Diabetes Complications. *Lancet Diabetes Endocrinol* (2016) 4(6):537–47. doi: 10.1016/S2213-8587(16)30010-9
3. World Health Organization. *A Report About Dementia*. (2020). Available at: https://www.who.int/news-room/fact-sheets/detail/dementia (Accessed November 2, 2020).
4. Assuncao N, Sudo FK, Drummond C, De Felice FG, Mattos P. Metabolic Syndrome and Cognitive Decline in the Elderly: A Systematic Review. *PloS One* (2018) 13(3):1–16. doi: 10.1371/journal.pone.0194990
5. Rawlings AM, Sharrett AR, Schneider ALC, Coresh J, Albert M, Couper D, et al. Diabetes in Midlife and Cognitive Change Over 20 Years. *Ann Intern Med* (2014) 161(11):785. doi: 10.7326/M14-0737
6. Xue M, Xu W, Ou Y-N, Cao X-P, Tan M-S, Tan L, et al. Diabetes Mellitus and Risks of Cognitive Impairment and Dementia: A Systematic Review and Meta-Analysis of 144 Prospective Studies. *Ageing Res Rev* (2019) 55:100944. doi: 10.1016/j.arr.2019.100944
7. Palta P, Schneider ALC, Biessels GJ, Touradji P, Hill-Briggs F. Magnitude of Cognitive Dysfunction in Adults With Type 2 Diabetes: A Meta-Analysis of Six Cognitive Domains and the Most Frequently Reported Neuropsychological Tests Within Domains. *J Int Neuropsychol Soc* (2014) 20(3):278–91. doi: 10.1017/S1355617713001483
8. Sadanand S, Balachandar R, Bharath S. Memory and Executive Functions in Persons With Type 2 Diabetes: A Meta-Analysis. *Diabetes Metab Res Rev* (2016) 32(2):132–42. doi: 10.1007/s00125-009-1571-9
9. van den Berg E, Reijmer YD, de Bresser J, Kessels RPC, Kappelle LJ, Biessels GJ. A 4 Year Follow-Up Study of Cognitive Functioning in Patients With Type 2 Diabetes Mellitus. *Diabetologia* (2010) 53(1):58–65. doi: 10.1007/s00125-009-1571-9
10. Moran C, Beare R, Wang W, Callisaya M, Srikanth V. Type 2 Diabetes Mellitus, Brain Atrophy, and Cognitive Decline. *Neurology* (2019) 92(8):e823–30. doi: 10.1212/WNL.0000000000006955
11. Geijselaers SLC, Sep SJS, Stehouwer CDA, Biessels GJ. Glucose Regulation, Cognition, and Brain MRI in Type 2 Diabetes: A Systematic Review. *Lancet Diabetes Endocrinol* (2015) 3(1):75–89. doi: 10.1016/S2213-8587(14)70148-2
12. Tuligenga RH, Dugravot A, Tabák AG, Elbaz A, Brunner EJ, Kivimäki M, et al. Midlife Type 2 Diabetes and Poor Glycaemic Control as Risk Factors for Cognitive Decline in Early Old Age: A Post-Hoc Analysis of the Whitehall II Cohort Study. *Lancet Diabetes Endocrinol* (2014) 2(3):228–35. doi: 10.1016/S2213-8587(13)70192-X
13. Zhang Q-Q, Li W-S, Liu Z, Zhang H-L, Ba Y-G, Zhang R-X. Metformin Therapy and Cognitive Dysfunction in Patients With Type 2 Diabetes: A Meta-Analysis and Systematic Review. *Med (Baltimore)* (2020) 99(10):e19378. doi: 10.1097/MD.0000000000019378
14. Martínez-González MA, Buil-Cosiales P, Corella D, Bulló M, Fitó M, Vioque J, et al. Cohort Profile: Design and Methods of the PREDIMED-Plus Randomized Trial. *Int J Epidemiol* (2019) 48(2):387–8. doi: 10.1093/ije/dyy225
15. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the Metabolic Syndrome. *Circulation* (2009) 120(16):1640–5. doi: 10.1161/CIRCULATIONAHA.109.192644
16. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis Model Assessment: Insulin Resistance and β-Cell Function From Fasting Plasma Glucose and Insulin Concentrations in Man. *Diabetologia* (1985) 28(7):412–9. doi: 10.1007/BF00280883
17. American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2021. *Diabetes Care* (2021) 44 (Supplement 1):S15–33. doi: 10.2337/dc21-S002
18. Schröder H, Fitó M, Estruch R, Martínez-González MA, Corella D, Salas-Salvadó J, et al. A Short Screener Is Valid for Assessing Mediterranean Diet Adherence Among Older Spanish Men and Women. *J Nutr* (2011) 141 (6):1140–5. doi: 10.3945/jn.110.135566
19. Elosua R, Marrugat J, Molina L, Pons S, Pujol E. Validation of the Minnesota Leisure Time Physical Activity Questionnaire in Spanish Men. *Am J Epidemiol* (1994) 39(12):1197–209. doi: 10.1093/oxfordjournals.aje.a116966
20. Elosua R, Garcia M, Aguilar A, Molina L, Covas M-I, Marrugat J. Validation of the Minnesota Leisure Time Physical Activity Questionnaire in Spanish Women. *Med Sci Sport Exerc* (2000) 32(8):1431–7. doi: 10.1097/00005768-200008000-00011
21. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An Inventory for Measuring Depression. *Arch Gen Psychiatry* (1961) 4(6):561. doi: 10.1001/archpsyc.1961.01710120031004
22. Ingraham LJ, Aiken CB. An Empirical Approach to Determining Criteria for Abnormality in Test Batteries With Multiple Measures. *Neuropsychology* (1996) 10(1):120–4. doi: 10.1037/0894-4105.10.1.120
23. Blesa R, Pujol M, Aguilar M, Santacruz P, Bertran-Serra I, Hernández G, et al. Clinical Validity of the "Mini-Mental State" for Spanish Speaking Communities. *Neuropsychologia* (2001) 39(11):1150–7. doi: 10.1016/s0028-3932(01)00055-0
24. del Ser Quijano T, García de Yébenes MJ, Sánchez Sánchez F, Frades Payo B, Rodríguez Laso Á, Bartolomé Martínez MP, et al. Evaluación Cognitiva Del Anciano. Datos Normativos De Una Muestra Poblacional Española De Más De 70 Años. *Med Clin (Barc)* (2004) 122(19):727–40. doi: 10.1157/13062190
25. Ganguli M, Belle S, Ratcliff G, Seaberg E, Huff FJ, Von der Porten K, et al. Sensitivity and Specificity for Dementia of Population-Based Criteria for Cognitive Impairment: The MoVIES Project. *J Gerontol* (1993) 48(4):152–61. doi: 10.1093/geronj/48.4.M152
26. de Waal T, Pannekoek J, Scholtus S. *Handbook of Statistical Data Editing and Imputation*. Hoboken, NJ: John Wiley & Sons (2011).
27. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *J R Stat Soc Ser B* (1995) 57 (1):289–300. doi: 10.1111/j.2517-6161.1995.tb02031.x
28. Feinkohl I, Price JF, Strachan MWJ, Frier BM. The Impact of Diabetes on Cognitive Decline: Potential Vascular, Metabolic, and Psychosocial Risk Factors. *Alzheimers Res Ther* (2015) 7(1):46. doi: 10.1186/s13195-015-0130-5
29. Mansur RB, Lee Y, Zhou AJ, Carmona NE, Cha DS, Rosenblat JD, et al. Determinants of Cognitive Function in Individuals With Type 2 Diabetes Mellitus: A Meta-Analysis. *Ann Clin Psychiatry* (2018) 30(1):38–50.

30. Monette MCE, Baird A, Jackson DL. A Meta-Analysis of Cognitive Functioning in Nondemented Adults With Type 2 Diabetes Mellitus. *Can J Diabetes* (2014) 38(6):401–8. doi: 10.1016/j.jcjd.2014.01.014
31. Marseglia A, Dahl Aslan AK, Fratiglioni L, Santoni G, Pedersen NL, Xu W. Cognitive Trajectories of Older Adults With Prediabetes and Diabetes: A Population-Based Cohort Study. *J Gerontol Ser A* (2018) 73(3):400–6. doi: 10.1093/gerona/glx112
32. Wennberg AMV, Hagen CE, Gottesman RF, Zipunnikov V, Kaufmann CN, Albert MS, et al. Longitudinal Association Between Diabetes and Cognitive Decline: The National Health and Aging Trends Study. *Arch Gerontol Geriatr* (2017) 72:39–44. doi: 10.1016/j.archger.2017.05.005
33. Zhang X, Jiang X, Han S, Liu Q, Zhou J. Type 2 Diabetes Mellitus Is Associated With the Risk of Cognitive Impairment: A Meta-Analysis. *J Mol Neurosci* (2019) 68(2):251–60. doi: 10.1007/s12031-019-01290-3
34. Zheng F, Yan L, Yang Z, Zhong B, Xie W. HbA1c, Diabetes and Cognitive Decline: The English Longitudinal Study of Ageing. *Diabetologia* (2018) 61 (4):839–48. doi: 10.1007/s00125-017-4541-7
35. Karvani M, Simos P, Stavrakaki S, Kapoukranidou D. Neurocognitive Impairment in Type 2 Diabetes Mellitus. *Hormones* (2019) 18(4):523–34. doi: 10.1007/s42000-019-00128-2
36. Ganguli M, Beer JC, Zmuda JM, Ryan CM, Sullivan KJ, Chang CH, et al. Aging, Diabetes, Obesity, and Cognitive Decline: A Population-Based Study. *J Am Geriatr Soc* (2020) 68(5):991–8. doi: 10.1111/jgs.16321
37. Lutski M, Weinstein G, Goldbourt U, Tanne D. Insulin Resistance and Future Cognitive Performance and Cognitive Decline in Elderly Patients With Cardiovascular Disease. *J Alzheimer's Dis* (2017) 57(2):633–43. doi: 10.3233/JAD-161016
38. Crane PK, Walker R, Hubbard RA, Li G, Nathan DM, Zheng H, et al. Glucose Levels and Risk of Dementia. *N Engl J Med* (2013) 369(6):540–8. doi: 10.1056/NEJMoa1215740
39. Launer LJ, Miller ME, Williamson JD, Lazar RM, Gerstein HC, Murray AM, et al. Effects of Intensive Glucose Lowering on Brain Structure and Function in People With Type 2 Diabetes (ACCORD MIND): A Randomised Open-Label Substudy. *Lancet Neurol* (2011) 10(11):969–77. doi: 10.1016/S1474-4422(11)70188-0
40. Biessels GJ, Despa F. Cognitive Decline and Dementia in Diabetes Mellitus: Mechanisms and Clinical Implications. *Nat Rev Endocrinol* (2018) 14 (10):591–604. doi: 10.1038/s41574-018-0048-7
41. Abner EL, Nelson PT, Kryscio RJ, Schmitt FA, Fardo DW, Woltjer RL, et al. Diabetes Is Associated With Cerebrovascular But Not Alzheimer's Disease Neuropathology. *Alzheimer's Dement* (2016) 12(8):882–9. doi: 10.1016/j.jalz.2015.12.006
42. Whitmer RA. Hypoglycemic Episodes and Risk of Dementia in Older Patients With Type 2 Diabetes Mellitus. *JAMA* (2009) 301(15):1565–72. doi: 10.1001/jama.2009.460
43. Lin C-H, Sheu WHH. Hypoglycaemic Episodes and Risk of Dementia in Diabetes Mellitus: 7-Year Follow-Up Study. *J Intern Med* (2013) 273(1):102–10. doi: 10.1111/joim.12000
44. Gómez-Martínez C, Babio N, Júlvez J, Becerra-Tomás N, Martínez-González MA, Corella D, et al. Longitudinal Associations Between Glycemic Status and Cognitive Function in Older Participants at High Risk of Cardiovascular Disease: Two-Year Follow-Up in the PREDIMED-Plus Study. *Res Square* (2021) 1:1–30. doi: 10.21203/rs.3.rs-768645/v1

Conflict of Interest: JS-S serves on the board of the International Nut and Dried Fruit Council and receives grant support through this institution. He also served on the Executive Committee of the Instituto Danone, Spain, and on the Scientific Committee of the Danone International Institute. He has received research support from the Patrimonio Comunal Olivarero, Spain, and Borges S.A., Spain. He receives consulting fees or travel expenses from Eroski Foundation, the Instituto Danone, Spain, Mundipharma and Abbot Laboratories. ER reports grants, personal fees, non-financial support and others from California Walnut Commission and Alexion, personal fees, non-financial support and others from Ferrer International and Danone, and personal fees from Amarin, outside the submitted work. FF-A reports consultation fees from Novo Nordisk and editor-in-Chief honoraria from Wiley.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Citation: *Gómez-Martínez C, Babio N, Júlvez J, Becerra-Tomás N, Martínez-González MÁ, Corella D, Castañer O, Romaguera D, Vioque J, Alonso-Gómez ÁM, Wärnberg J, Martínez JA, Serra-Majem L, Estruch R, Tinahones FJ, Lapetra J, Pintó X, Tur JA, López-Miranda J, Bueno-Cavanillas A, Gaforio JJ, Matía-Martín P, Daimiel L, Martín-Sánchez V, Vidal J, Vázquez C, Ros E, Dalsgaard S, Sayón-Orea C, Sorlí JV, de la Torre R, Abete I, Tojal-Sierra L, Barón-López FJ, Fernández-Brufal N, Konieczna J, García-Ríos A, Sacanella E, Bernal-López MR, Santos-Lozano JM, Razquin C, Alvarez-Sala A, Goday A, Zulet MA, Vaquero-Luna J, Diez-Espino J, Cuenca-Royo A, Fernández-Aranda F, Bulló M and Salas-Salvadó J (2021) Glycemic Dysregulations Are Associated With Worsening Cognitive Function in Older Participants at High Risk of Cardiovascular Disease: Two-Year Follow-up in the PREDIMED-Plus Study. Front. Endocrinol. 12:754347. doi: 10.3389/fendo.2021.754347*

UNIVERSITAT ROVIRA I VIRGILI
Psychology and Disease: Unveiling Emerging Perspectives on Their Interplay
Carlos Gómez Martínez

CHAPTER 6:
COVID-19 AND COGNITIVE FUNCTION

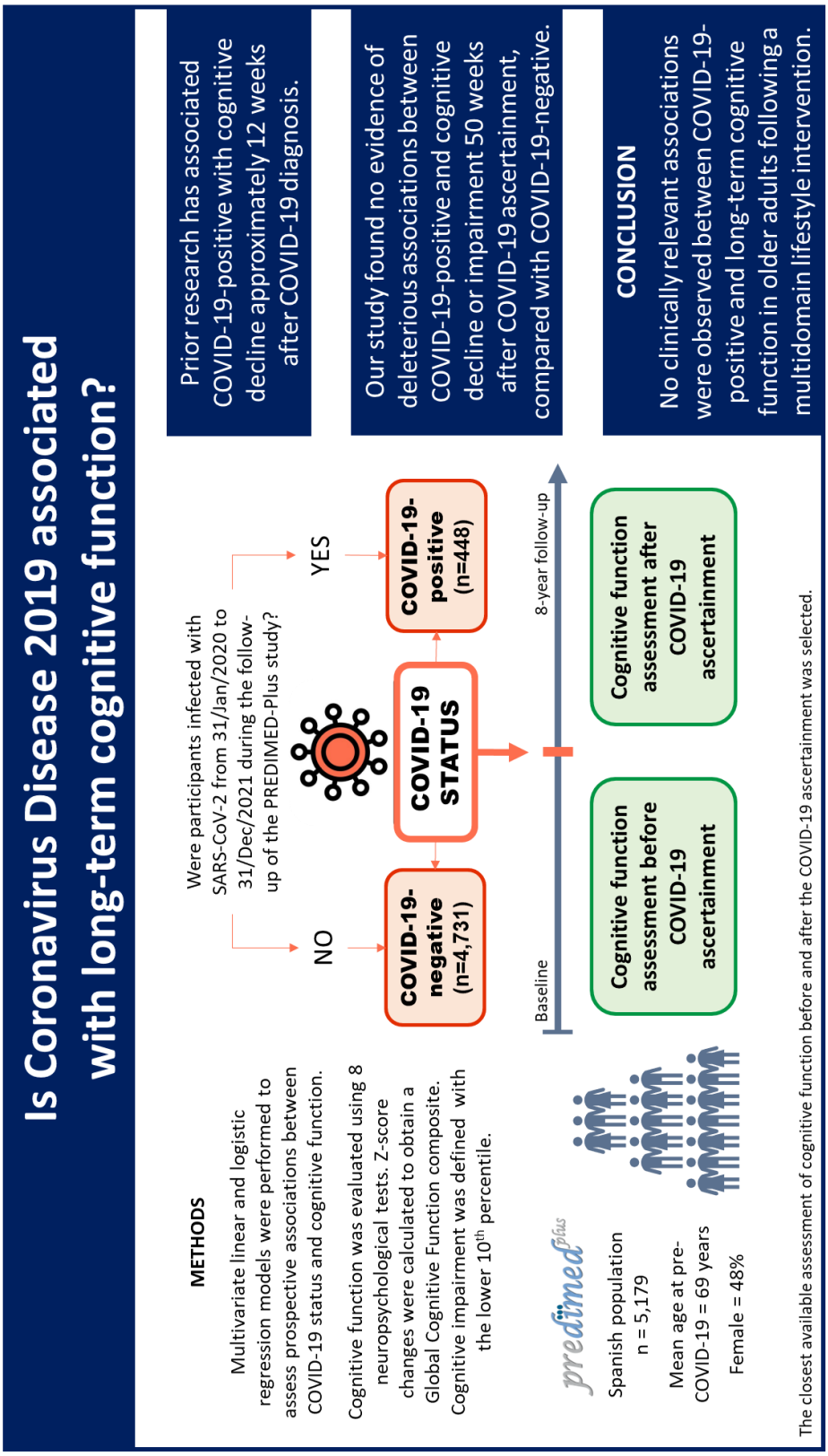


Figure 11. Graphical abstract of Chapter 6. COVID-19 and cognitive function.

Aging and Disease
www.aginganddisease.org
Early access date: July 21, 2024
http://dx.doi.org/10.14336/AD.2024.0380

Original Article

COVID-19 and Cognitive Decline in Older Adults with High-Cardiovascular Risk: A Post Hoc Analysis

Sangeetha Shyam[1,2,3#,*], Carlos Gómez-Martínez[1,2,3#], Jiaqi Ni[1,2,3], José J. Gaforio[4,5], Miguel Ángel Martínez-González[3,6,7], Dolores Corella[3,8], J. Alfredo Martínez[3,9,10], Ángel M. Alonso-Gómez[3,11], Julia Wärnberg[3,12], Jesús Vioque[4,13], Dora Romaguera[3,14], José López-Miranda[3,15], Ramon Estruch[3,16], Francisco J Tinahones[3,17], José Lapetra[3,18], Lluís Serra-Majem[3,19], Aurora Bueno-Cavanillas[4,20, 21], Josep A. Tur[3,14,22], Vicente Martín-Sánchez[4,23], Xavier Pintó[3,24], Miguel Delgado-Rodríguez[10,25], Pilar Matía-Martín[26], Josep Vidal[27,28], Clotilde Vázquez[3,29], Lidia Daimiel[3,30,31], Emilio Ros[32], Fernando Fernandez-Aranda[3,33], Adrián Hernández-Cacho[1,2,3], Pilar Buil-Cosiales[3,6,34], Jose V Sorli[3,8], Olga Castañer[4,35], Antonio Garcia-Rios[3,15], Alejandro Oncina-Canovas[4,13], Napoleón Pérez-Farinós[12], Mar Nafria[14], Rosa Casas[3,16], Silvia Martínez-Diz[4,20,21,36], Lucas Tojal-Sierra[11], Gómez-Pérez AM[3,17], Estefania Toledo[3,6], Rebeca Fernández-Carrión[3,8], Álvaro Morán Bayón[10,23], Jose David Torres-Peña[3,15], Laura Compañ-Gabucio[4,13], Zenaida Vázquez-Ruiz[3,6], Nancy Babio[1,2,3], Montserrat Fitó[3,35], Jordi Salas-Salvadó[1,2,3*]

[1]Universitat Rovira i Virgili, Departament de Bioquímica i Biotecnologia, Unitat de Nutrició, Reus, Spain. [2]Institut d'Investigació Sanitària Pere Virgili (IISPV), Reus, Spain. [3]Centro de Investigación Biomédica en Red Fisiopatología de la Obesidad y la Nutrición (CIBEROBN), Institute of Health Carlos III, Madrid, Spain. [4]CIBER de Epidemiología y Salud Pública (CIBERESP), Instituto de Salud Carlos III, Madrid, Spain. [5]Departamento de Ciencias de la Salud, Instituto Universitario de Investigación en Olivar y Aceites de Oliva, Universidad de Jaén, Jaén, Spain. [6]University of Navarra, Department of Preventive Medicine and Public Health, IdiSNA, Pamplona, Spain. [7]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA. [8]Department of Preventive Medicine, University of Valencia, Valencia, Spain. [9]Department of Nutrition, Food Sciences, and Physiology, Center for Nutrition Research, University of Navarra, Pamplona, Spain. [10]Precision Nutrition and Cardiometabolic Health Program. IMDEA Food, CEI UAM + CSIC, Madrid, Spain. [11]Bioaraba Health Research Institute, Cardiovascular, Respiratory and Metabolic Area; Osakidetza Basque Health Service, Araba University Hospital; University of the Basque Country UPV/EHU, Vitoria-Gasteiz, Spain. [12]EpiPHAAN research group, University of Málaga - Instituto de Investigación Biomédica en Málaga (IBIMA), Málaga, Spain. [13]Instituto de Investigación Sanitaria y Biomédica de Alicante. Universidad Miguel Hernández (ISABIAL-UMH). Alicante, Spain. [14]Health Research Institute of the Balearic Islands (IdISBa), Palma de Mallorca, Spain. [15]Lipids and Atherosclerosis Unit, Department of Internal Medicine, Maimonides Biomedical Research Institute of Cordoba (IMIBIC), Reina Sofia University Hospital, University of Cordoba, Av. Menéndez Pidal s/n, 14004 Cordoba, Spain. [16]Department of Internal Medicine, Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS), Hospital Clinic, and Institut de Recerca en Nutrició i Seguretat Alimentaria (INSA-UB); University of Barcelona, Barcelona, Spain. [17]Virgen de la Victoria Hospital, Department of Endocrinology, Instituto de Investigación Biomédica de Málaga (IBIMA). University of Málaga, Málaga, Spain. [18]Department of Family Medicine, Research Unit, Distrito Sanitario Atención Primaria Sevilla, Sevilla, Spain. [19]Research Institute of Biomedical and Health Sciences (IUIBS), University of Las Palmas de Gran Canaria & Centro Hospitalario Universitario Insular Materno Infantil (CHUIMI), Canarian Health Service, Las Palmas de Gran Canaria, Spain. [20]Department of Preventive Medicine and Public Health, University of Granada, Granada, Spain. [21]Instituto de Investigación

***Correspondence should be addressed to:** Dr. Sangeetha Shyam and Prof Jordi Salas-Salvadó, Universitat Rovira i Virgili, Departament de Bioquímica i Biotecnologia, Food, Nutrition, Development and Mental Health Group (ANUT-DSM), Human Nutrition Unit, Reus, Spain. Email: sangeetha.shyam@urv.cat and jordi.salas@urv.cat. #These authors contributed equally to this work.

Biosanitaria ibs. GRANADA, Granada, Spain. [22]Research Group on Community Nutrition & Oxidative Stress, University of Balearic Islands, Research Institute of Health Sciences (IUNICS), Palma de Mallorca, Spain. [23]Institute of Biomedicine (IBIOMED), University of León, León, Spain. [24]Lipids and Vascular Risk Unit, Internal Medicine, Hospital Universitario de Bellvitge-Institut d'Investigacions biomèdiques de Bellvitge (IDIBELL), Hospitalet de Llobregat, Barcelona Spain. [26]Department of Endocrinology and Nutrition, Instituto de Investigación Sanitaria Hospital Clínico San Carlos (IdISSC), Madrid, Spain. [27]CIBER Diabetes y Enfermedades Metabólicas (CIBERDEM), Instituto de Salud Carlos III (ISCIII), Madrid, Spain. [28]Department of Endocrinology, Institut d` Investigacions Biomédiques August Pi Sunyer (IDIBAPS), Hospital Clinic, University of Barcelona, Barcelona, Spain. [29]Department of Endocrinology and Nutrition, Hospital Fundación Jimenez Díaz. Instituto de Investigaciones Biomédicas IISFJD. University Autonoma, Madrid, Spain. [30]Nutritional Control of the Epigenome Group. Precision Nutrition and Obesity Program. IMDEA Food, CEI UAM + CSIC, Madrid, Spain. [31]Departamento de Ciencias Farmacéuticas y de la Salud, Faculty de Farmacia, Universidad San Pablo-CEU, CEU Universities, Boadilla del Monte, Spain. [32]Lipid Clinic, Department of Endocrinology and Nutrition, Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS), Hospital Clínic, Barcelona, Spain. [33]Psychology Department, University Hospital of Bellvitge-ICS, Hospitalet del Llobregat (Barcelona), Spain. [34]Servicio Navarro de salud, Primary Health Care, Navarra, Spain. [35]Unit of Cardiovascular Risk and Nutrition, Institut Hospital del Mar de Investigaciones Médicas Municipal d'Investigació Médica (IMIM), Barcelona, Spain. [36]Preventive Medicine and Public Health Service, Hospital Universitario Virgen de las Nieves, Granada, Spain.

[Received April 4, 2024; Revised May 21, 2024; Accepted May 21, 2024]

ABSTRACT: Cognitive decline has been reported as a short-term sequela in patients hospitalized for coronavirus disease-19 (COVID-19). Whether COVID-19 is associated with late cognitive impairment in older free-living individuals with high cardiovascular risk, a group at greater risk of cognitive decline, is unknown. We determined this association of COVID-19 through a longitudinal evaluation of post-COVID-19 cognitive performance and impairment as post hoc analysis in 5,179 older adults (48% female) with mean (SD) age 68.5 (5.0) years, body mass index 31.7 (3.7) kg/m^2, harboring ≥ 3 criteria for metabolic syndrome (e.g., hypertension, hyperlipidemia, hyperglycemia etc.) enrolled in PREDIMED-Plus trial. Pre- and post-COVID-19 cognitive performance was ascertained from scheduled assessments conducted using a battery of neuropsychological tests, including 5 domains: Global Cognitive Function, General Cognitive Function, Execution Function, Verbal Fluency and Attention domains, which were standardized for the cohort. Cognitive impairment was defined as the bottom 10 percentile of the sample. Multivariable linear and logistic regression models assessed the association of COVID-19 with cognitive decline and impairment, respectively. After a mean 50-week follow-up, no significant associations were observed between COVID-19 status and post-COVID-19 scores of all tapped neuropsychological domains, except Global Cognitive Function (GCF). When fully adjusted, COVID-19 was marginally associated with higher (better) post-pandemic GCF score (βadj (95% CI): 0.06 (0.00, 0.13) p=.05). However, the odds for post-COVID-19 cognitive impairment in GCF domain were not associated with the disease (ORadj (95% CI): 0.90 (0.53, 1.51) p=.68). In the PREDIMED-Plus cohort, COVID-19 status and cognitive impairment determined 50 weeks post-infection showed no association in older adults at high cardiovascular risk. This suggests that cognitive changes observed shortly after COVID-19 revert over time. However, cautious interpretation is warranted as these data were obtained within the framework of a clinical trial encouraging a healthy lifestyle.

Key words: COVID-19, Cognition, Older adults, PREDIMED-Plus

INTRODUCTION

Cognitive impairment, a major determinant of poor health and mortality in older adults [1], is a common neuropsychological sequela of coronavirus disease 2019 (COVID-19)[2–5]. Cognitive deficits post-COVID-19 have been reported in several cognitive domains [6], associating COVID-19 with cognitive impairment and dementia [6, 7]. These COVID-19-related cognitive deficits occur through structural and functional brain changes [2, 3].

Several individual-level characteristics including cardiovascular risks such as obesity, diabetes, hypertension, and depression are thought to influence COVID-19-related cognitive decline [8]. As older age is

associated with an increased risk for severe COVID-19 [9], infection-related cognitive deficits could be a health concern among older adults, specifically those with cardiovascular risk factors. Hence, we examined older adults enrolled in the PREDIMED-Plus trial, the association of COVID-19 status with cognitive impairment measured at 1-year post-infection. From a public health perspective, such a long-term assessment in older adults with cardiometabolic risks informs if there is a need for sustained cognitive support in older adults with a high propensity for dementia.

MATERIALS AND METHODS

Study design and participants

This longitudinal analysis was conducted within the framework of PREDIMED-Plus [10], an ongoing, multicenter, randomized controlled lifestyle trial in Spain for the primary prevention of cardiovascular disease. Eligible participants were older adults (55-75 years) with overweight/obesity (included BMI range: 27-40 kg/m^2) and ≥3 criteria for metabolic syndrome (MetS).

The trial recruited participants between 2013 and 2016, who were randomized to an intervention (IG) or control group (CG). IG encouraged energy-reduced Mediterranean diet (MedDiet) and physical activity and provided behavioural support to achieve/maintain weight loss. CG followed an *ad libitum* MedDiet. Participants provided written informed consent to a protocol approved by the institutional review boards of the participating centers (http://www.predimedplus.com).

Exposure: COVID-19 status

The occurrence of COVID-19 was defined from the pandemic onset to 31st December 2021 as adjudicated by the PREDIMED-Plus Clinical Event Ascertainment Committee. The ascertainment was based on the annual review of participant medical records by collaborating physicians [11], in accordance with CDC 2020 guidelines using PCR SARS-Cov-2, IgG tests [12]. Participants who did not have a confirmed COVID-19-positive diagnosis were considered COVID-19-negative. Subsequently, COVID-19 status was established dichotomously (positive/negative) and defined as exposure.

Identifying pre- and post-COVID-19 data

For COVID-19-positive participants, the last available data prior to COVID-19 diagnosis was the pre-COVID-19 assessment, and the first evaluation after the COVID-19 diagnosis date was the post-COVID-19 assessment. In COVID-19 negative participants, the most recent data before the first known COVID-19 case in Spain (31st January 2020) was the pre-COVID-19, and the subsequent available measurement was the post-COVID-19 data. The duration between pre- and post-COVID-19 cognitive assessment visits was calculated in weeks.

Outcome Ascertainment

Cognitive function assessment and post-COVID-19 cognitive impairment

In PREDIMED-Plus, a neuropsychological battery of 8 cognitive tests assessed cognitive function at baseline and every 2 years [10]. These cognitive tests psychometrically evaluated for Spanish populations include the Mini-Mental State Examination (MMSE)[13], the Clock Drawing Test (CDT) [14], the Verbal Fluency Test animals (VFT-a) and letter "p" (VFT-p) categories[15], the Digit Span Test forward (DST-f) and backward (DST-b) sections, and the Trail Making Test A (TMT-A) and B (TMT-B) sections [16].

From these 8 tests, 5 cognitive domains were derived using z-scores, as prescribed in neuropsychological handbooks [17, 18]. These included the Global Cognitive Function (GCF), General Cognitive Function (genCF), Executive Function, Verbal Fluency, and Attention domains. Global Cognitive Function is defined as a composite of all 8 tests, with inversion of TMT-A and TMT-B scores, as higher scores reflect lower cognitive performance in these two tests. The General Cognitive Function domain included the MMSE and the CDT, the Executive Function domain included the VFT-a, VFT-p, DST-b, and TMT-B, the Verbal Fluency domain included the VFT-a and VFT-p, and the Attention domain included the DST-f and TMT-A tests.

Post-COVID-19 cognitive assessments.

Post-COVID-19 cognitive function was evaluated as aggregate performance in 5 cognitive domains assessed at the post-COVID-19 visit and estimated as z-score (number of SDs from the cohort mean, at pre-COVID-19 visit).

Global Cognitive Function composite score at the post-COVID-19 assessment was obtained using the following formula: Global Cognitive Function (post-COVID-19) = [zMMSE post-COVID-19 + zCDT post-COVID-19 + zVFT-a post-COVID-19 + zVFT-p post-COVID-19 + zDST-f post-COVID-19 + zDST-b post-COVID-19 + (-zTMT-A post-COVID-19) + (-zTMT-B post-COVID-19)]/8. Thereafter, the Global Cognitive Function composite score at the post-COVID-19 assessment was further standardized using the mean and

standard deviation of the Global Cognitive Function composite score at the pre-COVID-19 assessment [19].

Post-COVID-19 cognitive impairment for each cognitive domain was determined as a dichotomous variable (yes/no) using the bottom 10th percentile of cognitive function [20].

Table 1. Participant characteristics at the pre-COVID-19 visit according to COVID-19 status.

Characteristics	COVID Status			
	Total population (n=5,179)	Negative (n=4,731)	Positive (n=448)	p-value
Sex (female)[b]	2,473 (47.8%)	2,291 (48.4%)	182 (40.6%)	<0.01
Age (in years) #	68.5 ± 5.0	68. 4 ± 5.0	69.1 ± 5.1	0.01
Allocation to Intervention arm [b]	2,488 (48.04%)	2,272 (48.0%)	216 (48.2%)	0.94
Educational level [b]				0.04
Primary school or less	2,570 (49.62%)	2,373 (50.2%)	197 (44. 0%)	
High school	1,498 (28.92%)	1,356 (28.7%)	142 (31.7%)	
College	1,111 (21.45%)	1,002 (20.75%)	109 (24.3%)	
Marital status #				0.54
Single, divorced or separated	633 (12.2%)	583 (12.3%)	50 (11.2%)	
Married	3,959 (76.4%)	3, 607 (76.2%)	352 (78.6%)	
Widowed	587 (11.3%)	541 (11. 4%)	46 (10.3%)	
Smoking status [b]				0.001
Never smoker	2,331 (45.0%)	2,155 (45.6%)	176 (39.3%)	
Former smoker	2,237 (43.19%)	2,007 (42.4%)	230 (51.3%)	
Current smoker	611 (11.80%)	569 (12.0%)	42 (9.4%)	
Physical activity (METs min/week) #	3,063 ± 2,450	3,043 ± 2,424	3,281 ± 2,698	0.05
Alcohol intake (g/day) #	9.6 ± 13.3	9.5 ± 13.3	10.3 ± 13.9	0.22
MeDiet adherence score (er-MEDAS; range: 0-17 points) #	11.7 ± 2.8	11.6 ± 2.8	11.8 ± 2.6	0.21
Body mass index (kg/m^2) #	31.7 ± 3.7	31.7 ± 3.7	32.1 ± 3.7	0.04
Hypertension [b]	4,332 (83.65%)	3,968 (83. 9%)	364 (81.3%)	0.15
Hyperlipidemia [b]	3,619 (69.88 %)	3,317 (70.1%)	302 (67.4%)	0.23
Type 2 diabetes [b]	1,559 (30.1%)	1,409 (29.8%)	150 (33. 5%)	0.10
Depressive symptomatology#	715 (13.82%)	664 (14.0%)	51 (11.4%)	0.12
Received 1 dose of COVID-19# vaccine before event	39 (0.75%)	0 (0%)	39 (8.7%)	<0.001
Time from COVID-19 status ascertainment to post-COVID-19 cognitive assessment (weeks)	43.7 ± 28.6	43.1 ± 28.5	49.9 ± 29.4	<0.001
Time between pre- and post-COVID-19 cognitive assessments (weeks)*	105.5 ± 6.2	105.5 ± 6.2	104.2 ± 6.1	<0.001

Abbreviations: MeDiet, Mediterranean diet; er-MEDAS, 17-point energy-restricted Mediterranean Diet Adherence Screener score.
Data are n (%) or mean ± SD for categorical and quantitative variables, respectively.
Chi-square is used for categorical variables and t-test for quantitative variables.
*The time was estimated for Global Cognitive Function domain measurements (n=4,838).
[b] Data obtained at baseline
#Measured at the pre-COVID-19 visit

Covariates

Sociodemographic, lifestyle, and history of disease covariates data were assessed by trained staff and ascertained at baseline or at the pre-COVID-19 assessment based on the data available in the PREDIMED-Plus database at the time of analysis. Physical activity was evaluated using the Regicor Short Physical Activity Questionnaire [21], and depressive symptoms using the Spanish version of the Beck Depression Inventory-II, which specifies a depressive symptomatology risk using a cut-off of >13 points[22, 23]. The adherence to the Mediterranean diet was assessed with the 17-point energy-restricted Mediterranean Adherence Screener (er-MEDAS), validated in the Spanish population [24].

For the main analysis, covariates were obtained from baseline or pre-COVID-19 visits. Covariates at baseline include sex (man; woman), recruitment center size (>400; 300–400; 250–300; <250 participants), educational level (<high school; high school; college), intervention group allocation, smoking status (never; former smoker; current

smoker), and prevalence of type 2 diabetes (no; yes), hypertension (no; yes), and hyperlipidemia (no; yes). Covariates at the pre-COVID-19 assessment include participant's age (years), marital status (single, divorced or separated; married; widower), body mass index (BMI; kg/m^2), physical activity (METs min/week), alcohol intake adding the quadratic term (g/day), the respective cognitive function assessment (linear score), depressive symptomatology (no; yes), and having received at least one dose of COVID-19 vaccination (no; yes). Furthermore, the time elapsed between COVID-19 event status determination and the post-COVID-19 cognitive function assessment (in weeks) was included as a covariate.

Statistical analyses

This analysis used the PREDIMED-Plus database dated September 2023, merged with COVID-19 data. Missing covariates (<1%) were imputed as either the mean (continuous) or mode (categorical). Z-score of changes in cognitive domains were compared between COVID-19 positive and negative participants, adjusting for covariates. Linear and logistic regression models were used to assess associations between COVID-19 status (no/yes) and post-COVID-19 cognitive decline (post-COVID-19 z-scores) and impairment (absence/presence) for all cognitive domains. Crude, minimally adjusted, and three other models adjusting for potential covariates were tested. Supplementary analyses were performed for each cognitive test, using an alternative definition of cognitive impairment (1.5 SD below cohort pre-COVID-19 mean), and replacing pre-COVID-19 BMI, lifestyle and depression data with post-COVID-19 measurements.

Table 2. Comparison of changes of performance in various cognitive domains (z scores) from pre- to post-COVID-19 between COVID-19 cases and control (not infected) participants in the PREDIMED-Plus study.

Cognitive domain	COVID-19 Status						
	Positive			Negative			
	n	Change (95% CI)	p-value[1]	n	Change (95% CI)	p-value[1]	p-value[2]
Global Cognitive Function	377	-0.09 (-0.15, -0.03)	<0.01	4,461	-0.18 (-0.19, -0.16)	<0.001	0.06
General Cognitive Function	381	-0.15 (-0.27, -0.04)	<0.01	4,535	-0.30 (-0.33, -0.27)	<0.001	0.11
Executive Function	439	-0.08 (-0.14, -0.03)	<0.01	4,267	-0.10 (-0.11, -0.08)	<0.001	0.42
Verbal Fluency	445	-0.07 (-0.14, -0.00)	0.05	4,719	-0.07 (-0.09, -0.05)	<0.001	0.42
Attention	440	-0.04 (-0.04, 0.11)	0.36	4,680	-0.10 (-0.12, -0.07)	<0.001	0.23

Abbreviations: COVID-19, Coronavirus disease 2019; n, number of participants; 95% CI, 95% confidence interval.
p-value1 calculated using paired t-test to assess differences of z-scores from pre-COVID-19 to post-COVID-19 assessments within groups.
p-value2 calculated using ANCOVA to assess differences of z-score changes using delta method between COVID-19 status (negative/positive), adjusting for the respective cognitive domain performance at pre-COVID-19 (linear z-score), low and high Mediterranean diet adherence COVID-19 vaccine (no/yes), time elapsed between ascertainment of COVID-19 status and post-COVID-19 cognitive assessment (weeks), intervention group, center size (<250; 250-300, 300-400; ≥400 participants recruited), randomized as couples (no/yes), sex, smoking status (smoker; former smoker; never smoker), , educational level (primary school; secondary school; college), pre-COVID-19 covariates (age (in years), marital status (single, divorced or separated; married; widower), body mass index (kg/m2, and depressive symptomatology (no/yes)), physical activity (METs min/week), alcohol intake (g/day, adding the quadratic term), and prevalence of hypertension (no/yes), hypercholesterolemia (no/yes), type 2 diabetes (no/yes) at enrolment.
The Global Cognitive Function domain was obtained by averaging all cognitive z-scores. The General Cognitive Function domain was obtained by averaging z-scores of the Mini-Mental State Examination and Clock Drawing Test. The Executive Function domain was obtained by averaging z-scores of the Verbal Fluency Test animals, Verbal Fluency Test letter "p", Trail Making Test B, and the Digit Span Test backward. The Verbal Fluency domain was obtained by averaging z-scores of the Verbal Fluency Test animals and Verbal Fluency Test letter "p". The Attention domain was obtained by averaging z-scores of the Trail Making Test A and the Digit Span Test forward.

RESULTS

Of the 6,874 PREDIMED-Plus participants, 5,179 were included in this analysis inclusive of 448 COVID-19 positive cases (Supplementary Fig. 1). COVID-19-positive cases were more likely to be male, older, have higher education and BMI, and smoked less frequently compared to COVID-19-negative participants (Table 1).

Cognitive assessments post-COVID-19 in infected participants were performed at a mean (SD) of 50(29) weeks after infection, with only 13% assessed within 3 months of infection. Most (74%) post-COVID-19 assessments were performed 6 months post-infection.

Irrespective of COVID-19 status, all participants experienced reductions in scores of several cognitive domains from pre- to post-COVID-19 assessment, indicating cognitive decline. However, these changes did not differ by COVID-19 status when adjusted for potential covariates (Table 2, all p≥0.06).

No significant associations were observed between COVID-19 status and post-COVID-19 assessments for GenCF, Executive Function, Verbal Fluency, and Attention domains (Table 3, all p≥0.06). Accordingly, COVID-19 was not associated with post-COVID-19 cognitive impairment in these domains (Table 3, all p≥0.52). COVID-19 positive status was marginally associated with GCF measured post-COVID-19 (β_{adj} (95% CI): 0.06 (0.00, 0.13) p=0.05). However, cognitive impairment in GCF was not associated with COVID-19 (OR_{adj} (95% CI): 0.90 (0.53, 1.51) p=0.68).

No association between COVID-19 and cognitive decline or impairment was observed for any individual cognitive test (Supplementary Table S1). An alternative definition of cognitive impairment and the use of post-COVID-19 variables in supplementary analyses did not change the results (Supplementary Table 2).

Table 3. Association of COVID-19 with 50-week post-infection cognitive performance and impairment.

	Linear (β (95% CI))	p-value	Logistic (OR (95% CI))	p-value
Global Cognitive Function (n=4,838)				
Model 1	0.11 (-0.01, 0.22)	0.07	0.82 (0.57, 1.20)	0.31
Model 2	0.07 (0.01, 0.13)	0.03	0.87 (0.52, 1.45)	0.59
Model 3	0.06 (-0.00, 0.12)	0.05	0.91 (0.53, 1.54)	0.72
Model 4	0.06 (0.00, 0.13)	0.05	0.90 (0.53, 1.51)	0.68
Model 5	0.07 (0.01, 0.14)	0.02	0.87 (0.51, 1.48)	0.60
General Cognitive Function (n = 4,916)				
Model 1	0.10 (-0.01, 0.23)	0.08	0.86 (0.60, 1.24)	0.42
Model 2	0.11 (0.00, 0.22)	0.05	0.85 (0.57, 1.28)	0.43
Model 3	0.09 (-0.02, 0.20)	0.11	0.86 (0.57, 1.31)	0.50
Model 4	0.10 (-0.01, 0.23)	0.08	0.87 (0.58, 1.32)	0.52
Model 5	0.10 (-0.01, 0.23)	0.08	0.86 (0.57, 1.29)	0.46
Executive Function (n= 5,066)				
Model 1	0.07(-0.03,0.18)	0.16	0.84 (0.59, 1.19)	0.32
Model 2	0.02(-0.04, 0.08)	0.46	0.88 (0.56, 1.39)	0.59
Model 3	0.02(-0.04, 0.08)	0.46	0.91 (0.57, 1.43)	0.67
Model 4	0.02(-0.03, 0.08)	0.40	0.92 (0.58, 1.47)	0.74
Model 5	0.03(-0.03, 0.09)	0.37	0.90 (0.57, 1.43)	0.65
Verbal Fluency (n = 5,164)				
Model 1	0.07 (-0.02, 0.17)	0.14	1.02 (0.68, 1.53)	0.91
Model 2	0.03 (-0.05, 0.10)	0.47	1.02 (0.68, 1.52)	0.94
Model 3	0.03 (-0.05, 0.10)	0.47	1.02 (0.68, 1.54)	0.91
Model 4	0.03 (-0.04, 0.10)	0.43	1.02 (0.68, 1.54)	0.90
Model 5	0.03 (-0.04, 0.10)	0.41	1.00 (0.67, 1.50)	0.99
Attention (n= 5,120)				
Model 1	0.08 (-0.03, 0.19)	0.16	1.03 (0.74, 1.42)	0.88
Model 2	0.06 (-0.02, 0.14)	0.16	1.08 (0.72, 1.63)	0.71
Model 3	0.05 (-0.03, 0.13)	0.24	1.11 (0.73, 1.69)	0.62
Model 4	0.05 (-0.03, 0.13)	0.22	1.11 (0.73, 1.69)	0.62
Model 5	0.07 (-0.01, 0.15)	0.09	1.04 (0.68, 1.58)	0.86

Abbreviations: COVID-19, Coronavirus disease 2019; n, number of participants; β: beta coefficient from linear regression, OR: Odds ratio and 95% CI: 95% confidence interval.

Linear regression models presented using β (95% CI) tested the associations between COVID-19 status (no/yes) and post-COVID-19 cognitive assessment (Z score: standardized change from pre-COVID-19 assessment).

Logistic regression models using OR (95% CI) tested the associations between COVID-19 status (no/yes) and longitudinal post-COVID-19 cognitive impairment (absence/presence) in the 5 cognitive domains assessed using ≤10^{th} percentile performance for the cohort as a cut-off.

Model 1: crude model.

Model 2: adjusted by the respective cognitive domain performance at pre-COVID-19 (linear z-score), receipt of one dose of COVID-19 vaccine (no/yes), and time elapsed between COVID-19 status and post-COVID-19 cognitive assessment (in weeks).

Model 3: Model 2 + additional adjustments for intervention group allocation, recruitment center size (<250; 250-300, 300-400; ≥400 participants), sex, educational level (primary school; secondary school; college) smoking status (smoker; former smoker; never smoker), pre-COVID-19 variables((age (years), marital status (single, divorced or separated; married; widower), body mass index (kg/m^2), adherence to Mediterranean Diet score (on a 17-point scale), physical activity (METs min/week), and alcohol intake (g/day, adding the quadratic term)).

Model 4: Model 3+ additional adjustments for participants' disease prevalence at enrollment (diabetes, hypertension hypercholesterolemia) and elevated depressive symptomatology at pre-COVID-19 visit.
Model 5: uses a minimal adjustment identified using a directed acyclic graph (DAG). This model includes sex, intervention group allocation, educational level (primary school; secondary school; college), smoking status (smoker; former smoker; never smoker), pre-COVID-19 variables (age (years), body mass index (kg/m^2), adherence to Mediterranean Diet score (on a 17-point scale), physical activity (METs min/week), and alcohol intake (g/day, adding the quadratic term)), enrollment data on prevalence of diabetes(yes/no), prevalence of hypertension(yes/no), respective cognitive domain performance at pre-COVID-19 (linear z-score), and receipt of one dose of COVID-19 vaccine at pre-COVID-19 visit (no/yes).

DISCUSSION

In a Spanish cohort of older adults with overweight/ obesity and MetS, we observed a small but significant cognitive decline between pre- and post-COVID-19 assessments, consistent with evaluations from the UK during the pandemic [25]. Nevertheless, contradicting several previous studies, we found that COVID-19 itself was not associated with cognitive decline or impairment post-infection, and even noted a small positive association for GCF with COVID-19 positive status, although clinically irrelevant. Earlier studies were limited in their ability to provide unbiased long-term estimates as they oftentimes lacked suitable controls or baseline cognitive scores, used hospitalized patients, self-reported cognitive measures, or measured cognition shortly after COVID-19 infection [4–7]. Our post-infection cognitive assessments were measured, on average, 1 year after diagnosis. Thus, the lack of association between COVID-19 and cognitive dysfunction documented here is likely to reflect the natural resolution with time [6]. It should also be noted that cognitive deficits were not detected in individuals who had reported a full recovery from COVID-19 [26]. Given that all participants included in this analysis were able to attend follow-up visits after COVID-19, it is probable that most cases included here were mild to moderate in severity and had a full recovery.

Our study aligns with recent recommendations for robust post-COVID-19 cognitive dysfunction evaluation [27]. We measured several cognitive domains using culturally validated methodology at pre- and post-COVID-19 visits, facilitating adjustment for individuals' pre-COVID-19 data in both COVID-19-infected and similar controls without evidence of infection. The use of objective, validated, cognitive assessments is a particular strength of this study. It has been noted that a reliance on self-report instruments for the assessment of post-COVID-19 evaluation of cognitive dysfunction can produce skewed estimates due to the well-established dissonance between subjective and objective cognitive data. Additionally, utilizing the PREDIMED-Plus data allowed for accounting of recognized confounders of cognitive decline, and the analysis close to 1-year after infection provides a comprehensive perspective. Supplementary analyses including the use of post-COVID-19 covariates and alternative definitions of cognitive decline were consistent with the main findings, attesting to the robustness of our analysis. However, we acknowledge that we did not have data to account for COVID-19 severity, hospitalization, or infection strain which could determine post-COVID-19 sequalae [2, 4, 5]. Furthermore, we were unable to account for sleep duration and quality in the analysis, which may be associated with cognitive health, as we did not possess these data for the entire PREDIMED-Plus cohort. Therefore, residual confounding, while unlikely, cannot be discounted. The small number of COVID-19 cases in this cohort, despite reflecting the national prevalence at this time [28], could make this analysis underpowered to detect small but clinically significant differences in cognitive outcomes. It is also likely that misclassification of cases could have occurred as undiagnosed asymptomatic infections could have been labelled as COVID-19-negative. However, we also believe that this to have been highly unlikely as strategies for COVID-19 testing were stringent in Spain between 2020 and 2021, the period of COVID-19 ascertainment covered in this analysis. During this period, Spain was attempting to increase COVID-19 vaccination coverage and public health systems for COVID-19 testing were robust. Also, as described earlier, we included participants who attended both the pre-and post-COVID-19 cognitive assessments. Hence, it is highly likely that the analysis excluded those who developed severe complications. Thus, caution is required when extrapolating the results, as these findings may be generalizable only to those with mild and moderate COVID-19 who recovered without severe post-COVID-19 complications.

We recognize that our participants were enrolled in a lifestyle intervention program encouraging MedDiet in all participants and additional behavioral strategies for weight loss in the IG [10]. This could have attenuated any association of COVID-19 with cognition. It may also have been interesting to study structural brain changes through imaging studies to determine if changes in cognition parallel with changes in brain structure or function. However, current findings hold implications for public health preventive strategies, particularly in the context of documented detrimental lifestyle changes during COVID-19 restrictions [29] and campaigns to fight the spread of COVID-19 largely neglecting lifestyle improvement[29]. Considering the predicted increase in pandemics and the aging populations worldwide, strategies promoting healthy lifestyles could be crucial for public health.

In conclusion, among PREDIMED-Plus participants, there was no long-term association between COVID-19

status and cognitive decline or impairment. These findings must be interpreted in the context of a clinical trial that encouraged adherence to a healthy lifestyle, as the absence of evidence does not represent evidence of no effect.

Acknowledgements

The authors wish to thank the PREDIMED-Plus participants and staff for their engagement, as well as the primary care centres involved in the study. We also thank the Cerca Programme of the Generalitat de Catalunya, the CIBEROBN, CIBERESP and CIBERDEM initiatives of Instituto de Salud Carlos III in Spain.

This work was supported by a project grant from the Fundación Francisco Soria Melguizo. The project also received support from the Community of Madrid and the European Union, through the European Regional Development Fund (ERDF)-REACT-EU resources of the Madrid Operational Program 2014–2020, in the action line of R+D+i projects in response to COVID-19, FACINGLCOVID -CM. The PREDIMED-Plus trial was supported by the official Spanish Institutions for funding scientific biomedical research, CIBER Fisiopatología de la Obesidad y Nutrición (CIBEROBN) and Instituto de Salud Carlos III (ISCIII), through the Fondo de Investigación para la Salud (FIS), which is co-funded by the European Regional Development Fund (six coordinated FIS projects leaded by JS-S and JVi, including the following projects: PI13/00673, PI13/00492, PI13/00272, PI13/01123, PI13/00462, PI13/00233, PI13/02184, PI13/00728, PI13/01090, PI13/01056, PI14/01722, PI14/00636, PI14/00618, PI14/00696, PI14/01206, PI14/01919, PI14/00853, PI14/01374, PI14/00972, PI14/00728, PI14/01471, PI16/00473, PI16/00662, PI16/01873, PI16/01094, PI16/00501, PI16/00533, PI16/00381, PI16/00366, PI16/01522, PI16/01120, PI17/00764, PI17/01183, PI17/00855, PI17/01347, PI17/00525, PI17/01827, PI17/00532, PI17/00215, PI17/01441, PI17/00508, PI17/01732, PI17/00926, PI19/00957, PI19/00386, PI19/00309, PI19/01032, PI19/00576, PI19/00017, PI19/01226, PI19/00781, PI19/01560, PI19/01332, PI20/01802, PI20/00138, PI20/01532, PI20/00456, PI20/00339, PI20/00557, PI20/00886, PI20/01158, PI21/01617, PI21/01214, PI21/00767, PI21/00465, PI17/00214, PI20/00012, CP21/00097); the Especial Action Project entitled: Implementación y evaluación de una intervención intensiva sobre la actividad física Cohorte PREDIMED-Plus grant to JS-S; the European Research Council (Advanced Research Grant 2014–2019; agreement #340918) granted to MÁM-G.; the Recercaixa (number 2013ACUP00194) grant to JS-S; grants from the Consejería de Salud de la Junta de Andalucía (PI0458/2013, PS0358/2016, PI0137/2018); the PROMETEO/2017/017, PROMETEO 21/2021 and the AICO/2021/347 grants from the Generalitat Valenciana; the SEMERGEN grant. This research was also partially funded by EU-H2020 Grants (Eat2beNICE/ H2020-SFS-2016-2; and the Horizon 2020 PRIME study (Prevention and Remediation of Insulin Multimorbidity in Europe; grant agreement #847879). S.G.S is a recipient of the Maria Zambrano Fellowship with funding support from the Ministry of Universities and the Recovery, Transformation and Resilience Plan, Spain. The Fellowship is "Funded by the European Union – NextGenerationEU". CG-M receives a predoctoral scholarship (2020PMF-PIPF-37) from URV. JN is supported by a predoctoral grant from Ministerio de Ciencia, Innovación y Universidades (FPU 20/00385). AH-C is supported by a predoctoral grant from Martí Franquès – INVESTIGO research fellowship funded and supported by NextGenerationEU, Servicio Público de Empleo Estatal and Universitat Rovira i Virgili (2022PMF-INV-01). JS-S was partially supported by ICREA under the ICREA Academia program. We thank the CERCA Programme/Generalitat de Catalunya for institutional support. The Institut de Recerca en Nutrició i Seguretat Alimentaria (INSA-UB). The University of Barcelona, Barcelona, Spain, is recognized as a Maria de Maeztu Unit of Excellence grant CEX2021-001234-M) funded by MICIN/AEI/FEDER, UE.

Author contributions

Conceptualization; JSS, MF, MAM, DC, JAM, ÁMAG, JW, JV, DR, JLM, RE, FJT, JL, JLSM, ABC, JAT, VMS, XP, PMM, JV, CV, LD, ER, FFA, MDR, NB, SS, CGM; JN. Data curation; Investigation; JSS, MF, MÁM, DC, JAM, AMAG, JW, JV, DR, JLM, RE, FJT, JL, JLSM, ABC, JAT, VMS, XP, PMM, JV, CV, LD, ER, FFA, MDR, NB, SS, CGM; JN. Formal Analysis & Methodology; SS, CGM; JN, NB, JSS. Funding acquisition; JSS, MF, MAM, DC, JAM, AMAG, JW, JV, DR, JLM, RE, FJT, JL, JLSM, ABC, JAT, VMS, XP, PMM, JV, LD, ER, FFA, and MDR. Project Administration; Resources; Software; Supervision; JSS & MF. Writing - original draft; SS, CGM; JN, JSS. Writing - review & editing: All authors.

Competing interests

The funders had no role in the "design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication."

Data and materials availability: The study protocol of PREDIMDED-Plus including its statistical analysis plan has been published earlier and can be downloaded from https://www.predimedplus.com/. Data and variables collected in PREDIMED-Plus and the procedure for request of data or samples are outlined here. The datasets generated and analyzed during the current study are not publicly available due to data regulations and for ethical reasons, considering that this information might compromise research participants' consent because our participants only gave their consent for the use of their data by the original team of investigators. However, collaboration for data analyses can be requested by sending a letter to the PREDIMED-Plus Steering Committee (predimed_plus_scommittee@googlegroups.com). The request will then be passed to all the members of the PREDIMED-Plus Steering Committee for deliberation.

Conflict of interest

FFA acknowledges consulting fees from Novo Nordisk and Wiley as EIC for the European Eat Dis Rev. He has also received honoraria for lectures and support for travel/meetings from Novo Nordisk. He discloses his honorary participation in the Data Safety Monitoring Board or Advisory Board of Sustain-Consortium-Germany. ER has received honoraria for presentations and support for attending meetings/travel from the California Walnut Commission, Alexion and the Spanish Atherosclerosis Society. He has also received consulting fees from Alexion. He participates in the Data Safety Monitoring Board or Advisory Board of the PREDIMED-Plus Clinical Trial. RE has received research grants from Instituto de Salud Carlos III, Madrid, Spain. He has received honoraria for presentations from Fundacion Cerveza y Salud, Spain; Instituto Cervantes, Albuquerque, USA; Instituto Cervantes, Milan, Italy; Instituto Cervantes, Tokyo, Japan; Fundacion Bosch i Gimpera, Spain; Wine and Culinary International Forum; Pernaud Richart; Mexico; Fundacion Dieta Mediterranea, Barcelona, Spain. He has received support for travel or meetings or conference organizations from ERAB, Belgium, Brewers of Europe, Belgium, and Sociedad Española de Nutrición (SEN). He has served on the Advisory Board of Cerveza y Salud, Spain. JSS reported receiving consulting fees from the Eroski Foundation. He has also received grants and support for attending meetings/travel from the Nut and Dried Fruit Foundation. He is an honorary Member of the International Advisory Board of the Project "Effect of cashew nut supplementation on glycemic status and lipid profile in type 2 diabetes subjects", Member of the Scientific Advisory Committee of the European PEGASO project (Personalized Guidance Services for Optimizing lifestyle management in teenagers through awareness, motivation and engagement) and Member of the Scientific Committee of Danone Institute International. He received personal fees for serving as a Member of the Institute Danone Advisory Board. SS has received consulting fees from Abbott Sdn Bhd. Other authors declare no potential conflict of interest.

Supplementary Materials

The Supplementary data can be found online at: www.aginganddisease.org/EN/10.14336/AD.2024.0380.

References

[1] Duan J, Lv YB, Gao X, Zhou JH, Kraus VB, Zeng Y, et al. (2020). Association of cognitive impairment and elderly mortality: differences between two cohorts ascertained 6-years apart in China. BMC Geriatrics, 20:29.

[2] Guo P, Benito Ballesteros A, Yeung SP, Liu R, Saha A, Curtis L, et al. (2022). COVCOG 1: Factors Predicting Physical, Neurological and Cognitive Symptoms in Long COVID in a Community Sample. A First Publication from the COVID and Cognition Study. Front Aging Neurosci, 14:804922–804922.

[3] Ali Awan H, Najmuddin Diwan M, Aamir A, Ali M, Di Giannantonio M, Ullah I, et al. (2021). SARS-CoV-2 and the Brain: What Do We Know about the Causality of 'Cognitive COVID? J Clin Med, 10:3441.

[4] Ferrucci R, Dini M, Rosci C, Capozza A, Groppo E, Reitano MR, et al. (2022). One-year cognitive follow-up of COVID-19 hospitalized patients. Eur J Neurol, 29:2006–2014.

[5] del Corral T, Menor-Rodríguez N, Fernández-Vega S, Díaz-Ramos C, Aguilar-Zafra S, López-de-Uralde-Villanueva I (2024). Longitudinal study of changes observed in quality of life, psychological state cognition and pulmonary and functional capacity after COVID-19 infection: A six- to seven-month prospective cohort. J Clin Nurs, 33:89–102

[6] Schou TM, Joca S, Wegener G, Bay-Richter C (2021). Psychiatric and neuropsychiatric sequelae of COVID-19-A systematic review. Brain Behav Immun, 97:328-348.

[7] Ceban F, Ling S, Lui LMW, Lee Y, Gill H, Teopiz KM, et al. (2022). Fatigue and cognitive impairment in Post-COVID-19 Syndrome: A systematic review and meta-analysis. Brain Behav Immun, 101:93-135.

[8] Valdes E, Fuchs B, Morrison C, Charvet L, Lewis A, Thawani S, et al. (2022). Demographic and social determinants of cognitive dysfunction following hospitalization for COVID-19. J Neurol Sci, 438: 120146-120146.

[9] Channappanavar R, Perlman S (2020). Age-related susceptibility to coronavirus infections: role of impaired

and dysregulated host immunity. J Clin Invest, 130: 6204-6213.

[10] Martínez-González MA, Buil-Cosiales P, Corella D, Bulló M, Fitó M, Vioque J, et al. (2019). Cohort Profile: Design and methods of the PREDIMED-Plus randomized trial. Int J Epidemiol, 48:387-388o.

[11] Shyam S, Gómez-Martínez C, Paz-Graniel I, Gaforio JJ, Martínez-González MÁ, Corella D, et al. (2023). Coronavirus disease 2019 is associated with long-term depressive symptoms in Spanish older adults with overweight/obesity and metabolic syndrome. Psychol Med, 1-11.

[12] McFee, RB (2020). COVID-19 laboratory testing/CDC guidelines. Disease-a-month, *66*(9): 101067.

[13] Blesa R (2001). Normalisation of cognitive and functional instruments for dementia. Clinical validity of the "mini-mental state" for Spanish speaking communities. Neuropsychologia, 39:1150–1157.

[14] Ser Quijano T del, García de Yébenes MJ, Sánchez Sánchez F, Frades Payo B, Rodríguez Laso Á, Bartolomé Martínez MP, et al. (2004). Evaluación cognitiva del anciano. Datos normativos de una muestra poblacional española de más de 70 años. Medicina Clínica, 122:727–740.

[15] Peña-Casanova J, Quiñones-Úbeda S, Gramunt-Fombuena N, Quintana-Aparicio M, Aguilar M, Badenes D, et al. (2009). Spanish Multicenter Normative Studies (NEURONORMA Project): Norms for Verbal Fluency Tests. Arch Clin Neuropsychol, 24:395-411.

[16] Llinàs-Reglà J, Vilalta-Franch J, López-Pousa S, Calvó-Perxas L, Torrents Rodas D, Garre-Olmo J (2017). The Trail Making Test: Association with Other Neuropsychological Measures and Normative Values for Adults Aged 55 Years and Older from a Spanish-Speaking Population-Based Sample. Assessment, 24:183-196.

[17] Strauss E, Sherman EMS, Spreen O (2006). A compendium of neuropsychological tests: Administration, norms, and commentary, 3rd ed. Oxford University Press, 1216.

[18] Lezak MD, Howieson DB, Bigler ED, Tranel D (2012). Neuropsychological assessment, 5th ed. Oxford University Press, 1161.

[19] Zheng F, Yan L, Yang Z, Zhong B, Xie W (2018). HbA1c, diabetes and cognitive decline: the English Longitudinal Study of Ageing. Diabetologia, 61:839-848.

[20] Ganguli M, Belle S, Ratcliff G, Seaberg E, Huff FJ, von der Porten K, et al. (1993). Sensitivity and specificity for dementia of population-based criteria for cognitive impairment: the MoVIES project. J Gerontol, 48:M152-161.

[21] Molina L, Sarmiento M, Peñafiel J, Donaire D, Garcia-Aymerich J, Gomez M, et al. (2017). Validation of the Regicor Short Physical Activity Questionnaire for the Adult Population. PLoS One, 12:e0168148.

[22] Sanz J, Perdigón AL, Vázquez C (2003). Adaptación española del Inventario para la Depresión de Beck-ll (BDI-II): 2. Propiedades psicométricas en población general. [The Spanish adaptation of Beck's Depression Inventory-ll (BDI-II): 2. Psychometric properties in the general population. Clínica y Salud, 14:249–280.

[23] Sanz Fernández J (2013). 50 years of the Beck Depression Inventory: recommendations for using the Spanish adaptation of the BDI-II in clinical practice. Papeles del Psicólogo, 34:161-168

[24] Filippou CD, Thomopoulos CG, Kouremeti MM, Sotiropoulou LI, Nihoyannopoulos PI, Tousoulis DM, et al. (2021). Mediterranean diet and blood pressure reduction in adults with and without hypertension: A systematic review and meta-analysis of randomized controlled trials. Clin Nutr, 40:3191-3200.

[25] Corbett A, Williams G, Creese B, Hampshire A, Hayman V, Palmer A, et al. (2023). Cognitive decline in older adults in the UK during and after the COVID-19 pandemic: a longitudinal analysis of PROTECT study data. Lancet Healthy Longev, 4:e591-e599.

[26] Cheetham NJ, Penfold R, Giunchiglia V, Bowyer V, Sudre CH, Canas LS, et al. (2023). The effects of COVID-19 on cognitive performance in a community-based cohort: a COVID symptom study biobank prospective cohort study. eClinicalMedicine, 62:102086

[27] Becker JH, Vannorsdall TD, Weisenbach SL (2023). Evaluation of Post–COVID-19 Cognitive Dysfunction: Recommendations for Researchers. JAMA Psychiatry, 80:1085-1086.

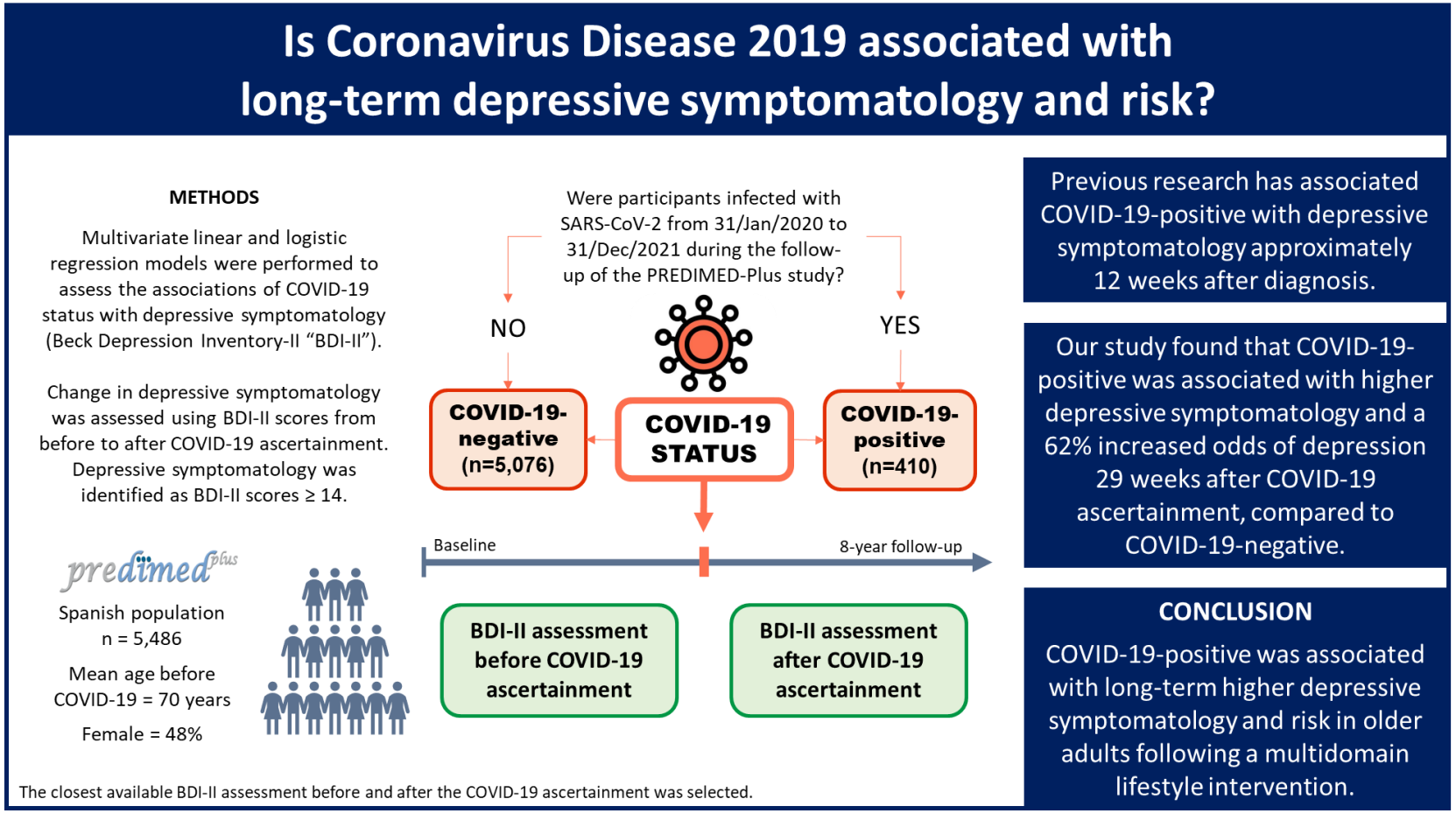
[28] Pollán M, Pérez-Gómez B, Pastor-Barriuso R, Oteo J, Hernán MA, Pérez-Olmeda M, et al. (2020). Prevalence of SARS-CoV-2 in Spain (ENE-COVID): a nationwide, population-based seroepidemiological study. Lancet, 396:535-544.

[29] Waterink L, Bakker ED, Visser LNC, Mangialasche F, Kivipelto M, Deckers K, et al. (2022). Changes in Brain-Health Related Modifiable Risk Factors in Older Adults After One Year of COVID-19-Restrictions. Front Psychiatry, 13:877460.

UNIVERSITAT ROVIRA I VIRGILI
Psychology and Disease: Unveiling Emerging Perspectives on Their Interplay
Carlos Gómez Martínez

CHAPTER 7:
COVID-19 AND DEPRESSIVE SYMPTOMATOLOGY

Figure 12. Graphical abstract of Chapter 7. COVID-19 and depressive symptomatology.



Psychological Medicine

cambridge.org/psm

Coronavirus disease 2019 is associated with long-term depressive symptoms in Spanish older adults with overweight/obesity and metabolic syndrome

Sangeetha Shyam[1,2,3], Carlos Gómez-Martínez[1,2,3], Indira Paz-Graniel[1,2,3], José J. Gaforio[4,5], Miguel Ángel Martínez-González[1,6,7], Dolores Corella[1,8], Montserrat Fitó[1,9], J. Alfredo Martínez[1,10,11], Ángel M. Alonso-Gómez[1,12], Julia Wärnberg[1,13], Jesús Vioque[4,14], Dora Romaguera[1,15], José López-Miranda[1,16], Ramon Estruch[1,17], Francisco J. Tinahones[1,18], José Manuel Santos-Lozano[1,19], J. Luís Serra-Majem[1,20], Aurora Bueno-Cavanillas[4,21], Josep A. Tur[1,22], Vicente Martín Sánchez[4,11,23], Xavier Pintó[1,24], María Ortiz Ramos[25], Josep Vidal[26,27], Maria Mar Alcarria[28], Lidia Daimiel[1,29,30], Emilio Ros[1,31], Fernando Fernandez-Aranda[1,32,33], Stephanie K. Nishi[1,2,3,34], Oscar García Regata[35], Estefania Toledo[1,6], Jose V. Sorli[1,8], Olga Castañer[9], Antonio Garcia-Rios[1,16], Rafael Valls-Enguix[36], Napoleon Perez-Farinos[1,13], M. Angeles Zulet[1,10], Elena Rayó-Gago[15], Rosa Casas[1,17], Mario Rivera-Izquierdo[21], Lucas Tojal-Sierra[1,12], Miguel Damas-Fuentes[18], Pilar Buil-Cosiales[1,6,37], Rebeca Fernández-Carrion[1,8], Albert Goday[9], Patricia J. Peña-Orihuela[1,16], Laura Compañ-Gabucio[4,14], Javier Diez-Espino[1,6,37], Susanna Tello[9], Ana González-Pinto[38], Víctor de la O[1,6], Miguel Delgado-Rodríguez[11,39], Nancy Babio[1,2,3] and Jordi Salas-Salvadó[1,2,3]

Original Article

Cite this article: Shyam S *et al* (2023). Coronavirus disease 2019 is associated with long-term depressive symptoms in Spanish older adults with overweight/obesity and metabolic syndrome. *Psychological Medicine* 1–11. https://doi.org/10.1017/S0033291723002313

Received: 9 March 2023
Revised: 20 July 2023
Accepted: 21 July 2023

Keywords:
COVID-19; depression; older adults; PREDIMED-Plus; SARS-CoV-2

Corresponding author:
Sangeetha Shyam;
Email: Sangeetha.shyam@urv.cat;
Nancy Babio;
Email: nancy.babio@urv.cat

Abstract

Background. The coronavirus disease 2019 (COVID-19) has serious physiological and psychological consequences. The long-term (>12 weeks post-infection) impact of COVID-19 on mental health, specifically in older adults, is unclear. We longitudinally assessed the association of COVID-19 with depression symptomatology in community-dwelling older adults with metabolic syndrome within the framework of the PREDIMED-Plus cohort.

Methods. Participants ($n = 5486$) aged 55–75 years were included in this longitudinal cohort. COVID-19 status (positive/negative) determined by tests (e.g. polymerase chain reaction severe acute respiratory syndrome coronavirus 2, IgG) was confirmed via event adjudication (410 cases). Pre- and post-COVID-19 depressive symptomatology was ascertained from annual assessments conducted using a validated 21-item Spanish Beck Depression Inventory-II (BDI-II). Multivariable linear and logistic regression models assessed the association between COVID-19 and depression symptomatology.

Results. COVID-19 in older adults was associated with higher post-COVID-19 BDI-II scores measured at a median (interquartile range) of 29 (15–40) weeks post-infection [fully adjusted $\beta = 0.65$ points, 95% confidence interval (CI) 0.15–1.15; $p = 0.011$]. This association was particularly prominent in women ($\beta = 1.38$ points, 95% CI 0.44–2.33, $p = 0.004$). COVID-19 was associated with 62% increased odds of elevated depression risk (BDI-II ≥ 14) post-COVID-19 when adjusted for confounders (odds ratio; 95% CI 1.13–2.30, $p = 0.008$).

Conclusions. COVID-19 was associated with long-term depression risk in older adults with overweight/obesity and metabolic syndrome, particularly in women. Thus, long-term evaluations of the impact of COVID-19 on mental health and preventive public health initiatives are warranted in older adults.

Background

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) evolved into a global pandemic since its emergence in 2019

(Guo et al., 2022). Despite largely affecting the respiratory system, COVID-19's impact on the cardiovascular, gastrointestinal, and neurologic systems has been recognized (Sparks et al., 2020). Long-term physical and mental health consequences of COVID-19 are increasingly understood as more data become available (Lopez-Leon et al., 2021).

Depression is a potentially serious mental health consequence of COVID-19, with its prevalence post-COVID-19 depending on the individual's age and the timing of depression assessment in relation to the infection (Pano et al., 2021). While depression is common in the acute 4-weeks post-infection, there are scarce data on its long-term prevalence (>12 weeks after the diagnosis of COVID-19) (Mazza et al., 2020; Renaud-Charest et al., 2021). Recently, a meta-analysis determined the frequency of depressive symptoms ≥ 12 weeks post-infection in COVID-19-positive men and women aged over 19 years, with varying degrees of COVID-19 severity, including both hospitalized and non-hospitalized populations and those with and without comorbidities. In this heterogeneous group, the frequency of depressive symptoms ranged between 11% and 28%, while clinically significant depression and/or severe depressive symptoms affected 3–12% of the participants, at >12 weeks after COVID-19 (Renaud-Charest et al., 2021). While the long-term impact of COVID-19 on depression in the general population may be small, the effects appear to be severe in older age groups (Klaser et al., 2021), specifically in older women and those with prior depressive tendencies (Mazza et al., 2020; Meng et al., 2020; Renaud-Charest et al., 2021).

Older age and cardiometabolic risks increase susceptibility to severe COVID-19 (Channappanavar & Perlman, 2020; Mueller, McNamara, & Sinclair, 2020; Wee, 2021), and depression is more prevalent in those with metabolic syndrome and diabetes (Dunbar et al., 2008; Khaledi, Haghighatdoost, Feizi, & Aminorroaya, 2019). The mental health consequence of COVID-19 in older adults with metabolic disturbances is of specific concern because depression is associated with lower adherence to treatment (Castro et al., 2021), poorer prognosis (Dunbar et al., 2008; Khaledi et al., 2019), and higher risk of mortality in community-dwelling older adults (Wei et al., 2019). While affecting mortality and quality of life in older adults with high cardiometabolic risk, the long-term impact of COVID-19 on depression symptoms will also represent a burden for healthcare systems. Therefore, understanding the impact of COVID-19 on older adults with comorbidities will facilitate early identification and management of the mental health sequelae of COVID-19 in this population. Existing evidence on the topic is highly heterogeneous in terms of the location, age, and sex of individuals and time of depressive symptoms assessment post-COVID-19. Few studies include an unexposed control group to quantify the impact of COVID-19 on depression (Renaud-Charest et al., 2021). These limitations make it challenging to inform practice with existing information.

Thus, we examined the association of COVID-19 with depressive symptomatology in older adults with overweight/obesity and metabolic syndrome enrolled in the PREDIMED-Plus trial in Spain. We hypothesized that a positive diagnosis of COVID-19 would be associated with higher post-COVID-19 scores for depressive symptoms in comparison to a COVID-19 negative status. We also investigated if sex, time of post-COVID-19 depression assessment, and pre-existing depressive symptomatology affected this association.

Methods

Study design and participants

This analysis involved older women and men enrolled in the PREDIMED-Plus trial, a multicentre, randomized controlled clinical trial in Spain (Martínez-González et al., 2019). PREDIMED-Plus is an existing longitudinal cohort of 6874 community-dwelling older adults with overweight/obesity and metabolic syndrome. At enrolment, participants were free from cardiovascular disease, cancers, major depressive disorder, and other major chronic conditions. The trial aims to assess in this cohort the effectiveness of an energy-reduced Mediterranean diet, physical activity, and behavioural support intervention on the primary prevention of cardiovascular disease in comparison to an *ad libitum* Mediterranean diet without advice to increase physical activity or reduce energy intake. The ongoing trial began its recruitment in 2013 and is scheduled to be completed in 2024. A detailed study protocol has been published earlier (Martínez-González et al., 2019; Salas-Salvadó et al., 2018) (see supplementary methods).

The PREDIMED-Plus protocol has been approved by the institutional review boards of all participating centres in accordance with the Declaration of Helsinki. All enrolled participants provided written informed consent. This study is registered at the International Standard Randomized Controlled Trial (ISRCT; http://www.isrctn.com/ISRCTN89898870).

The cohort has validated assessments of depression that were obtained before the onset of the COVID-19 pandemic as well as ongoing follow-up measurements. The PREDIMED-Plus database also contains data on demography and clinical status that could confound the relationship between COVID-19 and depression. Thus, the PREDIMED-Plus cohort provides a unique opportunity to evaluate the association of COVID-19 with depressive symptomatology in older adults with overweight/obesity and metabolic syndrome.

Ascertainment of variables

Exposure: SARS-CoV-2 infection

For the primary analysis, the main exposure was a confirmed COVID-19 event in a participant (positive/negative) as adjudicated by the Clinical Event Ascertainment Committee of the trial. The clinical event determination was based on the information from participant medical records reviewed annually by the participating physicians (CDC, 2020). Overall, 410 participants in this analysis were COVID-19 positive. Participants who did not have a confirmed/probable COVID-19-positive diagnosis were considered COVID-19 negative (i.e. assumed to have not experienced the infection). The COVID-19 status accordingly established as a dichotomous variable (positive/negative) was used to define the exposure.

A supplementary analysis was performed using a subsample ($n = 3982$) of the PREDIMED-Plus participants who had undergone serology testing with SARS-CoV-2 IgG ELISA Kits. These tests obtained between 3 March 2020, and 25 December 2021, classified participants as COVID-19 negative ($n = 3698$)/COVID-19 positive ($n = 287$). COVID-19 status was accordingly defined as a dichotomous predictor variable in the supplementary analysis (see supplementary methods for details).

Outcome: depression assessment

Depression assessment in the PREDIMED-Plus. As per the PREDIMED-Plus protocol, participants' complete annual

https://doi.org/10.1017/S0033291723002313 Published online by Cambridge University Press

assessments of depressive symptomatology were performed using the validated 21-item Spanish version of the Beck Depression Inventory-II (BDI-II) (Fernández, Valverde, & Perdigón, 2003). Each item in the BDI-II has four possible answers with scores ranging from 0 to 3 in accordance with symptom severity. Thus, the sum total of the BDI-II score ranges between 0 and 63 points, with higher scores indicating a higher propensity for depression.

Identifying pre- and post-COVID-19 measurements. From the annual assessments of depressive symptomatology, a pre-COVID-19 and a post-COVID-19 measurements were identified for each participant based on their COVID-19 event status. For COVID-19-positive participants, the last available BDI-II assessment prior to the COVID-19 diagnosis date was ascertained as the pre-COVID-19 measurement. In these participants, the BDI-II score available from the first post-COVID-19 follow-up visit was ascertained as the post-COVID-19 BDI-II score. For COVID-19-negative participants, the date of identification of the first COVID-19 case in Spain (31 January 2020) was used as a hinge to identify BDI-II scores from comparable time points as COVID-19-positive participants. Thus, in COVID-19-negative participants, BDI-II scores from a visit before 31 January 2020 indicated pre-COVID-19 measurement and those from the subsequent visit were used as post-COVID-19 measurement (online Supplementary Fig. S1). The duration between pre- and post-COVID-19 depression measurements and the time elapsed from the COVID-19 event at post-COVID-19 depression measurements were calculated in weeks. Time elapsed at post-COVID-19 depression measurement was further categorized as ≤12 weeks and >12 weeks to stratify the time-dependent effects of COVID-19 on depression (Klaser et al., 2021; Renaud-Charest et al., 2021).

Categorizing post-COVID-19 depression risk as the outcome variable. For the primary analysis, the post-COVID-19 BDI-II score was used as a continuous outcome. BDI-II scores have also been categorized to identify the risk of depression: scores 0–13 indicate minimal risk, and scores ≥ 14 identify elevated risk (Becker, Steer, & Brown, 1996). For a secondary analysis, we categorized elevated depression risk accordingly and treated it as a binary outcome. In addition, since a cut-off ≥ 12 had an adequate specificity index and diagnostic concordance and detects major depressive episodes in 93% of Spanish individuals (Sanz Fernández, 2013), a supplementary analysis using a cut-off ≥ 12 was also conducted.

Assessment of confounder variables

Data on potentially relevant confounders were also obtained from the PREDIMED-Plus database (See supplementary methods). Pre-COVID-19 visit covariates used in the models included age (years), marital status (levels: single/divorced, married or widow/widower), adherence to the Mediterranean diet (er-MEDAS score), alcohol consumption (g/day), total physical activity (METs min/week), and body mass index (BMI; kg/m^2). For other confounders including sex (man/woman), education (<high school, high school, and university), intervention group (A/B), recruitment centre size (>400, 300–400, 250–300, and <250), smoking status (never/former smoker/current smoker), the prevalence of type 2 diabetes mellitus (yes/no), hypercholesterolemia (yes/no), hypertension (yes/no), and cognitive performance [Mini-Mental State Examination (MMSE) scores], and study baseline data were used to reduce missing data. Since the time elapsed since COVID-19 can impact depression assessments (Renaud-Charest et al., 2021), this duration (weeks) was adjusted for confounding in regression models. Since pre- and post-COVID-19 BDI-II scores were highly correlated, pre-COVID-19 BDI-II scores were adjusted as a covariate in all models.

Statistical analyses

The present analysis was conducted as a prospective cohort study using the PREDIMED-Plus database with the COVID-19 event status updated until 31 December 2021. All other data (depression outcomes and confounder data) were sourced from the database that was updated until 4 November 2022. This allowed for sourcing depression assessments before and after COVID-19 and enabled the inclusion of both acute (<12 weeks) and long-term (≥12 weeks) associations of COVID-19 on depressive symptomatology. We included participants who had completed depression questionnaire assessments both before and after the ascertainment of COVID-19 event status.

In a preliminary cross-sectional exploration, we compared the characteristics and the timing of depression assessment of COVID-19-negative and positive participants using the Chi-Square and Mann–Whitney *U* tests, as appropriate.

The primary analysis evaluated the longitudinal relationship of COVID-19 on post-infection depression symptomatology (BDI-II scores) using linear regression models, considering the COVID-19-negative status as the reference category. In addition to the unadjusted crude model, three other models were tested. Model 1 adjusted for age, sex, education, marital status, intervention group, recruitment centre size, pre-COVID-19 BDI-II scores, and time since COVID-19 for depression assessments as confounders. Model 2 additionally adjusted for the presence of obesity (BMI ≥ 30 kg/m^2), type 2 diabetes mellitus, hypertension, hypercholesterolemia, and cognitive performance on recruitment to the trial. Model 3 also adjusted for lifestyle factors including scores of adherence to the Mediterranean diet, total physical activity levels, smoking status, and alcohol consumption. Alcohol consumption was used as a quadratic term in the model to accommodate for a nonlinear relationship with the outcome. All analyses were conducted with robust estimates of the variance to correct for intracluster correlation. This procedure was used to control for the allocation of household members into the same intervention group without randomization.

A secondary logistic regression analysis using the same models developed for the main analysis was performed with elevated depression risk post-COVID-19 (BDI-II cut-off ≥ 14) as a binary outcome.

Furthermore, to negate over-adjustments, a directed acyclic graph (DAG) (Textor, van der Zander, Gilthorpe, Liśkiewicz, & Ellison, 2016) was modelled (online Supplementary Fig. S2) and a minimal adjustment set was identified for both the linear and logistic regression models. This minimal model adjusted only for pre-COVID-19 depression scores. An additional supplementary logistic regression analysis was undertaken using a BDI-II score ≥ 12 as the cut-off for elevated depression risk.

Effect modification of the association by potential confounders [age group (≤70 or >70 years), sex, intervention group, disease conditions, and time elapsed post-COVID-19] was assessed by introducing product terms in the multivariable model. Further, sub-analyses that stratified results by factors that showed significant interaction (sex, presence of pre-COVID-19 high depression risk, and time elapsed post-COVID-19 during depression

https://doi.org/10.1017/S0033291723002313 Published online by Cambridge University Press

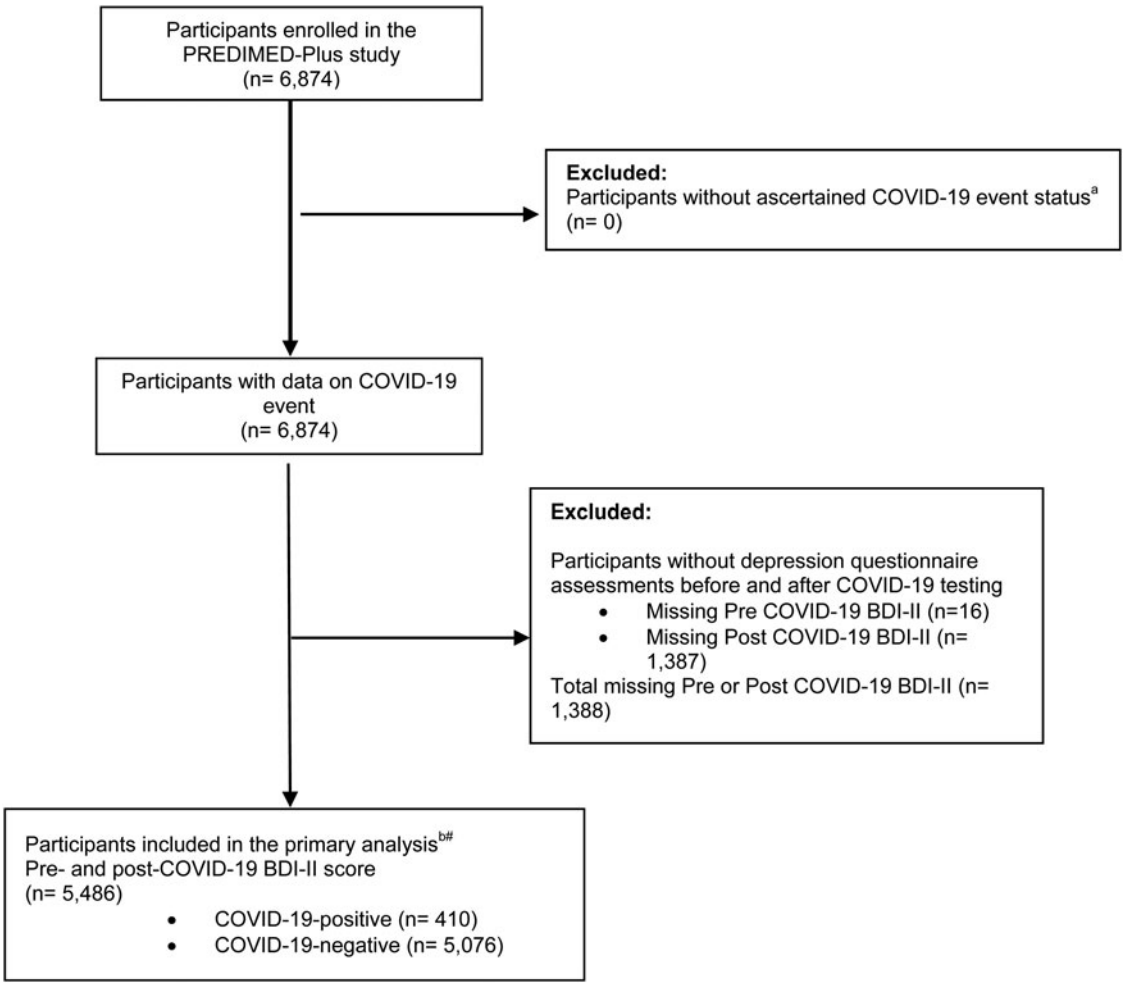


Figure 1. Flow diagram for PREDIMED-Plus participants included in the analysis to evaluate the impact of COVID-19 on depression. BDI-II, Beck Depression Inventory-II; BMI, body mass index; COVID-19, coronavirus disease 2019; MMSE, Mini-Mental State Examination. [a]Analysis used COVID-19 event confirmation data from the PREDIMED-Plus database updated until December 2021. [b]Analysis used depressive and covariate assessments from the PREDIMED-Plus database updated until November 2022. [#]Age, sex, education, intervention group, recruitment centre, smoking status, physical activity, adherence to the Mediterranean diet, BMI, prevalence of baseline diabetes, hypertension, and hypercholesterolemia had no missing data for this analysis. Marital status: 12/5486 (0.2%) missing data. Missing data were replaced with the mode of the variable for the cohort. Alcohol consumption: 15/5486 (0.3%) missing data. Missing data were replaced with cohort mean consumption by gender (*men = 17.47; women = 4.59 g/day). MMSE data: 135/5486 missing data (2.4%). No imputation was performed for missing data.

assessments) were undertaken. Finally, supplementary linear and logistic analyses were conducted in the sub-sample with serology results to ascertain COVID-19 status.

Data were analysed using the Stata 14 software (StataCorp, College Station, TX, USA), and statistical significance was set at a two-tailed p value <0.05 (see supplementary methods for details).

Results

This analysis included a total of 5486 PREDIMED-Plus participants (51.7% men) with a median [interquartile range (IQR)] age of 69.7 (7.4) years (Fig. 1). Table 1 shows their characteristics stratified by COVID-19 event status. At the pre-COVID-19 visit, participants had a median (IQR) BDI-II score of 5 (8), and these scores did not significantly differ by COVID-19 status. Approximately 14% of the participants included in this analysis had elevated depression risk at the pre-COVID-19 visit with no significant difference in the prevalence between COVID-19-positive and COVID-19-negative individuals. A COVID-19-positive status was associated with the male sex. COVID-19-positive participants were also more likely to report having been former smokers. All other factors evaluated were comparable in COVID-19-positive and COVID-19-negative individuals at the pre-COVID-19 visit.

Post-COVID-19 depression assessments in COVID-19-positive participants were on average assessed 23 weeks post-infection. The duration between pre- and post-COVID-19 depression assessments was significantly shorter in COVID-19-positive *v.* COVID-19-negative participants ($p < 0.001$, Table 1). However, the mean difference in duration between pre- and post-COVID-19 depression assessments between those who had and did not have the infection was <5 days.

Table 2 evaluates the longitudinal association of COVID-19 on BDI-II scores over a median (IQR) duration of 29.4 (24.7) weeks post-COVID-19 in the cohort. In the fully adjusted model, SARS-CoV-2 infection was significantly associated with post-COVID-19 BDI-II scores [β (95% confidence interval (CI)) 0.65 (0.15–1.15), $p = 0.011$].

https://doi.org/10.1017/S0033291723002313 Published online by Cambridge University Press

Table 1. Participant characteristics according to COVID-19 status

Characteristics	Full sample ($n = 5486$)	COVID-19 status		p Value[a]
		Positive ($n = 410$)	Negative ($n = 5076$)	
Sociodemographic data				
Age at pre-COVID visit, years[b]	69.7 (7.4)	69.7 (7.6)	69.7 (7.3)	0.64
Men, *n* (%)	2836 (51.7)	239 (58.3)	2597 (51.2)	<0.01
Education level, *n* (%)[c]				0.14
Less than high school	2730 (49.8)	188 (45.9)	2542 (50.1)	
High school or equivalent	1560 (28.4)	118 (28.8)	1442 (28.4)	
University	1196 (21.8)	104 (25.4)	1092 (21.5)	
Civil status, *n* (%)[d]				0.43
Single or divorced	678 (12.4)	52(12.7)	626 (12.3)	
Married	4135 (75.4)	316 (77.1)	3819 (75.2)	
Widow/widower	673 (12.3)	42 (10.2)	631 (12.4)	
Intervention group (Group B)	2649 (48.3)	195 (47.6)	2454 (48.4)	0.76
Lifestyle habits				
Smoking habit, *n* (%)[c]				<0.01
Never smoker	2477 (45.1)	163 (39.8)	2314 (45.6)	
Former smoker	2352 (42.9)	205 (50.0)	2147(42.3)	
Current smoker	657 (12.0)	42 (10.2)	615 (12.1)	
17-item MedDiet score[b,d,e]	12(4)	12(4)	12(4)	0.97
Total physical activity, METs min/week[b,d]	2545 (2853)	2654 (3040)	2544 (2853)	0.75
Alcohol consumption, g/day[b,d]	4.0 (11.3)	4.5 (12.6)	3.8 (11.3)	0.06
Anthropometry, clinical and cognitive data				
BMI, kg/m^2[b,d]	31.4 (5.3)	31.7 (5.3)	31.3(5.3)	0.09
Obesity; BMI $\geq$ 30, *n* (%)[d]	3515 (64.1)	275 (67.1)	3240 (63.8)	0.18
Diabetes, *n* (%)[c]	1621 (29.6)	122 (29.8)	1499 (29.5)	0.92
Hypercholesterolaemia, *n* (%)[c]	3842 (70.0)	272 (66.3)	3570 (70.3)	0.09
Hypertension, *n* (%)[c]	4591 (83.7)	330(80.5)	4261 (84.0)	0.08
MMSE scores[b,c,e]	29 (3)	29 (2)	29 (3)	0.31
Depression data				
BDI-II scores[b,c]				
Pre-COVID-19	5 (8)	4 (8)	5 (8)	0.14
Post-COVID-19	5 (7)	5 (8)	5 (7)	0.62
Elevated depression risk, *n* (%)[c]	1077 (19.7)	71 (17.3)	1006 (19.9)	0.21
Elevated depression risk, pre-COVID-19, *n* (%)[d]	758 (13.8)	53 (12.9)	705 (13.9)	0.65
Elevated depression risk, post-COVID-19, *n* (%)	661 (12.1)	58 (14.2)	603 (11.9)	0.18
Time between pre- and post-COVID-19 depression measurements, weeks[f]	53.0 (51.0–55.1)	52.3 (50.0–54.6)	53.0 (51.1–53.3)	<0.001
Time elapsed from COVID-19 at post-COVID-19 depression assessment, weeks[f]	29.4 (15–39.7)	22.7 (11.1–37.1)	30.7 (15.6–39.9)	<0.001

BDI-II scores, Beck Depression Inventory-II; BMI, body mass index; COVID-19, coronavirus disease 2019; IQR, interquartile range; MedDiet, Mediterranean diet; MMSE, Mini-Mental State Examination.
Data are *n* (%) or median (IQR) for categorical and quantitative variables, respectively, unless specified.
[a]p Values for comparisons between groups were tested using the Mann–Whitney test (owing to the skewed nature of the distribution) or χ^2, as appropriate.
[b]Data are presented as median (IQR).
[c]Data are from study baseline.
[d]Data from pre-COVID-19 measurement.
[e]Notes on scales: BDI-II Scores range between 0 and 63. Elevated depression risk is described as BDI-II scores $\geq$ 14. MMSE scores range between 0 and 30; the higher the scores greater the cognitive performance. Possible MedDiet scores range between 0 and 17. Higher MedDiet scores represent higher adherence to the Mediterranean diet.
[f]Duration data are presented as median (25th–75th percentile).

https://doi.org/10.1017/S0033291723002313 Published online by Cambridge University Press

Table 2. Longitudinal association of COVID-19 status with post-infection depression assessments (BDI-II scores)[a] in the PREDIMED-Plus cohort (β [95% CI])

	Total ($n = 5486$)			Men ($n = 2836$)			Women ($n = 2650$)		
	β[b]	95% CI	p value	β[b]	95% CI	p value	β[b]	95% CI	p value
Unadjusted crude model	0.19	−0.46 to 0.83	0.57	−0.20	−0.91 to 0.52	0.59	1.21	0.13–2.30	0.03
Model 1[c]	0.70	0.21–1.19	0.01	0.07	−0.44 to 0.59	0.79	1.56	0.66–2.46	<0.01
Model 2	0.64	0.14–1.14	0.01	0.11	−0.41 to 0.63	0.67	1.40	0.47–2.34	<0.01
Model 3	0.65	0.15–1.15	0.01	0.13	−0.39 to 0.65	0.63	1.40	0.45–2.34	<0.01

BDI-II, Beck Depression Inventory-II; CI, confidence interval; COVID-19, coronavirus disease 2019; MMSE, Mini-Mental State Examination.
Linear regression model: exposure = COVID-19 status (positive or negative); outcome: post-COVID-19 BDI-II score. Reference category: COVID-19-negative status.
The crude model only uses COVID-19 status (positive or negative) as the predictor variable in the model.
Model 1: Adjusted for age, sex, education, marital status, intervention group, cluster randomization, recruitment centre size, pre-COVID-19 BDI-II scores, and time since infection for post-COVID-19 depression assessments.
Model 2: Model 1 in addition adjusted for the presence of obesity, diabetes mellitus, hypertension, hypercholesterolemia, and baseline cognition (MMSE scores).
Model 3: Model 2 in addition adjusted for adherence to Mediterranean diet scores, smoking status, physical activity, and alcohol consumption.
[a]Depression assessment from the first scheduled follow-up visit after COVID-19 was used to calculate post-COVID-19 BDI-II scores.
[b]β (95% CI) was calculated using linear regression models.
[c]Sex is included as a predictor for the analysis of the total sample in Model 1. A stratified analysis by sex was conducted to determine differences, if any, in the impact of COVID-19 on depression measurements.

Table 3 summarises the positive association between a SARS-CoV-2 infection and elevated depression risk post-COVID-19 in this group of older adults at high cardiometabolic risk. In the final model, COVID-19 was associated with a 62% increase in the odds of observing elevated depression risk post-COVID-19 in the cohort [odds ratio (OR), 95% CI 1.13–2.30, $p = 0.008$].

These results remained unchanged in the supplementary analysis using a minimal adjustment model (online Supplementary Analysis 1: Supplementary Table S1). In addition, the results of logistic regression quantifying the longitudinal association between COVID-19 and elevated depression risk post-COVID-19 remained unchanged when the cut-off for BDI-II to identify the heightened risk was lowered to 12 points (online Supplementary Analysis 2, Supplementary Table S1).

Evaluation of interactions

Significant interactions ($p < 0.01$) with COVID-19 were observed for sex and the presence of pre-COVID-19 elevated depression risk (online Supplementary Fig. S3). Fully adjusted predicted post-COVID-19 BDI-II scores and probabilities of elevated depression risk in the stratified sub-analysis undertaken for these factors are visualised in online Supplementary Fig. S4.

Sex

At the pre-COVID visit, 68% of the participants who exhibited depressive symptomatology were women ($p < 0.001$). In women, a positive COVID-19 event was associated with an increase in BDI-II scores measured post-COVID-19 [β (95% CI) 1.38 (0.44–2.33), $p = 0.004$, Table 2] in the fully adjusted model. Similarly, a positive COVID-19 status in women was associated with an 82% increase in heightened depression risk post-COVID-19, even when controlled for potential confounders including pre-COVID-19 BDI-II scores (OR, 95% CI 1.17–2.86; $p = 0.008$, Table 3). However, these associations were not significant in men.

Elevated depression risk pre-COVID-19

Elevated depression risk pre-COVID-19 was positively associated with a similar assessment at the post-COVID-19 visit. Approximately 50% ($n = 377$) of those who recorded BDI-II scores ≥14 ($n = 758$) and 6% ($n = 284$) of those who scored <14 at the pre-COVID-19 visit exhibited elevated depression risk at their post-COVID-19 visit. Table 4 stratifies the prospective association between SARS-CoV-2 infection and elevated depression risk post-COVID-19, by pre-COVID-19 depression risk levels. In individuals with BDI-II scores <14 at the prior visit, a positive COVID-19 event was associated with a 72% increase in the risk of elevated depression post-COVID-19, in the fully adjusted model (OR, 95% CI 1.17–2.62; $p = 0.008$, Table 4).

A significant interaction was also observed between the timing of depression assessment and COVID-19 status ($p < 0.05$). Results stratified by timing of post-COVID-19 depression assessment are shown in online Supplementary Table S2. While the directionality of the relationship between a COVID-19-positive status and depression scores remained consistent, these associations were statistically significant only among participants who had their depression assessment conducted after 12 weeks following COVID-19 diagnosis (COVID-19-positive participants) or after 12 weeks following the first confirmed case of COVID-19 in Spain (COVID-19-negative participants).

In the replication analysis in the subsample with serology results to confirm COVID-19 status, the directionality of the results remained unchanged. However, the association was no longer statistically significant ($n = 3801$, 284 cases of COVID-19) (online Supplementary Table S3).

Discussion

We examined the association of COVID-19 with depressive symptomatology in older adults with overweight/obesity and metabolic syndrome enrolled in the PREDIMED-Plus trial in Spain. Spain with an increasingly ageing population was among the European countries most affected by the pandemic (Pollán et al., 2020). COVID-19 was associated with a small but significant and persistent increase in post-infection depression scores in this population. These findings add to the existing global evidence on the mental health consequences of COVID-19 (Deng et al., 2021; Klaser et al., 2021; Meng et al., 2020; Renaud-Charest et al., 2021).

https://doi.org/10.1017/S0033291723002313 Published online by Cambridge University Press

Table 3. Longitudinal association between COVID-19 status and post-infection elevated depression risk in the PREDIMED-Plus cohort [OR (95% CI)]

Depressive symptomatology	Total ($n = 5486$)			Men ($n = 2836$)			Women ($n = 2650$)		
	OR[a]	95% CI	p Value	OR[a]	95% CI	p Value	OR[a]	95% CI	p Value
Unadjusted crude model	1.22	0.91–1.63	0.18	1.11	0.68–1.81	0.69	1.47	1.01–2.13	0.04
Model 1[b]	1.67	1.19–2.34	<0.01	1.40	0.78–2.50	0.26	1.92	1.26–2.95	<0.01
Model 2	1.59	1.11–2.27	0.01	1.36	0.74–2.49	0.32	1.82	1.16–2.84	<0.01
Model 3	1.62	1.13–2.30	<0.01	1.38	0.76–2.53	0.30	1.83	1.17–2.87	<0.01

BDI-II scores, Beck Depression Inventory-II; COVID-19, coronavirus disease 2019; CI, confidence interval; MMSE, Mini-Mental State Examination; OR, odds ratio.
Logistical regression model: exposure = COVID-19 status (positive or negative); outcome = elevated depression risk post-COVID-19. Reference category: COVID-19-negative status.
Model 1: Adjusted for age, sex, education, marital status, intervention group, cluster randomization, recruitment centre size, pre-COVID-19 BDI-II scores, duration post-COVID-19 measurements.
Model 2: Model 1 additionally adjusted for the presence of obesity, diabetes mellitus, hypertension, hypercholesterolemia, and baseline cognition (MMSE scores).
Model 3: Model 2 additionally adjusted for adherence to Mediterranean diet scores, smoking status, physical activity, and alcohol consumption.
[a]OR (95% CI) was calculated using logistic regression models.
[b]Sex included as a predictor for the analysis of the total sample in Model 1. A stratified analysis by sex was conducted to determine differences, if any, in the impact of COVID-19 on depression measurements.
[c]Elevated depression risk is defined as BDI-II score ≥ 14, absence of elevated depression risk as BDI-II score < 14. Depression assessment from the first scheduled follow-up visit after the COVID-19 infection was used to categorize post-COVID-19 depressive symptomatology.

Post-infection increases in depressive symptomatology associated with infections that have a prolonged convalescence have biological and psychological bases (Kim, Yoo, Lee, Lee, & Shin, 2018). Biologically, the escalation of depressive symptoms after COVID-19 stems from increased inflammation (Lyra e Silva, Barros-Aragão, De Felice, & Ferreira, 2022; Mazza et al., 2020). COVID-19 is a hyperinflammatory disease with systemic and brain inflammation, leading to acute and persistent neurological and psychological disturbances (Lyra e Silva et al., 2022). COVID-19 could also be a stress-inducing traumatic event, and patients who experience traumatic events are known to have higher inflammation markers (Fernández-Sevillano et al., 2022). Proinflammatory cytokines are associated with the development of depression, irrespective of baseline scores, indicating that inflammation temporally precedes and increases the depression risk (Martínez-Cengotitabengoa et al., 2016). In addition, the increased depression risk in Middle East Respiratory Syndrome (MERS) patients quarantined in the hospital was ascribed to psychological factors including tension, fear, anger, mistrust, uncertainty, and depressed mood due to the infection itself and the subsequent isolation during quarantine (Kim et al., 2018), socioeconomic and family consequences. These mechanisms could collectively explain the association of COVID-19 with increased depressive symptomatology. In addition, the pandemic nature of

Table 4. Longitudinal association between COVID-19 status and depressive symptomatology in the PREDIMED-Plus cohort, stratified by depression risk at pre-COVID-19 assessment (OR[a] or β[b] coefficients and 95% CI)

	Elevated depression risk at pre-COVID-19 visit ($n = 758$)			Minimal risk at pre-COVID-19 visit ($n = 4728$)		
	Effect size	95% CI	p Value	Effect size	95% CI	p Value
Post COVID BDI-II scores [β (95% CI)][a]						
Unadjusted crude model	−0.10	−2.47 to 2.26	0.93	0.33	−0.19 to 0.86	0.21
Model 1	0.27	−1.92 to 2.45	0.81	0.53	−0.02 to 1.08	0.06
Model 2	−0.06	−2.37 to 2.25	0.96	0.48	−0.08 to 1.03	0.09
Model 3	0.17	−2.78 to 2.52	0.90	0.50	−0.05 to 1.05	0.08
Depressive symptomatology post-COVID19 [OR (95% CI)][b]						
Unadjusted crude model	0.97	0.56 to 1.70	0.92	1.61	1.09 to 2.36	0.02
Model 1	1.00	0.56 to 1.79	1.00	1.78	1.19 to 2.65	<0.01
Model 2	0.87	0.47 to 1.61	0.66	1.73	1.15 to 2.60	<0.01
Model 3	0.92	0.49 to 1.72	0.78	1.74	1.16 to 2.62	<0.01

BDI-II scores, Beck Depression Inventory-II; COVID-19, coronavirus disease 2019; CI, confidence interval; MMSE, Mini-Mental State Examination; OR, odds ratio.
Elevated depression risk is defined as BDI-II score ≥ 14, minimal depression risk as BDI-II score < 14. Depression assessment from the first scheduled follow-up visit after the COVID-19 infection was used to evaluate post-COVID-19 depressive symptomatology.
Reference category: COVID-19-negative status.
Model 1: Adjusted for age, sex, education, marital status, intervention group, cluster randomization, recruitment centre size, pre-COVID-19 BDI-II scores, and time since infection for post-COVID-19 depression assessments.
Model 2: Model 1 additionally adjusted for the presence of obesity, diabetes mellitus, hypertension, hypercholesterolemia, and baseline cognition (MMSE scores).
Model 3: Model 2 additionally adjusted for adherence to Mediterranean diet scores, smoking status, physical activity, and alcohol consumption.
[a]β coefficient (95% CI) was calculated using linear regression models. Exposure = COVID-19 status (positive or negative); outcome: post-COVID-19 BDI-II scores.
[b]OR (95% CI) was calculated using logistic regression models. Exposure = COVID-19 status (positive or negative); outcome = elevated depressive risk post-COVID-19 (yes/no).

https://doi.org/10.1017/S0033291723002313 Published online by Cambridge University Press

the COVID-19 outbreak and the widespread adoption of public health measures could have compounded the association of COVID-19 with depressive symptoms. Therefore, it is likely that the magnitude of the impact of COVID-19 on mental health, specifically among the vulnerable including older adults, is more prominent in comparison to common acute illnesses.

While the association between COVID-19 and depression risk was statistically significant, the effect size was small, and hence, its clinical significance is debatable. Nevertheless, the effect of COVID-19 on depressive symptoms is in line with the repeated calls for mental health interventions in older adults, particularly in older women surviving COVID-19 (Mazza et al., 2020; Meng et al., 2020; Renaud-Charest et al., 2021). Moreover, contrary to the existing understanding that prior mental health conditions make individuals particularly vulnerable to the psychological impact of COVID-19 (Mazza et al., 2020; Meng et al., 2020; Renaud-Charest et al., 2021), we found that COVID-19 was significantly associated with elevated depressive risk post-infection in PREDIMED-Plus participants without a similar risk at the pre-COVID-19 visit. These results provide new insights into the need for holistic management of COVID-19 in older adults who were more vulnerable to infection and had poorer survival rates in the initial phases of the pandemic, owing to senescence and comorbidity-related changes in the immune system (Mueller et al., 2020). Aging attenuates coping strategies (Meng et al., 2020), while self-awareness of the aging-related increased the risk of mortality from the pandemic and poorer coping tendencies could contribute to increased and persistent depressive tendencies in older adults experiencing COVID-19. Furthermore, poorer physical health increases the risk for poorer mental health post-COVID-19 (Robinson, Sutin, Daly, & Jones, 2022). Hence, among older adults at high cardiometabolic health risk, preventive mental health interventions to manage depressive symptomatology may be required irrespective of pre-COVID-19 mental health status.

Previous reports suggest that the mental health effects of COVID-19 are transitory and attenuate 12 weeks after the infection (Klaser et al., 2021; Renaud-Charest et al., 2021). However, we found no evidence to support this contention. The observed lack of significance of the results in the group with post-COVID-19 assessments conducted within 12 weeks of the date of infection could be due to insufficient statistical power in this group. Nevertheless, consistent results in the group that had their depression assessments performed 12 weeks or later after SARS-CoV-2 infection confirms that COVID-19 posed an extended mental health risk in this group of older adults with heightened metabolic risks, even in the absence of depression in pre-COVID-visits.

We could attribute this extended mental health consequence of COVID-19 to both the physiological consequences of COVID-19 and the prolonged lockdown instituted as public health measures to stem the spread of the disease. However, we have recently shown, albeit in a sub-sample of this cohort, that the lockdown was not associated with an increase in depressive symptomatology (Paz-Graniel et al., 2023). Thus, it is highly likely that the persistent depressive symptomatology seen in this group is predominantly a consequence of the disease. These findings reemphasize that COVID-19-induced increases in depressive symptoms could be larger and more persistent in comparison to smaller changes observed for anxiety disorder symptoms and overall mental health functioning measures (Robinson et al., 2022). With the increasing concern over 'Long-COVID', it is important to further monitor the long-term psychological impact of COVID-19 in older adults, specifically concerning depressive symptoms, even in the absence of depression in pre-COVID-visits.

Our study has limitations. First, BDI-II scores were self-reported and are not interpreted as a bonafide diagnosis of the presence/absence of depression. Nevertheless, BDI-II has been validated and used widely in Spain with sufficient specificity to identify individuals at the heightened risk for depression (Sanz Fernández, 2013). Second, while social and economic outcomes of the pandemic contribute to depression post-COVID-19 (Renaud-Charest et al., 2021), this analysis did not account for regional variation in lockdown severity and its economic/social consequences. We believe that with adjustments for the recruitment centre size and education, we could have partially accounted for these factors. Third, some COVID-19-negative patients may have had asymptomatic infections that went undiagnosed, resulting in misclassification of cases. This is unlikely because we scrutinized all medical records during 2020 and 2021 when public health strategies for COVID-19 testing were stringent as the nation was in the process of maximizing vaccination coverage. We also recognize that protecting the integrity of the main trial precludes obtaining updated data for covariates such as the prevalence of diabetes, hypercholesterolemia, or hypertension for this analysis. However, the minimal adjustment model shows that the association may be independent of these variables. Furthermore, the results from the sub-sample with positive serology go in the same direction as the primary analysis, suggesting minimal effects of misclassification on this analysis. Finally, this analysis uses data from participants in a clinical trial and may not be widely generalizable.

Nevertheless, this analysis adds strong data to the existing evidence on the mental health sequelae of COVID-19 in a vulnerable group of older adults with overweight/obesity and metabolic syndrome. The sufficiently large PREDIMED-Plus cohort with scheduled data assessments from before the onset of the pandemic and after helps establish the impact of COVID-19 on depressive symptomatology in the cohort while adjusting for the time for depression determinations, an important confounder of this relationship (Renaud-Charest et al., 2021). Furthermore, the similar time frame within which the pre- and post-COVID-19 assessments were obtained in all participants controls for many extraneous factors that could have increased the depression risk, independently of infection status. Moreover, COVID-19 event adjudication was performed by an independent committee removing any potential bias in the ascertainment of cases. Supplementary analyses using a lower cut-off for depression risk and serology results from a sub-sample confirmed the directionality of the results from the main analysis. Finally, we believe that the identification of a minimal adjustment set using a DAG to investigate the relationships involved in this analysis also removes concerns of over-adjustments in the models.

Our analyses do not consider vaccination status and type, the severity of COVID-19 infection, the infection strain or the treatment modality used, or the need for hospitalization among the COVID-19-positive participants. However, current evidence for the impact of these factors on post-COVID-19 depressive symptoms is inconsistent (Chen, Aruldass, & Cardinal, 2022; Mazza et al., 2020; Renaud-Charest et al., 2021). It is possible that the severity of COVID-19 in the early days of the pandemic differed from those that occurred later. We found that while several of the strains reported in 2020 and 2021 caused severe infections, the

https://doi.org/10.1017/S0033291723002313 Published online by Cambridge University Press

omicron variant reported after November 2021 produced milder disease. However, only 46 cases in our cohort were diagnosed after November 2021, and we do not possess data on strain causing COVID-19 in our cohort to tease out these effects. Also, vaccination in Spain started on 27 December 2020, and the possibility that it might have influenced depression outcomes is restricted to approximately 4% of our population who had received at least one dose of the vaccine at the time of post-COVID-19 depression measurements. Nevertheless, considering these factors in future analyses will facilitate identifying sub-groups that would specifically benefit from mental health interventions. We also propose that future studies investigate the trajectory of depressive symptoms in COVID-19 patients using repeated measurements post-infection. Such an evaluation will help better understand the time-dependent mental health effects of COVID-19.

Implications for practice

Overall, our findings support a call for mental health interventions to tackle increased depressive tendencies post-COVID-19 infection in older adults, particularly in women. Furthermore, in this Spanish cohort of older adults with overweight/obesity and metabolic syndrome, the association between COVID-19 and depressive symptoms was persistent and observable after 12 weeks post-COVID-19. Importantly, strategies to mitigate depression should be extended to older adults with cardiometabolic health risks, who do not exhibit heightened depressive symptomatology prior to a SARS-CoV-2 infection.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291723002313.

Acknowledgements. The authors wish to thank the PREDIMED-Plus participants and staff for their engagement, as well as the primary care centres involved in the study. We also thank the Cerca Programme of the Generalitat de Catalunya, the CIBEROBN, CIBERESP, and CIBERDEM initiatives of Instituto de Salud Carlos III in Spain. We are grateful to Dr Jesús Francisco García Gavilán for his input on the methodology used in this manuscript. INSA-Ma María de Maeztu Unit of Excellence (grant CEX2021-001234-M funded by MICIN/AEI/FEDER, UE).

Author contributions. All authors (1) made substantial contributions to the study concept or the data analysis or interpretation; (2) drafted the manuscript or revised it critically for the important intellectual concept; (3) approved the final version of the manuscript to be published; and (4) agreed to be accountable for all aspects of the work.

Financial support. This work was supported by a project grant from the Fundación Francisco Soria Melguizo. The PREDIMED-Plus trial was supported by the official Spanish Institutions for funding scientific biomedical research, CIBER Fisiopatología de la Obesidad y Nutrición (CIBEROBN) and Instituto de Salud Carlos III (ISCIII), through the Fondo de Investigación para la Salud (FIS), which is co-funded by the European Regional Development Fund (six coordinated FIS projects leaded by J. S.-S. and J. Vi., including the following projects: PI13/00673, PI13/00492, PI13/00272, PI13/01123, PI13/00462, PI13/00233, PI13/02184, PI13/00728, PI13/01090, PI13/01056, PI14/01722, PI14/00636, PI14/00618, PI14/00696, PI14/01206, PI14/01919, PI14/00853, PI14/01374, PI14/00972, PI14/00728, PI14/01471, PI16/00473, PI16/00662, PI16/01873, PI16/01094, PI16/00501, PI16/00533, PI16/00381, PI16/00366, PI16/01522, PI16/01120, PI17/00764, PI17/01183, PI17/00855, PI17/01347, PI17/00525, PI17/01827, PI17/00532, PI17/00215, PI17/01441, PI17/00508, PI17/01732, PI17/00926, PI19/00957, PI19/00386, PI19/00309, PI19/01032, PI19/00576, PI19/00017, PI19/01226, PI19/00781, PI19/01560, PI19/01332, PI20/01802, PI20/00138, PI20/01532, PI20/00456, PI20/00339, PI20/00557, PI20/00886, PI20/01158); the Especial Action Project entitled: Implementación y evaluación de una intervención intensiva sobre la actividad física Cohorte PREDIMED-Plus grant to J. S.-S.; the European Research Council (Advanced Research Grant 2014–2019; agreement #340918) granted to M. Á. M.-G.; the Recercaixa (number 2013ACUP00194) grant to J. S.-S.; grants from the Consejería de Salud de la Junta de Andalucía (PI0458/2013, PS0358/2016, and PI0137/2018); the PROMETEO/2017/017 and PROMETEO 21/2021 grants from the Generalitat Valenciana; the SEMERGEN grant; Juan de la Cierva-Incorporación research grant (IJC2019-042420-I) of the Spanish Ministry of Economy, Industry and Competitiveness and European Social Funds. This research was also partially funded by EU-H2020 Grants (Eat2beNICE/ H2020-SFS-2016-2); and the Horizon 2020 PRIME study (Prevention and Remediation of Insulin Multimorbidity in Europe; grant agreement #847879). S. G. S. was a recipient of the Maria Zambrano Fellowship with funding support from the Ministry of Universities and the Recovery, Transformation and Resilience Plan, Spain. The Fellowship is 'Funded by the European Union – NextGenerationEU'. S. K. N. was supported by a postdoctoral fellowship from the Canadian Institutes of Health Research (CIHR, MFE-171207). C. G.-M. was supported by a predoctoral grant from the University of Rovira I Virgili (2020PMF-PIPF-37). J. S.-S. was partially supported by ICREA under the ICREA Academia program. We thank CERCA Programme/Generalitat de Catalunya for institutional support. The funders had no role in study design, data collection and analysis, the decision to publish, or the preparation of the manuscript.

Competing interest. The authors have no conflict of interests to declare.

Ethical standards. The authors assert that the studies involving human participants were reviewed and approved by the study and were conducted in compliance with the guidelines of the Declaration of Helsinki. The study was approved by the Institutional Review Boards of all participating centres. The patients/participants provided their written informed consent to participate in this study.

[1]Centro de Investigación Biomédica en Red Fisiopatología de la Obesidad y la Nutrición (CIBEROBN), Institute of Health Carlos III, Madrid, Spain; [2]Departament de Bioquímica i Biotecnologia, Grup Alimentació, Nutrició, Desenvolupament i Salut Mental, Unitat de Nutrició Humana, Universitat Rovira i Virgili, Reus, Spain; [3]Institut d'Investigació Sanitària Pere Virgili (IISPV), Reus, Spain; [4]CIBER de Epidemiología y Salud Pública (CIBERESP), Instituto de Salud Carlos III (ISCIII), Madrid, Spain; [5]Departamento de Ciencias de la Salud, Instituto Universitario de Investigación en Olivar y Aceites de Oliva, Universidad de Jaén, Jaén, Spain; [6]Department of Preventive Medicine and Public Health, Instituto de Investigación Sanitaria de Navarra (IdiSNA), University of Navarra, Pamplona, Spain; [7]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA; [8]Department of Preventive Medicine, University of Valencia, Valencia, Spain; [9]Unit of Cardiovascular Risk and Nutrition, Institut Hospital del Mar de Investigaciones Médicas Municipal d'Investigació Médica (IMIM), Barcelona, Spain; [10]Department of Nutrition, Food Sciences, and Physiology, Center for Nutrition Research, University of Navarra, Pamplona, Spain; [11]Precision Nutrition and Cardiometabolic Health Program, IEA Food, CEI UAM + CSIC, Madrid, Spain; [12]Bioaraba Health Research Institute, Cardiovascular, Respiratory and Metabolic Area; Osakidetza Basque Health Service, Araba University Hospital; University of the Basque Country UPV/EHU, Vitoria-Gasteiz, Spain; [13]EpiPHAAN Research Group, School of Health Sciences, University of Málaga – Instituto de Investigación Biomédica en Málaga (IBIMA), Málaga, Spain; [14]Instituto de Investigación Sanitaria y Biomédica de Alicante, Universidad Miguel Hernández (ISABIAL-UMH), Alicante, Spain; [15]Health Research Institute of the Balearic Islands (IdISBa), Palma de Mallorca, Spain; [16]Department of Internal Medicine, Maimonides Biomedical Research Institute of Cordoba (IMIBIC), Reina Sofia University Hospital, University of Cordoba, Cordoba, Spain; [17]Department of Internal Medicine, Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS), Hospital Clinic, University of Barcelona, Barcelona, Spain; Institut de Recerca en Nutrició i Seguretat Alimentaria (INSA-UB), University of Barcelona, Barcelona, Spain; [18]Department of Endocrinology, Virgen de la Victoria Hospital, Instituto de Investigación Biomédica de Málaga (IBIMA), University of Málaga, Málaga, Spain;

[19]Department of Family Medicine, Research Unit, Distrito Sanitario Atención Primaria Sevilla, Sevilla, Spain; [20]Research Institute of Biomedical and Health Sciences (IUIBS), University of Las Palmas de Gran Canaria & Centro Hospitalario Universitario Insular Materno Infantil (CHUIMI), Canarian Health Service, Las Palmas de Gran Canaria, Spain; [21]Department of Preventive Medicine and Public Health, University of Granada, Granada, Spain; [22]Research Group on Community Nutrition & Oxidative Stress, University of Balearic Islands, Palma de Mallorca, Spain; [23]Institute of Biomedicine (IBIOMED), University of León, León, Spain; [24]Lipids and Vascular Risk Unit, Internal Medicine, Hospital Universitario de Bellvitge-IDIBELL, Hospitalet de Llobregat – Barcelona, Barcelona, Spain; [25]Department of Endocrinology and Nutrition, Instituto de Investigación Sanitaria Hospital Clínico San Carlos (IdISSC), Madrid, Spain; [26]CIBER Diabetes y Enfermedades Metabólicas (CIBERDEM), Instituto de Salud Carlos III (ISCIII), Madrid, Spain; [27]Department of Endocrinology, Institut d`Investigacions Biomédiques August Pi Sunyer (IDIBAPS), Hospital Clinic, University of Barcelona, Barcelona, Spain; [28]Department of Endocrinology and Nutrition, Hospital Fundación Jimenez Díaz, Instituto de Investigaciones Biomédicas IISFJD, University Autonoma, Madrid, Spain; [29]Nutritional Control of the Epigenome Group, Precision Nutrition and Obesity Program, IMDEA Food, CEI UAM + CSIC, Madrid, Spain; [30]Departamento de Ciencias Farmacéuticas y de la Salud, Faculty de Farmacia, Universidad San Pablo-CEU, CEU Universities, Boadilla del Monte, Spain; [31]Lipid Clinic, Department of Endocrinology and Nutrition, Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS), Hospital Clínic, Barcelona, Spain; [32]Psychoneurobiology of Eating and Addictive Behaviors Group, Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), Barcelona, Spain; [33]Department of Psychiatry, University Hospital of Bellvitge and University of Barcelona, Barcelona, Spain; [34]Toronto 3D (Diet, Digestive Tract and Disease) Knowledge Synthesis and Clinical Trials Unit, Toronto, ON, Canada; [35]Department of Internal Medicine, OSI ARABA, University Hospital Araba, Vitoria-Gasteiz, Spain; [36]Health Care Centre Raval-Elche, Elche, Spain; [37]Atención Primaria, Servicio Navarro de Salud, Pamplona, Spain; [38]Department of Psychiatry, Bioaraba Health Research Institute, Osakidetza Basque Health Service, Araba University Hospital; University of the Basque Country UPV/EHU, CIBERSAM, Vitoria-Gasteiz, Spain and [39]Division of Preventive Medicine, Faculty of Medicine, University of Jaén, Jaén, Spain

References

Becker, A. B., Steer, R. A., & Brown, G. K. (1996). *BDI-II: Beck depression inventory-second edition manual*. San Antonio, TX: The Psychological Corporation.

Castro, A., Roca, M., Ricci-Cabello, I., García-Toro, M., Riera-Serra, P., Coronado-Simsic, V., … Gili, M. (2021). Adherence to lifestyle interventions for treatment of adults with depression: A systematic review and meta-analysis. *International Journal of Environmental Research and Public Health*, *18*(24), 13268. doi:10.3390/ijerph182413268

CDC. (2020, February 11). Labs. Retrieved December 12, 2022, from Centers for Disease Control and Prevention website: https://www.cdc.gov/coronavirus/2019-ncov/lab/serology-testing.html

Channappanavar, R., & Perlman, S. (2020). Age-related susceptibility to coronavirus infections: Role of impaired and dysregulated host immunity. *The Journal of Clinical Investigation*, *130*(12), 6204–6213. doi:10.1172/JCI144115

Chen, S., Aruldass, A. R., & Cardinal, R. N. (2022). Mental health outcomes after SARS-CoV-2 vaccination in the United States: A national cross-sectional study. *Journal of Affective Disorders*, *298*(Pt A), 396–399. doi:10.1016/j.jad.2021.10.134

Deng, J., Zhou, F., Hou, W., Silver, Z., Wong, C. Y., Chang, O., … Zuo, Q. K. (2021). The prevalence of depression, anxiety, and sleep disturbances in COVID-19 patients: A meta-analysis. *Annals of the New York Academy of Sciences*, *1486*(1), 90–111. doi:10.1111/nyas.14506

Dunbar, J. A., Reddy, P., Davis-Lameloise, N., Philpot, B., Laatikainen, T., Kilkkinen, A., … Janus, E. D. (2008). Depression: An important comorbidity with metabolic syndrome in a general population. *Diabetes Care*, *31*(12), 2368–2373. doi:10.2337/dc08-0175

Fernández, J. S., Valverde, C. V., & Perdigón, A. L. (2003). Adaptación española del Inventario para la Depresión de Beck-II (BDI-II): 2. Propiedades psicométricas en población general. *Clínica y salud: Investigación Empírica en Psicología*, *14*(3), 249–280.

Fernández-Sevillano, J., González-Ortega, I., MacDowell, K., Zorrilla, I., López, M. P., Courtet, P., … González-Pinto, A. (2022). Inflammation biomarkers in suicide attempts and their relation to abuse, global functioning and cognition. *The World Journal of Biological Psychiatry*, *23*(4), 307–317. doi:10.1080/15622975.2021.1988703

Guo, P., Benito Ballesteros, A., Yeung, S. P., Liu, R., Saha, A., Curtis, L., … Cheke, L. G. (2022). COVCOG 1: Factors predicting physical, neurological and cognitive symptoms in long COVID in a community sample. A first publication from the COVID and cognition study. *Frontiers in Aging Neuroscience*, *14*, 804922. doi:10.3389/fnagi.2022.804922

Khaledi, M., Haghighatdoost, F., Feizi, A., & Aminorroaya, A. (2019). The prevalence of comorbid depression in patients with type 2 diabetes: An updated systematic review and meta-analysis on huge number of observational studies. *Acta Diabetologica*, *56*(6), 631–650. doi:10.1007/s00592-019-01295-9

Kim, H.-C., Yoo, S.-Y., Lee, B.-H., Lee, S. H., & Shin, H.-S. (2018). Psychiatric findings in suspected and confirmed Middle East Respiratory Syndrome patients quarantined in hospital: A retrospective chart analysis. *Psychiatry Investigation*, *15*(4), 355–360. doi:10.30773/pi.2017.10.25.1

Klaser, K., Thompson, E. J., Nguyen, L. H., Sudre, C. H., Antonelli, M., Murray, B., … Steves, C. J. (2021). Anxiety and depression symptoms after COVID-19 infection: Results from the COVID symptom study app. *Journal of Neurology, Neurosurgery and Psychiatry*, *92*(12), 1254–1258. doi:10.1136/jnnp-2021-327565

Lopez-Leon, S., Wegman-Ostrosky, T., Perelman, C., Sepulveda, R., Rebolledo, P. A., Cuapio, A., & Villapol, S. (2021). More than 50 long-term effects of COVID-19: A systematic review and meta-analysis. *Scientific Reports*, *11*(1), 16144. doi:10.1038/s41598-021-95565-8

Lyra e Silva, N. M., Barros-Aragão, F. G. Q., De Felice, F. G., & Ferreira, S. T. (2022). Inflammation at the crossroads of COVID-19, cognitive deficits and depression. *Neuropharmacology*, *209*, 109023. doi:10.1016/j.neuropharm. 2022.109023

Martínez-Cengotitabengoa, M., Carrascón, L., O'Brien, J. T., Díaz-Gutiérrez, M.-J., Bermúdez-Ampudia, C., Sanada, K., … González-Pinto, A. (2016). Peripheral inflammatory parameters in late-life depression: A systematic review. *International Journal of Molecular Sciences*, *17*(12), 2022. doi:10.3390/ijms17122022

Martínez-González, M. A., Buil-Cosiales, P., Corella, D., Bulló, M., Fitó, M., Vioque, J., … Salas-Salvadó, J. (2019). Cohort profile: Design and methods of the PREDIMED-Plus randomized trial. *International Journal of Epidemiology*, *48*(2), 387–388o. doi:10.1093/ije/dyy225

Mazza, M. G., De Lorenzo, R., Conte, C., Poletti, S., Vai, B., Bollettini, I., … Benedetti, F. (2020). Anxiety and depression in COVID-19 survivors: Role of inflammatory and clinical predictors. *Brain, Behavior, and Immunity*, *89*, 594–600. doi:10.1016/j.bbi.2020.07.037

Meng, H., Xu, Y., Dai, J., Zhang, Y., Liu, B., & Yang, H. (2020). Analyze the psychological impact of COVID-19 among the elderly population in China and make corresponding suggestions. *Psychiatry Research*, *289*, 112983. doi:10.1016/j.psychres.2020.112983

Mueller, A. L., McNamara, M. S., & Sinclair, D. A. (2020). Why does COVID-19 disproportionately affect older people? *Aging* (*Albany NY*), *12* (10), 9959–9981. doi:10.18632/aging.103344

Pano, O., Martínez-Lapiscina, E. H., Sayón-Orea, C., Martinez-Gonzalez, M. A., Martinez, J. A., & Sanchez-Villegas, A. (2021). Healthy diet, depression and quality of life: A narrative review of biological mechanisms and primary prevention opportunities. *World Journal of Psychiatry*, *11*(11), 997–1016. doi:10.5498/wjp.v11.i11.997

Paz-Graniel, I., Babio, N., Nishi, S. K., Martínez-González, MÁ, Corella, D., Fitó, M., … Salas-Salvadó, J. (2023). How did the COVID-19 lockdown pandemic affect the depression symptomatology in Mediterranean older adults with metabolic syndrome? *Depression and Anxiety*, *2023*, e6765950. doi:10.1155/2023/6765950

Pollán, M., Pérez-Gómez, B., Pastor-Barriuso, R., Oteo, J., Hernán, M. A., Pérez-Olmeda, M., … Villa, A. V. de la. (2020). Prevalence of SARS-CoV-2 in Spain (ENE-COVID): A nationwide, population-based seroepidemiological study. *The Lancet*, *396*(10250), 535–544. doi:10.1016/S0140-6736(20)31483-5

Renaud-Charest, O., Lui, L. M. W., Eskander, S., Ceban, F., Ho, R., Di Vincenzo, J. D., … McIntyre, R. S. (2021). Onset and frequency of

https://doi.org/10.1017/S0033291723002313 Published online by Cambridge University Press

depression in post-COVID-19 syndrome: A systematic review. *Journal of Psychiatric Research*, *144*, 129–137. doi:10.1016/j.jpsychires.2021.09.054

Robinson, E., Sutin, A. R., Daly, M., & Jones, A. (2022). A systematic review and meta-analysis of longitudinal cohort studies comparing mental health before versus during the COVID-19 pandemic in 2020. *Journal of Affective Disorders*, *296*, 567–576. doi:10.1016/j.jad.2021.09.098

Salas-Salvadó, J., Díaz-López, A., Ruiz-Canela, M., Basora, J., Fitó, M., Corella, D., … PREDIMED-Plus investigators. (2018). Effect of a lifestyle intervention program with energy-restricted Mediterranean diet and exercise on weight loss and cardiovascular risk factors: One-year results of the PREDIMED-Plus trial. *Diabetes Care*, *42*(5), 777–788. doi:10.2337/dc18-0836

Sanz Fernández, J. (2013). 50 years of the Beck Depression Inventory: Recommendations for using the Spanish adaptation of the BDI-II in clinical practice [Info:eu-repo/semantics/article]. Retrieved November 23, 2022, from https://eprints.ucm.es/id/eprint/36450/

Sparks, M. A., South, A. M., Badley, A. D., Baker-Smith, C. M., Batlle, D., Bozkurt, B., … Garovic, V. D. (2020). Severe acute respiratory syndrome coronavirus 2, COVID-19, and the renin-angiotensin system. *Hypertension*, *76*(5), 1350–1367. doi:10.1161/HYPERTENSIONAHA.120.15948

Textor, J., van der Zander, B., Gilthorpe, M. S., Liśkiewicz, M., & Ellison, G. T. (2016). Robust causal inference using directed acyclic graphs: The R package 'dagitty'. *International Journal of Epidemiology*, *45*(6), 1887–1894. doi:10.1093/ije/dyw341

Wee, A. K. H. (2021). COVID-19's toll on the elderly and those with diabetes mellitus – is vitamin B12 deficiency an accomplice? *Medical Hypotheses*, *146*, 110374. doi:10.1016/j.mehy.2020.110374

Wei, J., Hou, R., Zhang, X., Xu, H., Xie, L., Chandrasekar, E. K., … Goodman, M. (2019). The association of late-life depression with all-cause and cardiovascular mortality among community-dwelling older adults: Systematic review and meta-analysis. *The British Journal of Psychiatry*, *215*(2), 449–455. doi:10.1192/bjp.2019.74

VI. DISCUSSION

UNIVERSITAT ROVIRA I VIRGILI
Psychology and Disease: Unveiling Emerging Perspectives on Their Interplay
Carlos Gómez Martínez

Discussion

In this section we discuss the findings of the seven manuscripts included in the results section of the current doctoral thesis. The discussion section comprises a general discussion and an evaluation of the strengths and limitations of the reported investigations.

One of the primary areas of focus in the general discussion is the role of impulsivity in increasing the incidence of type 2 diabetes and cardiovascular disease events, with a particular emphasis on its relationships with dietary patterns and potential interaction and mediation effects. Additionally, glycemic-related dysregulations were observed to contribute to increased impulsivity. In light of these findings, a potential detrimental feedback loop between impulsivity and poorer glycemic status is further discussed, providing a potential rationale for the mechanisms underlying this suggested vicious cycle. Furthermore, associations between glycemic dysregulations and cognitive decline are presented. Finally, an overview of the associations between positive COVID-19 cases and cognitive function, as well as depressive symptomatology, is provided.

GENERAL DISCUSSION

The main findings of *Chapter 2* and *Chapter 3* suggest that higher trait impulsivity is associated with an increased risk of developing cardiovascular disease and type 2 diabetes, respectively. These associations were assessed over a median follow-up period of eight years in approximately 50,000 adult participants from the general French population. The results of *Chapter 1* indicate that trait impulsivity was positively associated with adherence to unhealthy dietary patterns and inversely with healthy dietary patterns, with diet being a recognized risk factor for type 2 diabetes and cardiovascular disease.

Personality traits are supposed to determine a specific range of behaviors from all the possible actions that can be performed in response to a particular stimulus[26,264], such as palatable food[126]. This further interacts with the concrete mood of the individual and the specific environmental and situational cues that are present at the time the behavior is performed[19,26,265]. Accordingly, personality traits are hypothesized to precede behaviors, and consequently the onset of noncommunicable chronic diseases[1,2,19,42]. Type 2 diabetes and cardiovascular disease are among the leading causes of noncommunicable disease prevalence and mortality worldwide[130,156], and personality traits have been proposed to be important characteristics that influence the risk of developing these chronic diseases[1,19,42]. In line with this, although higher levels of the personality trait of impulsivity have been associated with poor glycemic status and increased cardiovascular disease risk through elevated HbA1c levels and unhealthy lifestyle behaviors[25,57,59,60], the potential relationships between trait impulsivity and the risk of developing an incident type 2 diabetes or cardiovascular disease event has never been examined prior to the current work.

As the manuscript examining the relationship between trait impulsivity and the prospective risk of developing type 2 diabetes was published close to the presentation of this dissertation, no additional findings were reported in the scientific literature. A similar pattern was observed in the manuscript assessing relationships between trait impulsivity and incident cardiovascular disease, which is currently being submitted to a peer-reviewed journal. Consequently, the discussion of *Chapter 2* and *Chapter 3* in the Results section of the present doctoral thesis provide an up-to-date comparison with previous

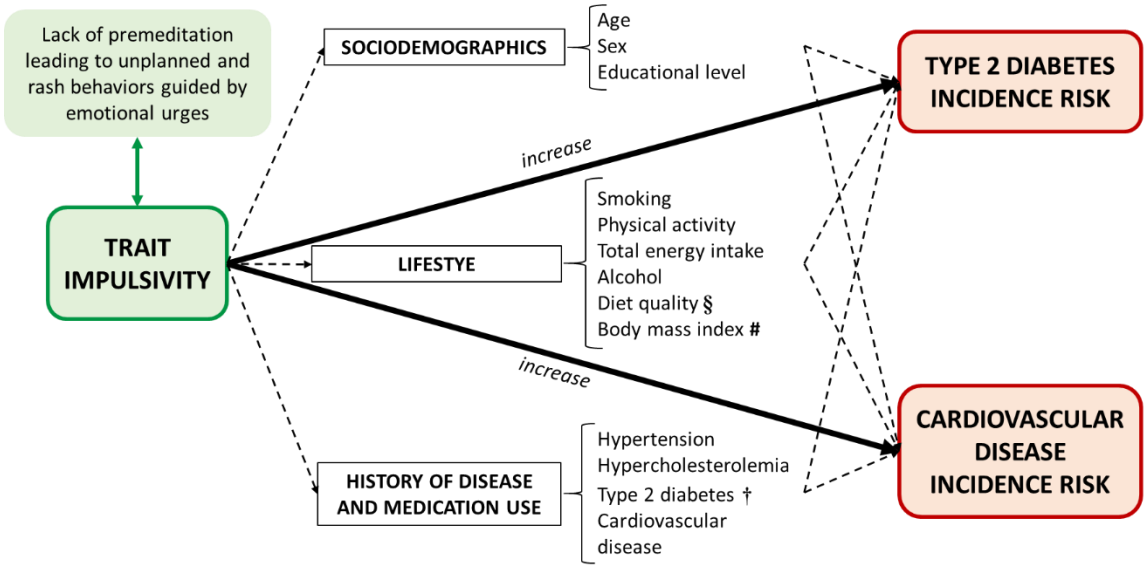
related research and proposed mechanisms. However, a brief and overall description of potential pathways is detailed below.

Potential shared mechanisms explaining the findings reported in *Chapter 2* and *Chapter 3* could be based on the mind-heart-body framework, the neural substrates of impulsivity, and impulsivity-related neurotransmitters. The mind-heart-body framework states that these three components are interconnected, and that psychological factors such as personality traits may have an influence on the heart and the body[42]. This provides a theoretical framework for examining the associations of trait impulsivity with cardiometabolic risk. Indeed, some neural brain areas underlying impulsivity, such as limbic and prefrontal cortex regions[34,266,267], have been shown to be linked to neuroendocrine signals to the heart and vasculature and vice versa[268]. Furthermore, the hypothalamus contains glucose-sensing neurons and is postulated to interact in the regulation of glucose homeostasis[269], in which impulsivity seems to play a role in these interplays[270]. With regard to neurotransmitters, serotonin and dopamine, which are related to impulsivity[271], have been shown to interact with heart muscles affecting heart rate variability and glucose metabolism[272–275]. Indeed, serotonin and dopamine receptors have been proposed as potential therapeutic targets for individuals with diabetes and cardiovascular disease[272–275]. However, the potential benefits of targeting these receptors to improve cardiometabolic health remain to be fully explored.

The onset of type 2 diabetes and cardiovascular disease is influenced by a variety of factors, including sociodemographic, lifestyle, history of disease, and medication use[112,137]. Additional mechanisms related to the findings of *Chapter 2* and *Chapter 3* may involve trait impulsivity idiosyncrasies such as a tendency to act rashly in response to emotional states, deficits in attention and planning, and a propensity for risky and unpredictable behavior[32,260,262]. Previous research has linked impulsivity to an increased occurrence of risk factors associated with type 2 diabetes and cardiovascular disease[24,25,45,46,56,276–284], suggesting that impulsivity not only directly elevates the risk of these diseases but also indirectly influences their incidence by promoting behaviors that exacerbate cardiometabolic risk factors. Within this rationale, the findings of *Chapter 3* found a positive mediation effect of body mass index on the relationship between trait impulsivity and incident type 2 diabetes. Interestingly, the findings of *Chapter 2* reveal that individuals with type 2 diabetes and lower impulsivity exhibited a protective effect

by reducing the incidence rates of cardiovascular disease. These direct and indirect associations are illustrated in **Figure 13**.

Figure 13. Relationships of trait impulsivity with type 2 diabetes and cardiovascular risk factors and incidence.



Note: The solid lines represent the findings reported in Chapter 2 and Chapter 3. The dashed lines indicate a potential indirect pathway from trait impulsivity to an increased risk of developing type 2 diabetes and cardiovascular disease through an increased occurrence of type 2 diabetes and cardiovascular disease risk factors. The bibliographic references supporting the associations of the dashed lines can be found in the Supplementary Online Material of Chapter 2 for cardiovascular disease and in Chapter 3 for type 2 diabetes. Additionally, detrimental associations between trait impulsivity and adherence to dietary patterns were described in Chapter 1 and indicated by the symbol: #. Moreover, a detrimental mediating effect of body mass index between trait impulsivity and incident type 2 diabetes was reported in Chapter 3 and indicated by the symbol: §. Furthermore, an interaction effect of type 2 diabetes prevalence between trait impulsivity and incident cardiovascular disease was reported in Chapter 2 and indicated by the symbol: †.

Another potential indirect pathway between impulsivity and the risk of developing type 2 diabetes and cardiovascular disease is supported by the findings presented in *Chapter 1*. This work showed associations between trait impulsivity and adherence to dietary patterns over a three-year follow-up period in a cohort of more than 450 Spanish older adults at high risk of cardiovascular disease. Specifically, increases in trait impulsivity were associated with increases in adherence to the Western diet. This unhealthy dietary pattern has been linked to an elevated risk of developing chronic diseases[121], while a

decreased adherence has been associated with an enhanced state of health[107,108]. These results are in line with previous cross-sectional studies[56,127] and recent research showing that a high energy intake exacerbated the genetic susceptibility to impulsivity[285]. These results may be explained due to some individuals may perceive the consumption of desirable foods, which often have a nutritionally deficient profile, as a challenge. This phenomenon has led to the emergence of the term "food addiction", in which impulsivity has been identified as a pivotal factor due to its intrinsic connection to reward sensitivity[286,287]. Individuals with high impulsivity often experience difficulties in delaying immediate urges, which may contribute to the development of food addiction and unhealthy dietary habits, thereby partially explaining the findings of our study. Remarkably, we observed an interaction effect by intervention group in the associations between trait impulsivity and four healthy dietary patterns. In the framework of the PREDIMED-Plus study, in which this research was performed, both the control and intervention groups received an active intervention. However, the control group was provided with "ad libitum" Mediterranean diet recommendations, whereas the intervention group was further encouraged to adhere to an energy-restricted Mediterranean diet and to engage in increased physical activity, together with more regular visits with dietitians. When results were stratified, it was observed that individuals in the intervention group with high impulsivity had lower adherence to healthy plant-based diets. These unfavorable relationships were not found in the control group. This interaction effect suggests that individuals with elevated impulsivity may encounter difficulties in adhering to healthy plant-based diets when undergoing an intensive multidomain lifestyle intervention.

In summary, the findings of *Chapter 1*, *Chapter 2*, and *Chapter 3* have contributed to the existing corpus of evidence by indicating first-time prospective associations between trait impulsivity, adherence to dietary patterns, and the incidence of type 2 diabetes and cardiovascular disease. These findings suggest that trait impulsivity represents a psychological risk factor that should be considered in the development of strategies aimed at preventing cardiometabolic diseases. Furthermore, dietary intervention programs for the prevention of these chronic diseases should consider that individuals with higher levels of impulsivity may encounter challenges in following healthy diets.

The main findings of *Chapter 4* indicate that several glycemic-related dysregulations were prospectively associated with increased impulsivity in an adult older Mediterranean population having high cardiovascular risk.

The manuscript presented in *Chapter 4* was contemporaneous with the presentation of this doctoral thesis, and new evidence studying these associations was not yet available in the scientific literature. Therefore, the discussion in the corresponding Results section remains up-to-date. Remarkably, this scientific paper suggests a potential detrimental positive feedback loop between facets of impulsivity and glycemic dysregulations, with a detailed rationale for the underlying mechanisms provided below.

The current state of research on this topic primarily focuses on studying associations, and therefore establishing causal relationships from glycemic dysregulations to increased impulsivity, or vice versa, is challenging. Nevertheless, evidence from observational and review studies demonstrated correlations between insulin-related and glucose levels, the presence of type 2 diabetes, the management and control of type 2 diabetes, and assessments of trait and/or behavioral impulsivity across both healthy and cardiometabolically unhealthy populations[25,59,60,84,85,87–89,288–292]. Accordingly, although not all studies supported these findings[184–186], there appears to be a reciprocal relationship between poor glycemic status and heightened impulsivity. Moreover, the findings of *Chapter 3* and *Chapter 4* provide additional support for the hypothesis that this potential vicious cycle exists. Specifically, these investigations indicate that higher levels of impulsivity were associated with an increased risk of developing type 2 diabetes, as well as HbA1c levels, type 2 diabetes, and poor diabetes control were positively associated with increases in impulsivity facets.

Figure 14. Potential mechanisms underlying the proposed detrimental feedback loop between impulsivity and glycemic dysregulation.

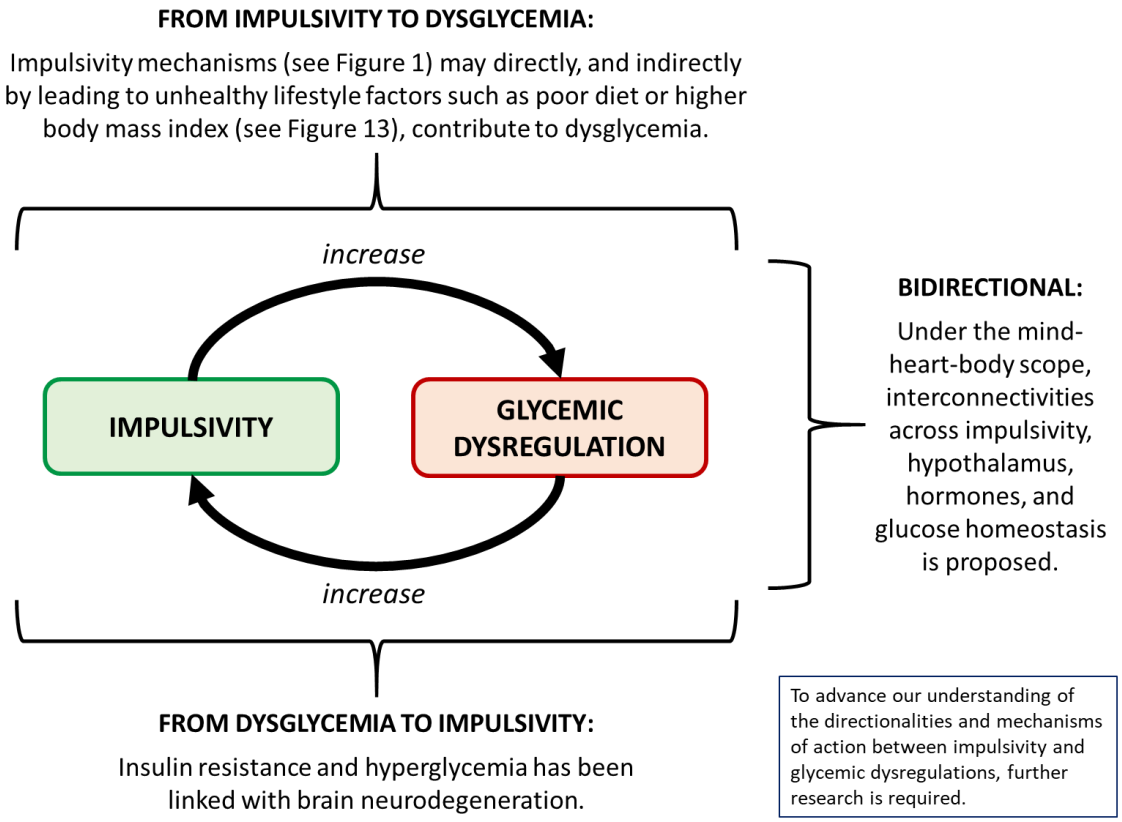


Figure 14 illustrates some of the potential mechanisms that may explain the suggested detrimental feedback loop between facets of impulsivity and glycemic dysregulations. Firstly, impulsive characteristics (see **Figure 1**) may directly influence glucose impairments, but may also indirectly contribute to a poor glycemic status resulting from the adoption of unhealthier lifestyle factors, as it was displayed in **Figure 13**. Some of these indirect pathways can be through characteristic unhealthy dietary choices of individuals with higher impulsivity[55,56,127,293]. In fact, the interplay between impulsivity, food addiction, emotional eating, and increased susceptibility to the reward system, particularly through dopaminergic action in the nucleus accumbens, has been proposed as crucial in explaining how impulsivity can lead to overeating, poor dietary habits, and obesity[286,287,294–296], which may subsequently increase the risk of glycemic impairments. Indeed, the results of *Chapter 1* are at least partially aligned with these explanations. In addition, *Chapter 3* identified a pathway whereby heightened impulsivity results in an elevated body mass index, which in turn increases the risk of developing type 2 diabetes.

This unfavorable mediation effect of body mass index in the associations between impulsivity and incident type 2 diabetes may be explained by idiosyncratic impulsivity features (see **Figure 1**), in which brain neural pathways underlying impulsivity seem to play an important role in weight gain and glycemic impairments[290,297]. Secondly, the bidirectional relationship between impulsivity and glycemic dysregulations can be sustained under the scope of psychoneuroendocrinology. The hypothalamus has been linked to impulsivity, and its role in hormone release is crucial in regulating behaviors that may contribute to glycemic impairments[42,270,298–301]. Furthermore, the hypothalamus is also susceptible to insulin and glucose action[269,302–304]. Accordingly, and within the broader context of mind-heart-body interconnectivities[42], hypotheses may be formulated regarding reciprocal associations between trait impulsivity, hypothalamic action in hormone release, impulsive behaviors, and glycemic dysregulations. It is important to note that this is a speculative potential mechanism, although its plausibility is supported by current literature, which may promote new research lines in the future. Finally, glycemic dysregulations may modulate impulsivity through brain cell damage. Insulin resistance and its subsequent hyperglycemia has been found to be associated with deleterious effects on endothelial function and oxidative stress, and the presence of type 2 diabetes has been linked to brain atrophy and neurodegeneration[305–308].

The principal findings of *Chapter 5* indicate that multiple glycemic dysregulations were associated with a decline in cognitive function over a two-year follow-up period in Spanish older adults who were at high risk of cardiovascular disease.

Our findings are aligned with subsequent evidence that emerged after the publication of our manuscript[309–312]. Insulin receptors and components of the insulin signaling pathway are distributed throughout the brain, particularly in regions associated with cognitive function[313]. In addition, insulin resistance results in hyperglycemia, which in turn leads to impaired brain function via the accumulation of advanced glycation end products, glucose neurotoxicity, and oxidative stress[314]. Indeed, a recent systematic review including participants without metabolic syndrome or diabetes found that high blood glucose levels were associated with greater amyloid burden, brain atrophy, and reduced cortical thickness[309]. However, this systematic review stated that in these cardiometabolic healthy populations, the associations between blood glucose levels and cognitive dysfunction were inconclusive[309]. In contrast, another recent systematic review reported that participants with metabolic syndrome exhibited a decline in global cognitive

function, although these associations were less pronounced when examining specific domains[310]. However, the corpus of evidence demonstrates a robust relationship between prevalent type 2 diabetes and poor diabetes control with cognitive decline and impairment[311,312]. For example, the hypothesis that brain insulin resistance may lead to Alzheimer's disease has been termed "diabetes-related cognitive dysfunction" or "type 3 diabetes"[315,316]. In general, the results of our study indicated comparable findings to those just reported. However, our investigation showed a borderline association between poor glycemic control and global cognitive function in participants with type 2 diabetes over a two-year period. This finding may suggest that longer time periods may be required to elucidate these detrimental associations, as observed by other investigations with longer follow-ups[80,81,317,318].

In summary, the evidence suggests that as glycemic dysregulation becomes more pronounced, the relationship between these heightened cardiometabolic disturbances and cognitive dysfunction becomes more consistent. This highlights the importance of assessing glycemic status to evaluate the intrinsic harmful effect of glycemic dysregulation, which in turn elevates cardiometabolic impairments and related comorbidities, such as cognitive impairments that may ultimately lead to dementia.

The primary conclusion of *Chapter 6* is that individuals who experienced COVID-19 did not develop cognitive decline or impairment. In contrast, *Chapter 7* indicates that those who experienced COVID-19 exhibited increased depressive symptomatology and heightened risk of developing depression. These associations were observed in over 5,000 older adults living in Spain who were at high risk for cardiovascular disease.

Both manuscripts were recently published, and as COVID-19 is a recent topic of investigation, contemporary research is included in this discussion. In relation to cognitive function, a meta-analysis of 43 studies found that 32% of individuals experienced cognitive fatigue and 22% experienced cognitive impairment at least 12 weeks after being infected with SARS-CoV-2[319]. Additionally, a recent study conducted in England with approximately 113,000 participants found significant cognitive declines 12 weeks after experiencing COVID-19, compared to those who tested negative[320]. However, this study reported small Cohen effect sizes for cognitive decline among participants without severe COVID-19, with standard deviation decreases ranging from 0.2 to 0.4, which have been considered non-clinically relevant[203]. Indeed, there were no

significant inverse associations between COVID-19 and cognitive function in our study. These discrepancies may be explained by the differences in the length of follow-up for cognitive assessments after a COVID-19 diagnosis. Our study included a notably longer follow-up period, which may suggest that cognitive function could return to baseline levels after the commonly reported short-term detrimental impact of SARS-CoV-2 infection on cognition[319–323]. In fact, recovery from some psychological sequelae of COVID-19 has been previously documented[324]. Other potential explanations include the lack of control groups without SARS-CoV-2 infection in some studies in this field, as well as the absence of cognitive assessments prior to COVID-19 diagnosis. These characteristics have recently been identified as a significant limitation when analyzing the potential effect of SARS-CoV-2 infection[203]. Additionally, the COVID-19 pandemic negatively impacted modifiable risk factors related to brain health, but the active lifestyle intervention of the PREDIMED-Plus study, even during the Spanish governmental restrictions[237], might have mitigated the adverse effects of COVID-19 on cognitive function in our population.

In relation to depression, systematic reviews and meta-analyses have consistently demonstrated the adverse effects of COVID-19 on mental health across various populations, age groups, and stages of the pandemic. These reviews have demonstrated a significant negative impact of COVID-19 on depressive symptoms, with rates of depression and related disorders being higher than those observed before the outbreak[198,199,202,325–328]. Specifically, two additional systematic reviews reported that individuals with a positive SARS-CoV-2 infection experienced higher levels of depressive symptomatology and clinically significant depression approximately 12 weeks post-infection[200,329]. Our study extends this knowledge by showing that these adverse associations persist even after considerably longer follow-up periods. Potential mechanisms underlying this relationship include neural, neuroimmune, and intestinal microbiota effects[202].

In conclusion, our studies indicated that experiencing COVID-19 was associated with elevated depressive symptomatology and an increased risk of developing depressive disorders. However, no such association was observed between SARS-CoV-2 infection and cognitive dysfunction. These findings emphasize the importance of long-term monitoring of the effects of COVID-19, particularly regarding the trajectory of cognitive impairment and its potential association with dementia. Furthermore, it is important to

examine whether the observed increase in depression rates due to the pandemic will revert to the levels observed prior to the outbreak.

STRENGTHS AND LIMITATIONS

It is important to acknowledge the limitations and strengths of the present doctoral thesis.

One of the primary constraints of the present dissertation is its observational nature, which only permits the examination of associations and restricts the ability to infer causality. Other limitations include the fact that the analyses were conducted using data from two distinct populations: Spanish adult older individuals with overweight/obesity and metabolic syndrome, and a general French population older than 18 years old. Consequently, the results obtained from the Spanish population are not generalizable to other populations with more favorable health status profiles, and the results from the French cohort should be replicated in diverse populations to confirm the results found. One of the primary research topics of this work is impulsivity. Impulsivity is a broad psychological construct, and throughout the manuscripts included in this dissertation, it was assessed using various methods. In the manuscripts assessing trait impulsivity, it was employed the Barratt Impulsiveness Scale 11 or the UPPS-P Impulsive Behavior Scale questionnaires. This raises the question of whether the results obtained will be interchangeable depending on the trait impulsivity questionnaire used. In any case, these constructs were probably the two most used questionnaires around the world for assessing trait impulsivity, and this would facilitate comparisons with future studies. Additionally, both questionnaires showed at least acceptable internal consistency as assessed by Cronbach alpha. One of our studies further included the assessment of behavioral impulsivity, in which we used several neuropsychological evaluations for its assessment. This allowed to capture the extensive behavioral impulsivity features, but also difficult the interpretation of results with other studies not including the same behavioral impulsivity features. Moreover, it is important to recognize that the participants in the studies conducted under the PREDIMED-Plus framework were engaged in an active lifestyle intervention. This may have influenced the observed associations, although all the analyses were adjusted for this significant confounding factor and its potential interaction effect was also assessed.

The current research presents strengths that should be also noticed. Firstly, the majority of the findings presented in this dissertation are original and have not been previously reported in the literature. The studies examining prospective relationships between trait

impulsivity and the incidence of type 2 diabetes and cardiovascular disease, as well as between trait impulsivity and adherence to dietary patterns, represent a previously unexplored area of research. Secondly, our manuscript relating impulsivity and glycemic status put forth novel perspectives on the assessment and understanding of impulsivity. Given the multifaceted nature of impulsivity, which encompasses multiple traits and behavioral characteristics, a domain of trait impulsivity and a domain of behavioral impulsivity were obtained. Subsequently, a global impulsivity composite score was obtained by merging the two domains. This approach permits a more comprehensive examination of impulsivity as a global construct, an investigation of the specific trait and behavioral impulsivity domains, and an examination of the particular subfactors of the trait and behavioral impulsivity features. Thirdly, it should be noted that some of our manuscripts included a notably large number of participants. Subsequently, public health policies designed to reduce the global health burden may consider some of our findings to be relevant. Fourth, all of our manuscripts included the inclusion of several confounding factors, such as sociodemographic, lifestyle, and history of disease and medication use. Therefore, some residual confounding effects might be present in our results, but efforts to minimize this potential bias were performed. Finally, several sensitivity analyses were conducted in our investigations, which strengthened the robustness of our findings.

VII. CONCLUSIONS

UNIVERSITAT ROVIRA I VIRGILI
Psychology and Disease: Unveiling Emerging Perspectives on Their Interplay
Carlos Gómez Martínez

CONCLUSIONS

The conclusions of this doctoral thesis are presented in response to each of the aims previously formulated.

Aim 1: To prospectively examine the associations between levels of trait impulsivity and adherence to healthy and unhealthy dietary patterns within the context of the PREDIMED-Plus-Cognition cohort (462 Spanish older adults at high risk of cardiovascular disease over three years of follow-up).

- Trait impulsivity was found to be positively associated with adherence to the unhealthy Western dietary pattern and negatively associated with adherence to six of the eight healthy dietary patterns assessed, including the Mediterranean diet.
- An interaction by intervention group was identified in some of the studied associations, and the results were also stratified. The results of this interaction suggest that individuals following an intensive lifestyle intervention may encounter additional challenges in adhering to recommendations for healthy plant-based diets.
- Overall, the results suggest that trait impulsivity is an important psychological factor to consider when making dietary recommendations, particularly for individuals with metabolic syndrome and overweight or obesity.

Aim 2: To prospectively examine the associations between levels of trait impulsivity and the risk of incident cardiovascular disease within the context of the NutriNet-Santé cohort (48,377 general French adults over eight years of follow-up).

- Individuals with higher levels of trait impulsivity exhibited a 27% increased risk of developing cardiovascular disease events.
- An interaction by type 2 diabetes status was identified and results were further stratified. In participants without type 2 diabetes, similar results were observed as those in the total population, although detrimental associations were borderline significant. In participants with type 2 diabetes and lower impulsivity, a 58% reduction in the risk of developing cardiovascular disease events was observed.
- Overall, these results suggest that trait impulsivity is an important psychological feature to account for cardiovascular disease prevention strategies in the general population.

Aim 3: To prospectively examine the associations between levels of trait impulsivity and the risk of developing type 2 diabetes within the context of the NutriNet-Santé cohort (48,135 general French adults over eight years of follow-up).

- A 1 standard deviation increase in trait impulsivity was associated with a 10% higher risk of developing type 2 diabetes.
- Body mass index was found to have an incremental mediation effect in the detrimental associations observed between trait impulsivity and the risk of developing type 2 diabetes.
- Overall, these results suggest that trait impulsivity is an important psychological feature to account for type 2 diabetes prevention strategies in the general population.

Aim 4: To prospectively examine the associations of insulin resistance, glycated hemoglobin, type 2 diabetes prevalence, and type 2 diabetes control with the global impulsivity composite, as well as with trait and behavioral impulsivity domains, within the context of the PREDIMED-Plus- Cognition cohort (487 Spanish older adults at high risk of cardiovascular disease over three years of follow-up).

- Baseline and changes in insulin resistance, as evaluated by HOMA-IR, were not associated with any measure of impulsivity.
- Baseline and changes in glucose levels, as assessed by HbA1c, were prospectively and positively associated with changes in the Global, Trait, and Behavioral Impulsivity domains.
- Individuals with type 2 diabetes at baseline showed a prospective increase in the Global Impulsivity domain.
- Individuals with type 2 diabetes and poor diabetes control at baseline exhibited prospective increases in the Global Impulsivity domain. Participants with type 2 diabetes at baseline who experienced changes to a poor diabetes control exhibited prospective increases in the Global and Trait Impulsivity domains.
- Overall, prospective relationships between glycemic-related dysregulations and increases in facets of impulsivity were observed. These results suggest that glycemic dysregulations increase impulsivity, potentially increasing medical and psychological impulsivity-related comorbidities, at least in populations at high risk of cardiovascular disease.

Aim 5: To prospectively examine the associations of insulin resistance, glycated hemoglobin, type 2 diabetes prevalence, type 2 diabetes control, and diabetes medication use with cognitive function changes over two years of follow-up within the context of the PREDIMED-Plus cohort (6,874 Spanish older adults at high risk of cardiovascular disease over two years of follow-up).

- HOMA-IR and HbA1c levels at baseline were inversely associated with changes in the Global Cognitive Function score.
- A status of prediabetes at baseline was not associated with changes in cognitive function.
- The presence of type 2 diabetes at baseline, particularly with longer diabetes duration, was inversely associated with changes in the Global Cognitive Function score.
- In participants with type 2 diabetes at baseline, a poor diabetes control was borderline and inversely associated with changes in the Global Cognitive Function score, and only significant decreases in the phonological verbal fluency performance were observed.
- The use of insulin medication was prospectively and inversely associated with changes in the Global Cognitive Function score.
- Overall, in only two years of follow-up, prospective associations between several glycemic-related dysregulations and worsening cognitive function were observed. These results suggest that even over a relatively short follow-up period, glycemic impairments can worsen cognitive function, at least in populations at high risk of cardiovascular disease.

Aim 6: To prospectively examine the associations of COVID-19 status (negative/positive) with cognitive impairment and changes in cognitive function before and after COVID-19 status ascertainment within the context of the PREDIMED-Plus cohort (50 weeks after COVID-19 status ascertainment in 5,179 Spanish older adults at high risk of cardiovascular disease).

- COVID-19 was not associated with worsening cognitive function 50 weeks after COVID-19 ascertainment.
- COVID-19 was not associated with the odds of developing cognitive impairment 50 weeks after COVID-19 ascertainment.

- These findings suggest the necessity for further investigation into the potential long-term impact of COVID-19 on cognitive impairment.

Aim 7: To prospectively examine the associations of COVID-19 status (negative/positive) with depressive risk and changes in depressive symptomatology before and after COVID-19 status ascertainment within the context of the PREDIMED-Plus cohort (29 weeks after COVID-19 status ascertainment in 5,486 Spanish older adults at high risk of cardiovascular disease).

- Individuals who experienced COVID-19 showed higher depressive symptomatology 29 weeks after COVID-19 ascertainment.
- Individuals who experienced COVID-19 showed a 62% increase in the odds of depression 29 weeks after COVID-19 ascertainment.
- These findings advocate for the necessity of monitoring the trajectory of depressive symptoms and disorders over the forthcoming post-COVID-19 decades.

VIII. GLOBAL AND FUTURE INSIGHTS

UNIVERSITAT ROVIRA I VIRGILI
Psychology and Disease: Unveiling Emerging Perspectives on Their Interplay
Carlos Gómez Martínez

GLOBAL AND FUTURE INSIGHTS

The findings of this doctoral thesis highlight the intricate relationships between psychological factors, cardiometabolic health, and the impact of infectious diseases such as COVID-19. Over the past century, while life expectancy has increased, there has also been a concomitant rise in chronic diseases, cognitive impairments, and mental health conditions. This research specifically highlights the relevance of trait impulsivity, glycemic dysregulations, and COVID-19 as important factors influencing these health outcomes.

The evidence presented indicated that higher trait impulsivity is longitudinally associated with an unfavorable adherence to dietary patterns in individuals with overweight or obesity and metabolic syndrome at high risk of cardiovascular disease. Moreover, this personality trait was linked to an increased risk of developing type 2 diabetes and cardiovascular disease in the general population. These findings underscore the importance of assessing and managing trait impulsivity as a component of cardiometabolic chronic disease prevention strategies. By understanding and gaining more knowledge of how impulsivity affects dietary habits, public health initiatives can be better tailored to address these psychological barriers, potentially reducing the incidence of cardiometabolic diseases through improved adherence to healthy diets. The findings of this thesis strongly support the integration of psychological assessments into routine public health care, particularly for individuals at high risk of metabolic syndrome, diabetes and cardiovascular disease. Given the evident links between trait impulsivity, poor dietary adherence, and the occurrence of cardiometabolic chronic diseases, public health strategies should consider incorporating tailored psychological interventions designed to mitigate the tendency to act on impulse for promoting healthier lifestyle patterns and health status.

This thesis further elucidates the relationship between glycemic dysregulations and cognitive function. The findings of our study indicate that insulin resistance, the prevalence of type 2 diabetes, poor glycemic control, and the use of insulin treatment were all associated with a decline in cognitive function within the PREDIMED-Plus study. In light of the rapid decline in cognitive function observed over the course of just two years, there is a need for interventions that can ameliorate these adverse relationships.

Furthermore, results from the PREDIMED-Plus-cognition study revealed that elevated HbA1c levels, the presence of type 2 diabetes, and inadequate glycemic control were associated with increased impulsivity over time, underscoring the interdependence of metabolic and psychological health. These findings highlight the necessity for integrated approaches that address both the physical and psychological aspects of health. Future research should consider the development of comprehensive strategies that integrate glycemic management and cognitive health preservation, further accounting for the fact that poorer glycemic health could also promote unbeneficial lifestyle behaviors by increasing impulsivity.

The COVID-19 pandemic has introduced significant challenges to both physical and mental health. The findings under the framework of the PREDIMED-Plus study indicate that individuals who tested positive for COVID-19 had a 62% increased risk of developing depressive symptoms 29 weeks after diagnosis, compared to those who did not contract the virus. In contrast, no significant associations were identified between positive COVID-19 cases and cognitive dysfunction 50 weeks after diagnosis. These findings reinforce the necessity for long-term monitoring of the cognitive and mental health consequences of COVID-19. This will help to ensure that no additional cognitive impairments arise and increase the certainty of the COVID-19 impact on depressive symptomatology rates in the forthcoming decades, as the ongoing nature of the pandemic necessitates continued research to fully understand its impact on cognitive and mental health. The implementation of public health policies should prioritize the integration of mental health support for individuals who have survived the consequences of SARS-CoV-2 infection. The provision of ongoing psychological supervision for those affected, particularly those with preexisting conditions or severe COVID-19 illness, is of the great importance in order to prevent the progression of depressive symptoms into more severe mental health disorders.

While this thesis has contributed significant insights, there are also several avenues for future research in this field that warrant further investigation. First, exploring the neural substrates of impulsivity and their connections to cardiometabolic health could facilitate the identification of more precise targets for interventions. A deeper comprehension of the manner in which impulsivity interacts with the regulation of glucose homeostasis via the hypothalamus and other brain regions could also facilitate the development of novel therapeutic strategies. Furthermore, this understanding could potentially be extended to

the prevention of cardiovascular disease. Additional research on neurotransmitters, such as serotonin and dopamine or other molecules, may facilitate the development of pharmacological treatments for both psychological and physical health, as their role in linking impulsivity with cardiometabolic outcomes represents a promising avenue for further research.

This thesis hypothesizes the existence of a potential feedback loop between impulsivity and glycemic dysregulations, potentially opening new future lines of research. This suggests that interventions designed to reduce the prevalence of type 2 diabetes, for instance by improving glycemic control, could have advantageous effects in mitigating glycemic impairments while concurrently reducing impulsivity and its associated risky behaviors that contribute to a poorer physical and mental health status. Therefore, future research should consider the examination of these bidirectional relationships in diverse populations over extended periods and with a larger number of participants, in order to gain a more comprehensive understanding of the nature of these interconnectivities. This will facilitate a more comprehensive understanding of the emergence and evolution of these interrelated dynamics over time. The optimal approach would be to promote psychological interventions that have been demonstrated to reduce impulsivity, such as increasing mindfulness activities, lifestyle interventions to reduce glycemic impairments, or a combination of both. This would provide the opportunity to assess the feasibility of integrating these recommendations into more comprehensive general health policies aimed at reducing glycemic diseases and related psychological disturbances associated with higher impulsivity.

In conclusion, this doctoral research has significantly advanced the understanding of how psychological factors, particularly impulsivity, interact with health outcomes. The associations between impulsivity, glycemic dysregulations, cardiovascular disease, and cognitive dysfunction emphasize the necessity for integrated health approaches that address both psychological and medical health aspects. Furthermore, the findings of this thesis advocate for the necessity of addressing the mental health consequences of the COVID-19 pandemic, as well as monitoring the cognitive function. Future research should be built on these approaches and explore holistic psychological and lifestyle interventions with the goal of reducing the global burden of disease and enhancing population quality of life in the context of the post-pandemic era.

IX. REFERENCES

UNIVERSITAT ROVIRA I VIRGILI
Psychology and Disease: Unveiling Emerging Perspectives on Their Interplay
Carlos Gómez Martínez

REFERENCES

1. Harper, R. G. *Personality-Guided Therapy in Behavioral Medicine. American Psychological Association* (American Psychological Association, Washington, DC, 2004). doi:10.1037/10650-000.

2. Galli, F., Tanzilli, A., Pompili, M. & Bagby, M. Editorial: Personality and Disease: New Directions in Modern Research. *Front Psychol* **12**, 828337 (2022).

3. Remes, O., Mendes, J. F. & Templeton, P. Biological, Psychological, and Social Determinants of Depression: A Review of Recent Literature. *Brain Sci* **11**, 1633 (2021).

4. Leventhal, H., Weinman, J., Leventhal, E. A. & Phillips, L. A. Health Psychology: The Search for Pathways between Behavior and Health. *Annu Rev Psychol* **59**, 477–505 (2008).

5. Rumsfeld, J. S. Health Status and Clinical Practice. *Circulation* **106**, 5–7 (2002).

6. Rubin, R. Exploring the Relationship Between Depression and Dementia. *JAMA* **320**, 961 (2018).

7. Stephan, Y., Sutin, A. R., Luchetti, M., Aschwanden, D. & Terracciano, A. Personality and Risk of Incident Stroke in 6 Prospective Studies. *Stroke* **54**, 2069–2076 (2023).

8. Jokela, M. *et al.* Personality and risk of diabetes in adults: Pooled analysis of 5 cohort studies. *Health Psychology* **33**, 1618–1621 (2014).

9. Stoney, C. M., Kaufmann, P. G. & Czajkowski, S. M. Cardiovascular disease: Psychological, social, and behavioral influences: Introduction to the special issue. *American Psychologist* **73**, 949–954 (2018).

10. Kuo, W. *et al.* The association between psychological stress and metabolic syndrome: A systematic review and meta-analysis. *Obesity Reviews* **20**, 1651–1664 (2019).

11. Segerstrom, S. C. & Miller, G. E. Psychological Stress and the Human Immune System: A Meta-Analytic Study of 30 Years of Inquiry. *Psychol Bull* **130**, 601–630 (2004).

12. Kiecolt-Glaser, J. K., McGuire, L., Robles, T. F. & Glaser, R. Emotions, Morbidity, and Mortality: New Perspectives from Psychoneuroimmunology. *Annu Rev Psychol* **53**, 83–107 (2002).

13. Walker, E. R., McGee, R. E. & Druss, B. G. Mortality in Mental Disorders and Global Disease Burden Implications. *JAMA Psychiatry* **72**, 334 (2015).

14. Seligman, M. E. P. & Csikszentmihalyi, M. Positive psychology: An introduction. *American Psychologist* **55**, 5–14 (2000).

15. Valenzuela, M. J. & Sachdev, P. Brain reserve and dementia: a systematic review. *Psychol Med* **36**, 441–454 (2006).

16. Uchino, B. N. Social Support and Health: A Review of Physiological Processes Potentially Underlying Links to Disease Outcomes. *J Behav Med* **29**, 377–387 (2006).

17. Irwin, A. *et al.* Mindfulness, disordered eating, and impulsivity in relation to glycemia among adolescents with type 1 diabetes and suboptimal glycemia from the Flexible Lifestyles Empowering Change (FLEX) intervention trial. *Pediatr Diabetes* **23**, 516–526 (2022).

18. Fekih-Romdhane, F., Malaeb, D., Hallit, S. & Obeid, S. Does mindfulness moderate the association between impulsivity and well-being in Lebanese university students? *Int J Environ Health Res* **34**, 1397–1409 (2023).

19. Friedman, H. S. & Kern, M. L. Personality, Well-Being, and Health. *Annu Rev Psychol* **65**, 719–742 (2014).

20. Moeller, F. G., Barratt, E. S., Dougherty, D. M., Schmitz, J. M. & Swann, A. C. Psychiatric Aspects of Impulsivity. *American Journal of Psychiatry* **158**, 1783–1793 (2001).

21. Dalley, J. W. & Robbins, T. W. Fractionating impulsivity: neuropsychiatric implications. *Nat Rev Neurosci* **18**, 158–171 (2017).

22. Kopetz, C. E., Woerner, J. I. & Briskin, J. L. Another look at impulsivity: Could impulsive behavior be strategic? *Soc Personal Psychol Compass* **12**, e12385 (2018).

23. Hollander, E. & Rosen, J. Impulsivity. *Journal of Psychopharmacology* **14**, S39–S44 (2000).

24. Emery, R. L. & Levine, M. D. Questionnaire and behavioral task measures of impulsivity are differentially associated with body mass index: A comprehensive meta-analysis. *Psychol Bull* **143**, 868–902 (2017).

25. Emery, R. L. *et al.* Impulsivity and midlife cardiometabolic risk: The role of maladaptive health behaviors. *Health Psychology* **39**, 642–654 (2020).

26. Svrakic, D. M., Przybeck, T. R. & Cloninger, C. R. Mood states and personality traits. *J Affect Disord* **24**, 217–226 (1992).

27. Fleeson, W. Toward a structure- and process-integrated view of personality: Traits as density distributions of states. *J Pers Soc Psychol* **80**, 1011–1027 (2001).

28. Sharma, L., Markon, K. E. & Clark, L. A. Toward a theory of distinct types of 'impulsive' behaviors: A meta-analysis of self-report and behavioral measures. *Psychol Bull* **140**, 374–408 (2014).

29. Roberts, B. W. & DelVecchio, W. F. The rank-order consistency of personality traits from childhood to old age: A quantitative review of longitudinal studies. *Psychol Bull* **126**, 3–25 (2000).

30. Caspi, A., Roberts, B. W. & Shiner, R. L. Personality Development: Stability and Change. *Annu Rev Psychol* **56**, 453–484 (2005).

31. Liu, M., Argyriou, E. & Cyders, M. A. Developmental Considerations for Assessment and Treatment of Impulsivity in Older Adults. in *Current Topics in Behavioral Neurosciences* (eds. de Wit, H. & Jentsch, J. D.) vol. 47 165–177 (Springer Cham, Berlin/Heidelberg, Germany, 2020).

32. Lynam, D. R., Smith, G. T., Whiteside, S. P. & Cyders, M. A. *The UPPS–P: Assessing Five Personality Pathways to Impulsive Behavior*. (Purdue University, West Lafayette, 2006).

33. Creswell, K. G., Wright, A. G. C., Flory, J. D., Skrzynski, C. J. & Manuck, S. B. Multidimensional assessment of impulsivity-related measures in relation to externalizing behaviors. *Psychol Med* **49**, 1678–1690 (2019).

34. Bari, A. & Robbins, T. W. Inhibition and impulsivity: Behavioral and neural basis of response control. *Prog Neurobiol* **108**, 44–79 (2013).

35. Dalley, J. W., Everitt, B. J. & Robbins, T. W. Impulsivity, Compulsivity, and Top-Down Cognitive Control. *Neuron* **69**, 680–694 (2011).

36. Brewster, B. M., Pasqualini, M. S. & Martin, L. E. Functional Brain Connectivity and Inhibitory Control in Older Adults: A Preliminary Study. *Front Aging Neurosci* **14**, 125 (2022).

37. Chamberlain, S. R., Stochl, J., Redden, S. A. & Grant, J. E. Latent traits of impulsivity and compulsivity: toward dimensional psychiatry. *Psychol Med* **48**, 810–821 (2018).

38. Carr, M. M., Wiedemann, A. A., Macdonald-Gagnon, G. & Potenza, M. N. Impulsivity and compulsivity in binge eating disorder: A systematic review of behavioral studies. *Prog Neuropsychopharmacol Biol Psychiatry* **110**, 110318 (2021).

39. Moore, F. R. *et al.* Impulsivity, aggression, and suicidality relationship in adults: A systematic review and meta-analysis. *EClinicalMedicine* **45**, 101307 (2022).

40. Kalenscher, T., Ohmann, T. & Güntürkün, O. The neuroscience of impulsive and self-controlled decisions. *International Journal of Psychophysiology* **62**, 203–211 (2006).

41. Buckholtz, J. W. *et al.* Dopaminergic Network Differences in Human Impulsivity. *Science (1979)* **329**, 532–532 (2010).

42. Levine, G. N. *et al.* Psychological Health, Well-Being, and the Mind-Heart-Body Connection: A Scientific Statement From the American Heart Association. *Circulation* **143**, E763–E783 (2021).

43. Stautz, K. & Cooper, A. Impulsivity-related personality traits and adolescent alcohol use: A meta-analytic review. *Clin Psychol Rev* **33**, 574–592 (2013).

44. Herman, A. M. & Duka, T. Facets of impulsivity and alcohol use: What role do emotions play? *Neurosci Biobehav Rev* **106**, 202–216 (2019).

45. Bos, J., Hayden, M. J., Lum, J. A. G. & Staiger, P. K. UPPS-P impulsive personality traits and adolescent cigarette smoking: A meta-analysis. *Drug Alcohol Depend* **197**, 335–343 (2019).

46. Kale, D., Stautz, K. & Cooper, A. Impulsivity related personality traits and cigarette smoking in adults: A meta-analysis using the UPPS-P model of impulsivity and reward sensitivity. *Drug Alcohol Depend* **185**, 149–167 (2018).

47. Bénard, M. *et al.* Association between Impulsivity and Weight Status in a General Population. *Nutrients* **9**, 217 (2017).

48. Pandey, A. *et al.* Effectiveness of Universal Self-regulation–Based Interventions in Children and Adolescents. *JAMA Pediatr* **172**, 566 (2018).

49. Rung, J. M. & Madden, G. J. Experimental reductions of delay discounting and impulsive choice: A systematic review and meta-analysis. *J Exp Psychol Gen* **147**, 1349–1381 (2018).

50. Anderson, A. C., Youssef, G. J., Robinson, A. H., Lubman, D. I. & Verdejo-Garcia, A. Cognitive boosting interventions for impulsivity in addiction: a systematic review and meta-analysis of cognitive training, remediation and pharmacological enhancement. *Addiction* **116**, 3304–3319 (2021).

51. Schag, K. *et al.* IMPULS: Impulsivity-Focused Group Intervention to Reduce Binge Eating Episodes in Patients with Binge Eating Disorder – A Randomised Controlled Trial. *Psychother Psychosom* **88**, 141–153 (2019).

52. Schag, K. *et al.* Food-related impulsivity assessed by longitudinal laboratory tasks is reduced in patients with binge eating disorder in a randomized controlled trial. *Sci Rep* **11**, 8225 (2021).

53. İnce, B. *et al.* Can we change binge eating behaviour by interventions addressing food-related impulsivity? A systematic review. *J Eat Disord* **9**, 38 (2021).

54. Treasure, J., Duarte, T. A. & Schmidt, U. Eating disorders. *The Lancet* **395**, 899–911 (2020).

55. Stevenson, R. J. Psychological correlates of habitual diet in healthy adults. *Psychol Bull* **143**, 53–90 (2017).

56. Bénard, M. *et al.* Impulsivity is associated with food intake, snacking, and eating disorders in a general population. *Am J Clin Nutr* **109**, 117–126 (2019).

57. van den Berk-Clark, C. The role of impulsivity on health behavior related to cardiovascular disease among young adults. *Psychol Trauma* **13**, 271–276 (2021).

58. Allen, M. T., Hogan, A. M. & Laird, L. K. The relationships of impulsivity and cardiovascular responses: The role of gender and task type. *International Journal of Psychophysiology* **73**, 369–376 (2009).

59. Hadj-Abo, A., Enge, S., Rose, J., Kunte, H. & Fleischhauer, M. Individual differences in impulsivity and need for cognition as potential risk or resilience factors of diabetes self-management and glycemic control. *PLoS One* **15**, e0227995 (2020).

60. Wainwright, K., Romanowich, P. & Crabtree, M. A. Associations between impulsivity and self-care adherence in individuals diagnosed with Type 2 or prediabetes. *PLoS One* **17**, e0263961 (2022).

61. Gomila, T. & Calvo, P. Directions for an Embodied Cognitive Science: Toward an Integrated Approach. in *Handbook of Cognitive Science* (eds. Gomila, T. & Calvo, P.) 1–25 (Elsevier, Amsterdam, the Netherrlands, 2008). doi:10.1016/B978-0-08-046616-3.X0001-1.

62. Pozo, J. I. *Adquisición de Conocimiento: Cuando La Carne Se Hace Verbo*. vol. 2 (Morata, Madrid, Spain, 2006).

63. Kiely, K. M. Cognitive Function. in *Encyclopedia of Quality of Life and Well-Being Research* (ed. Michalos, A.) 974–978 (Springer, Dordrech, Netherlands, 2014). doi:10.1007/978-94-007-0753-5_426.

64. Sachdev, P. S. *et al.* Classifying neurocognitive disorders: the DSM-5 approach. *Nat Rev Neurol* **10**, 634–642 (2014).

65. Tucker-Drob, E. M. Cognitive Aging and Dementia: A Life-Span Perspective. *Annu Rev Dev Psychol* **1**, 177–196 (2019).

66. Bishop, N. A., Lu, T. & Yankner, B. A. Neural mechanisms of ageing and cognitive decline. *Nature* **464**, 529–535 (2010).

67. Roberts, R. O. *et al.* Higher risk of progression to dementia in mild cognitive impairment cases who revert to normal. *Neurology* **82**, 317–325 (2014).

68. Mitchell, A. J. & Shiri-Feshki, M. Rate of progression of mild cognitive impairment to dementia - meta-analysis of 41 robust inception cohort studies. *Acta Psychiatr Scand* **119**, 252–265 (2009).

69. World Health Organization. A report about dementia. *September 21, 2020* https://www.who.int/news-room/fact-sheets/detail/dementia.

70. Pais, R., Ruano, L., P. Carvalho, O. & Barros, H. Global Cognitive Impairment Prevalence and Incidence in Community Dwelling Older Adults—A Systematic Review. *Geriatrics* **5**, 84 (2020).

71. Bai, W. *et al.* Worldwide prevalence of mild cognitive impairment among community dwellers aged 50 years and older: a meta-analysis and systematic review of epidemiology studies. *Age Ageing* **51**, afac173 (2022).

72. Avan, A. & Hachinski, V. Global, regional, and national trends of dementia incidence and risk factors, 1990–2019: A Global Burden of Disease study. *Alzheimer's & Dementia* **19**, 1281–1291 (2023).

73. Nichols, E. *et al.* Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. *Lancet Public Health* **7**, e105–e125 (2022).

74. Davies, G. *et al.* Study of 300,486 individuals identifies 148 independent genetic loci influencing general cognitive function. *Nat Commun* **9**, 2098 (2018).

75. Livingston, G. *et al.* Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *The Lancet* **396**, 413–446 (2020).

76. Lourida, I. *et al.* Association of Lifestyle and Genetic Risk With Incidence of Dementia. *JAMA* **322**, 430 (2019).

77. Meng, X. *et al.* Multidomain lifestyle interventions for cognition and the risk of dementia: A systematic review and meta-analysis. *Int J Nurs Stud* **130**, 104236 (2022).

78. Whitty, E. *et al.* Efficacy of lifestyle and psychosocial interventions in reducing cognitive decline in older people: Systematic review. *Ageing Res Rev* **62**, 101113 (2020).

79. Coley, N., Giulioli, C., Aisen, P. S., Vellas, B. & Andrieu, S. Randomised controlled trials for the prevention of cognitive decline or dementia: A systematic review. *Ageing Res Rev* **82**, 101777 (2022).

80. Rawlings, A. M. *et al.* Diabetes in Midlife and Cognitive Change Over 20 Years. *Ann Intern Med* **161**, 785–793 (2014).

81. Tuligenga, R. H. *et al.* Midlife type 2 diabetes and poor glycaemic control as risk factors for cognitive decline in early old age: a post-hoc analysis of the Whitehall II cohort study. *Lancet Diabetes Endocrinol* **2**, 228–235 (2014).

82. Spauwen, P. J. J., Kohler, S., Verhey, F. R. J., Stehouwer, C. D. A. & van Boxtel, M. P. J. Effects of Type 2 Diabetes on 12-Year Cognitive Change: Results from the Maastricht Aging Study. *Diabetes Care* **36**, 1554–1561 (2013).

83. Zheng, F., Yan, L., Yang, Z., Zhong, B. & Xie, W. HbA1c, diabetes and cognitive decline: the English Longitudinal Study of Ageing. *Diabetologia* **61**, 839–848 (2018).

84. Riby, L. M. *et al.* Impulsiveness, postprandial blood glucose, and glucoregulation affect measures of behavioral flexibility. *Nutrition Research* **48**, 65–75 (2017).

85. Hawkins, M. A. W., Gunstad, J., Calvo, D. & Spitznagel, M. B. Higher fasting glucose is associated with poorer cognition among healthy young adults. *Health Psychology* **35**, 199–202 (2016).

86. Epstein, L. H. *et al.* Delay Discounting, Glycemic Regulation and Health Behaviors in Adults with Prediabetes. *Behavioral Medicine* **47**, 194–204 (2021).

87. Lebeau, G. *et al.* Delay discounting of gains and losses, glycemic control and therapeutic adherence in type 2 diabetes. *Behavioural Processes* **132**, 42–48 (2016).

88. Reach, G. *et al.* Patients' impatience is an independent determinant of poor diabetes control. *Diabetes Metab* **37**, 497–504 (2011).

89. Lansing, A. H., Stanger, C., Crochiere, R., Carracher, A. & Budney, A. Delay discounting and parental monitoring in adolescents with poorly controlled type 1 diabetes. *J Behav Med* **40**, 864–874 (2017).

90. World Health Organization. A report about depression. *World Health Organization* (2023).

91. Herrman, H. *et al.* Reducing the global burden of depression: a Lancet–World Psychiatric Association Commission. *The Lancet* **393**, e42–e43 (2019).

92. Marx, W. *et al.* Major depressive disorder. *Nat Rev Dis Primers* **9**, 44 (2023).

93. Bangasser, D. A. & Cuarenta, A. Sex differences in anxiety and depression: circuits and mechanisms. *Nat Rev Neurosci* **22**, 674–684 (2021).

94. Lim, G. Y. *et al.* Prevalence of Depression in the Community from 30 Countries between 1994 and 2014. *Sci Rep* **8**, 2861 (2018).

95. Hu, T. *et al.* Prevalence of depression in older adults: A systematic review and meta-analysis. *Psychiatry Res* **311**, 114511 (2022).

96. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (5th Ed.)*. (American Psychiatric Association, Washington, DC, 2013).

97. Moussavi, S. *et al.* Depression, chronic diseases, and decrements in health: results from the World Health Surveys. *The Lancet* **370**, 851–858 (2007).

98. Gold, S. M. *et al.* Comorbid depression in medical diseases. *Nat Rev Dis Primers* **6**, 69 (2020).

99. Melin, E. O. *et al.* Depression was associated with younger age, female sex, obesity, smoking, and physical inactivity, in 1027 patients with newly diagnosed type 2 diabetes: a Swedish multicentre cross-sectional study. *BMC Endocr Disord* **22**, 273 (2022).

100. Graham, E. A. *et al.* Measures of depression and risk of type 2 diabetes: A systematic review and meta-analysis. *J Affect Disord* **265**, 224–232 (2020).

101. Hare, D. L., Toukhsati, S. R., Johansson, P. & Jaarsma, T. Depression and cardiovascular disease: a clinical review. *Eur Heart J* **35**, 1365–1372 (2014).

102. Malik, S., Wells, A. & Wittkowski, A. Emotion regulation as a mediator in the relationship between attachment and depressive symptomatology: A systematic review. *J Affect Disord* **172**, 428–444 (2015).

103. Rodríguez-Rey, R., Garrido-Hernansaiz, H. & Collado, S. Psychological Impact and Associated Factors During the Initial Stage of the Coronavirus (COVID-19) Pandemic Among the General Population in Spain. *Front Psychol* **11**, 1540 (2020).

104. Cénat, J. M. *et al.* The global evolution of mental health problems during the COVID-19 pandemic: A systematic review and meta-analysis of longitudinal studies. *J Affect Disord* **315**, 70–95 (2022).

105. Tapsell, L. C., Neale, E. P., Satija, A. & Hu, F. B. Foods, Nutrients, and Dietary Patterns: Interconnections and Implications for Dietary Guidelines. *Advances in Nutrition* **7**, 445–454 (2016).

106. Fabiani, R., Naldini, G. & Chiavarini, M. Dietary Patterns and Metabolic Syndrome in Adult Subjects: A Systematic Review and Meta-Analysis. *Nutrients* **11**, 2056 (2019).

107. Casas, R. Dietary Pattern and Nutrients Intake on Chronic Diseases. *Nutrients* **15**, 3399 (2023).

108. Cena, H. & Calder, P. C. Defining a Healthy Diet: Evidence for the Role of Contemporary Dietary Patterns in Health and Disease. *Nutrients* **12**, 334 (2020).

109. Ambrosini, G. L. Childhood dietary patterns and later obesity: a review of the evidence. *Proceedings of the Nutrition Society* **73**, 137–146 (2014).

110. Seifu, C. N., Fahey, P. P., Hailemariam, T. G., Frost, S. A. & Atlantis, E. Dietary patterns associated with obesity outcomes in adults: an umbrella review of systematic reviews. *Public Health Nutr* **24**, 6390–6414 (2021).

111. Batis, C., Mendez, M. A., Sotres-Alvarez, D., Gordon-Larsen, P. & Popkin, B. Dietary pattern trajectories during 15 years of follow-up and HbA1c, insulin resistance and diabetes prevalence among Chinese adults. *J Epidemiol Community Health (1978)* **68**, 773–779 (2014).

112. Ley, S. H. *et al.* Contribution of the Nurses' Health Studies to Uncovering Risk Factors for Type 2 Diabetes: Diet, Lifestyle, Biomarkers, and Genetics. *Am J Public Health* **106**, 1624–1630 (2016).

113. Salas-Salvadó, J., Becerra-Tomás, N., Papandreou, C. & Bulló, M. Dietary Patterns Emphasizing the Consumption of Plant Foods in the Management of Type 2 Diabetes: A Narrative Review. *Advances in Nutrition* **10**, S320–S331 (2019).

114. Gibbs, J., Gaskin, E., Ji, C., Miller, M. A. & Cappuccio, F. P. The effect of plant-based dietary patterns on blood pressure: a systematic review and meta-analysis of controlled intervention trials. *J Hypertens* **39**, 23–37 (2021).

115. Shan, Z. *et al.* Association Between Healthy Eating Patterns and Risk of Cardiovascular Disease. *JAMA Intern Med* **180**, 1090 (2020).

116. Liu, Y.-H. *et al.* Dietary Pattern, Diet Quality, and Dementia: A Systematic Review and Meta-Analysis of Prospective Cohort Studies. *Journal of Alzheimer's Disease* **78**, 151–168 (2020).

117. Shan, Z. *et al.* Healthy Eating Patterns and Risk of Total and Cause-Specific Mortality. *JAMA Intern Med* **183**, 142 (2023).

118. Cordain, L. *et al.* Origins and evolution of the Western diet: health implications for the 21st century. *Am J Clin Nutr* **81**, 341–354 (2005).

119. Rauber, F. & Levy, R. B. Ultra-processed foods and cardiovascular disease. *Nat Rev Cardiol* **21**, 213–214 (2024).

120. Srour, B. *et al.* Ultraprocessed Food Consumption and Risk of Type 2 Diabetes among Participants of the NutriNet-Santé Prospective Cohort. *JAMA Intern Med* **180**, 283–291 (2020).

121. Clemente-Suárez, V. J., Beltrán-Velasco, A. I., Redondo-Flórez, L., Martín-Rodríguez, A. & Tornero-Aguilera, J. F. Global Impacts of Western Diet and Its Effects on Metabolism and Health: A Narrative Review. *Nutrients* **15**, 2749 (2023).

122. Christ, A., Lauterbach, M. & Latz, E. Western Diet and the Immune System: An Inflammatory Connection. *Immunity* **51**, 794–811 (2019).

123. Toi, P. L. *et al.* Preventive Role of Diet Interventions and Dietary Factors in Type 2 Diabetes Mellitus: An Umbrella Review. *Nutrients* **12**, 2722 (2020).

124. Doundoulakis, I. *et al.* Effects of dietary interventions on cardiovascular outcomes: a network meta-analysis. *Nutr Rev* **82**, 715–725 (2024).

125. Opie, R. S., O'Neil, A., Itsiopoulos, C. & Jacka, F. N. The impact of whole-of-diet interventions on depression and anxiety: a systematic review of randomised controlled trials. *Public Health Nutr* **18**, 2074–2093 (2015).

126. Leng, G. *et al.* The determinants of food choice. *Proceedings of the Nutrition Society* **76**, 316–327 (2017).

127. Lumley, J., Stevenson, R. J., Oaten, M. J., Mahmut, M. & Yeomans, M. R. Individual differences in impulsivity and their relationship to a Western-style diet. *Pers Individ Dif* **97**, 178–185 (2016).

128. Leitch, M. A., Morgan, M. J. & Yeomans, M. R. Different subtypes of impulsivity differentiate uncontrolled eating and dietary restraint. *Appetite* **69**, 54–63 (2013).

129. Sarmugam, R. & Worsley, A. Dietary Behaviours, Impulsivity and Food Involvement: Identification of Three Consumer Segments. *Nutrients* **7**, 8036–8057 (2015).

130. World Health Organization. A report about cardiovascular diseases. *June 11, 2021* https://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds).

131. Libby, P. & Theroux, P. Pathophysiology of Coronary Artery Disease. *Circulation* **111**, 3481–3488 (2005).

132. Webb, A. J. S. & Werring, D. J. New Insights Into Cerebrovascular Pathophysiology and Hypertension. *Stroke* **53**, 1054–1064 (2022).

133. Haunstetter, A. & Izumo, S. Apoptosis. *Circ Res* **82**, 1111–1129 (1998).

134. Amini, M., Zayeri, F. & Salehi, M. Trend analysis of cardiovascular disease mortality, incidence, and mortality-to-incidence ratio: results from global burden of disease study 2017. *BMC Public Health* **21**, 401 (2021).

135. Li, Y., Cao, G., Jing, W., Liu, J. & Liu, M. Global trends and regional differences in incidence and mortality of cardiovascular disease, 1990−2019: findings from 2019 global burden of disease study. *Eur J Prev Cardiol* **30**, 276–286 (2023).

136. Münzel, T. *et al.* Environmental risk factors and cardiovascular diseases: a comprehensive expert review. *Cardiovasc Res* **118**, 2880–2902 (2022).

137. Mozaffarian, D., Wilson, P. W. F. & Kannel, W. B. Beyond Established and Novel Risk Factors. *Circulation* **117**, 3031–3038 (2008).

138. Livingstone, K. M. *et al.* Diet quality indices, genetic risk and risk of cardiovascular disease and mortality: a longitudinal analysis of 77 004 UK Biobank participants. *BMJ Open* **11**, e045362 (2021).

139. Lehert, P., Villaseca, P., Hogervorst, E., Maki, P. M. & Henderson, V. W. Individually modifiable risk factors to ameliorate cognitive aging: a systematic review and meta-analysis. *Climacteric* **18**, 678–689 (2015).

140. Rana, J. S., Nieuwdorp, M., Jukema, J. W. & Kastelein, J. J. P. Cardiovascular metabolic syndrome - an interplay of, obesity, inflammation, diabetes and coronary heart disease. *Diabetes Obes Metab* **9**, 218–232 (2007).

141. Wilson, P. W. F., D'Agostino, R. B., Parise, H., Sullivan, L. & Meigs, J. B. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. *Circulation* **112**, 3066–3072 (2005).

142. Koene, R. J., Prizment, A. E., Blaes, A. & Konety, S. H. Shared Risk Factors in Cardiovascular Disease and Cancer. *Circulation* **133**, 1104–1114 (2016).

143. Celano, C. M., Daunis, D. J., Lokko, H. N., Campbell, K. A. & Huffman, J. C. Anxiety Disorders and Cardiovascular Disease. *Curr Psychiatry Rep* **18**, 101 (2016).

144. Wang, X. *et al.* Association of Cardiovascular Health With Life Expectancy Free of Cardiovascular Disease, Diabetes, Cancer, and Dementia in UK Adults. *JAMA Intern Med* **183**, 340 (2023).

145. Gardener, H. *et al.* Ideal Cardiovascular Health and Cognitive Aging in the Northern Manhattan Study. *J Am Heart Assoc* **5**, e002731 (2016).

146. Tini, G. *et al.* Alzheimer's Disease and Cardiovascular Disease: A Particular Association. *Cardiol Res Pract* **2020**, 1–10 (2020).

147. Yusuf, S. *et al.* Modifiable risk factors, cardiovascular disease, and mortality in 155 722 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. *The Lancet* **395**, 795–808 (2020).

148. O'Connor, E. A., Evans, C. V., Rushkin, M. C., Redmond, N. & Lin, J. S. Behavioral Counseling to Promote a Healthy Diet and Physical Activity for Cardiovascular Disease Prevention in Adults With Cardiovascular Risk Factors. *JAMA* **324**, 2076 (2020).

149. Fretheim, A. *et al.* Comparative effectiveness of antihypertensive medication for primary prevention of cardiovascular disease: systematic review and multiple treatments meta-analysis. *BMC Med* **10**, 33 (2012).

150. Cai, T. *et al.* Associations between statins and adverse events in primary prevention of cardiovascular disease: systematic review with pairwise, network, and dose-response meta-analyses. *BMJ* **374**, n1537 (2021).

151. Delgado-Lista, J. *et al.* Long-term secondary prevention of cardiovascular disease with a Mediterranean diet and a low-fat diet (CORDIOPREV): a randomised controlled trial. *The Lancet* **399**, 1876–1885 (2022).

152. Naci, H. & Ioannidis, J. P. A. Comparative effectiveness of exercise and drug interventions on mortality outcomes: metaepidemiological study. *Br J Sports Med* **49**, 1414–1422 (2015).

153. Stürmer, T., Hasselbach, P. & Amelang, M. Personality, lifestyle, and risk of cardiovascular disease and cancer: follow-up of population based cohort. *BMJ* **332**, 1359 (2006).

154. Kivimäki, M. & Steptoe, A. Effects of stress on the development and progression of cardiovascular disease. *Nat Rev Cardiol* **15**, 215–229 (2018).

155. American Diabetes Association Professional Practice Committee. 6. Glycemic Targets: Standards of Medical Care in Diabetes-2022. *Diabetes Care* **45**, S83–S96 (2022).

156. World Health Organization. A report about diabetes. *June 8, 2020* https://www.who.int/health-topics/diabetes.

157. Saltiel, A. R. & Kahn, C. R. Insulin signalling and the regulation of glucose and lipid metabolism. *Nature* **414**, 799–806 (2001).

158. Zaccardi, F., Webb, D. R., Yates, T. & Davies, M. J. Pathophysiology of type 1 and type 2 diabetes mellitus: a 90-year perspective. *Postgrad Med J* **92**, 63–69 (2016).

159. Rooney, M. R. *et al.* Global Prevalence of Prediabetes. *Diabetes Care* **46**, 1388–1394 (2023).

160. Magliano, D. J. *et al.* Trends in incidence of total or type 2 diabetes: systematic review. *BMJ* **366**, l5003 (2019).

161. Khan, M. A. B. *et al.* Epidemiology of Type 2 Diabetes – Global Burden of Disease and Forecasted Trends. *J Epidemiol Glob Health* **10**, 107 (2019).

162. Gregory, G. A. *et al.* Global incidence, prevalence, and mortality of type 1 diabetes in 2021 with projection to 2040: a modelling study. *Lancet Diabetes Endocrinol* **10**, 741–760 (2022).

163. Liu, J. *et al.* Trends in the incidence of diabetes mellitus: results from the Global Burden of Disease Study 2017 and implications for diabetes mellitus prevention. *BMC Public Health* **20**, 1415 (2020).

164. Lin, X. *et al.* Global, regional, and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2025. *Sci Rep* **10**, 14790 (2020).

165. de Groot, M., Golden, S. H. & Wagner, J. Psychological conditions in adults with diabetes. *American Psychologist* **71**, 552–562 (2016).

166. Bellou, V., Belbasis, L., Tzoulaki, I. & Evangelou, E. Risk factors for type 2 diabetes mellitus: An exposure-wide umbrella review of meta-analyses. *PLoS One* **13**, e0194127 (2018).

167. Dendup, T., Feng, X., Clingan, S. & Astell-Burt, T. Environmental Risk Factors for Developing Type 2 Diabetes Mellitus: A Systematic Review. *Int J Environ Res Public Health* **15**, 78 (2018).

168. Chen, M. *et al.* The Effect of Lifestyle Intervention on Diabetes Prevention by Ethnicity: A Systematic Review of Intervention Characteristics Using the TIDieR Framework. *Nutrients* **13**, 4118 (2021).

169. García-Molina, L. *et al.* Improving type 2 diabetes mellitus glycaemic control through lifestyle modification implementing diet intervention: a systematic review and meta-analysis. *Eur J Nutr* **59**, 1313–1328 (2020).

170. Zhou, X. *et al.* Cost-effectiveness of Diabetes Prevention Interventions Targeting High-risk Individuals and Whole Populations: A Systematic Review. *Diabetes Care* **43**, 1593–1616 (2020).

171. Zhou, Z., Sun, B., Huang, S., Zhu, C. & Bian, M. Glycemic variability: adverse clinical outcomes and how to improve it? *Cardiovasc Diabetol* **19**, 102 (2020).

172. Winkley, K. *et al.* Psychological interventions to improve glycemic control in adults with type 2 diabetes: a systematic review and meta-analysis. *BMJ Open Diabetes Res Care* **8**, e001150 (2020).

173. Viana, L. V., Gomes, M. B., Zajdenverg, L., Pavin, E. J. & Azevedo, M. J. Interventions to improve patients' compliance with therapies aimed at lowering glycated hemoglobin (HbA1c) in type 1 diabetes: systematic review and meta-analyses of randomized controlled clinical trials of psychological, telecare, and educational interventions. *Trials* **17**, 94 (2016).

174. Padhi, S., Nayak, A. K. & Behera, A. Type II diabetes mellitus: a review on recent drug based therapeutics. *Biomedicine & Pharmacotherapy* **131**, 110708 (2020).

175. Khursheed, R. *et al.* Treatment strategies against diabetes: Success so far and challenges ahead. *Eur J Pharmacol* **862**, 172625 (2019).

176. Geijselaers, S. L. C., Sep, S. J. S., Stehouwer, C. D. A. & Biessels, G. J. Glucose regulation, cognition, and brain MRI in type 2 diabetes: a systematic review. *Lancet Diabetes Endocrinol* **3**, 75–89 (2015).

177. Profenno, L. A., Porsteinsson, A. P. & Faraone, S. V. Meta-Analysis of Alzheimer's Disease Risk with Obesity, Diabetes, and Related Disorders. *Biol Psychiatry* **67**, 505–512 (2010).

178. Whitmer, R. A. Hypoglycemic Episodes and Risk of Dementia in Older Patients With Type 2 Diabetes Mellitus. *JAMA* **301**, 1565–1572 (2009).

179. Xue, M. *et al.* Diabetes mellitus and risks of cognitive impairment and dementia: A systematic review and meta-analysis of 144 prospective studies. *Ageing Res Rev* **55**, 100944 (2019).

180. Sadanand, S., Balachandar, R. & Bharath, S. Memory and executive functions in persons with type 2 diabetes: a meta-analysis. *Diabetes Metab Res Rev* **32**, 132–142 (2016).

181. Crane, P. K. *et al.* Glucose Levels and Risk of Dementia. *New England Journal of Medicine* **369**, 540–548 (2013).

182. Nooyens, A. C. J., Baan, C. A., Spijkerman, A. M. W. & Verschuren, W. M. M. Type 2 Diabetes and Cognitive Decline in Middle-Aged Men and Women: The Doetinchem Cohort Study. *Diabetes Care* **33**, 1964–1969 (2010).

183. Fischer, A. L., de Frias, C. M., Yeung, S. E. & Dixon, R. A. Short-term longitudinal trends in cognitive performance in older adults with type 2 diabetes. *J Clin Exp Neuropsychol* **31**, 809–822 (2009).

184. Klement, J. *et al.* Effects of blood glucose on delay discounting, food intake and counterregulation in lean and obese men. *Psychoneuroendocrinology* **89**, 177–184 (2018).

185. Testa, G. *et al.* Impulsive Personality Traits Predicted Weight Loss in Individuals with Type 2 Diabetes after 3 Years of Lifestyle Interventions. *J Clin Med* **11**, 3476 (2022).

186. Eriksson, A.-K. *et al.* Personality traits and abnormal glucose regulation in middle-aged Swedish men and women. *Diabetes Res Clin Pract* **95**, 145–152 (2012).

187. John, O., Naumann, L. & Soto CJ. Paradigm shift to the integrative big five trait taxonomy: History, measurement, and conceptual issues. in *Handbook of personality: Theory and research, 3rd ed.* (eds. Jhon OP, Robins RW & Pervin LA) 114–158 (The Guilford Press, 2008).

188. Stephan, Y., Sutin, A. R., Luchetti, M., Canada, B. & Terracciano, A. Personality and HbA1c: Findings from six samples. *Psychoneuroendocrinology* **120**, 104782 (2020).

189. World Health Organization. A report about COVID-19. *World Health Organization* https://www.who.int/news-room/fact-sheets/detail/coronavirus-disease-(covid-19) (2023).

190. Centers for Disease Control and Prevention. A report about COVID-19. *Centers for Disease Control and Prevention* https://www.cdc.gov/coronavirus/2019-ncov/your-health/about-covid-19.html (2024).

191. Centers for Disease Control and Prevention. A report about long COVID. *Centers for Disease Control and Prevention* https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html (2024).

192. Cosentino, F. *et al.* Cardiometabolic risk management: insights from a European Society of Cardiology Cardiovascular Round Table. *Eur Heart J* **44**, 4141–4156 (2023).

193. Clift, A. K. *et al.* Living risk prediction algorithm (QCOVID) for risk of hospital admission and mortality from coronavirus 19 in adults: national derivation and validation cohort study. *BMJ* **371**, m3731 (2020).

194. Khunti, K., Valabhji, J. & Misra, S. Diabetes and the COVID-19 pandemic. *Diabetologia* **66**, 255–266 (2023).

195. Giacca, M. & Shah, A. M. The pathological maelstrom of COVID-19 and cardiovascular disease. *Nature Cardiovascular Research* **1**, 200–210 (2022).

196. Hampshire, A. *et al.* Associations between dimensions of behaviour, personality traits, and mental-health during the COVID-19 pandemic in the United Kingdom. *Nat Commun* **12**, 4111 (2021).

197. Azevedo, F. *et al.* Social and moral psychology of COVID-19 across 69 countries. *Sci Data* **10**, 272 (2023).

198. Ludwig-Walz, H., Dannheim, I., Pfadenhauer, L. M., Fegert, J. M. & Bujard, M. Increase of depression among children and adolescents after the onset of the COVID-19 pandemic in Europe: a systematic review and meta-analysis. *Child Adolesc Psychiatry Ment Health* **16**, 109 (2022).

199. Hawes, M. T., Szenczy, A. K., Klein, D. N., Hajcak, G. & Nelson, B. D. Increases in depression and anxiety symptoms in adolescents and young adults during the COVID-19 pandemic. *Psychol Med* **52**, 3222–3230 (2022).

200. Mazza, M. G., Palladini, M., Poletti, S. & Benedetti, F. Post-COVID-19 Depressive Symptoms: Epidemiology, Pathophysiology, and Pharmacological Treatment. *CNS Drugs* **36**, 681–702 (2022).

201. Santomauro, D. F. *et al.* Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. *The Lancet* **398**, 1700–1712 (2021).

202. Zhu, C., Zhang, T., Li, Q., Chen, X. & Wang, K. Depression and Anxiety During the COVID-19 Pandemic: Epidemiology, Mechanism, and Treatment. *Neurosci Bull* **39**, 675–684 (2023).

203. Becker, J. H., Vannorsdall, T. D. & Weisenbach, S. L. Evaluation of Post–COVID-19 Cognitive Dysfunction: Recommendations for Researchers. *JAMA Psychiatry* **80**, 1085 (2023).

204. Alberti, K. G. *et al.* Harmonizing the Metabolic Syndrome. *Circulation* **120**, 1640–1645 (2009).

205. Estruch, R. *et al.* Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. *New England Journal of Medicine* **378**, e34 (2018).

206. Nigg, C. R. *et al.* Stages of Change Across Ten Health Risk Behaviors for Older Adults. *Gerontologist* **39**, 473–482 (1999).

207. Martínez-González, M. A. *et al.* Cohort Profile: Design and methods of the PREDIMED-Plus randomized trial. *Int J Epidemiol* **48**, 387–388o (2019).

208. Salas-Salvadó, J. *et al.* Effect of a Lifestyle Intervention Program With Energy-Restricted Mediterranean Diet and Exercise on Weight Loss and Cardiovascular Risk Factors: One-Year Results of the PREDIMED-Plus Trial. *Diabetes Care* **42**, dc180836 (2018).

209. Fernández-Ballart, J. D. *et al.* Relative validity of a semi-quantitative food-frequency questionnaire in an elderly Mediterranean population of Spain. *British Journal of Nutrition* **103**, 1808–1816 (2010).

210. Schröder, H. *et al.* A Short Screener Is Valid for Assessing Mediterranean Diet Adherence among Older Spanish Men and Women. *J Nutr* **141**, 1140–1145 (2011).

211. Schröder, H. *et al.* Validity of the energy-restricted Mediterranean Diet Adherence Screener. *Clinical Nutrition* **40**, 4971–4979 (2021).

212. Molina, L. *et al.* Validation of the Regicor Short Physical Activity Questionnaire for the Adult Population. *PLoS One* **12**, e0168148 (2017).

213. Thomas, S., Reading, J. & Shephard, R. J. Revision of the Physical Activity Readiness Questionnaire (PAR-Q). *Canadian Journal of Sport Sciences* **17**, 338–45 (1992).

214. Topolski, T. D. *et al.* The Rapid Assessment of Physical Activity (RAPA) Among Older Adults. *Prev Chronic Dis* **3**, A118 (2006).

215. Martínez-González, M. A., López-Fontana, C., Varo, J. J., Sánchez-Villegas, A. & Martinez, J. A. Validation of the Spanish version of the physical activity questionnaire used in the Nurses' Health Study and the Health Professionals' Follow-up Study. *Public Health Nutr* **8**, 920–927 (2005).

216. Jones, C. J., Rikli, R. E. & Beam, W. C. A 30-s Chair-Stand Test as a Measure of Lower Body Strength in Community-Residing Older Adults. *Res Q Exerc Sport* **70**, 113–119 (1999).

217. Folstein, M. F., Folstein, S. E. & McHugh, P. R. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* **12**, 189–198 (1975).

218. Shulman, K. I. Clock-drawing: is it the ideal cognitive screening test? *Int J Geriatr Psychiatry* **15**, 548–561 (2000).

219. Armitage, S. G. An analysis of certain psychological tests used for the evaluation of brain injury. *Psychol Monogr* **60**, i–48 (1946).

220. Benton, A. L. Differential behavioral effects in frontal lobe disease. *Neuropsychologia* **6**, 53–60 (1968).

221. Newcombe, F. *Missle Wounds Ofthe Brain. A Study of Psychological Deficit*. (Oxford University Press, London, England, 1969).

222. Test Battery Army Individual. *Manual of Directions and Scoring*. (War Department, Adjutant General's Office, Washington, DC, 1944).

223. Vilagut, G. *et al.* The Spanish version of the Short Form 36 Health Survey: a decade of experience and new developments. *Gac Sanit* **19**, 135–150 (2005).

224. Beck, A. T., Steer, R. A. & Brown, G. K. *Manual for the Beck Depression Inventory-II. Psychological Assessment* (Psychological Corporation, San Antonio, TX, 1996).

225. Wallston, K. A., Strudler Wallston, B. & DeVellis, R. Development of the Multidimensional Health Locus of Control (MHLC) Scales. *Health Educ Monogr* **6**, 160–170 (1978).

226. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (4th Ed., Text Revised)*. *American Psychiatric Association* (American Psychiatric Association, Washington, DC, 2000).

227. Gearhardt, A. N., Corbin, W. R. & Brownell, K. D. Preliminary validation of the Yale Food Addiction Scale. *Appetite* **52**, 430–436 (2009).

228. Rosa, A. R. *et al.* Validity and reliability of the Functioning Assessment Short Test (FAST) in bipolar disorder. *Clinical Practice and Epidemiology in Mental Health* **3**, 1–8 (2007).

229. Wilson, B. A., Alderman, N., Burgess, P. W., Emslie, H. & Evans, J. J. *BADS: Behavioural Assessment of the Dysexecutive Syndrome*. (Thames Valley Test Company, Suffolk, England, 1996).

230. Nasreddine, Z. S. *et al.* The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* **53**, 695–9 (2005).

231. Golden, C. *Manual STROOP-Test de Colores y Palabras*. *TEA Ediciones, S. A.* (TEA Ediciones, Madrid, Spain, 2001).

232. Smith, A. *Symbol Digit Modalities Test*. *Western Psychological Services* (Western Psychological Services, Los Angeles, California, 1973).

233. Schmidt, M. Rey Auditory Verbal Learning Test: A Handbook. in (Los Angeles, CA, 1996).

234. Shin, M.-S., Park, S.-Y., Park, S.-R., Seol, S.-H. & Kwon, J. S. Clinical and empirical applications of the Rey–Osterrieth Complex Figure Test. *Nat Protoc* **1**, 892–899 (2006).

235. Bechara, A., Damasio, A. R., Damasio, H. & Anderson, S. W. Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition* **50**, 7–15 (1994).

236. Keith Conners, C., Sitarenios, G. & Ayearst, L. E. Conners' Continuous Performance Test Third Edition. in *Encyclopedia of Clinical Neuropsychology* 929–933 (Springer International Publishing, Cham, 2018). doi:10.1007/978-3-319-57111-9_1535.

237. Paz-Graniel, I. *et al.* Impact of COVID-19 pandemic on the PREDIMED-Plus randomized clinical trial: Effects on the interventions, participants follow-up, and adiposity. *Front Nutr* **9**, 1098269 (2023).

238. Gan, Z. H., Cheong, H. C., Tu, Y.-K. & Kuo, P.-H. Association between Plant-Based Dietary Patterns and Risk of Cardiovascular Disease: A Systematic Review and Meta-Analysis of Prospective Cohort Studies. *Nutrients* **13**, 3952 (2021).

239. Satija, A. *et al.* Plant-Based Dietary Patterns and Incidence of Type 2 Diabetes in US Men and Women: Results from Three Prospective Cohort Studies. *PLoS Med* **13**, e1002039 (2016).

240. Becerra-Tomás, N. *et al.* Mediterranean diet, cardiovascular disease and mortality in diabetes: A systematic review and meta-analysis of prospective cohort studies and randomized clinical trials. *Crit Rev Food Sci Nutr* **60**, 1207–1227 (2020).

241. Chiuve, S. E. *et al.* Alternative Dietary Indices Both Strongly Predict Risk of Chronic Disease. *J Nutr* **142**, 1009–1018 (2012).

242. Chiavaroli, L. *et al.* Portfolio Dietary Pattern and Cardiovascular Disease: A Systematic Review and Meta-analysis of Controlled Trials. *Prog Cardiovasc Dis* **61**, 43–53 (2018).

243. Fung, T. T. Adherence to a DASH-Style Diet and Risk of Coronary Heart Disease and Stroke in Women. *Arch Intern Med* **168**, 713 (2008).

244. Morris, M. C. *et al.* MIND diet slows cognitive decline with aging. *Alzheimer's & Dementia* **11**, 1015–1022 (2015).

245. *Summary Report about Food Planet Health: Healthy Diets From Sustainable Food Systems*. https://eatforum.org/eat-lancet-commission/eat-lancet-commission-summary-report/ (2019).

246. Gómez-Martínez, C. *et al.* Impulsivity is longitudinally associated with healthy and unhealthy dietary patterns in individuals with overweight or obesity and metabolic syndrome within the framework of the PREDIMED-Plus trial. *International Journal of Behavioral Nutrition and Physical Activity* **19**, 101 (2022).

247. Matthews, D. R. *et al.* Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* **28**, 412–419 (1985).

248. American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2021. *Diabetes Care* **44**, S15–S33 (2021).

249. Verdejo-García, A., Lozano, Ó., Moya, M., Alcázar, M. Á. & Pérez-García, M. Psychometric Properties of a Spanish Version of the UPPS–P Impulsive Behavior Scale: Reliability, Validity and Association With Trait and Cognitive Impulsivity. *J Pers Assess* **92**, 70–77 (2010).

250. Bechara, A., Damasio, H., Tranel, D. & Damasio, A. R. Deciding Advantageously Before Knowing the Advantageous Strategy. *Science (1979)* **275**, 1293–1295 (1997).

251. Blesa, R. *et al.* Clinical validity of the 'mini-mental state' for Spanish speaking communities. *Neuropsychologia* **39**, 1150–7 (2001).

252. del Ser Quijano, T. *et al.* Evaluación cognitiva del anciano. Datos normativos de una muestra poblacional española de más de 70 años. *Med Clin (Barc)* **122**, 727–740 (2004).

253. Peña-Casanova, J. *et al.* Spanish multicenter normative studies (NEURONORMA project): Norms for verbal fluency tests. *Archives of Clinical Neuropsychology* **24**, 395–411 (2009).

254. Shao, Z., Janse, E., Visser, K. & Meyer, A. S. What do verbal fluency tasks measure? Predictors of verbal fluency performance in older adults. *Front Psychol* **5**, 772 (2014).

255. Llinàs-Reglà, J. *et al.* The Trail Making Test. *Assessment* **24**, 183–196 (2017).

256. Kortte, K. B., Horner, M. D. & Windham, W. K. The Trail Making Test, Part B: Cognitive Flexibility or Ability to Maintain Set? *Appl Neuropsychol* **9**, 106–109 (2002).

257. Centers for Disease Control and Prevention (CDC). COVID-19 Testing: What You Need to Know. https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/testing.html#types-of-tests (2024).

258. Hercberg, S. *et al.* The Nutrinet-Santé Study: a web-based prospective study on the relationship between nutrition and health and determinants of dietary patterns and nutritional status. *BMC Public Health* **10**, 242 (2010).

259. Craig, C. L. *et al.* International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc* **35**, 1381–95 (2003).

260. Patton, J. H., Stanford, M. S. & Barratt, E. S. Factor structure of the Barratt Impulsiveness Scale. *J Clin Psychol* **51**, 768–774 (1995).

261. Baylé, F. J. *et al.* [Factor analysis of french translation of the Barratt impulsivity scale (BIS-10)]. *Can J Psychiatry* **45**, 156–65 (2000).

262. Stanford, M. S. *et al.* Fifty years of the Barratt Impulsiveness Scale: An update and review. *Pers Individ Dif* **47**, 385–395 (2009).

263. World Health Organization. *International Statistical Classification of Diseases and Related Health Problems, 10th Revision, 5th Ed. World Health Organization* vol. 1 (World Health Organization, France, 2016).

264. Eisenlohr-Moul, T. A. & Owens, S. A. *Encyclopedia of Personality and Individual Differences*. *Encyclopedia of Personality and Individual Differences* (Springer, Cham, 2020). doi:10.1007/978-3-319-28099-8.

265. Dubois, J., Eberhardt, F., Paul, L. K. & Adolphs, R. Personality beyond taxonomy. *Nat Hum Behav* **4**, 1110–1117 (2020).

266. Kozak, K. *et al.* The neurobiology of impulsivity and substance use disorders: implications for treatment. *Ann N Y Acad Sci* **1451**, 71–91 (2019).

267. Koob, G. F. & Volkow, N. D. Neurobiology of addiction: a neurocircuitry analysis. *Lancet Psychiatry* **3**, 760–773 (2016).

268. Ginty, A. T., Kraynak, T. E., Fisher, J. P. & Gianaros, P. J. Cardiovascular and autonomic reactivity to psychological stress: Neurophysiological substrates and links to cardiovascular disease. *Autonomic Neuroscience* **207**, 2–9 (2017).

269. Hirschberg, P. R., Sarkar, P., Teegala, S. B. & Routh, V. H. Ventromedial hypothalamus glucose-inhibited neurones: A role in glucose and energy homeostasis? *J Neuroendocrinol* **32**, e12773 (2020).

270. Noble, E. E. *et al.* Hypothalamus-hippocampus circuitry regulates impulsivity via melanin-concentrating hormone. *Nat Commun* **10**, 4923 (2019).

271. Dalley, J. W. & Roiser, J. P. Dopamine, serotonin and impulsivity. *Neuroscience* **215**, 42–58 (2012).

272. Neumann, J., Hofmann, B., Dhein, S. & Gergs, U. Role of Dopamine in the Heart in Health and Disease. *Int J Mol Sci* **24**, 5042 (2023).

273. Rieder, M., Gauchel, N., Bode, C. & Duerschmied, D. Serotonin: a platelet hormone modulating cardiovascular disease. *J Thromb Thrombolysis* **52**, 42–47 (2021).

274. Lopez Vicchi, F. *et al.* Dopaminergic drugs in type 2 diabetes and glucose homeostasis. *Pharmacol Res* **109**, 74–80 (2016).

275. Oh, C.-M., Park, S. & Kim, H. Serotonin as a New Therapeutic Target for Diabetes Mellitus and Obesity. *Diabetes Metab J* **40**, 89 (2016).

276. Steinberg, L. *et al.* Age differences in sensation seeking and impulsivity as indexed by behavior and self-report: Evidence for a dual systems model. *Dev Psychol* **44**, 1764–1778 (2008).

277. Moustafa, A. A., Tindle, R., Frydecka, D. & Misiak, B. Impulsivity and its relationship with anxiety, depression and stress. *Compr Psychiatry* **74**, 173–179 (2017).

278. Cross, C. P., Copping, L. T. & Campbell, A. Sex differences in impulsivity: A meta-analysis. *Psychol Bull* **137**, 97–130 (2011).

279. Schwartz, J. A., Connolly, E. J. & Alsolami, A. Within-Individual Changes in Impulsivity and Sensation Seeking from Childhood to Early Adulthood and Educational Attainment. *J Youth Adolesc* **51**, 2190–2204 (2022).

280. Castañer, M. *et al.* Impulsivity and physical activity: A T-Pattern detection of motor behavior profiles. *Physiol Behav* **219**, 112849 (2020).

281. Mõttus, R. *et al.* The associations between personality, diet and body mass index in older people. *Health Psychology* **32**, 353–360 (2013).

282. Fuemmeler, B. F., Østbye, T., Yang, C., McClernon, F. J. & Kollins, S. H. Association between attention-deficit/hyperactivity disorder symptoms and obesity and hypertension in early adulthood: a population-based study. *International Journal of Obesity* **35**, 852–862 (2010).

283. Sutin, A. R. *et al.* Cholesterol, triglycerides, and the Five-Factor Model of personality. *Biol Psychol* **84**, 186–191 (2010).

284. Fields, S. A., Schueler, J., Arthur, K. M. & Harris, B. The Role of Impulsivity in Major Depression: A Systematic Review. *Curr Behav Neurosci Rep* **8**, 38–50 (2021).

285. Xie, T. *et al.* Do Poor Diet and Lifestyle Behaviors Modify the Genetic Susceptibility to Impulsivity in the General Population? *Nutrients* **15**, 1625 (2023).

286. Maxwell, A. L., Gardiner, E. & Loxton, N. J. Investigating the relationship between reward sensitivity, impulsivity, and food addiction: A systematic review. *European Eating Disorders Review* **28**, 368–384 (2020).

287. Pivarunas, B. & Conner, B. T. Impulsivity and emotion dysregulation as predictors of food addiction. *Eat Behav* **19**, 9–14 (2015).

288. Gailliot, M. T. & Baumeister, R. F. The Physiology of Willpower: Linking Blood Glucose to Self-Control. *Personality and Social Psychology Review* **11**, 303–327 (2007).

289. Sun, D.-M. *et al.* Decision-making in primary onset middle-age type 2 diabetes mellitus: a BOLD-fMRI study. *Sci Rep* **7**, 10246 (2017).

290. Testa, G. *et al.* Transdiagnostic Perspective of Impulsivity and Compulsivity in Obesity: From Cognitive Profile to Self-Reported Dimensions in Clinical Samples with and without Diabetes. *Nutrients* **13**, 4426 (2021).

291. Liu, N. *et al.* The Relationship between Trait Impulsivity and Everyday Executive Functions among Patients with Type 2 Diabetes Mellitus: The Mediating Effect of Negative Emotions. *J Diabetes Res* **2023**, 1–11 (2023).

292. Eckstrand, K. L. *et al.* An insulin resistance associated neural correlate of impulsivity in type 2 diabetes mellitus. *PLoS One* **12**, e0189113 (2017).

293. Guerrieri, R., Nederkoorn, C., Schrooten, M., Martijn, C. & Jansen, A. Inducing impulsivity leads high and low restrained eaters into overeating, whereas current dieters stick to their diet. *Appetite* **53**, 93–100 (2009).

294. Meule, A., de Zwaan, M. & Müller, A. Attentional and motor impulsivity interactively predict 'food addiction' in obese individuals. *Compr Psychiatry* **72**, 83–87 (2017).

295. VanderBroek-Stice, L., Stojek, M. K., Beach, S. R. H., vanDellen, M. R. & MacKillop, J. Multidimensional assessment of impulsivity in relation to obesity and food addiction. *Appetite* **112**, 59–68 (2017).

296. Loxton, N. J. The Role of Reward Sensitivity and Impulsivity in Overeating and Food Addiction. *Curr Addict Rep* **5**, 212–222 (2018).

297. Steward, T., Miranda-Olivos, R., Soriano-Mas, C. & Fernández-Aranda, F. Neuroendocrinological mechanisms underlying impulsive and compulsive behaviors in obesity: a narrative review of fMRI studies. *Rev Endocr Metab Disord* **20**, 263–272 (2019).

298. Montoliu, T., Hidalgo, V. & Salvador, A. Personality and Hypothalamic–Pituitary–Adrenal Axis in Older Men and Women. *Front Psychol* **11**, 983 (2020).

299. Soliemanifar, O., Soleymanifar, A. & Afrisham, R. Relationship between Personality and Biological Reactivity to Stress: A Review. *Psychiatry Investig* **15**, 1100–1114 (2018).

300. McEwen, B. S. Hormones and behavior and the integration of brain-body science. *Horm Behav* **119**, 104619 (2020).

301. Eisenlohr-Moul, T. A. & Owens, S. A. Hormones and Personality. in *Encyclopedia of Personality and Individual Differences* 2010–2032 (Springer, Cham, 2020). doi:10.1007/978-3-319-24612-3_762.

302. Heni, M. *et al.* Nasal insulin changes peripheral insulin sensitivity simultaneously with altered activity in homeostatic and reward-related human brain regions. *Diabetologia* **55**, 1773–1782 (2012).

303. Scherer, T., Sakamoto, K. & Buettner, C. Brain insulin signalling in metabolic homeostasis and disease. *Nat Rev Endocrinol* **17**, 468–483 (2021).

304. Ruud, J., Steculorum, S. M. & Brüning, J. C. Neuronal control of peripheral insulin sensitivity and glucose metabolism. *Nat Commun* **8**, 15259 (2017).

305. Monnier, L. *et al.* Activation of Oxidative Stress by Acute Glucose Fluctuations Compared With Sustained Chronic Hyperglycemia in Patients With Type 2 Diabetes. *JAMA* **295**, 1681 (2006).

306. Ceriello, A. *et al.* Oscillating Glucose Is More Deleterious to Endothelial Function and Oxidative Stress Than Mean Glucose in Normal and Type 2 Diabetic Patients. *Diabetes* **57**, 1349–1354 (2008).

307. Moran, C., Beare, R., Wang, W., Callisaya, M. & Srikanth, V. Type 2 diabetes mellitus, brain atrophy, and cognitive decline. *Neurology* **92**, e823–e830 (2019).

308. Callisaya, M. L. *et al.* Type 2 diabetes mellitus, brain atrophy and cognitive decline in older people: a longitudinal study. *Diabetologia* **62**, 448–458 (2019).

309. Kirvalidze, M. *et al.* The role of glucose in cognition, risk of dementia, and related biomarkers in individuals without type 2 diabetes mellitus or the metabolic syndrome: A systematic review of observational studies. *Neurosci Biobehav Rev* **135**, 104551 (2022).

310. Koutsonida, M., Markozannes, G., Bouras, E., Aretouli, E. & Tsilidis, K. K. Metabolic syndrome and cognition: A systematic review across cognitive domains and a bibliometric analysis. *Front Psychol* **13**, 981379 (2022).

311. Luo, A. *et al.* Type 2 diabetes mellitus-associated cognitive dysfunction: Advances in potential mechanisms and therapies. *Neurosci Biobehav Rev* **137**, 104642 (2022).

312. Lin, Y., Gong, Z., Ma, C., Wang, Z. & Wang, K. Relationship between glycemic control and cognitive impairment: A systematic review and meta-analysis. *Front Aging Neurosci* **15**, 1126183 (2023).

313. Werner, H. & LeRoith, D. Insulin and insulin-like growth factor receptors in the brain: Physiological and pathological aspects. *European Neuropsychopharmacology* **24**, 1947–1953 (2014).

314. Hamed, S. A. Brain injury with diabetes mellitus: evidence, mechanisms and treatment implications. *Expert Rev Clin Pharmacol* **10**, 409–428 (2017).

315. McCrimmon, R. J., Ryan, C. M. & Frier, B. M. Diabetes and cognitive dysfunction. *The Lancet* **379**, 2291–2299 (2012).

316. de la Monte, S. M. & Wands, J. R. Alzheimer's Disease is Type 3 Diabetes—Evidence Reviewed. *J Diabetes Sci Technol* **2**, 1101–1113 (2008).

317. Yaffe, K. *et al.* Diabetes, glucose control, and 9-year cognitive decline among older adults without dementia. *Arch Neurol* **69**, 1170–1175 (2012).

318. Rawlings, A. M. *et al.* The association of late-life diabetes status and hyperglycemia with incident mild cognitive impairment and dementia: The ARIC study. *Diabetes Care* **42**, 1248–1264 (2019).

319. Ceban, F. *et al.* Fatigue and cognitive impairment in Post-COVID-19 Syndrome: A systematic review and meta-analysis. *Brain Behav Immun* **101**, 93–135 (2022).

320. Hampshire, A. *et al.* Cognition and Memory after Covid-19 in a Large Community Sample. *New England Journal of Medicine* **390**, 806–818 (2024).

321. Houben, S. & Bonnechère, B. The Impact of COVID-19 Infection on Cognitive Function and the Implication for Rehabilitation: A Systematic Review and Meta-Analysis. *Int J Environ Res Public Health* **19**, 7748 (2022).

322. Miners, S., Kehoe, P. G. & Love, S. Cognitive impact of COVID-19: looking beyond the short term. *Alzheimers Res Ther* **12**, 170 (2020).

323. Becker, J. H. *et al.* Assessment of Cognitive Function in Patients After COVID-19 Infection. *JAMA Netw Open* **4**, e2130645 (2021).

324. Schou, T. M., Joca, S., Wegener, G. & Bay-Richter, C. Psychiatric and neuropsychiatric sequelae of COVID-19 – A systematic review. *Brain Behav Immun* **97**, 328–348 (2021).

325. Madigan, S. *et al.* Changes in Depression and Anxiety Among Children and Adolescents From Before to During the COVID-19 Pandemic. *JAMA Pediatr* **177**, 567 (2023).

326. Thompson, E. J. *et al.* Psychological distress, depression, anxiety, and life satisfaction following COVID-19 infection: evidence from 11 UK longitudinal population studies. *Lancet Psychiatry* **9**, 894–906 (2022).

327. Silva, C. *et al.* Depression in older adults during the COVID-19 pandemic: A systematic review. *J Am Geriatr Soc* **71**, 2308–2325 (2023).

328. Seighali, N. *et al.* The global prevalence of depression, anxiety, and sleep disorder among patients coping with Post COVID-19 syndrome (long COVID): a systematic review and meta-analysis. *BMC Psychiatry* **24**, 105 (2024).

329. Renaud-Charest, O. *et al.* Onset and frequency of depression in post-COVID-19 syndrome: A systematic review. *J Psychiatr Res* **144**, 129–137 (2021).

X. APPENDICES

UNIVERSITAT ROVIRA I VIRGILI
Psychology and Disease: Unveiling Emerging Perspectives on Their Interplay
Carlos Gómez Martínez

MANUSCRIPT CONTRIBUTIONS

(1) **Gómez-Martínez C**, Babio N, Júlvez J, Becerra-Tomás N, Martínez-González MÁ, Corella D, Castañer O, Romaguera D, Vioque J, Alonso-Gómez ÁM, Wärnberg J, Martínez JA, Serra-Majem L, Estruch R, Tinahones FJ, Lapetra J, Pintó X, Tur JA, López-Miranda J, Bueno-Cavanillas A, Gaforio JJ, Matía-Martín P, Daimiel L, Martín-Sánchez V, Vidal J, Vázquez C, Ros E, Dalsgaard S, Sayón-Orea C, Sorlí JV, de la Torre R, Abete I, Tojal-Sierra L, Barón-López FJ, Fernández-Brufal N, Konieczna J, García-Ríos A, Sacanella E, Bernal-López MR, Santos-Lozano JM, Razquin C, Alvarez-Sala A, Goday A, Zulet MA, Vaquero-Luna J, Diez-Espino J, Cuenca-Royo A, Fernández-Aranda F, Bulló M, Salas-Salvadó J. Glycemic Dysregulations Are Associated With Worsening Cognitive Function in Older Participants at High Risk of Cardiovascular Disease: Two-Year Follow-up in the PREDIMED-Plus Study. *Frontiers in Endocrinology*. 2021. Doi: 10.3389/fendo.2021.754347.
IF: 6.1 (2021)
Q1 (33/146) in Endocrinology & Metabolism

(2) **Gómez-Martínez C**, Babio N, Júlvez J, Nishi SK, Fernández-Aranda F, Martínez-González MA, Cuenca-Royo A, Fernández R, Jiménez-Murcia S, de la Torre R, Pintó X, Bloemendaal M, Fitó M, Corella D, Arias Al, Salas-Salvadó J. Impulsivity is longitudinally associated with healthy and unhealthy dietary patterns in individuals with overweight or obesity and metabolic syndrome within the framework of the PREDIMED-Plus trial. *International Journal of Behavioral Nutrition and Physical Activity*. 2022. Doi: 10.1186/s12966-022-01335-8.
IF: 8.7 (2022)
D1 (7/88) in Nutrition & Dietetics

(3) **Gómez-Martínez C**, Babio N, Camacho-Barcia L, Júlvez J, Nishi SK, Vázquez Z, Forcano L, Álvarez-Sala A, Cuenca-Royo A, de la Torre R, Fanlo-Maresma M, Tello S, Corella D, Vásquez AA, Dalsgaard S, Franke B, Fernández-Aranda F, Salas-Salvadó J. Glycated hemoglobin, type 2 diabetes, and poor diabetes control are positively associated with impulsivity changes in aged individuals with overweight or obesity and metabolic syndrome. Ann N Y Acad Sci. 2024 Aug 16. doi: 10.1111/nyas.15205
IF: 4.1 (2023)
Q1 (24/134) in Multidisciplinary Sciences

(4) **Gómez-Martínez C**, Paolassini-Guesnier P, Fezeu L, Srour B, Hercberg S, Touvier M, Babio N, Salas-Salvadó J, Péneau S. Trait impulsivity is associated with an increased risk of type 2 diabetes incidence in adults over 8 years of follow-up: results from the NutriNet-Santé cohort. BMC Med. 2024 Aug 15;22(1):332. Doi: 10.1186/s12916-024-03540-7.
IF: 7.0 (2023)
D1 (23/325) in Medicine, General & Internal

(5) Shyam S*, **Gómez-Martínez C***, Ni J, Gaforio JJ, Martínez-González MÁ, Corella D, Martínez JA, Alonso-Gómez ÁM, Wärnberg J, Vioque J, Romaguera D, López-Miranda J, Estruch R, Tinahones FJ, Lapetra J, Serra-Majem L, Bueno-Cavanillas A, Tur JA, Martín-Sánchez V, Pintó X, Delgado-Rodríguez M, Matía-Martín P, Vidal J, Vázquez C, Daimiel L, Ros E, Fernandez-Aranda F, Hernández-Cacho A, Buil-Cosiales P, Sorli JV, Castañer O, Garcia-Rios A, Oncina-Canovas A, Pérez-Farinós N, Nafria M, Casas R, Martínez-Diz S, Tojal-Sierra L, Am

GP, Toledo E, Fernández-Carrión R, Bayón ÁM, Torres-Peña JD, Compañ-Gabucio L, Vázquez-Ruiz Z, Babio N, Fitó M, Salas-Salvadó J. COVID-19 and Cognitive Decline in Older Adults with High-Cardiovascular Risk: A Post Hoc Analysis. Aging Dis. 2024 Jul 21. doi: 10.14336/AD.2024.0380. * Equal contribution.
IF: 7.0 (2023)
D1 (6/74) in Geriatrics & Gerontology

(6) Shyam S, **Gómez-Martínez C**, Paz-Graniel I, Gaforio JJ, Martínez-González MA, Corella D, Fitó M, Alonso-Gómez AM, Wärnberg J, Vioque J, Romaguera D, López-Miranda J, Estruch R, Tinhaones FJ, Santos-Lozano JM, Serra-Majem JL, Bueno-Cavanillas A, Tur JA, Martín-Sánchez V, Pintó X, Ortiz-Ramos M, Damiel L, Ros E, Fernández-Aranda F, Nishi SK, García-Regata O, Toledo E, Sorlí JV, Castañer O, García-Ríos A, Valls-Enguix R, Pérez-Farinós N, Zulet MA, Rayó-Gago E, Casas R, Riviera-Izquierdo M, Tojal-Sierra L, Dama-Fuentes M, Buil-Cosiales P, Fernández-Carrión R, Goday A, Peña-Orihuela PJ, Compañ-Gabucio L, Diez-Espino J, Tello S, González-Pinto A, de la O V, Delgado-Rodríguez M, Babio N, Salas-Salvadó J. Coronavirus disease 2019 is associated with long-term depressive symptoms in Spanish older adults with overweight/obesity and metabolic syndrome. *Psychological Medicine*. 2023. Doi: 10.1017/S0033291723002313.
IF: 5.9 (2023)
1D (7/92) in Psychology

(7) Garcidueñas-Fimbres TE, **Gómez-Martínez C**, Pascual-Compte M, Jurado-Castro JM, Leis R, Moreno LA, Navas-Carretero S, Codoñer-Franch P, Echeverria AM, Pastor-Villaescusa B, López-Rubio A, Moroño-García S, de Miguel-Etayo P, Martínez JA, Velasco-Aguayo I, Vázquez-Cobela R, Escribano J, Miguel-Berges ML, de la Torre-Aguilar MJ, Gil-Campos M, Salas-Salvadó J, Babio N. Adherence to a healthy lifestyle behavior composite score and cardiometabolic risk factors in Spanish children from the CORALS cohort. *European Journal of Pediatrics*. 2022. Doi: 10.1007/s00431-023-05389-z.
IF: 3.6 (2022)
Q1 (23/130) in Pediatrics

(8) K Nishi S, Babio N, **Gómez-Martínez C**, Martinez-Gonzalez MA, Ros E, Corella D, Castañer O, Martinez JA, Alonso-Gómez AM, Wärnberg J, Vioque J, Romaguera D, López-Miranda J, Estruch R, Tinahones FJ, Lapetra J, Serra-Majem L, Bueno-Cavanillas A, Tur JA, Sánchez VM, Pintó X, Delgado-Rogríguez M, Matía-Martín P, Vidal J, Vazquez C, Daimiel L, Razquin C, Coltell O, Becerra Tomás N, de la Torre R Fornell, Itziar Abete, Carolina Sorto-Sanchez, Francisco Javier Barón-López, Signes-Pastor AJ, Konieczna J, García-Ríos A, Casas R, Gómez-Pérez AM, Santos-Lozano JM, García-Arellano A, Guillem-Saiz P, Ni J, Soria-Florido MT, Zulet MA, Vaquero-Luna J, Toledo E, Fitó M, Salas-Salvadó J. Mediterranean, DASH, and MIND Dietary Patterns and Cognitive Function: The 2-Year Longitudinal Changes in an Older Spanish Cohort. *Frontiers in Aging Neuroscience*. 2021. Doi: 10.3389/fnagi.2021.782067.
IF: 5.7 (2021)
Q1 (66/274) in Neurosciences

(9) Garcidueñas-Fimbres TE, Paz-Graniel I, **Gómez-Martínez C**, Jurado-CastroJM, Leis R, Escribano J, Moreno LA, Navas-Carretero S, Portoles O, Pérez-Vega KA, Gil-Campos M,López-Rubio A, Rey-Reñones C, Miguel-Etayo PD, Martínez JA, Flores-Rojas K, Vázquez-Cobela R,Luque V, Miguel-Berges ML, Pastor-Villaescusa B, Llorente-Cantarero FJ, Salas-Salvadó J, Babio N. Associations Between Eating Speed, Diet Quality, Adiposity and Cardiometabolic Risk Factors. *Journal of Pediatrics*. 2022. Doi: 10.1016/j.jpeds.2022.08.024.

IF: 5.1 (2022)
1D (12/130) in Pediatrics

(10) Testa G, Camacho-Barcia L, **Gómez-Martínez C**, Mora-Maltas B, de la Torre R, Pintó X, Corella D, Granero R, Cuenca-Royo A, Jiménez-Murcia S, Babio N, Fernández-Barrión R, Esteve-Luque V, Forcano L, Ni J, Malcampo M, De las Heras-Delgado S, Fitó M, Salas-Salvadó J, Fernández-Aranda F. Impulsive Personality Traits Predicted Weight Loss in Individuals with Type 2 Diabetes after 3 Years of Lifestyle Interventions. *Journal of Clinical Medicine*. 2022. Doi: 10.3390/jcm11123476.
IF: 3.9 (2022)
Q2 (58/167) in Medicine, General & Internal

(11) Camacho-Barcia L, Munguía L, Lucas I, de la Torre R, Salas-Salvadó J, Pintó X, Corella D, Granero R, Jiménez-Murcia S, González-Monje I, Esteve-Luque V, Cuenca-Royo A, **Gómez-Martínez C**, Paz-Graniel I, Forcano L, Fernández-Aranda F. Metabolic, Affective and Neurocognitive Characterization of Metabolic Syndrome Patients with and without Food Addiction. Implications for Weight Progression. *Nutrients*. 2021. Doi: 10.3390/nu13082779.
IF: 6.7 (2021)
Q1 (15/90) in Nutrition & Dietetics

(12) Cano-Ibáñez N, Serra-Majem L, Martín-Peláez S, Martínez-González MA, Salas-Salvadó J, Corella D, Lassale C, Alfredo Martínez J, Alonso-Gómez AM, Wärnberg J, Vioque J, Romaguera D, López-Miranda J, Estruch R, Gómez-Pérez AM, Santos-Lozano JM, Fernández-Aranda F, Bueno-Cavanillas A, Tur JA, Martín V, Pintó X, Delgado-Rodríguez M, Matía P, Vidal J, Cárdenas JJ, Daimiel L, Ros E, Buil-Cosiales P, Becerra-Tomás N, Saiz C, Muñoz MA, Abete I, Tojal-Sierra L, Fernández-Barceló O, Bernabé-Casanova A, Konieczna J, García-Ríos A, Casas R, Bernal-López MR, Lapetra J, Toledo E, **Gómez-Martínez C**, Coltell O, Malcampo-Manrúbia M, Zulet MA, Sorto-Sánchez C, Gea A, Hernández-Fleta J, Castañer-Niño O, Sánchez-Villegas A. Association between the Prime Diet Quality Score and depressive symptoms in a Mediterranean population with metabolic syndrome. Cross-sectional and 2-year follow-up assessment from PREDIMED-PLUS study. *British Journal of Nutrition*. 2021. Doi: 10.1017/S0007114521004323.
IF: 4.1 (2021)
Q3 (48/90) in Nutrition & Dietetics

(13) Soldevila-Domenech N, Cuenca-Royo A, Babio N, Forcano L, Nishi S, Vintró-Alcaraz C, **Gómez-Martínez C**, Jiménez-Murcia S, Fernández-Carrión R, Gomis-González M, Alvarez-Sala A, Carlos S, Pintó X, Corella D, Díez-Espino J, Castañer O, Fernández-Aranda F, Salas-Salvadó J, de la Torre R. Metformin Use and Cognitive Function in Older Adults With Type 2 Diabetes Following a Mediterranean Diet Intervention. *Frontiers in Nutrition*. 2021. Doi: 10.3389/fnut.2021.742586.
IF: 6.6 (2021)
Q1 (16/80) in Nutrition & Dietetics

(14) Testa G, Mora-Maltas B,Camacho-Barcia L, Granero R, Lucas I, Agüera Z, Jiménez-Murcia S, Baños R, Bertaina-Anglade V, Botella C, Bulló M, Casanueva FF, Dalsgaard S, Fernández-Real JM, Franke B, Frühbeck G, Fitó M, **Gómez-Martínez C**, Pintó X, Poelmans G, Tinahones FJ, De La Torre R, Salas-Salvadó J, Serra-Majem L, Vos S, Wimberley T, Fernández-Aranda F. Transdiagnostic Perspective of Impulsivity and Compulsivity in Obesity: From Cognitive Profile

to Self-Reported Dimensions in Clinical Samples with and without Diabetes. *Nutrients*. 2021. Doi: 10.3390/nu13124426.
IF: 6.7 (2021)
Q1 (15/90) in Nutrition & Dietetics

(15) Ni J, Nishi SK, Babio N, Martínez-González MA, Corella D, Castañer O, Martínez JA, Alonso-Gómez ÁM, Gómez-Gracia E, Vioque J, Romaguera D, López-Miranda J, Estruch R, Tinahones FJ, Lapetra J, Serra-Majem L, Bueno-Cavanillas A, Tur JA, Martín-Sánchez V, Pintó X, Gaforio JJ, Barabash-Bustelo A, Vidal J, Vázquez C, Daimiel L, Ros E, Toledo E, Clotell O, **Gómez-Martínez C,** Zomeño MD, Donat-Vargas C, Goicolea-Güemez L, Bouzas C, Garcia-de-la-Hera M, Chaplin A, Garcia-Rios A, Casas R, Cornejo-Pareja I, Santos-Lozano JM, Rognoni T, Saiz C, Paz-Ganiel I, Malcampo M, Sánchez-Villegas A, Salaverria-Lete I, García-Arellano A, Schröder H, Salas-Salvadó J. Dairy Product Consumption and Changes in Cognitive Performance: Two-Year Analysis of the PREDIMED-Plus Cohort. *Molecular Nutrition and Food Research*. 2022. Doi: 10.1002/mnfr.202101058.
IF: 5.2 (2022)
Q1 (34/142) in Food Science & Technology

(16) Cano-Ibáñez N, Serra-Majem L, Martín-Peláez S, Martínez-González MA, Salas-Salvadó J, Corella D, Lassale C, Alfredo Martínez J, Alonso-Gómez AM, Wärnberg J, Vioque J, Romaguera D, López-Miranda J, Estruch R, Gómez-Pérez AM, Lapetra J, Férnandez-Arando F, Bueno-Cavanillas A, Tur JA, Cubelos N, Pintó X, Gaforio JJ, Matía P, Vidal J, Calderón C, Daimiel L, Ros E, Gea A, Babio N, Giménez-Alba IM, Zomño-Fajardo MD, Abete I, Tojal Sierra L, Romero-Galisteo RO, García de la Hera M, Martín-Padillo M, García-Ríos A, Casas RM, Fernández-García JC, Santos-Lozano JM, Toledo E, Becerra-Tomás N, Sorlí JV, Schröder H, Zulet MA, Sorto-Sánchez C, Diez-Espino J, **Gómez-Martínez C**, Fitó M, Sánchez-Villegas A. Dietary diversity and Depression: Cross-sectional and longitudinal analyses in Spanish adult population with Metabolic Syndrome. Findings from PREDIMED-PLUS Trial. *Public Health Nutrition*. 2022. Doi: 10.1017/S1368980022001525.
IF: 3.2 (2022)
Q3 (56/88) in Nutrition & Dietetics

(17) Martín-Peláez S, Serra-Majem L, Cano-Ibáñez N, Martínez-González MA, Salas-Salvadó J, Corella D, Lassale C, Martínez JA, Alonso-Gómez AM, Wärnberg J, Vioque J, Romaguera D, López-Miranda J, Estruch R, Tinahones FJ, Lapetra J, Fernández-Aranda F, Bueno-Cavanillas A, Tur JA, Martín V, Pintó X, Delgado-Rodríguez M, Matía P, Vidal J, Vázquez C, Daimiel L, Ros E, Toledo E, Nishi SK, Sorli JV, Malcampo M, Zulet MA, Moreno-Rodríguez A, Cueto-Galán R, Vivancos-Aparicio D, Colom A, García-Ríos A, Casas R, Bernal-López MR, Santos-Lozano JM, Vázquez Z, **Gómez-Martínez C**, Ortega-Azorín C, del Val JL, Abete I, Goikoetxea-Bahon A, Pascual E, Becerra-Tomás N, Chillarón JJ, Sánchez-Villegas A. Contribution of cardiovascular risk factors to depressive status in the PREDIMED-PLUS Trial. A cross-sectional and a 2-year longitudinal study. *PLOS ONE*. 2022. Doi: 10.1371/journal.pone.0265079.
IF: 3.7 (2022)
Q1 (23/133) in Multidisciplinary Sciences

(18) Nishi SK, Babio N, Paz-Graniel I, Serra-Majem L, Vioque J, Fitó M, Corella D, Bueno-Cavanillas A, Tur JA, Diez-Ricote L, Martínez JA, G**ómez-Martínez C**, González-Botella A, Castañer O, Álvarez-Sala A, Montesdeoca-Mendoza C, Fanlo-Maresma M, Cano-Ibáñez N, Bouzas C, Daimiel L, Zulet MA, Sievenpiper JL, Rodriguez KL, Vázquez-Ruiz Z, Salas-Salvadó

J. Water intake, hydration status and 2-year changes in cognitive performance: a prospective cohort study. *BMC Medicine*. 2023. Doi: 10.1186/s12916-023-02771-4.
IF: 7.0 (2023)
1D (23/325) in Medicine, General & Internal

(19) Rognoni T, Fernández-Matarrubia M, Martínez-González MA, Salas-Salvadó J, Corella D, Castañer O, Alfredo-Martínez J, Alonso-Gómez MA, Gómez-García E, Vioque J, Romaguera D, López-Miranda J, Estruch R, Tinhaones FJ, Santos-Lozano JM, Serra-Majem L, Cano-Ibañez N, Tur JA, Micó-Pérez R, Pintó X, Delgado-Rodríguez M, Ortiz-Ramos M, Martín-Vidal J, Vázquez C, Daimiel L, Ros E, Goñi-Ruiz N, Babio N, Sorlí JV, Schröder H, García-Ríos A, Compañ-Gabucio L, Wärnberg J, Zulet MA, Chaplin A, Sacanella E, Bouzalmate-Hajjaj A, Tojal-Sierra L, Damas-Fuentes M, Vázquez Z, **Gómez-Martínez C**, Saiz C, Malcampo M, Ortiz-Morales AM, Martínez-Áviles V, García-Gavilán J, Abete I, Fitó M, Toledo E. Two-year changes in physical activity and concurrent changes in cognitive function in a cohort of adults with metabolic syndrome. *Journal of Alzheimer's Disease*. 2023. Doi: 10.3233/JAD-230105.
IF: 3.4 (2023)
Q2 (116/310) in Neurosciences

(20) Baenas I, Camacho-Barcia L, Granero R, Razquin C, Corella D, **Gómez-Martínez C**, Castañer-Niño O, Martínez JA, Wärnberg J, Vioque J, Romaguera D, López-Miranda J, Estruch R, Tinahones FJ, Lapetra J, Serra-Majem JL, Cano-Ibañez N, Tur JA, Martín-Sánchez V, Pintó X, Gaforio JJ, Matía-Martín P, Vidal J, Vázquez C, Daimiel L, Ros E, Jiménez-Murcia S, Dalsgaard S, García-Arellano A, Babio N, Sorlí JV, Lassale C, García-de-la-Hera M, Gómez-García E, Zulet MA, Konieczna J, Martín-Peláez S, Tojal-Sierra L, Basterra-Gortari FJ, de las Heras-Delgado S, Portoles O, Muñoz-Pérez MÁ, Arenas-Larriva AP, Compañ-Gabucio L, Eguaras S, Shyam S, Fitó M, Baños RM, Salas-Salvadó J, Fernández-Aranda F. Association between type 2 diabetes and depressive symptoms after a 1-year follow-up in an older adult Mediterranean population. *Journal of Endocrinological Investigation*. 2023. Doi: 10.1007/s40618-023-02278-y.
IF: 5.4 (2023)
Q1 (34/145) in Endocrinology & Metabolism

PARTICIPATION IN CONFERENCES

Date: 14-17/Apr/2021
Conference: DNSG 2021 (38th International Symposium on Diabetes and Nutrition).
Type: Oral presentation
Modality: Online
International/*national*: International
Contribution title: Longitudinal associations between glycemic status and cognitive dysfunction in older participants at high risk of cardiovascular disease: Two-year results of the PREDIMED-Plus study.
Authors: **Gómez-Martínez C**, Babio N, Júlvez J, Becerra-Tomás N, Martínez-González MÁ, Corella D, Castañer O, Romaguera D, Vioque J, Alonso-Gómez ÁM, Wärnberg J, Martínez JA, Serra-Majem L, Estruch R, Tinahones FJ, Lapetra J, Pintó X, Tur JA, López-Miranda J, Bueno-Cavanillas A, Gaforio JJ, Matía-Martín P, Daimiel L, Martín-Sánchez V, Vidal J, Vázquez C, Ros E, Dalsgaard S, Sayón-Orea C, Sorlí JV, de la Torre R, Abete I, Tojal-Sierra L, Barón-López FJ, Fernández-Brufal N, Konieczna J, García-Ríos A, Sacanella E, Bernal-López MR, Santos-Lozano JM, Razquin C, Alvarez-Sala A, Goday A, Zulet MA, Vaquero-Luna J, Diez-Espino J, Cuenca-Royo A, Fernández-Aranda F, Bulló M, Salas-Salvadó J.

Date: 28/Apr//2022
Conference: Sessió científica CCNIEC 2022 (Centre Català de la Nutrició de l'Institut d'Estudis Catalans).
Type: Oral presentation by invitation.
Modality: In-person.
International/*national*: International.
Contribution title: Impulsivity is longitudinally associated with healthy and unhealthy dietary patterns in individuals with overweight or obesity and metabolic syndrome.
Authors: **Gómez-Martínez C**, Babio N, Júlvez J, Nishi SK, Fernández-Aranda F, Martínez-González MA, Cuenca-Royo A, Fernández R, Jiménez-Murcia S, de la Torre R, Pintó X, Bloemendaal M, Fitó M, Corella D, Arias Al, Salas-Salvadó J.

Date: 16-19/Jun/2022
Conference: DNSG 2022 (39th International Symposium on Diabetes and Nutrition).
Type: Oral presentation.
Modality: In-person.
International/*national*: International.
Contribution title: Impulsivity is longitudinally associated with healthy and unhealthy dietary patterns in individuals with overweight or obesity and metabolic syndrome.
Authors: **Gómez-Martínez C**, Babio N, Júlvez J, Nishi SK, Fernández-Aranda F, Martínez-González MA, Cuenca-Royo A, Fernández R, Jiménez-Murcia S, de la Torre R, Pintó X, Bloemendaal M, Fitó M, Corella D, Arias Al, Salas-Salvadó J.

Date: 16-19/Jun/2022
Conference: DNSG 2022 (39th International Symposium on Diabetes and Nutrition).
Type: Oral presentation.
Modality: In-person.

International/national: International.
Contribution title: Dairy Product Consumption and Changes in Cognitive Performance: Two-Year Analysis of the PREDIMED-Plus Cohort.
Authors: Ni J, Nishi SK, Babio N, Martínez-González MA, Corella D, Castañer O, Martínez JA, Alonso-Gómez ÁM, Gómez-Gracia E, Vioque J, Romaguera D, López-Miranda J, Estruch R, Tinahones FJ, Lapetra J, Serra-Majem L, Bueno-Cavanillas A, Tur JA, Martín-Sánchez V, Pintó X, Gaforio JJ, Barabash-Bustelo A, Vidal J, Vázquez C, Daimiel L, Ros E, Toledo E, Clotell O, **Gómez-Martínez C,** Zomeño MD, Donat-Vargas C, Goicolea-Güemez L, Bouzas C, Garcia-de-la-Hera M, Chaplin A, Garcia-Rios A, Casas R, Cornejo-Pareja I, Santos-Lozano JM, Rognoni T, Saiz C, Paz-Ganiel I, Malcampo M, Sánchez-Villegas A, Salaverria-Lete I, García-Arellano A, Schröder H, Salas-Salvadó J.

Date: 16-19/Jun/2022
Conference: DNSG 2022 (39th International Symposium on Diabetes and Nutrition).
Type: Oral presentation.
Modality: In-person.
International/national: International.
Contribution title: Adherence to a healthy lifestyle behavior composite score and cardiometabolic risk factors in Spanish children from the CORALS cohort.
Authors: Garcidueñas-Fimbres TE, **Gómez-Martínez C**, Pascual-Compte M, Jurado-Castro JM, Leis R, Moreno LA, Navas-Carretero S, Codoñer-Franch P, Echeverria AM, Pastor-Villaescusa B, López-Rubio A, Moroño-García S, de Miguel-Etayo P, Martínez JA, Velasco-Aguayo I, Vázquez-Cobela R, Escribano J, Miguel-Berges ML, de la Torre-Aguilar MJ, Gil-Campos M, Salas-Salvadó J, Babio N.

Date: 06-08/Sep/2022
Conference: PRIME 4th General Assembly Meeting (PRIME H2020 PROJECT).
Type: Oral presentation.
Modality: In-person.
International/national: International.
Contribution title: Type 2 diabetes, insulin resistance, and glycated hemoglobin were positively and longitudinally associated with impulsivity in a senior population with metabolic syndrome.
Authors: **Gómez-Martínez C**, Babio N, Camacho-Barcia L, Júlvez J, Nishi SK, Vázquez Z, Forcano L, Álvarez-Sala A, Cuenca-Royo A, de la Torre R, Fanlo-Maresma M, Tello S, Corella D, Arias Vásquez A, Dalsgaard S, Franke B, Fernández-Aranda F, Salas-Salvadó J.

Date: 15-16/Nov/2022
Congress: XIII Simposio CIBERobn.
Contribution title: Impulsive personality traits predicted weight loss in individuals with type 2 diabetes after 3 years of lifestyle interventions.
Type: Poster.
Modality: In-person.
International/national: National.
Authors: Testa G, Camacho-Barcia L, **Gómez-Martínez C**, Mora-Maltas B, de la Torre R, Pintó X, Corella D, Granero R, Cuenca-Royo A, Jiménez-Murcia S, Babio N, Fernández-Barrión R, Esteve-Luque V, Forcano L, Ni J, Malcampo M, De las Heras-Delgado S, Fitó M, Salas-Salvadó J, Fernández-Aranda F.

Date: 15-18/Jun/2023
Conference: DNSG 2023 (40th International Symposium on Diabetes and Nutrition).
Type: Oral presentation.
Modality: In-person.
International/*national*: International.
Contribution title: Impulsivity is associated with higher risk to develop type 2 diabetes and cardiovascular disease over 8 years of follow-up in the NutriNet-Santé cohort.
Authors: **Gómez-Martínez C**, Paolassini-Guesnier P, Srour B, Fezeu L, Babio N, Salas-Salvadó J, Hercberg S, Touvier M, Péneau S.

Date: 22/Jun/2023
Conference: PhD Day (IISPV: Institut d'Investigació Sanitària Pere Virgili).
Type: Oral presentation.
Modality: In-person.
International/*national*: National.
Contribution title: Impulsivity is associated with higher risk to develop type 2 diabetes and cardiovascular disease over 8 years of follow-up in the NutriNet-Santé cohort.
Authors: **Gómez-Martínez C**, Paolassini-Guesnier P, Srour B, Fezeu L, Babio N, Salas-Salvadó J, Hercberg S, Touvier M, Péneau S.

Date: 16-18/Oct/2023
Conference: 33rd Alzheimer Europe Conference (Alzheimer Europe).
Type: Oral presentation.
Modality: In-person.
International/*national*: International.
Contribution title: COVID-19 and cognitive impairment in older adults: Longitudinal analysis from the PREDIMED-PLUS Cohort.
Authors: **Gómez-Martínez C,** Sangeetha Shyam, Ni J, Babio N, Salas-Salvadó J.

Date: 13-15/May/2024
Conference: PRIME 5th General Assembly Meeting (PRIME H2020 PROJECT).
Type: Oral presentation.
Modality: In-person.
International/*national*: International.
Contribution title: Glycated hemoglobin, type 2 diabetes, and poor diabetes control were positively associated with impulsivity changes.
Authors: **Gómez-Martínez C**, Babio N, Camacho-Barcia L, Júlvez J, Nishi SK, Vázquez Z, Forcano L, Álvarez-Sala A, Cuenca-Royo A, de la Torre R, Fanlo-Maresma M, Tello S, Corella D, Arias Vásquez A, Dalsgaard S, Franke B, Fernández-Aranda F, Salas-Salvadó J.

Date: 13-15/May/2024
Conference: PRIME 5th General Assembly Meeting (PRIME H2020 PROJECT).
Type: Oral presentation.
Modality: In-person.
International/*national*: International.
Contribution title: Lifestyle intervention effect aiming to weight loss and improve glycemic metabolism on novel neurology related-proteins and inflammation markers for cognitive decline.
Authors: **Gómez-Martínez C**, Paz-Graniel I, García-Gavilán J, Babio N, Salas-Salvadó J.

SCIENTIFIC DIVULGATION

Date: 01/Mar/2021
Divulgative journal: NutFruit Health Section (International Nut and Dried Fruit Council)
Contribution title: Protective Effects of Nut Consumption in Cognitive Dysfunction
Type: Divulgative publication article.
International/*national*: International.

Date: 30/Sep/2022
Workshop: "Taller Nit Europea de la Recerca".
*Contribution title: "*Explorem l'essència del menjar".
Type: Workshop.
Modality: In-person.
International/*national*: National.

Date: 30/ Sep /2022
Congress: "Conferencia Nit Europea de la Recerca".
Contribution title: "¿Puede un peor estado glicémico asociarse a una mayor impulsividad?"
Type: Congress.
Modality: In-person.
International/*national*: National.

Date: 18/Nov/2022
Congress: "Monòlegs del Club de la Ciència".
Contribution title: "Ràpid, a menjar!"
Type: Scientific monologue contest.
Modality: In-person.
International/*national*: National.

Date: 18/Nov/2022
Radio interview: "Radio Marca - Al límite".
Contribution title: "Las personas impulsivas tienden más a dietas poco equilibradas!"
Type: Radio interview.
Modality: Virutal.
International/*national*: National.

Date: 12/Nov/2022
Congress: "Conferencia Nit Europea de la Recerca".
Contribution title: "¿Puede un peor estado glicémico asociarse a una mayor impulsividad?"
Type: Congress.
Modality: In-person.
International/*national*: National.

Date: 22/May/2023.
Congress: Pint of Science.
Contribution title: Si puja la glucosa, mala PINTa OF SCIENCE.

Type: Oral presentation.
Modality: In-person.
International/*national*: National.

Date: 28/Sep/2023.
Congress: "Charla Nit Europea de la Recerca".
Contribution title: Que causa i desencadena el sucre en sang.
Type: Oral presentation.
Modality: In-person.
International/*national*: National.

Date: 17/Nov/2023.
Congress: "Setmana de la Ciència".
Contribution title: Que causa i desencadena el sucre en sang.
Type: Oral presentation.
Modality: In-person.
International/*national*: National.

Date: 26/Sep/2024.
Congress: "Microxerrada en la Nit Europea de la Recerca".
Contribution title: El paper de la psicologia en la salut pública.
Type: Oral presentation.
Modality: In-person.
International/*national*: National.

SCHOLARSHIPS AND AWARDS

Period: 01/Apr/2020-31/Jan/2022
Scholarship: PREDIMED-Plus project-related scholarship.
Institution: Institut d'Investigació Sanitària Pere i Virgili (IISPV).
Aim: To give monetary compensation for working in the PREDIMED-Plus project under the development of my PhD.

Period: 01/Feb/2021-31/Jan/2025
Scholarship: Beca Martí Franqués (2020PMF-PIPF-37).
Institution: Universitat Rovira i Virgili (URV).
Aim: To give monetary compensation for the development of my PhD.

Date: 18/Jun/2022
Award: Winner of the best short oral communication.
Institution: Diabetes Nutrition Study Group.
Prize: 1,000€.

Date: 18/Nov/2022
Award: Finalist in the contest of "Monòlegs del Club de la Ciència".
Institution: Fundació Catalana per a la Recerca i la Innovació (FCRI).

Period: 23/Jan/2023-26/Apr/2023
Scholarship: Erasmus+Internship.
Institution: Universitat Rovira i Virgili (URV).
Aim: To give monetary compensation for the mobility PhD training program in Paris.

Date: 16/Oct/2023-18/Oct/2023
Award: Winner of the “Bursaries for early-stage researchers”.
Institution: Alzheimer Europe.
Prize: 850€.

Period: 27/May/2024-07/Jun/2024
Scholarship: PRIME H2020 secondment.
Institution: PRIME H2020.
Aim: To give monetary compensation for performing a secondment at the Maastricht University.

MOBILITY

Period: 23/Jan/2023-26/Apr/2023 (93 days)
Reason: PhD mobility stage under the ERASMUS+Internship framwrok.
Host institution: Université Sorbonne Paris Nord and Université Paris Cité, INSERM, INRAE, CNAM, Center of Research in Epidemiology and StatisticS (CRESS), Nutritional Epidemiology Research Team (EREN), F-93017 Bobigny, France.
Host investigator and supervisor: Prof. Sandrine Péneau.
Tasks carried out: To extract a NutriNet-Santé database in order to perform the statistical analyses between trait impulsivity and the incidence of type 2 diabetes and cardiovascular disease on almost 50,000 French adult individuals participating in the NutriNet-Santé study, aiming to finally write scientific manuscripts and to do scientific translation.

Period: 27/May/2024-07/Jun/2024 (12 days)
Reason: Young researchers mobility stage under the European H2020 PRIME project.
Host institution: Department of Psychiatry and Neuropsychology, Alzheimer Center Limburg, School for Mental Health and Neuroscience, Maastricht University, Maastricht, the Netherlands.
Host investigators and collaborators: Dr. Willemijn Jansen, Dr. Stephanie Vos, and Dr. Veerle van Gils.
Tasks carried out: To perform statistical analyses and to write a scientific manuscript studying the associations of glycemic status and inflammation parameters with cognitive function changes and magnetic resonance imaging assessments in the Maastricht study cohort.