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Dietary intake of Perfluorooctanesulfonic acid (PFOS) and glucose homeostasis parameters in a non-diabetic senior population

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Abbreviations: BMI, Body mass index; CVD, Cardiovascular disease; Eds, Endocrine disruptors; er-MedDiet, Energy-reduced Mediterranean diet; EFSA, European Food Safety Authority; FFQs, Food frequency questionnaires; HbA1c, Glycated hemoglobin; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; LOD, Limit of detection; LB, lower bound; PFAS, Per- and polyfluoroalkyl substances; PFOS, Perfluorooctane sulfonate; SD, Standard deviation; TWI, Tolerable weekly intake; UB, Upper bound.

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ABSTRACT

Background: Endocrine disruptors (EDs) have emerged as potential contributors to the development of type-2 diabetes. Perfluorooctane sulfonate (PFOS), is one of these EDs linked with chronic diseases and gathered attention due to its widespread in food.
Objective: To assess at baseline and after 1-year of follow-up associations between estimated dietary intake (DI) of PFOS, and glucose homeostasis parameters and body-mass-index (BMI) in a senior population of 4600 non-diabetic participants from the PREDIMED-plus study.
Methods: Multivariable linear regression models were conducted to assess associations between baseline PFOS-DI at lower bound (LB) and upper bound (UB) established by the EFSA, glucose homeostasis parameters and BMI.
Results: Compared to those in the lowest tertile, participants in the highest tertile of baseline PFOS-DI in LB and UB showed higher levels of HbA1c [β-coefficient(CI)] [0.01 %(0.002 to 0.026), and [0.06 mg/dL(0.026 to 0.087), both p-trend $\leq$ 0.001], and fasting plasma glucose in the LB PFOS-DI [1.05 mg/dL(0.050 to 2.046),p-trend = 0.022]. Prospectively, a positive association between LB of PFOS-DI and BMI [0.06 kg/m^2(0.014 to 0.106) per 1-SD increment of energy-adjusted PFOS-DI was shown. Participants in the top tertile showed an increase in HOMA-IR [0.06(0.016 to 0.097), p-trend = 0.005] compared to participants in the reference tertile after 1-year of follow-up.
Discussion: This is the first study to explore the association between DI of PFOS and glucose homeostasis. In this study, a high baseline DI of PFOS was associated with a higher levels of fasting plasma glucose and HbA1c and with an increase in HOMA-IR and BMI after 1-year of follow-up.

1. Introduction

Type 2 diabetes mellitus (T2D) is a chronic metabolic disorder posing a significant global health challenge. In 2021, the International Diabetes Federation estimated that 1 in 10 adults were living with T2D and is predicted to rise to 1 in 9 adults by 2030 (IDF Diabetes Atlas 10th edition, 2023). The consequences of uncontrolled T2D are far-reaching and can lead to serious complications affecting various organ systems. Chronic hyperglycemia contributes, among others, to the development of microvascular and macrovascular complications, including diabetic retinopathy, stroke, and other cardiovascular diseases (Deshpande et al., 2008). To understand the multifactorial etiology of the T2D is crucial for establishing effective prevention and management strategies (Zimmet et al., 2001; Egede and Dagogo-Jack, 2005). Nowadays, it is known that there are multiple risk factors that lead to the development of T2D including genetic predisposition, age, sex, obesity status, smoking, physical inactivity, and unhealthy diet (Zimmet et al., 2001; Egede and Dagogo-Jack, 2005). However, in recent years, environmental and anthropogenic contaminants have emerged as potential contributors to the development and progression of this disease, with particular attention given to the role of endocrine disruptors (EDs) (Diamanti-Kandarakis et al., 2009; Gore et al., 2015; Wang et al., 2019).

Per- and polyfluoroalkyl substances (PFAS] are a diverse group of almost 15,000 anthropogenic chemicals (eBioMedicine, 2023). Since the 1940 s, these compounds have been extensively utilized due to their unique hydrophobic and lipophobic properties and molecular stability, making them highly stable and effective as water, grease, and stain resistants (Glüge et al., 2020; Paul et al., 2009). Despite their serious consequences on health, PFAS continue to be in use in various countries, contributing to the production of surfactants, lubricants, Teflon products, textiles, furniture, carpets, papers, and firefighting foams (Lau et al., 2004).

Perfluorooctane sulfonate (PFOS) is included in the PFAS family, and stands out as one of the most studied compounds (EFSA, 2020), it is an ED that has gathered considerable attention due to its widespread distribution and presence in foods specifically animal-origin products (Costopoulou et al., 2022; EFSA, 2020), and for its potential negative health effects. Due to its structural similarities to natural fatty acids, PFOS can bind to certain proteins and hormones, resulting in its long elimination half-life and bio-accumulation in the human body (Lindstrom et al., 2011; Heuvel et al., 1991). Furthermore, human exposure to PFAS is reported to start during gestation, potentially overpassing the placenta and persist through breastfeeding, leading to an important accumulation in body (Fábelová et al., 2023; Rovira et al., 2019). One of the key characteristics of PFOS is its notable persistence, characterized by high half-lives, which is estimated to range from 3.4 to 5.7 years (Rosato et al., 2024). PFOS is the most widely spread PFAS, and it has been used in various industrial and consumer applications. Consequently, it is accumulated in the food chain, being diet the main human exposure to this chemical (Olsen et al., 2007; EFSA, 2020). The chronic exposure and the long half-life of PFOS contribute to its accumulation in the body over time.

There is an increase amount of evidence examining the relationships between exposure to PFOS and the risk of obesity (Averina et al., 2021), anemia (Jain, 2021), dyslipidemia and mortality (Wen and Xu, 2022). In addition, previous studies have assessed the associations between PFAS exposure and increased risk of diabetes and glucose parameters (Xu

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et al., 2022; Brosset and Ngueta, 2023). However, other authors did not find consistent results (Han et al., 2021). In addition, the epidemiological evidence in senior population regarding dietary intake (DI) of PFOS, glycemic parameters and BMI is limited (Margolis and Sant, 2021; Qi et al., 2020) and despite the recognized susceptibility of specific groups to the adverse health effect of PFOS exposure, such as infants and pregnant women, the elderly populationis also a vulnerable group that is overlooked and needs to receive more attention. The elderly often experience a longer lifetime exposure to various contaminants, including PFOS, which may result in higher cumulative effects over time (Geller and Zenick, 2005). Additionally, age-related changes in metabolism, diminished organ function, and potential alterations in immune response can influence the way PFOS is absorbed, distributed, and eliminated (Palmer and Jensen, 2022).

Given the continuous increase in T2D and the significant anthropological and environmental exposures to PFOS, it is essential to evaluate in the context of the whole exposome, these chemicals and its impact on human health. In this way, we will be able to expand the understanding of the mechanism of this disease and to develop strategies for minimizing exposure (Lindstrom et al., 2011; Heuvel et al., 1991).

We hypothesized that high DI of PFOS has a detrimental impact on glycemic parameters and body mass index (BMI). Consequently, the overall objective of this study was to assess the associations between the estimated DI of PFOS and glucose homeostasis parameters and BMI in a cohort population from PREDIMED-Plus without diagnosed diabetes, cross-sectionally and longitudinally.

2. Materials and methods

2.1. Study design and population

The data of the PREDIMED-Plus (PREvención con DIeta MEDiterránea) cohort was used for the present cross-sectional and longitudinal study. PREDIMED-Plus is a currently ongoing randomized controlled trial taking place in 23 Spanish centers. The primary outcome of this trial is to evaluate the effect of an intensive weight loss intervention founded on a Mediterranean diet with reduced energy intake (er-MedDiet), promotion of physical activity, and behavioral support (intervention group), to and ad libitum Mediterranean diet following standard care advice (control group). The PREDIMED-Plus study aims to evaluate the incidence of cardiovascular disease (CVD) and mortality. Additional information about the PREDIMED-Plus study can be accessed at https://www.predimedplus.com, and has been described in prior publications (Sayón-Orea et al., 2019; Salas-Salvadó et al., 2019; Martínez-Gonzá lez et al., 2019). Participants were recruited in Spain (October 2013 - December 2016, including a total of 6,874) participants were randomly assigned to either the control group or the intervention group in a 1:1 ratio. Eligible participants were men (55–75 years) and women (60–75 years) with overweight or obesity (BMI = 27–40 kg/m2) and without a documented history of cardiovascular diseases (CVD) and met at least 3 criteria of metabolic syndrome (Alberti et al., 2005). In this present analysis, a total of 4,600 participants without diabetes were included in the cross-sectional assessment. They had complete baseline data from food frequency questionnaires (FFQs). Participants were excluded if their energy intake appeared implausible (Willet, 2012). Additionally, individuals with type 2 diabetes (T2D) were excluded from this analysis. For the prospective analysis, out of the initial 4,600 participants, 504 were further excluded due to insufficient FFQ

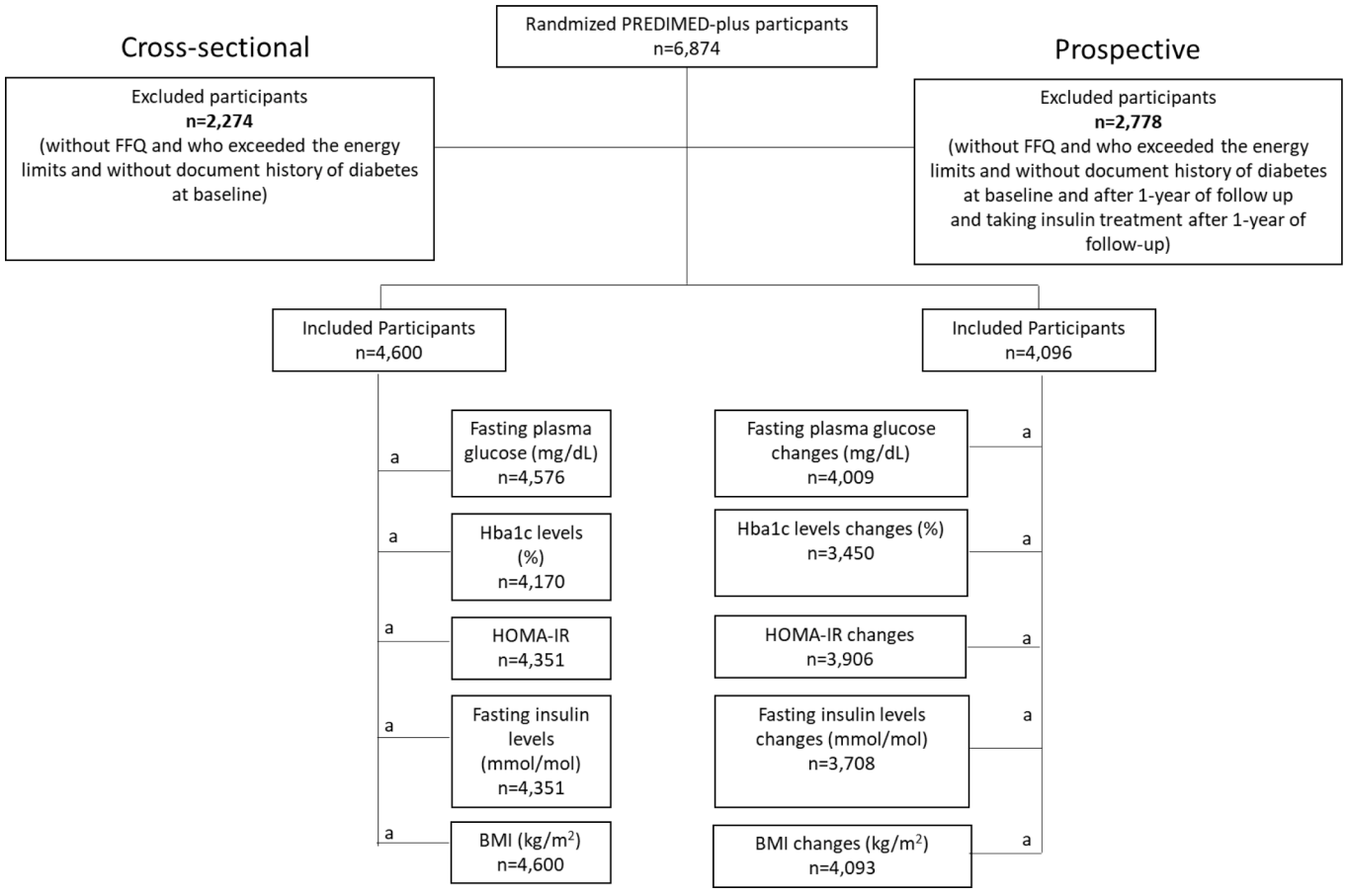

Fig. 1. Flow chart. a = Included participants for each outcome after excluding those with respective non-available measurements.

information, implausible energy intake, or because they had started insulin treatment during the one-year follow-up period (Fig. 1).

2.2. PFOS dietary intake assessment

To assess PFOS dietary intake, the study population underwent a validated face-to-face baseline food frequency questionnaire (FFQ) administered by trained staff members (De La Fuente-Arrillaga et al., 2010). Participants were asked to report their food consumption frequencies and quantity by this validated questionnaire (De La Fuente-Arrillaga et al., 2010). For the water intake assessment, a fluid-specific questionnaire that has been already validated as a tool for assessing intake of water and other types of beverages, was used in our population (Ferreira-Pêgo et al., 2016) (Supplementary Material, Figure S1).

We considered the most recent data on PFOS levels in food (measured in ng/g) (EFSA, 2020). These food items were grouped into appropriate food groups based on guidelines provided by the European Food Safety Authority (EFSA) (Supplementary Material, Table S2) (EFSA, 2020). To calculate the PFOS-DI, we also considered the previously mentioned consumption frequency. As a result, the dietary PFOS intake was expressed in ng/day.

The PFOS levels for each food group were obtained from earlier studies conducted by the EFSA, which assessed PFOS concentrations in a wide range of food samples from various European regions between 2012 and 2020. We primarily relied on data from 2020 as it represented the most up-to-date information (EFSA, 2020). In the DI estimation, we used the mean of the lower bound (LB) and upper bound (UB) levels within food categories defined by the EFSA.

It's important to note that the terms "lower bound" and "upper bound" refer to the range in which PFOS is detected. The LB represents the lowest value within that range, while the UB represents the highest estimated range for PFOS levels.

The mean LB is characterized by being the least conservative and also called "best case scenario" because when a non-detect is reported for a component, the concentration in the food is zero and the mean UB is characterized by being highly conservative and also called "worst case scenario" because when a non-detect is reported for a component, the concentration in food items is at the limit of detection (LOD). According to EFSA, when analyzing data on the presence of PFAS, results that fall below the LOD are considered left-censored. The recommended method for handling such data, involves a substitution approach. This method is particularly suitable for chemicals likely to be found in food such as PFOS, assigns a value of zero (minimum possible value) to results reported as < LOD LB. Simultaneously, an UB is determined by assigning the numerical value of LOD. The choice of LOD depends on the laboratory's reporting method. This approach ensures a cautious and realistic estimation of PFOS levels (EFSA, 2020). Consequently, in this study, both LB and UB were taken into consideration to estimate the lower and upper limits of dietary intake and exposure to PFOS in our study population (EFSA, 2020).

Therefore, the estimated DI of PFOS UB and LB (expressed in ng/day) was obtained from the following equation:

$$DI\ PFOS_{LB/UB}(ng/day) = \sum C_i \times A_i$$

Where DI represents the downward (LB) / upward (UB) Dietary intake of PFOS in ng/day; C_i represents the PFOS concentration of a specific food group (in ng/g); Ai signifies the quantity of a particular food item consumed, measured in grams per day (g/day).

2.3. Estimation of dietary exposure to PFOS

According to the EFSA, dietary exposure to PFOS was estimated in this cohort considering the LB (being this approach more realistic) (EFSA, 2020), following this equation:

$$Dietary\ exposure\ to\ PFOS(ng/kg\ of\ body\ weight/week) = \left(\left(\sum C_i \times A_i\right)/BW_i\right) \times 7$$

"Ci" refers to the PFOS concentration of a particular food group, measured in nanograms per gram (ng/g). "Ai" stands for the amount of that specific food consumed, expressed in grams per day (g/day). "BWi" represents the body weight of each participant, measured in kilograms (kg). To determine the weekly dietary exposure, the calculated result is multiplied by 7.

2.4. Outcomes

Samples for fasting plasma glucose and glycated hemoglobin (HbA1c) were obtained from our study cohort population and analyzed by a routine laboratory method. The fasting plasma insulin levels were measured centrally using an Elecsys immunoanalyzer (Roche Diagnostics, Meylan, France) with the assistance of an electrochemiluminescence immunoassay. To estimate insulin resistance, the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) index was used following this formula (Matthews et al., 1985):

$$HOMA - IR = Insulin_{(mU/mL)} \times glucose_{(mg/dL)}/405$$

Trained PREDIMED-Plus staff conducted assessments of various anthropometric variables at baseline and after 1-year of follow-up. The Body weight of our cohort population was measured two different times wearing light clothes. This was assessed using precise electronic calibrated scales. The average of the two measurements was used. Height was measured using a stadiometer mounted on a wall. BMI was obtained dividing the weight of each participant (in kilograms) by the square of height of each subject (in meters).

2.5. Assessment of covariates

Additional covariates were evaluated using general face-to-face questionnaires that collect information on socio-demographics (sex, marital status, age, and level of education), lifestyle (smoking habits and physical activity), history of type 2 diabetes and family history of cardiovascular diseases. Physical activity was assessed using a validated Minnesota-REGICOR Short Physical Activity questionnaire (Molina et al., 2017). Moreover, a validated 17-item questionnaire was used to assess the adherence to the Mediterranean diet (Schröder et al., 2011). Waist circumference was obtained for each participant measuring at the midpoint between the lowest rib and the iliac crest using a specialized tape.

2.6. Statistical analyses

The most updated database of the PREDIMED-PLUS study (from December 2020) was considered. The population was divided in tertiles of energy-adjusted PFOS intake, expressed as mean ± standard deviation (SD) for continuous variables and percentages (number) for categorical variables. Tertiles of PFOS dietary intake were adjusted for total energy intake (in ng/day), using the residual-regression method (Willett and Stampfer, 1986), where the first tertile corresponds to lower DI of PFOS, second tertile corresponds to medium DI of PFOS and third tertile corresponds to higher DI of PFOS.

To compare the baseline characteristics across these tertiles, the Chi-square test was used for categorical variables, and one-way ANOVA was applied for continuous variables.

Multivariable linear regression models were fitted to cross-sectionally and longitudinally assess the associations [β-coefficient (95 % confidence interval (CI)] between the baseline energy-adjusted DI of PFOS, glucose-related parameters (fasting plasma glucose, HbA1c, fasting plasma insulin and HOMA-IR) and BMI. These associations were explored considering both, tertiles of energy-adjusted DI of PFOS, and

Table 1
Main baseline characteristics of the included participants overall and across energy-adjusted total PFOS lower bound dietary intake tertiles.

	All	Energy-adjusted total PFOS lower bound dietary intake – (ng/d)			
		T1 n = 1,534 17.63 ± 3.50	**T2** n = 1,533 25.52 ± 1.94	**T3** n = 1,533 35.22 ± 5.93	**P-value**
Sex					
Women	50.3 (2,316)	42.9 (658)	50.7 (778)	57.4 (880)	< 0.001
Age (years) (n = 4,600)	64.9 ± 4.90	64.4 ± 5.07	65.3 ± 4.91	65.0 ± 4.69	< 0.001
Educational level (n = 4,600)					0.020
Up to primary	48.0 (2,209)	49.1 (754)	50.4 (772)	44.5 (683)	
Secondary	29.1 (1,339)	28.4 (436)	27.6 (423)	31.3 (480)	
University	22.9 (1,052)	22.4 (344)	22.0 (338)	24.1 (370)	
Marital status (n = 4,600)					0.211
Single	13.3 (613)	15.2 (233)	12.6 (193)	12.2 (187)	
Married	76.3 (3,508)	75.2 (1,154)	76.3 (1,170)	77.2 (1,184)	
Widowed	10.4 (479)	9.58 (147)	11.1 (170)	10.6 (162)	
Smoking status (n = 4,600)					0.001
Never	45.4 (2,088)	41.6 (638)	46.2 (708)	48.4 (742)	
Former	42.5 (1,953)	44.3 (679)	41.7 (639)	41.4 (635)	
Current	12.1 (559)	14.1 (217)	12.1 (186)	10.2 (156)	
Physical activity (MET min/week) (n = 4,600)	2499 ± 2318	2422 ± 2492	2403 ± 2124	2673 ± 2314	0.001
Waist circumference (cm) (n = 4,600)					
Men	111 ± 8.73	110 ± 8.76	111 ± 8.75	110 ± 8.65	0.114
Women	103 ± 9.03	103 ± 9.15	103 ± 9.15	103 ± 8.84	0.605
BMI (kg/m^2) (n = 4,600)	32.4 ± 3.42	32.4 ± 3.35	32.5 ± 3.45	32.4 ± 3.46	0.855
Adherence to Mediterranean diet MEDAS score (0–17 points) (n = 4,600)	8.44 ± 2.70	7.57 ± 2.61	8.49 ± 2.56	8.25 ± 2.67	< 0.001
Dietary assessment (n = 4,600)					
Fruits (g/d)	359 ± 208	321 ± 191	367 ± 199	389 ± 227	< 0.001
Vegetables (g/d)	327 ± 140	284 ± 127	325 ± 134	372 ± 144	< 0.001
Legumes (g/d)	20.5 ± 11.2	19.5 ± 11.4	20.7 ± 10.5	21.4 ± 11.5	< 0.001
Total cereals (g/d)	151 ± 78.3	162 ± 84.6	149 ± 77.5	141 ± 70.9	< 0.001
Biscuits (g/d)	27.7 ± 30.1	31.5 ± 33.9	28.7 ± 30.1	22.8 ± 24.9	< 0.001
Dairy products (g/d)	339 ± 198	346 ± 204	337 ± 198	336 ± 192	0.335
Red meat and derivatives (g/d)	80.9 ± 44.4	79.9 ± 45.8	81.4 ± 43.4	81.6 ± 43.9	0.548
White meat (g/d)	61.6 ± 33.8	55.8 ± 33.8	61.3 ± 31.5	67.7 ± 34.9	< 0.001
Fish and shellfish (g/d)	101 ± 47.3	57.5 ± 21.9	96.8 ± 21.5	150 ± 37.9	< 0.001
Nuts (g/d)	14.9 ± 16.9	14.4 ± 17.5	14.5 ± 16.2	16.0 ± 16.9	0.014
Total olive oil (g/d)	40.3 ± 16.7	39.9 ± 17.3	40.7 ± 16.2	40.4 ± 16.6	0.445
Virgin olive oil (g/d)	32.3 ± 20.7	31.2 ± 21.3	32.7 ± 20.8	32.9 ± 19.9	0.039
Total energy (Kcal/d)	2382 ± 554	2396 ± 585	2369 ± 552	2381 ± 524	0.405
Proteins (g/d)	97.2 ± 21.8	89.4 ± 21.0	96.3 ± 20.5	106 ± 20.8	< 0.001
Saturated fatty acids (g/d)	26.2 ± 8.49	26.5 ± 9.16	26.2 ± 8.31	26.0 ± 7.95	0.294
Polyunsaturated fatty acids (g/d)	18.0 ± 6.59	17.7 ± 6.89	17.9 ± 6.36	18.4 ± 6.48	0.021
Monounsaturated fatty acids (g/d)	53.9 ± 16.0	53.6 ± 16.7	53.9 ± 15.6	54.1 ± 15.8	0.644
Carbohydrates (g/d)	244 ± 73.2	255 ± 76.9	243 ± 73.3	235 ± 67.8	< 0.001
Dietary fiber (g/d)	26.2 ± 8.82	24.7 ± 8.66	26.3 ± 8.79	27.6 ± 8.76	< 0.001
Total sugar (g/d)	8.58 ± 13.2	10.2 ± 14.1	8.64 ± 13.2	6.90 ± 11.8	< 0.001
Water (mL/day)	1139 ± 267	1133 ± 269	1137 ± 263	1148 ± 268	0.305
Alcohol (g/day)	11.2 ± 14.9	12.5 ± 16.6	10.7 ± 14.4	10.3 ± 13.7	0.001
Fasting plasma insulin levels (mmol/mol) (n = 4,351)	18.4 ± 10.0	18.4 ± 10.4	18.6 ± 9.92	18.1 ± 9.84	0.394
Fasting plasma glucose levels (mg/dL) (n = 4,576)	102 ± 13.5	102 ± 14.2	103 ± 13.2	102 ± 12.9	0.152
HbA1c levels (%) (n = 4,170)	5.75 ± 0.39	5.73 ± 0.38	5.76 ± 0.41	5.77 ± 0.39	0.011

Abbreviations PFOS: Perfluorooctanesulfonic acid; CI: confidence interval; HbA1c: hemoglobin A1c; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; BMI: body mass index.
Data are expressed as means ± SD and percentages (number) for continuous and categorical variables, respectively. P-values for comparisons were tested by one-way ANOVA or Chi-square test, as appropriate across tertiles.

energy-adjusted DI of PFOS with one SD increment, continuous. For the prospective analysis, the outcome considered were the changes in aforementioned glucose-related parameters and BMI after 1-year of follow-up.

Three multivariable models were conducted considering several confounders: i) Model 1: sex and age-adjusted ii) Model 2: model 1 further adjusted for marital status (married, widowed, single or divorced or separated, or religious), physical activity (METs min/week), education level (primary or lower, secondary or academic, or graduate), the size of the recruitment center representing the total field center workload (<250, 250 to < 300, 300 to < 400, ≥400 randomized participants) and smoking status (never, former, or current) and BMI (kg/m^2); iii) Model 3: further adjusted for adherence to Mediterranean diet using the 17-item MEDAS score and family history of cardiovascular disease. For prospective analyses, model 3 was further adjusted for the intervention group, diabetes medications used and each respective baseline glucose-related parameter (Supplementary Material, Figure S2).

Moreover, we conducted sensitivity analyses considering the linear regression model 3 to assess the association between baseline energy-adjusted DI of PFOS in continuous (with 1 SD increment) and fasting plasma glucose or HbA1c depending on age (<65 years old ≥ 65 years old), sex (men or women) and weight status (overweight or obesity). In addition, sensitivity analysis was conducted after 1-year of follow-up using the linear regression model 3 to assess the association between baseline energy-adjusted DI of PFOS in continuous (with 1 SD increment) and changes in HOMA-IR depending on age (<65 years old or equal or ≥ 65 years old), sex (men or women), weight status (overweight or obesity) and allocation group (intervention or control group). No

significant interaction was observed for all cases (P-value > 0.05) using the likelihood ratio test.

P-value < 0.05 was considered as significant. All analyses were conducted with robust estimates of the variance to correct for intra-cluster (members of the same household) correlation and using the Stata 14 software program (StataCorp).

3. Results

A total of 4,600 participants with no diabetes from the PREDIMED-Plus cohort population (49.7 % men and 50.3 % women, with a mean (SD) age of 65 ± 4.90 years) were included in this analysis. In Table 1, the baseline characteristics of the participants overall and according to tertiles of total energy-adjusted dietary PFOS intake (ng/day) were presented.

Compared to participants in the lower DI tertile of PFOS, those participants the highest PFOS intake were more frequently women, were less frequently smokers, do more leisure-time physically activity, and showed lower adherence to the Mediterranean diet. They consume higher amounts of nuts, fruits and vegetables, fish and shellfish, legumes, white meat, dietary fiber, virgin olive oil, protein, and poly-unsaturated fatty acids. On the other hand, they consumed lower amounts of biscuits, cereals, sugar and alcohol.

In the present study the major food groups contributors to total DI of PFOS were fish and seafood (62 %), followed by eggs (25 %), and fruits and vegetables (8 %) (Fig. 2).

In our cross-sectional analysis (Table 2), positive associations were observed between the LB of energy-adjusted DI of PFOS and fasting plasma glucose and HbA1c levels, being the magnitude of these associations increased through the adjustment (β-coefficient [95 %CI]) (1.05 mg/dL [0.050 to 2.046] and 0.05 % [0.024 to 0.082], P for trend 0.022 and 0.001 for fasting plasma glucose and HbA1c, respectively, in the full adjusted model). In addition, we found a positive association between the UB of energy-adjusted DI of PFOS and HbA1c levels in the fully-adjusted model (β-coefficient [95 %CI]) (0.06 % [0.026 to 0.087], P for trend < 0.001. No other significant associations were found for the rest of glucose-related parameters in the LB nor the UB analysis. However, the direction of these associations goes in line with what was expected (higher fasting plasma insulin levels, higher HOMA-IR and higher BMI in the LB and UB of the highest tertile of PFOS DI).

In the prospective analysis (Table 3), a positive association between baseline energy-adjusted DI of PFOS in the LB (ng/day) and an increase in BMI after 1-year of follow-up (β coefficient [95 %CI] 0.06 kg/m^2 [0.014 to 0.106]) was shown. In addition, participants in the top tertile of baseline energy-adjusted DI of PFOS in the UB (ng/day) showed an increase in HOMA-IR (β-coefficient [95 %CI]; 0.06 [0.016 to 0.097]; P for trend = 0.005) compared to those in the first tertile after one year of follow-up. No other significant associations were observed for changes in fasting plasma glucose, HbA1c, fasting plasma insulin and BMI. In the sensitivity analysis energy-adjusted DI PFOS and fasting plasma glucose in the LB was positively associated only in overweight participants. Moreover, a higher baseline DI of PFOS was positively associated with higher levels of HbA1c in the LB as well as in the UB in participants < 65 years old. In addition, DI of PFOS was cross-sectionally associated with higher HbA1c in men and overweight participants in the UB. After 1-year of follow-up, baseline energy-adjusted PFOS intake (with 1 SD increment) was positively associated with an increase in HOMA-IR in participants < 65 years old (Supplementary Material, figures S3a-d and figures S4a-b).

4. Discussion

To the best of our knowledge, this is the first study to explore the association between DI of PFOS and glucose homeostasis. We found that in an adult Mediterranean population at high cardiovascular risk, high baseline DI of PFOS was associated with a higher levels of fasting plasma glucose and HbA1c and with an increase in HOMA-IR and BMI after 1-year of follow-up.

In our study, we found that fish and seafood, followed by eggs, and fruits and vegetables were the major food contributors to the total dietary intake of PFOS. These results are in line with other published articles (Fábelová et al., 2023; Rovira et al., 2019; Sznajder-Katarzyńska et al., 2018). A recent study conducted in Greece found that eggs, fish and seafood seem to be responsible for about 50 % of PFOS dietary exposure (Costopoulou et al., 2022). In addition, EFSA published a scientific opinion in 2020 stating that fish and seafood, fruits and vegetables contribute the most to the total PFOS DI (EFSA, 2020) for all ages. The high abundance of PFOS in animal-origin foods could be explained due the lipophilic properties of this chemical, which can lead to their accumulation and persistence in the food chain, being animal and animal-based products, especially seafood and eggs, the main sources to total PFOS dietary intake exposure. In addition, its presence in fruits and

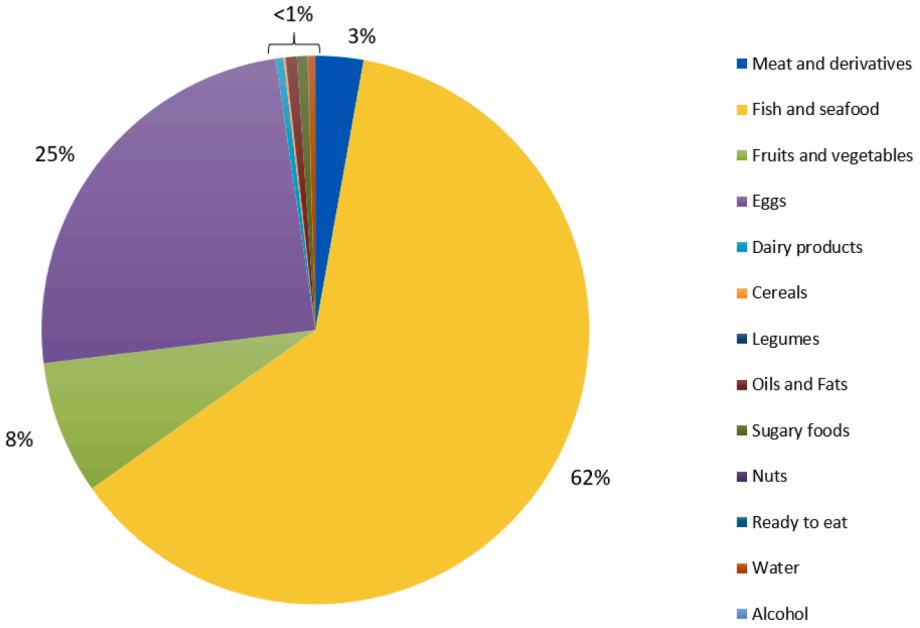

Fig. 2. Food groups contribution to the total dietary intake of PFOS.

Table 2
Cross-sectional baseline association between energy-adjusted dietary intake of PFOS and glucose-related parameters and body-mass-index.

	Energy-Adjusted dietary intake of PFOS across tertiles and in continuous with 1 SD increment in ng/d β coefficient (95 % CI)									
	LB					UB				
	T1	T2	T3	P-trend	Continuous with 1 SD increment	T1	T2	T3	P-trend	Continuous with 1 SD increment
Mean ± SD (ng/d)	17.62 ± 3.49	25.51 ± 1.94	35.21 ± 5.94			1104 ± 251	1738 ± 170	2552 ± 475		
Fasting plasma glucose (mg/dL) (n = 4,576)										
Model 1	**0 (ref)**	**1.15 (0.165 to 2.128)**	0.76 (-0.215 to 1.729)	0.079	0.18 (-0.206 to 0.576)	**0 (ref)**	0.94 (-0.037 to 1.924)	0.37 (-0.608 to 1.350)	0.531	0.12 (-0.276 to 0.520)
Model 2	**0 (ref)**	**1.20 (0.228 to 2.179)**	0.90 (-0.072 to 1.881)	**0.041**	0.25 (-0.146 to 0.639)	**0 (ref)**	**1.04 (0.065 to 2.02)**	0.53 (-0.453 to 1.516)	0.347	0.19 (-0.206 to 0.594)
Fully-adjusted	**0 (ref)**	**1.30 (0.316 to 2.289)**	**1.05 (0.050 to 2.046)**	**0.022**	0.29 (-0.107 to 0.693)	**0 (ref)**	**1.13 (0.143 to 2.128)**	0.67 (-0.341 to 1.685)	0.245	0.24 (-0.164 to 0.655)
Mean ± SD (ng/d)	17.53 ± 3.45	25.35 ± 1.91	35.01 ± 5.95			1096 ± 248	1721 ± 166	2531 ± 466		
HbA1c level (%) (n = 4,170)										
Model 1	**0 (ref)**	0.02 (-0.011 to 0.048)	0.03 (-0.000 to 0.057)	0.053	0.00 (-0.007 to 0.016)	**0 (ref)**	0.00 (-0.025 to 0.334)	**0.03 (0.000 to 0.059)**	**0.044**	**0.01 (-0.005 to 0.018)**
Model 2	**0 (ref)**	0.02 (-0.011 to 0.048)	**0.03 (0.005 to 0.063)**	**0.026**	0.01 (-0.004 to 0.019)	**0 (ref)**	0.00 (-0.025 to 0.033)	**0.04 (0.007 to 0.066)**	**0.013**	**0.01 (-0.002 to 0.022)**
Fully-adjusted	**0 (ref)**	0.03 (-0.001 to 0.058)	**0.05 (0.024 to 0.082)**	**0.001**	**0.01 (0.002 to 0.026)**	**0 (ref)**	0.01 (-0.013 to 0.045)	**0.06 (0.026 to 0.087)**	< **0.001**	**0.02 (0.006 to 0.030)**
Mean ± SD (ng/d)	17.59 ± 3.49	25.52 ± 1.94	35.26 ± 5.99			1102 ± 251	1737 ± 169	2553 ± 478		
Fasting plasma insulin (mmol/mol) (n = 4,351)										
Model 1	**0 (ref)**	0.49 (-0.243 to 1.219)	0.01 (-0.725 to 0.743)	0.948	−0.25 (-0.531 to 0.032)	**0 (ref)**	**0.97 (0.232 to 1.707)**	−0.01 (-0.724 to 0.702)	0.815	−0.22 (-0.498 to 0.049)
Model 2	**0 (ref)**	0.43 (-0.261 to 1.312)	0.12 (-0.573 to 0.824)	0.776	−0.23 (-0.501 to 0.039)	**0 (ref)**	0.93 (0.214 to 1.641)	0.14 (-0.546 to 0.829)	0.827	−0.19 (-0.456 to 0.077)
Fully-adjusted	**0 (ref)**	0.62 (-0.068 to 1.315)	0.48 (-0.222 to 1.186)	0.208	−0.02 (-0.099 to 0.058)	**0 (ref)**	1.15 (0.431 to 1.876)	0.52 (-0.182 to 1.217)	0.222	−0.05 (-0.324 to 0.216)

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Table 2 (*continued*)

	Energy-Adjusted dietary intake of PFOS across tertiles and in continuous with 1 SD increment in ng/d β coefficient (95 % CI)									
	LB					UB				
	T1	T2	T3	P-trend	Continuous with 1 SD increment	T1	T2	T3	P-trend	Continuous with 1 SD increment
Mean ± SD (ng/d)	17.59 ± 3.49	25.52 ± 1.94	35.26 ± 5.99			1102 ± 251	1737 ± 169	2553 ± 478		
HOMA-IR (n = 4,351)										
Model 1	**0 (ref)**	0.17 (-0.054 to 0.395)	0.02 (-0.205 to 0.238)	0.965	−0.07 (-0.149 to 0.017)	**0 (ref)**	**0.30 (0.073 to 0.529)**	−0.00 (-0.213 to 0.205)	0.798	0.06 (-0.139 to 0.022)
Model 2	**0 (ref)**	0.16 (-0.049 to 0.378)	0.07 (-0.139 to 0.274)	0.578	−0.05 (-0.131 to 0.027)	**0 (ref)**	0.30 (0.076 to 0.527)	0.05 (-0.150 to 0.258)	0.713	–0.04 (-0.117 to 0.040)
Fully-adjusted	**0 (ref)**	**0.21 (0.003 to 0.423)**	0.16 (-0.045 to 0.365)	0.166	−0.10 (-0.373 to 0.170)	**0 (ref)**	0.04 (0.130 to 0.591)	0.15 (-0.054 to 0.359)	0.229	−0.01 (-0.086 to 0.074)
Mean ± SD (ng/d)	17.63 ± 3.50	25.52 ± 1.94	35.22 ± 5.93			1105 ± 252	1739 ± 170	2553 ± 474		
BMI (kg/m^2) * (n = 4,600)										
Model 1	**0 (ref)**	0.05 (-0.194 to 0.288)	−0.07 (-0.316 to 0.169)	0.522	0.00 (-0.099 to 0.101)	**0 (ref)**	−0.02 (0.265 to 0.219)	−0.13 (-0.375 to 0.111)	0.275	−0.03 (-0.132 to 0.070)
Model 2	**0 (ref)**	0.07 (-0.172 to 0.305)	0.01 (-0.232 to 0.252)	0.960	0.04 (-0.058 to 0.143)	**0 (ref)**	0.00 (-0.239 to 0.244)	−0.04 (-0.287 to 0.199)	0.714	0.01 (-0.089 to 0.114)
Fully-adjusted	**0 (ref)**	0.13 (-0.111 to 0.370)	0.12 (-0.131 to 0.364)	0.381	0.08 (-0.017 to 0.188)	**0 (ref)**	0.07 (-0.175 to 0.313)	0.06 (-0.184 to 0.313)	0.631	0.06 (-0.044 to 0.163)

Abbreviations: PFOS: Perfluorooctanesulfonic acid; CI: confidence interval; HbA1c: hemoglobin A1c; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; LB: lower bound of energy-Adjusted dietary intake of PFOS; UB: upper bound of energy-Adjusted dietary intake of PFOS; BMI: body mass index; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance.
Linear regression models were fitted to assess the β-coefficients and its 95 % CI for glycemic index parameters across energy-adjusted total dietary PFOS intake and with 1 SD increment in ng/d. Model 1 adjusted for age and sex. Model 2: model 1 additionally adjusted for physical activity (MET min/week), marital status (single, married, widowed), smoking status (current, former, never), education level (up to primary, secondary, university) and the size of the recruitment center (<250, 250 to < 300, 300 to < 400, ≥400 and BMI (kg/m^2). Model 3: model 2 additionally adjusted for adherence to Mediterranean diet MEDAS score (0–17 points) and family history of cardiovascular diseases. All analyses were conducted with robust estimates of the variance to correct for intra-cluster correlation.

* Excluding BMI (kg/m^2) as a confounder in the models.

Table 3
Prospective association between baseline energy-adjusted dietary intake of PFOS and changes in glucose-related parameters and body-mass-index changes.

Energy-Adjusted dietary intake of PFOS across tertiles and in continuous with 1 SD increment in ng/d β coefficient (95 % CI)										
	LB					UB				
	T1	T2	T3	P-trend	Continuous with 1 SD increment	T1	T2	T3	P-trend	Continuous with 1 SD increment
Mean ± SD (ng/d)	17.7 ± 3.45	25.6 ± 1.95	35.1 ± 5.82			1109 ± 248	1741 ± 170	2546 ± 471		
Fasting plasma glucose changes (mg/dL) (n = 4,009)										
Model 1	**0 (ref)**	−0.27 (-1.209 to 0.669)	−0.54 (-1.480 to 0.391)	0.254	−0.17 (-0.551 to 0.200)	**0 (ref)**	−0.24 (-1.181 to 0.700)	−0.12 (-1.063 to 0.814)	0.815	−0.12 (-0.494 to 0.249)
Model 2	**0 (ref)**	−0.32 (-1.269 to 0.620)	−0.30 (-1.543 to 0.336)	0.209	−0.19 (-0.564 to 0.189)	**0 (ref)**	−0.32 (-1.263 to 0.625)	0.20 (-1.145 to 0.734)	0.692	−0.15 (-0.522 to 0.222)
Fully-adjusted	**0 (ref)**	0.02 (-0.841 to 0.881)	−0.21 (-1.075 to 0.662)	0.627	−0.08 (-0.431 to 0.260)	**0 (ref)**	−0.07 (-0.925 to 0.792)	0.05 (-0.812 to 0.915)	0.893	−0.07 (-0.412 to 0.268)
Mean ± SD (ng/d)	17.6 ± 3.39	25.4 ± 1.91	34.8 ± 5.82			**1101** ± 246	1724 ± 165	2517 ± 457		
HbA1c level changes (%) (n = 3,450)										
Model 1	**0 (ref)**	−0.01 (-0.032 to 0.018)	−0.02 (-0.045 to 0.006)	0.128	−0.00 (-0.015 to 0.007)	**0 (ref)**	−0.01 (-0.033 to 0.017)	−0.02 (-0.048 to 0.004)	0.095	−0.01 (-0.018 to 0.004)
Model 2	**0 (ref)**	−0.00 (-0.031 to 0.019)	−0.02 (-0.047 to 0.005)	0.113	−0.00 (-0.016 to 0.007)	**0 (ref)**	−0.01 (-0.032 to 0.018)	−0.02 (-0.049 to 0.003)	0.076	−0.01 (-0.019 to 0.004)
Fully-adjusted	**0 (ref)**	−0.00 (-0.027 to 0.019)	−0.01 (-0.039 to 0.010)	0.243	−0.00 (-0.015 to 0.007)	**0 (ref)**	−0.01 (-0.033 to 0.013)	−0.02 (-0.042 to 0.009)	0.200	−0.01 (-0.018 to 0.004)
Mean ± SD (ng/d)	17.7 ± 3.44	25.6 ± 1.95	35.1 ± 5.84			1109 ± 248	1744 ± 169	2547 ± 472		
Fasting plasma insulin levels changes (mmol/mol) (n = 3,708)										
Model 1	**0 (ref)**	−0.27 (-0.943 to 0.402)	0.33 (-0.559 to 1.218)	0.439	0.18 (-0.119 to 0.489)	**0 (ref)**	−0.55 (-1.217 to 0.119)	0.58 (-0.312 to 1.474)	0.168	0.27 (-0.037 to 0.583)
Model 2	**0 (ref)**	−0.26 (-0.944 to 0.414)	0.32 (-0.560 to 1.209)	0.445	0.18 (-0.118 to 0.489)	**0 (ref)**	−0.54 (-1.216 to 0.139)	0.60 (-0.315 to 1.518)	0.166	0.28 (-0.034 to 0.596)
Fully-adjusted	**0 (ref)**	−0.18 (-0.782 to 0.422)	0.37 (-0.419 to 1.152)	0.335	0.08 (-0.194 to 0.361)	**0 (ref)**	−0.29 (-0.926 to 0.346)	0.67 (-0.137 to 1.478)	0.086	0.19 (-0.105 to 0.479)

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Table 3 (*continued*)

Energy-Adjusted dietary intake of PFOS across tertiles and in continuous with 1 SD increment in ng/d β coefficient (95 % CI)										
	LB					**UB**				
	T1	**T2**	**T3**	**P-trend**	**Continuous with 1 SD increment**	**T1**	**T2**	**T3**	**P-trend**	**Continuous with 1 SD increment**
Mean ± SD (ng/d)	17.7 ± 3.43	25.6 ± 1.95	35.1 ± 5.82			1109 ± 246	1741 ± 169	2547 ± 470		
HOMA-IR changes (n = 3,906)										
Model 1	**0 (ref)**	−0.00 (-0.041 to 0.037)	0.03 (-0.009 to 0.065)	0.102	0.01 (-0.008 to 0.023)	**0 (ref)**	−0.55 (-1.217 to 0.119)	0.58 (-0.312 to 1.474)	**0.029**	0.01 (-0.005 to 0.025)
Model 2	**0 (ref)**	0.00 (-0.038 to 0.041)	0.02 (-0.013 to 0.062)	0.182	0.00 (-0.011 to 0.020)	**0 (ref)**	0.02 (-0.014 to 0.060)	0.04 (-0.001 to 0.080)	0.058	0.01 (-0.009 to 0.022)
Fully-adjusted	**0 (ref)**	0.00 (-0.039 to 0.040)	0.03 (-0.007 to 0.069)	0.101	0.01 (-0.007 to 0.024)	**0 (ref)**	0.03 (-0.010 to 0.069)	**0.06 (0.016 to 0.097)**	**0.005**	0.01 (-0.001 to 0.030)
Mean ± SD (ng/d)	17.7 ± 3.43	25.6 ± 1.95	35.1 ± 5.78			1116 ± 247	1748 ± 171	2552 ± 468		
BMI changes (kg/m^2) * (n = 4,093)										
Model 1	**0 (ref)**	0.01 (-0.106 to 0.136)	**0.13 (0.008 to 0.249)**	**0.033**	**0.07 (0.026 to 0.123)**	**0 (ref)**	−0.02 (-0.146 to 0.098)	0.08 (-0.035 to 0.205)	0.877	0.06 (0.010 to 0.111)
Model 2	**0 (ref)**	0.03 (-0.089 to 0.152)	**0.14 (0.021 to 0.262)**	**0.019**	**0.08 (0.030 to 0.127)**	**0 (ref)**	0.00 (-0.119 to 0.124)	0.10 (-0.019 to 0.220)	0.802	**0.06 (0.015 to 0.115)**
Fully-adjusted	**0 (ref)**	−0.05 (-0.162 to 0.061)	0.09 (-0.029 to 0.202)	0.117	**0.06 (0.014 to 0.106)**	**0 (ref)**	−0.08 (-0.193 to 0.033)	0.06 (-0.057 to 0.174)	0.230	0.05 (-0.001 to 0.094)

Abbreviations: PFOS: Perfluorooctanesulfonic acid; CI: confidence interval; HbA1c: hemoglobin A1c; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; LB: lower bound of energy-Adjusted dietary intake of PFOS; UB: upper bound of energy-Adjusted dietary intake of PFOS; BMI: body mass index; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance.
Linear regression models were fitted to assess the β-coefficients and its 95 % CI for glycemic index parameters across energy-adjusted total dietary PFOS intake and with 1 SD increment in ng/d. Model 1 adjusted for age and sex. Model 2: model 1 additionally adjusted for physical activity (MET min/week), marital status (single, married, widowed), smoking status (current, former, never), education level (up to primary, secondary, university) and the size of the recruitment center (<250, 250 to < 300, 300 to < 400, ≥400 and BMI (kg/m^2). Model 3: model 2 additionally adjusted for adherence to Mediterranean diet MEDAS score (0–17 points), family history of cardiovascular diseases, intervention group, each outcome at baseline and oral diabetes medications. All analyses were conducted with robust estimates of the variance to correct for intra-cluster correlation.

vegetables is due to the widespread contamination of soil and surface water which reach and can be stored in these food items (Bizkarguenaga et al., 2016; Domingo et al., 2012). Nevertheless, it is important to note that the significant contributors identified in this study may vary in other cohorts due to differences in lifestyle and dietary patterns.

Our results are in line with previous published papers, which assessed these chemicals in biological samples (serum and plasma). In Chinese adults an increase in serum PFOS was recently correlated with an increase in fasting plasma glucose, fasting plasma insulin and HOMA-IR (Zeeshan et al., 2021). In individuals at high risk of diabetes, cross-sectional positive associations were reported between plasma concentration of PFOS and different glucose-related measurements such as fasting glucose and insulin, HbA1C and HOMA-IR (Cardenas et al., 2017). Finally, a study conducted in adolescents and adults showed that PFOS concentrations levels increased HOMA-IR and beta-cell function (Lin et al., 2009).

The mechanisms explaining these associations are largely unknown. Limited studies suggest a potential effect of these EDs on pancreatic cells. For example, Qin et al., 2022 using *in vivo* and *in vitro* models found that PFOS exposure may disrupt calcium homeostasis and signaling within beta cells leading to an inability to secrete insulin in response to increased blood glucose levels (Qin et al., 2022). Therefore, based on the evidence of these seminal results more prospective and mechanistic studies to assess the specific effect of these chemicals on human health are needed.

As well as in other studies, in the current study an association between DI of PFOS and BMI was also found after 1-year of follow-up. In young adults, a positive association between serum PFOS and overweight was reported in individuals aged between 9 and 21 years old (Domazet et al., 2016). Furthermore, in a study involving 1612 Chinese adults, a positive association between blood PFOS concentration and a higher rate of overweight in women (Tian et al., 2019) was reported. Nelson et al., 2010 also found in men aged 60–80 years a positive association between PFOS exposure and BMI (Nelson et al., 2010).

The most updated tolerable weekly intake (TWI) of PFAS established by the EFSA in 2020 is 4.4 ng/kg of body weight/week (EFSA, 2020). In our study, the mean LB dietary exposure of the cohort was 2.17 ng/kg body weight/week, being this mean below the reference value. This result is in concordance with other Spanish and European populations such as from France, Belgium and Italy (Rovira et al., 2019; Cornelis et al., 2012; Yamada et al., 2014; Klenow et al., 2013). Even though PFOS is the largest contributor to the total dietary PFAS exposure (Barbo et al., 2023; Olsen et al., 2007; EFSA, 2020), our dietary exposure results could be slightly underestimated because other PFAS were not taken into consideration to perform the current the dietary exposure. Nevertheless, even with this current estimation obtained here, we saw a significant positive association between baseline higher DI of PFOS and fasting plasma glucose, HbA1c levels, HOMA-IR and BMI after 1-year of follow-up. Considering our results, the TWI of these perfluoralkyl compounds may have to be re-evaluated by the EFSA to get a more updated approach than the one from 2020.

Our study has several limitations that need to be mentioned. These findings cannot be applied to other subjects because the participants included in this analysis were senior individuals from the Mediterranean region who had overweight/obesity and metabolic syndrome. It's important to acknowledge that the use of a FFQ to evaluate food intake has certain limitations due to the possibility of measurement errors and it was not specifically designed and validated to assess to dietary exposure to PFOS. Nonetheless, despite this drawback, FFQs have been extensively employed as an epidemiological tool since the 1990 s (Shim et al., 2014). Furthermore, while PFOS constitutes the primary contributor to overall dietary PFAS exposure, it is worth noting that our assessment of dietary intake might be slightly underestimated. This is attributed to the fact that the current dietary intake assessment did not include other PFAS compounds in its calculations. In addition, it is important to note that this study exclusively examined exposure to PFOS through dietary sources and the concentrations were taken from available data and did not take into account other exposures such as inhalation or dermal contact or biological samples. However, it is worth mentioning that as before commented the major source of exposure to these chemicals is primarily through the diet and water.

To conclude, this is the first study to our knowledge that explores the association between DI of PFOS and glucose homeostasis. We found that in an adult Mediterranean population at high cardiovascular risk, high baseline DI of PFOS was associated with a higher levels of fasting plasma glucose and HbA1c and with an increase in HOMA-IR and BMI after 1-year of follow-up. These findings support the growing body of evidence linking the potential effect of PFOS intake on glucose homeostasis and insulin regulation. However, recognizing the broader PFAS categories and all different congeners is crucial for comprehensive evaluations of the overall impact of PFAS on human health, for this reason, the association remains complex and further large prospective studies using different population are necessary to warrant our results.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2024.108565.

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