Longitudinal changes in Mediterranean diet and transition between different obesity phenotypes

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ABSTRACT

Background & Aims: Little is known about the impact of specific dietary patterns on the development of obesity phenotypes. We aimed to determine the association of longitudinal changes in adherence to the traditional Mediterranean diet (MedDiet) with the transition between different obesity phenotypes.

Methods: Data of 5,801 older men and women at high cardiovascular risk from PREDIMED trial were used. Adherence to MedDiet was measured with the validated 14p-Mediterranean Diet Adherence Screener (MEDAS). Using the simultaneous combination of metabolic health- and body size-related parameters participants were categorized into one of four phenotypes: metabolically healthy and abnormal obese (MHO and MAO), metabolically healthy and abnormal non-obese (MHNO and MANO). Cox regression models with yearly repeated measures during 5-year of follow-up were built with use of Markov chain assumption.

Results: Each 2-point increase in MEDAS was associated with the following transitions: in MAO participants, with a 16% (95% CI 3-31%) greater likelihood of becoming MHO; in MHO participants with a 14% (3-23%) lower risk of becoming MAO; in MHNO participants with a 18% (5-30%) lower risk of becoming MHO. In MANO women, but not in men, MEDAS was associated with 20% (5-38%) greater likely of becoming MHNO (*p* for interaction by gender 0.014). No other significant associations were observed.

Conclusions: Better adherence to the traditional MedDiet is associated with transitions to healthier phenotypes, promoting metabolic health improvement in MAO, MANO (only in women), and MHO, as well as protecting against obesity incidence in MHNO subjects.

Keywords: Mediterranean diet; obesity phenotypes; transition probabilities; metabolically healthy obese; metabolically abnormal non-obese; the PREDIMED trial

Introduction

Undoubtedly, the overspread obesity epidemic is a life-threatening phenomenon of the XXI century. However, obesity is not a homogeneous condition, hence metabolic abnormalities and chronic disease risk may vary among obese subjects [1].

In this regard, different obesity phenotypes have been described recently. Among them, the metabolically healthy obese (MHO) phenotype has attracted much attention [1–3]. Despite excessive body size, MHO subjects have a better adipose tissue function, less ectopic fat storage, and are more insulin sensitive than metabolically abnormal obese (MAO) subjects [2]. Nevertheless, the effect of being MHO on health outcomes remains controversial, as MHO phenotype has also been associated with increased mortality, cardiovascular disease (CVD), type 2 diabetes (T2D), and lower quality of life than a lean phenotype [2,4]. Moreover, some recent studies evidenced that MHO phenotype is a transient state, in which one- to two-thirds of subjects tends to deteriorate toward MAO phenotype over time [5,6]. Conversely, there is a subset of non-obese subjects who show an abnormal metabolic profile – the concept of metabolically abnormal non-obese (MANO) phenotype – and consequently are also at increased cardiovascular and diabetes risk, when compared to metabolically healthy subjects [3,7]. Therefore, metabolic and body size phenotyping might be crucial to identify at risk subjects, and to optimize prevention and treatment strategies.

Until now, prevalence, nature, determinants and clinical implications of obesity phenotypes has been mainly studied, but the effect of lifestyle targeting transition from one to other phenotype has received less attention. Among limited number of studies that addressed this issue, many were only focused on MHO and MAO phenotypes [8–13], investigated short-term study period [8–11], used small sample size [8,9,11] or were cross-sectional comparisons of lifestyle factors among phenotypes [12,13]. It is hence unclear whether specific dietary factors would influence the evolution or transition between obesity phenotypes.

The Mediterranean Diet (MedDiet) has been associated with less weight gain [14–17], obesity prevention [14,18], reversion or lower incidence of the metabolic syndrome (MetS) [19,20], and reduction in the risk of developing cardiometabolic diseases such as T2D and CVD [21–23]. At such, the MedDiet has been proposed as a promising lifestyle factor to allow the transition to healthier obesity phenotypes, and reduction of long-term health risk [24].

Therefore, the aim of the present study was to evaluate the long-term association of changes in adherence to a traditional MedDiet with the possibility to transition between different obesity phenotypes defined jointly according to body size and metabolic health status, in men and women at high cardiovascular risk from the PREDIMED trial.

Methods

Design overview and participants

The present study was conducted within the framework of the PREDIMED study over the first 5-years of follow-up. Details on the study design have been previously described [22,25] and are on the website http://www.predimed.es/. Briefly, PREDIMED was a multicenter, randomized, controlled, CVD primary prevention trial, conducted in Spain during 2003-2010, which compared three dietary interventions: MedDiet supplemented with extra-virgin olive oil or nuts and a control low-fat diet. Men aged 55-80 yr and women aged 60-80 yr, free of CVD at enrolment, but at high CVD risk due to the presence of either T2D or at least three major risk factors, participated in the trial.

Of the total 7447 participants, those with no data available on the variables needed to determine obesity phenotypes, such as biochemical parameters at baseline and for at least 2 years of follow-up, were excluded from the analyses. Finally, a number of 5801 participants, 2437 (42%) men and 3364 (58%) women, was included in the present study. Selection of participants for analyses with the exclusion criteria is shown in **Supplementary Figure 1**.

The study protocol was approved by the institutional review boards of all recruiting centers according to the Declaration of Helsinki. The trial was registered at http://www.controlled-trials.com/ISRCTN35739639. Registration date: 5 October 2005.

Adherence to the Mediterranean diet

Adherence to the MedDiet was assessed with a 14-item Mediterranean diet adherence screener (MEDAS) (**Supplementary Table 1**), previously validated in adult Spanish population [26], repeatedly administered by trained dietitians at baseline and yearly during follow-up in a face-to-face interview. A value of 0 or 1 (not meeting or meeting the conditions) was recorded for each item. The final score ranged from 0 to 14; the higher the score, the better adherence to the MedDiet.

Anthropometric and biochemical parameters measurement

At baseline and at each annual visit, anthropometric parameters (body weight, height, waist circumference (WC)), systolic and diastolic blood pressure (SBP and DBP) were determined, and fasting blood samples were collected by trained staff. Body mass index (BMI) was calculated as weight (kg)/square of the height (m). Blood samples collected after overnight fast were used to determine fasting plasma glucose, HDL-cholesterol, and triglyceride concentrations with standard laboratory enzymatic methods.

Definition of obesity phenotypes

Obesity phenotype, as the outcome variable, was categorized into four groups based on body size (obesity presence/absence) and metabolic health status (MetS presence/absence). Obesity was defined according to the World Health Organization BMI classification as ≥ 30 kg/m^2 [27]. MetS was defined in accordance to the updated harmonized International Diabetes Federation and the American Heart Association/National Heart, Lung, and Blood Institute criteria [28]. The criteria for the MetS and cutoff points were as follows: abdominal obesity as a WC ≥ 102 cm (men) and ≥ 88 cm (women); fasting glucose ≥ 100 mg/dL (or drug treatment for elevated glucose), SBP ≥ 130 and/or DBP ≥ 85 mm Hg (or antihypertensive drug treatment); triglycerides ≥ 150 mg/dL (or drug treatment for elevated triglycerides); as well as HDL-cholesterol < 40 mg/dl (men) and < 50 mg/dl (women) (or drug treatment for reduced HDL-cholesterol).

According to these definitions, participants were classified as obese (BMI $\geqslant 30$ kg/m^2) or non-obese (BMI < 30 kg/m^2), and as metabolically healthy (0-2 of the criteria for MetS) or abnormal (≥ 3 of the criteria for MetS). Using the simultaneous combination of metabolic health and body size status participants were finally categorized into one of the four groups at baseline and yearly during follow-up as follows: MAO–metabolically abnormal obese, MHO–metabolically healthy obese, MANO–metabolically abnormal non-obese, and MHNO–metabolically healthy non-obese. Schematic illustration of obesity phenotypes definition is shown in **Figure 1**.

Moreover, due to the collinearity of BMI with WC, the variable obesity phenotype was re-calculated eliminating data on WC from the definition of MetS. In this case participants who met ≥ 2 of the criteria for MetS were considered metabolically abnormal.

Covariables assessment

A general medical questionnaire, a validated 137-item food-frequency questionnaire [29] and the Minnesota Leisure-Time Physical Activity Questionnaire [30] were administered on a yearly basis. Information from the food-frequency questionnaire was used to estimate intake of energy and nutrients (protein, carbohydrates, fat, types of fat, fibre and alcohol). For the present analyses, we used baseline data on age, sex, educational level (higher education/technician, secondary education, primary education/illiterate or missing data) and smoking status (never, current or former), as well as on nutrient intake. Furthermore, basal and yearly repeated measurements of total energy, alcohol intake, and physical activity were used as covariates in our models.

Statistical analyses

One-way analysis of variance (ANOVA) and chi-square tests (χ^2) (for continuous and categorical variables, respectively), followed by Bonferroni post-hoc test, were used to evaluate differences in baseline characteristics according to four groups of obesity phenotypes. Due to the concerns about sexual dimorphism, analyses were performed separately for men and women, and in the whole sample.

In order to study the natural course of four types of obesity phenotypes, we examined all transitions from any initial phenotype to any other one over the time period studied. Using basal and annual data on obesity phenotypes, we estimated unadjusted transition probabilities between MAO, MHO, MANO and MHNO states over follow-up time, overall, and in men and women separately.

The association of yearly repeated measurements of MEDAS across 5-year of follow-up (per 2-point increments) with the subsequent transition between the four types of obesity phenotypes was examined with use of Cox regression analyses. Firstly, we established the possible directions in which the transition can occur. For this we used Markov assumption, in which transition to the future states depends only on the current state, and transition movement happens only between proximate states [6].

Eight censored events used for Cox analysis were as follows: improvement in metabolic health in obese and non-obese participants (MAO → MHO, MANO → MHNO, respectively) and metabolic health deterioration in obese and non-obese participants (MHO → MAO, MHNO → MANO, respectively), obesity reversion in metabolically healthy and abnormal participants (MHO → MHNO, MAO → MANO, respectively) and obesity incidence in metabolically healthy and abnormal participants (MHNO → MHO, MANO → MAO, respectively). We considered only the first registered change in metabolic health status (MetS incidence/reversion) and body size (obesity incidence/reversion) for the analyses. Entry time was defined as the date at baseline; exit time was defined as the date of event (change in phenotype), last follow-up, death, or the date on which the participant was lost to follow-up, whichever occurred first.

Cox regression analyses were run separately for men and women, and in the whole sample. All models were stratified by recruiting center, sex (only for whole sample) and intervention group. A multivariable model was used after controlling for baseline age, educational level and smoking status, as well as yearly measured total energy intake, physical activity, and alcohol consumption.

We took into account departures from the randomization protocol, reported elsewhere [22]. Briefly, some participants (14%) were not individually allocated, but they were allocated in small clusters (defined as members of the same household, or members of the same small clinics). We used a robust variance estimator to account for intra-cluster correlations.

Moreover, plausible effect modifications by sex, age, diabetes status, and intervention group were assessed including an interactions term between MEDAS and these factors in the multivariable model, and subgroup analyses were conducted to explore consistency of the associations found across selected subsets of participants. For this, analyses were repeated for each subgroup separately according to sex, baseline diabetes status, age at enrollment (< 70 yr or ≥70 yr), and intervention group (combined MedDiets, control diet). The latter analysis across intervention and control groups was also adjusted for propensity scores (built with 30 baseline covariables) to control for minor (not clinically significant) imbalances in baseline covariables.

Finally, sensitivity analyses were conducted to test the robustness of the results: (1) adjusting only for age in a minimally adjusted model; (2) adjusting for yearly repeated measure of body weight, when studying transitions based on metabolic health status in obese and non-obese patients (MAO ↔ MHO, MANO ↔ MHNO); (3) excluding participants who developed CVD (myocardial infarction or stroke) or who died due to a cardiovascular disease during follow-up; (4) excluding WC from the definition of MetS, because of collinearity with BMI; (5) applying the last observation carried forward (LOCF) method to estimate the missing values in some variables (transition between different phenotypes, 14-p MEDAS, total energy intake, physical activity, and alcohol consumption) up to 5 years follow-up. The estimated values were imputed until event (change in phenotype), last follow-up, death, or the date on which the participant was lost to follow-up, whichever occurred first.

Statistical analyses were performed using Stata v15.0 program, with statistical significances set at $p < 0.05$.

Results

Characteristics of study participants according to baseline obesity phenotypes by sex are presented in **Table 1**. Overall, women were older, less physically active and less educated, consumed fewer total calories, and showed fewer smoking and drinking habits than men. Compared to men, a higher proportion of women had a MAO phenotype (40% of women versus 33% of men), whereas a higher proportion of men had a MHNO phenotype (33% of men versus 21% of women). The other two phenotypes (MHO: 8% of men and 12% of women; and MANO: 26% of men and 27% of women) were evenly distributed in both genders. As expected, metabolically abnormal men and women (MAO, MANO) were more likely to be diabetics compared to those who were metabolically healthy (MHO, MHNO). In both men and women, those with healthier phenotypes showed higher physical activity, higher adherence to the MedDiet, and lower saturated fats intake. Some associations were different in men and women. Women with MANO phenotype were significantly older than women with MHNO. Women with healthier phenotypes drank more alcohol, were smokers, and were more educated. Men with healthier phenotypes had a higher fibre intake. The higher proportion of smokers was observed in men with the MANO phenotype. Unhealthy phenotypes, due to metabolic health and/or body size status (MAO, MANO, MHO), were less educated, physically active, and had lower adherence to MedDiet, consumed more calories from saturated fats but less alcohol than MHNO subjects. The association between obesity phenotypes and sample characteristics in men and women combined can be found in **Supplementary Table 1**. Low compliance with MedDiet was primarily driven by lower consumption of nuts (**Supplementary Table 2**).

Figure 2 shows the probabilities to remain or change to another phenotype for each phenotype over the follow-up period. For an example 84.5% of MAO individuals at baseline will remain in this state over the 5-year period, 8% will transit to MANO, 6% to MHO, and only 1.55% to MHNO phenotype. To sum up, MAO phenotype showed the highest probability (85%) to remain in the initial phenotype over the 5-year period, followed by MHNO (75%), and MANO (73%). In turn, the highest probability (43%) to transition to another phenotype was observed among participants with MHO initial phenotype, who were more likely to become MAO (MHO → MAO, 31%), than any other phenotypes. Participants from non-obese phenotypes showed very low probability to transition to any obese phenotype, as MAO (an average 6%) or MHO (an average 2%). The observed transition patterns between obesity phenotypes were similar over 1 and 3 years of follow-up time (**Supplementary Table 3**). Transition probabilities in men and women separately are observed in **Supplementary Figure 2.** Overall men and women showed similar transition probabilities. Of note, 77% of MANO women remained in the same state during follow-up compared to 68% of men.

Figure 3, shows the association between longitudinal changes in adherence to the MedDiet and transition between obesity phenotypes. MedDiet was associated with different health benefits in all obesity phenotypes, promoting metabolic health and protecting against obesity. Focusing on the metabolic health status, we observed that increase in adherence to MedDiet was associated with transition to healthier metabolic phenotypes in metabolically abnormal obese (MAO → MHO) and non-obese participants (MANO → MHNO). In MAO participants, each 2-point increase in MEDAS was associated with a 16% (95% CI 3-31%) greater likelihood of becoming MHO; the association was of similar magnitude in men and women. In MANO subjects, MEDAS was associated with 12% (1-23%) greater likelihood of becoming MHNO; however, when this association was analyzed in men and women separately, we observed that adherence to MedDiet was associated with increased possibility of transition to MHNO phenotype (HR 1.20, 95% CI 1.05-1.38, p=0.007) in MANO women only (p-value for interaction 0.014). Furthermore, we found that in MHO participants, each 2-point increase in MEDAS was associated with a 14% (3-23%) decreased risk of metabolic health deterioration, with similar associations in men and women. Regarding obesity incidence, in MHNO subjects, each 2-point increase in MEDAS was associated with a 18% (5-30%) lower risk of transition to MHO phenotype. The association was more pronounced and only significative in MHNO women (women: HR 0.72, 95% CI 0.59-0.89, p=0.002; men: HR 0.90, 95% CI 0.73-1.11, p=0.324), albeit the interaction was not statistically significant. All other plausible transitions were neither statistically significant in the overall sample, nor in each gender separately.

According to subgroup analyses (**Table 2)**, we found a statistically significant interaction by intervention group (*p*-value for interaction 0.014) in the association between adherence to MedDiet and transition to MANO phenotype in MHNO participants, but within each subgroup, associations were null. Some other associations across subgroups with MEDAS were found, as in case of greater metabolic improvement in younger participants (<70 years), albeit the interactions were not statistically significant.

The observed associations did not change after performing sensitivity analyses (**Table 3**).

Discussion

Our analyses revealed that increase in adherence to MedDiet has a potential to exert differential health benefits for all four obesity phenotypes, promoting metabolic health improvement in MAO and MANO older men and women at high CVD risk, as well as protecting against metabolic health deterioration in MHO and obesity incidence in MHNO subjects. To best of our knowledge, this study is the first to examine the long-term association of traditional MedDiet with transition between four different obesity phenotypes.

The MAO or "at risk obese" with MetS represents the most severe phenotype regarding health outcomes and unfavourable natural course manifesting relative stability in that state over time [31]. We also confirmed these findings in our population, as the predicted transition probabilities over time showed the highest likelihood (85%) to remain in the initial state for MAO participants. Therefore, the development of strategies enabling the conversion from MAO into MHO might be of particular interest to lower the cardiometabolic risk in these subjects, although it might not completely eliminate the long term adverse health outcomes [24]. In this study, we found that MedDiet was associated with improvement in the metabolic health of MAO subjects, allowing their transition to MHO phenotype, and we have previously reported that PREDIMED intervention with MedDiets was able to significantly counteract the well-known adverse cardiovascular effects of adiposity [32]. Other studies have also shown that short-term lifestyle interventions, including intervention programme with physical activity and/or diet modification [9,11], and MedDiet counselling combined with vigorous training [8], were able to improve cardiometabolic risk parameters in MAO subjects. However, these studies did not evaluate specifically conversion from MAO into MHO.

Whether the concept of "healthy obesity" exists is still a topic of debate given contradictory findings regarding future morbidity and mortality. MHO phenotype is also a relatively unstable state. As shown in other studies, substantial proportion of MHO subjects become MAO over time [5,6], and the predicted probability of transition in our population was of 31%. Thus, it would be of interest to increase stability in healthy obesity over time. In our study we demonstrate that adherence to the MedDiet has a potential to prevent transition from MHO to MAO phenotype in men and women over 5 years of follow-up. The probability of transition was found similar in the magnitude for both sexes, although reached statistical significance only in women; potentially due to difference in the sample size between men and women. Previous intervention studies have addressed the effect of weight loss on the metabolic health in MHO subjects, yielding contradictory results. Some [10], but not all [8,11] studies reported that weight loss among MHO individuals paradoxically increased health risk by deteriorating their cadiometabolic status. Therefore, future studies are warranted to investigate the best approach to tackle obesity in those that are metabolically healthy.

Metabolically abnormal subjects within the non-obese population – a MANO phenotype – might constitute one of the most detrimental type among obesity phenotypes, due to an unfavourable health profile and even greater all-cause mortality than MHO subjects [33]. Despite this poor prognosis, Ruderman and colleagues suggested that individuals within this phenotype might be very responsive to dietary and lifestyle interventions, which could reduce their risk of cardiometabolic complications [34]. Other observational studies addressing the stability of the MANO phenotype also report on the substantial possibility of MANO individuals to transition to healthy non-obese state over time [6,31]. However, until now, specialized preventive and treatment strategies specific for MANO have not been developed. In this regard, findings from our study might be noteworthy, as we evidenced that long-term compliance with MedDiet in MANO individuals led to MetS reversion, particularly in women. The reason for this sex differences in the transition from MANO to MHNO is uncertain, but might be attributed to a different distribution of specific risk factors contributing to the MetS in MANO men and women, that may respond differently to MedDiet. For instance, MANO men showed the highest proportion of smokers, and this sub-group may be less responsive to changes in diet. On the other hand MANO men were slightly less likely to remain in their initial state compared to women; whether this greater fluidity across phenotypes reflect the younger age of men, or indicate that other factors beyond diet maybe more relevant for MANO men, is not known. Another explanation could be that, even though women were less educated and less physically active, they showed healthier lifestyle habits than men, and hence potentially could better comply with MedDiet and transit easier to healthier phenotypes. Future research should be conducted to deepen our understanding of these potential gender dimorphisms on the association between diet and obesity phenotypes.

The beneficial role of MedDiet, without an energy restriction and physical activity, in the reduction of body weight or weight gain has been evidenced previously in both prospective cohort studies [15,18] and interventional trials [16,17]. In the present study, we made a step forward evaluating association between traditional MedDiet and body size-related transitions in metabolically healthy and abnormal phenotypes. Interestingly, we observed that the adherence to MedDiet might be a useful tool to reduce the risk for obesity incidence in non-obese participants without MetS, but not in those with MetS. It could be that in case of MANO, better adherence to MedDiet might protect against obesity incidence in a two-step way, with a priori transition from MANO to MHNO phenotype. Furthermore, we found no association between a non-energy restricted MedDiet and obesity reversion either in MAO or in MHO phenotypes. Similarly, in the EPIC-Italy [15] and EPIC-PANACEA [14] studies, the relationship between MedDiet and less weight gain was present in persons of normal weight at baseline, but was not evident in those who were obese. It could well indicate that for weight loss in the obese, MedDiet alone is not sufficient, and it should be accompanied of energy restriction and/or increase of physical activity.

Our study has several strengths including large sample size of men and women, wide phenotypic spectrum (not only MAO and MHO), long-term follow-up during which data were collected yearly, the use of standardized protocols for the measurements of obesity and metabolic features, the exploration of different transitions potentiality with Markov chain assumption, the assessment of traditional MedDiet, with no energy-restrictions, additional supplementation or physical activity program, as well as the control for potential covariables and the inclusion of sensitivity analyses.

As far as the limitations are concerned, our study is based on the exploratory endpoints within PREDIMED framework. Although adherence to the MedDiet was assessed with use of previously validated questionnaire [26], the self-reporting method may always lead to measurement errors. However, data on diet were collected yearly to capture changes in adherence over 5 years, improving the validity of estimations; and a dietitian checked the questionnaire with the participant to ensure that there were no missing data. Furthermore, the cohort included elderly participants at high CVD risk from Mediterranean area, limiting the possibility to generalize our findings to other populations (younger, leaner, healthier, from other geographical areas). We classified participants as non-obese (BMI < 30 kg/m^2), including in this subgroup a great proportion of overweight participants (MANO, 91%; MHNO 81%). Moreover, we considered as metabolically healthy those participants who showed up to 2 components for MetS and those who, according to PREDIMED recruitment criteria, could present the burden of other features for CVD, such as family history of premature coronary heart disease or smoking history.

All in all, results from this study point out that increments in adherence to a traditional MedDiet is associated with differential transitions to healthier phenotypes, promoting metabolic health improvement in the phenotypes MAO and MANO, the latter in women only), as well as protecting against metabolic health deterioration in MHO and obesity incidence in MHNO subjects. Despite great interest in obesity phenotypes, existing guidelines do not provide indications regarding proper diagnosis and management of metabolically abnormal or healthy obese subjects, or those without excess weight but with unfavourable metabolic features. This study supports the relevance of the combined metabolic and body size phenotyping to improve early detection of subgroups at higher health risk. Moreover, our findings suggest that promotion of the MedDiet is a dietary strategy for preventing or treatment of obesity or MetS. These results add to the bulk of literature showing that the MedDiet is a sustainable and effective dietary pattern for the promotion of overall health, as reflected by the inclusion of this dietary pattern in relevant dietary guidelines worldwide. For future analysis, the important question remains to determine whether the transitions to healthier phenotypes associated with MedDiet may predict reduced cardiometabolic morbidity and mortality in those subjects.

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Statement of Authorship

K.J. and R.D. conceived this study and wrote the article. K.J., Y.A., M.M., B.N., T.E., M-G.MA., S.JV., S-S.J., E.R., R.E., A-G. A., S.H., L.J., S-M.Ll., P.X., G-B.M., D-L.A., G.JI, F.M., F.L., F.M., and R.D designed and conducted the project, and obtained the data. K.J., Y.A., B.N., T.E., and R.D. analyzed the data. All authors revised the manuscript for important intellectual content and read and approved the final manuscript. K.J. and R.D. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of Interest Statement

S-S.J. reports outside the submitted work serving on the board of and receiving grant support through his institution from the International Nut and Dried Fruit Council, and Eroski Foundation. Reports serving in the Executive Committee of the Instituto Danone Spain. Has received research support from California Walnut Commission, Sacramento CA, USA; Patrimonio Comunal Olivarero, Spain; La Morella Nuts, Spain; and Borges S.A., Spain. Reports receiving consulting fees or travel expenses from Danone; California Walnut Commission, Eroski Foundation, Nuts for Life, Australian Nut Industry Council, Nestlé, and Abbot Laboratories. E.R. reports outside the submitted work: grants, personal fees, non-financial support and other from California Walnut Commission; personal fees and non-financial support from Merck, Sharp & Dohme; grants, personal fees, non-financial support and other from Alexion; personal fees, non-financial support and other from Aegerion; grants and personal fees from Sanofi Aventis; personal fees, non-financial support and other from Ferrer International; grants from Amgen; grants from Pfizer; personal fees from Akcea; personal fees, non-financial support and other from Danone. K.J., Y.A., M.M., B.N., T.E., M-G.M.A., S.J.V., E.R., A-G.A.M., S.H., L.J., S-M.L., P.X., G-B.M., D-L.A., G.J.I., F.M., F.L., F.M., and R.D. declare no potential conflicts of interest.

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Figures and Legends

Figure 1. Schematic illustration of obesity phenotypes definition.

Abbreviations: BMI – body mass index; MetS – metabolic syndrome

Figure 2. Transition probabilities from MAO, MHO, MANO and MHNO over follow-up time in the whole study population.

Y axis shows transition probabilities and X axis indicates the baseline phenotypes. Each bar represents the sum of unadjusted transition probabilities from each baseline phenotype to any other one over the 5 years of follow-up on a scale of 0-100%.

Abbreviations: MAO – metabolically abnormal obese, MHO – metabolically healthy obese, MANO – metabolically abnormal non-obese, MHNO – metabolically healthy non-obese.

Figure 3. Relationship between longitudinal changes in adherence to the Mediterranean diet and transition between obesity phenotypes in men, women, and in the whole sample. Hazard ratios (95% CIs) of transitions between obesity phenotypes based on change in metabolic health status (MetS incidence/reversion) (a) and change in body size (obesity incidence/reversion) (b), calculated using Cox regression analyses with yearly repeated measures of 14-p MEDAS during 5 years of follow-up. Multivariable model adjusted for baseline age, smoking status and educational level, as well as yearly repeated measures of total energy intake, physical activity, and alcohol consumption was used for all analyses after stratification by recruitment center, sex (in case of whole sample) and intervention group. Robust standard errors to account for intracluster correlations were used.

Abbreviations: MAO – metabolically abnormal obese, MHO – metabolically healthy obese, MANO – metabolically abnormal non-obese, MHNO – metabolically healthy non-obese.

Supplementary material

Figure 1. Flow chart summarizing selection of the PREDIMED participants for obesity phenotypes analyses.

Table 1. Characteristics of the whole study population according to obesity phenotype at baseline.

Table 2. Quantitative (14-point) score of compliance with the Mediterranean Diet for the whole study population according to obesity phenotype at baseline.

Table 3. Transition probabilities from MAO, MHO, MANO and MHNO over 1, 3 and 5 years of follow-up time (a-c).

Figure 2. Transition probabilities from MAO, MHO, MANO and MHNO over follow-up time in men (a) and women (b).

Table 1. Characteristics of the study population by sex according to obesity phenotype at baseline.

a) Men n=2437 (42%)	**MAO n=797 (33%)**	**MHO n=196 (8%)**	**MANO n=638 (26%)**	**MHNO n=806 (33%)**	***p*-value**
Age (yrs)	65.5 (6.6)[a]	66.1 (6.3)[a,b]	66.4 (6.7)[b]	66.2 (6.4)[a,b]	0.051
Diabetes prevalence	481 (60%)[a]	40 (20%)[b]	412 (65%)[a]	343 (43%)[c]	<0.001
Physical activity (METs. min/day)	270 (281)[a]	295 (241)[a]	305 (318)[a]	366 (306)[b]	<0.001
MedDiet score (0 to 14 score)	8.56 (2.06)[a]	8.61 (2.09)[a,b]	8.70 (1.92)[a]	9.03 (1.96)[b]	<0.001
Total energy intake (kcal/day)	2495 (647)	2568 (619)	2483 (620)	2510 (605)	0.386
Protein (% of energy)	15.7 (2.6)	15.3 (2.3)	15.8 (2.7)	15.6 (2.7)	0.055
Carbohydrate (% of energy)	41.0 (7.8)	40.9 (7.4)	40.6 (7.5)	41.6 (7.4)	0.093
Fat (% of energy)	39.0 (6.9)	39.2 (6.7)	38.9 (7.2)	38.2 (7.0)	0.086
SFA (% of energy)	9.96 (2.14)[a]	9.86 (2.39)[a,b]	10.0 (2.3)[a]	9.58 (2.21)[b]	0.001
MUFA (% of energy)	19.5 (4.7)	19.7 (4.3)	19.4 (4.7)	19.1 (4.5)	0.135
PUFA (% of energy)	6.18 (2.07)	6.28 (2.05)	6.23 (2.03)	6.28 (1.98)	0.751
Alcohol (g/day)	15.8 (19.2)	17.3 (19.3)	17.1 (20.6)	16.6 (18.1)	0.520
Dietary fibre (g/day)	25.9 (9.0)[a]	26.1 (9.3)[a,b]	26.0 (9.0)[a,b]	27.2 (8.9)[b]	0.025
Educational level					
Higher education/Technician	91 (11%)	23 (12%)	88 (14%)	106 (13%)	0.579
Secondary education	165 (21%)	37 (19%)	133 (21%)	186 (23%)	
Primary education/Illiterate	530 (67%)	135 (69%)	412 (64%)	508 (63%)	
Missing data	11 (1%)	1 (0.5%)	5 (1%)	6 (1%)	
Smoking status					
Current	183 (23%)[a]	56 (29%)[a,b]	191 (30%)[a]	191 (24%)[b]	<0.001
Former	420 (53%)	92 (47%)	306 (48%)	366 (45%)	
b) Women n=3364 (58%)	**MAO n=1357 (40%)**	**MHO n=397 (12%)**	**MANO n=915 (27%)**	**MHNO n=695 (21%)**	***p*-value**
Age (yrs)	67.7 (5.7)[a,b]	67.5 (5.8)[a,b]	68.3 (5.9)[a]	67.3 (6.03)[b]	0.009
Diabetes prevalence	755 (56%)[a]	26 (7%)[b]	537 (59%)[a]	133 (19%)[c]	<0.001
Physical activity (METs. min/day)	144 (146)[a]	163 (156)[a,b]	185 (173)[b]	210 (186)[c]	<0.001
MedDiet score (0 to 14 score)	8.34 (1.92)[a]	8.60 (1.83)[a,b]	8.69 (1.93)[b]	8.97 (1.89)[c]	<0.001
Total energy intake (kcal/day)	2171 (580)	2192 (559)	2200 (574)	2227 (540)	0.203
Protein (% of energy)	17.1 (2.8)[a]	16.7 (2.8)[a,b]	16.9 (2.7)[a,b]	16.6 (2.7)[b]	0.003
Carbohydrate (% of energy)	42.4 (7.0)	42.5 (6.6)	42.3 (7.1)	42.4 (6.6)	0.984
Fat (% of energy)	39.7 (6.9)	39.9 (6.4)	39.8 (7.2)	39.6 (6.7)	0.904
SFA (% of energy)	10.1 (2.2)[a]	10.1 (2.2)[a,b]	9.95 (2.34)[a,b]	9.85 (2.17)[b]	0.022
MUFA (% of energy)	19.7 (4.9)	20.0 (4.5)	19.8 (4.9)	19.9 (4.4)	0.671
PUFA (% of energy)	6.19 (2.10)[a]	6.16 (2.10)[a,b]	6.44 (2.12)[b]	6.29 (1.99)[a,b]	0.027
Alcohol (g/day)	2.42 (5.25)[a]	3.09 (5.78)[a,b]	3.22 (6.27)[b]	4.47 (7.75)[c]	<0.001
Dietary fibre (g/day)	25.3 (9.5)	25.7 (9.9)	26.2 (9.7)	26.1 (9.3)	0.133
Educational level					
Higher education/Technician	37 (3%)[a]	14 (4%)[a,b]	38 (4%)[b]	62 (9%)[c]	<0.001
Secondary education	105 (8%)	39 (10%)	105 (11%)	109 (16%)	
Primary education/Illiterate	1207 (89%)	342 (86%)	765 (84%)	520 (75%)	
Missing data	8 (0.5%)	2 (0.5%)	7 (1%)	4 (1%)	
Smoking status					
Current	51 (4%)[a]	22 (6%)[a,b]	58 (6%)[b,c]	66 (10%)[c]	<0.001
Former	81 (6%)	22 (6%)	78 (9%)	61 (9%)	

Abbreviations: MAO – metabolically abnormal obese, MHO – metabolically healthy obese, MANO – metabolically abnormal non-obese, MHNO – metabolically healthy non-obese, SFA – saturated fatty acids, MUFA – monounsaturated fatty acids, PUFA – polyunsaturated fatty acids.

Data are expressed as means and SDs (continuous variables) or numbers and % (categorical variables). *P*-values were determined using one-way analysis of variance (ANOVA) (continuous variables) and chi-square test (χ^2) (categorical variables), followed by Bonferroni post-hoc test. Data not sharing a common letter (a, b and c) are significantly different ($p<0.05$).

Table 2. Relationship between longitudinal adherence to the Mediterranean diet and transition between obesity phenotypes by subgroups.

a) Hazard ratios (95% CIs) of transitions between obesity phenotypes based on change in metabolic health status (MetS incidence/reversion).

	MAO→MHO		**MHO→MAO**		**MANO→MHNO**		**MHNO→MANO**	
		p-value		*p*-value		*p*-value		*p*-value
MEDAS (for 2-point increase)	HR (95% CI)		HR (95% CI)		HR (95% CI)		HR (95% CI)	
Age	n= 1250→219		n= 336→186		n= 858→313		n= 897→340	
< 70 yr	1.24 (1.07 – 1.43)	0.003	0.86 (0.75 – 0.98)	0.029	1.15 (1.02 – 1.29)	0.017	0.97 (0.87 – 1.09)	0.646
	n= 688→121		n= 192→111		n= 538→182		n= 461→183	
≥ 70 yr	1.03 (0.83 – 1.27)	0.811	0.79 (0.63 – 0.99)	0.044	1.10 (0.94 – 1.28)	0.238	0.97 (0.83 – 1.14)	0.745
P for Interaction		*0.257*		*0.530*		*0.745*		*0.798*
Diabetes	n= 1123→88		n= 60→46		n= 859→250		n= 428→194	
Yes	1.08 (0.87 – 1.36)	0.483	0.91 (0.62 – 1.35)	0.649	1.07 (0.93 – 1.23)	0.329	0.94 (0.81 – 1.08)	0.380
	n= 815→252		n= 468→251		n= 537→245		n= 930→329	
No	1.13 (0.99 - 1.29)	0.071	0.82 (0.72 – 0.93)	0.003	1.15 (1.02 – 1.30)	0.027	0.99 (0.89 – 1.12)	0.930
P for Interaction		*0.526*		*0.017*		*0.640*		*0.242*
Group	n= 634→82		n= 180→85		n= 438→125		n= 395→147	
Control	1.12 (0.88 – 1.43)	0.367	0.84 (0.65 – 1.10)	0.215	1.22 (0.99 – 1.51)	0.061	0.85 (0.71 – 1.02)	0.082
	n= 1304→258		n= 348→212		n= 958→370		n= 963→376	
Intervention	1.18 (1.02 – 1.35)	0.024	0.88 (0.75 – 1.03)	0.109	1.07 (0.94 – 1.20)	0.305	1.02 (0.91 – 1.15)	0.693
P for Interaction		*0.840*		*0.733*		*0.617*		*0.014*

b) Hazard ratios (95% CIs) of transitions between obesity phenotypes based on change in body size (obesity incidence/reversion).

	MAO→MANO		MANO→MAO		MHO→MHNO		MHNO→MHO	
		p-value		*p*-value		*p*-value		*p*-value
MEDAS (for 2-point increase)	HR (95% CI)		HR (95% CI)		HR (95% CI)		HR (95% CI)	
Age	n= 1326→267		n= 898→156		n= 359→77		n= 959→116	
< 70 yr	1.04 (0.92 – 1.17)	0.523	0.96 (0.80 – 1.14)	0.627	1.12 (0.89 – 1.42)	0.329	0.86 (0.70 – 1.05)	0.133
	n= 726→168		n= 570→96		n= 208→54		n= 481→50	
≥ 70 yr	0.90 (0.77 – 1.05)	0.172	0.98 (0.79 – 1.21)	0.820	0.89 (0.64 – 1.25)	0.499	0.87 (0.69 – 1.10)	0.250
P for Interaction		*0.095*		*0.474*		*0.780*		*0.890*
Diabetes	n= 1168→255		n= 897→131		n= 63→22		n= 450→37	
Yes	1.00 (0.88 – 1.12)	0.948	0.94 (0.78 – 1.14)	0.515	1.38 (0.53 – 3.58)	0.508	0.75 (0.56 – 1.02)	0.066
	n= 884→180		n= 571→121		n= 504→109		n= 990→129	
No	0.98 (0.83 – 1.15)	0.769	0.95 (0.78 – 1.15)	0.586	1.01 (0.82 – 1.24)	0.962	0.84 (0.70 – 1.02)	0.076
P for Interaction		*0.447*		*0.867*		*0.105*		*0.317*
Group	n= 685→119		n= 476→62		n= 207→33		n= 437→38	
Control	0.97 (0.79 – 1.19)	0.771	0.92 (0.69 – 1.23)	0.566	1.27 (0.83 – 1.94)	0.279	0.72 (0.50 – 1.06)	0.093
	n= 1367→316		n= 992→190		n= 360→98		n= 1003→128	
Intervention	0.98 (0.87 – 1.11)	0.805	1.00 (0.85 – 1.19)	0.976	0.93 (0.72 – 1.20)	0.573	0.87 (0.71 – 1.06)	0.156
P for Interaction		*0.509*		*0.638*		*0.514*		*0.349*

Abbreviations: MAO – metabolically abnormal obese, MHO – metabolically healthy obese, MANO – metabolically abnormal non-obese, MHNO – metabolically healthy non-obese.

Analyses were performed using Cox regression with yearly repeated measures of 14-p MEDAS during 5 years of follow-up. Multivariable model adjusted for baseline age, smoking status and educational level, as well as yearly repeated measures of total energy intake, physical activity, and alcohol consumption, and stratified by recruitment center, sex and intervention group was used for all analyses. Robust standard errors to account for intracluster correlations were used.

Table 3. Sensitivity analyses of relationship between adherence to the Mediterranean diet and transitions between obesity phenotypes.

a) Hazard ratios (95% CIs) of transitions between obesity phenotypes based on change in metabolic health status (MetS incidence/reversion).

	MAO→MHO		**MHO→MAO**		**MANO→MHNO**		**MHNO→MANO**	
MEDAS (for 2-point increase)	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
	n=1938→343		n=528→297		n=1396→496		n=1358→525	
Minimally adjusted model#	1.16 (1.04 – 1.31)	0.011	0.86 (0.77 – 0.96)	0.008	1.12 (1.02 – 1.23)	0.017	0.95 (0.87 – 1.04)	0.304
	n=1938→340		n=528→296		n=1396→495		n=1358→523	
Adjusting for yearly weight (kg)*	1.17 (1.03 – 1.32)	0.012	0.85 (0.76 – 0.96)	0.008	1.12 (1.02 – 1.23)	0.022	0.96 (0.88 – 1.05)	0.413
	n=1871→334		n=513→289		n=1338→479		n=1322→508	
Excluding subjects with incident CV§	1.15 (1.02 – 1.30)	0.027	0.85 (0.76 – 0.96)	0.009	1.13 (1.02 – 1.24)	0.015	0.98 (0.89 – 1.07)	0.594
	n=2027→286		n=493→286		n=1995→388		n=803→403	
Excluding WC from MetS definition¶	1.25 (1.10 – 1.43)	0.001	0.88 (0.78 – 0.99)	0.031	1.15 (1.03 – 1.28)	0.013	0.96 (0.87 – 1.06)	0.421
	n=1938→369		n=528→329		n=1396→525		n=1358→562	
LOCF†	1.14 (1.01 – 1.28)	0.029	0.89 (0.80 – 0.98)	0.022	1.09 (1.00 – 1.19)	0.063	0.96 (0.88 – 1.05)	0.343

b) Hazard ratios (95% CIs) of transitions between obesity phenotypes based on change in body size (obesity incidence/reversion).

	MAO→MANO		**MANO→MAO**		**MHO→MHNO**		**MHNO→MHO**	
MEDAS (for 2-point increase)	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
	n=2052→437		n=1468→252		n=567→131		n=1440→166	
Minimally adjusted model#	0.98 (0.89 – 1.09)	0.759	0.97 (0.84 – 1.11)	0.628	1.03 (0.85 – 1.24)	0.782	0.81 (0.70 – 0.94)	0.005
	n=1983→418		n=1407→249		n=550→129		n=1399→161	
Excluding subjects with incident CV§	1.00 (0.90 – 1.10)	0.941	0.96 (0.83 – 1.10)	0.553	1.04 (0.86 – 1.26)	0.691	0.79 (0.68 – 0.93)	0.003
	n=2085→450		n=2045→299		n=514→114		n=848→117	
Excluding WC from MetS definition¶	0.97 (0.88 – 1.07)	0.543	0.95 (0.84 – 1.08)	0.457	1.08 (0.88 – 1.34)	0.457	0.75 (0.62 – 0.92)	0.006
	n=2052→495		n=1468→290		n=567→158		n=1440→195	
LOCF†	1.00 (0.91 – 1.09)	0.926	0.96 (0.85 – 1.09)	0.541	0.99 (0.83 – 1.18)	0.918	0.84 (0.73 – 0.97)	0.015

Abbreviations: MAO – metabolically abnormal obese, MHO – metabolically healthy obese, MANO – metabolically abnormal non-obese, MHNO – metabolically healthy non-obese, WC – waist circumference.

Analyses were performed using Cox regression with yearly repeated measures of 14p-Mediterranean Diet Adherence Screener (MEDAS) during 5 years of follow-up. Multivariable model adjusted for baseline age, smoking status and educational level, as well as yearly repeated measures of total energy intake, physical activity, and alcohol consumption, and stratified by recruitment center, sex and intervention group was used for all analyses, unless otherwise stated. Robust standard errors to account for intracluster correlations were used.
#Model was minimally adjusted for baseline age only.
*Multivariable model was additionally adjusted for yearly measured body weight.
§Participants who developed CV-related diseases (myocardial infarction or stroke) or who died by any cardiovascular mechanism during follow-up were excluded from the analyses.
¶The variable for metabolic status was re-calculated excluding WC from the definition of MetS.
†Last observation carried forward (LOCF) method was applied to impute the missing data during follow-up.

Figure 1.

	OBESE BMI ≥ 30 kg/m^2	**NON-OBESE** BMI < 30 kg/m^2
MetS PRESENCE ≥ 3 MetS factors	**MAO** metabolically abnormal obese	**MANO** metabolically abnormal non-obese
MetS ABSENCE 0-2 MetS factors	**MHO** metabolically healthy obese	**MHNO** metabolically healthy non-obese

Figure 2.

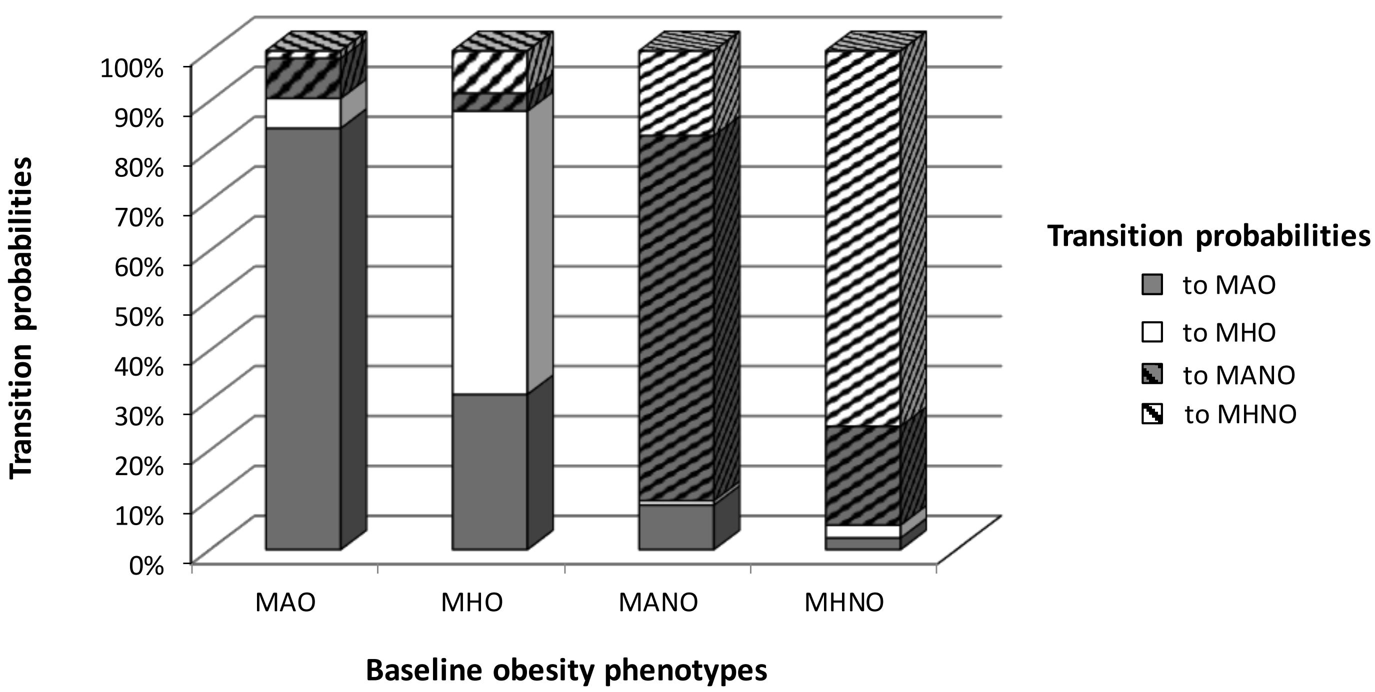

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Transition probabilities
MAO
MHO
MANO
MHNO
Baseline obesity phenotypes
Transition probabilities
to MAO
to MHO
to MANO
to MHNO

Figure 3.

MEDAS (for 2-point increase)	n		HR (95% CI)	*p*-value	*p for interaction*
MAO → MHO	698 → 132	Men	1.18 (0.98 - 1.41)	0.076	0.601
	1240 → 208	Women	1.15 (0.98 - 1.35)	0.087	
	1938 → 340	Whole sample	1.16 (1.03 - 1.31)	0.015	
MHO → MAO	175 → 107	Men	0.88 (0.73 - 1.06)	0.183	0.439
	353 → 190	Women	0.86 (0.74 - 1.00)	0.047	
	528 → 297	Whole sample	0.86 (0.77 - 0.97)	0.013	
MANO → MHNO	570 → 240	Men	1.01 (0.89 - 1.16)	0.833	0.014
	826 → 255	Women	1.20 (1.05 - 1.38)	0.007	
	1396 → 495	Whole sample	1.12 (1.01 - 1.23)	0.023	
MHNO → MANO	724 → 265	Men	1.00 (0.88 - 1.13)	0.973	0.905
	634 →258	Women	0.96 (0.84 - 1.10)	0.550	
	1358 → 523	Whole sample	0.97 (0.89 - 1.07)	0.572	
MAO → MANO	748 → 177	Men	1.01 (0.86 - 1.18)	0.894	0.676
	1304 → 258	Women	0.95 (0.84 - 1.08)	0.450	
	2052 → 435	Whole sample	0.98 (0.89 - 1.08)	0.714	
MANO → MAO	597 → 102	Men	1.03 (0.81 - 1.31)	0.795	0.651
	871 → 150	Women	0.92 (0.78 - 1.08)	0.311	
	1468 → 252	Whole sample	0.97 (0.84 - 1.11)	0.634	
MHO → MHNO	187 → 51	Men	1.20 (0.87 - 1.64)	0.272	0.126
	380 → 80	Women	0.96 (0.75 - 1.22)	0.719	
	567 → 131	Whole sample	1.04 (0.86 - 1.26)	0.700	
MHNO → MHO	768 → 88	Men	0.90 (0.73 - 1.11)	0.324	0.657
	672 → 78	Women	0.72 (0.59 - 0.89)	0.002	
	1440 → 166	Whole sample	0.82 (0.70 - 0.95)	0.010	

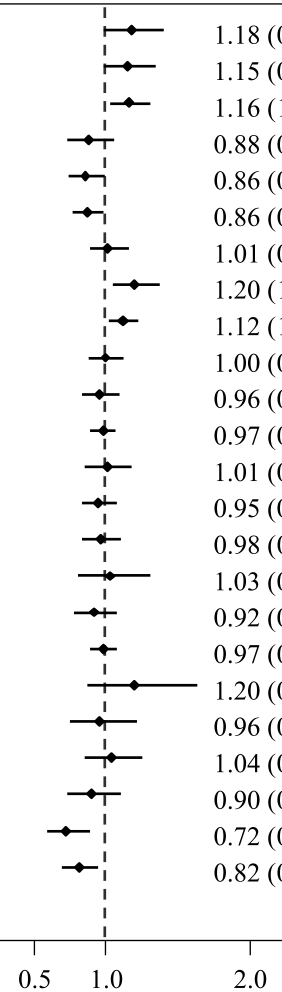
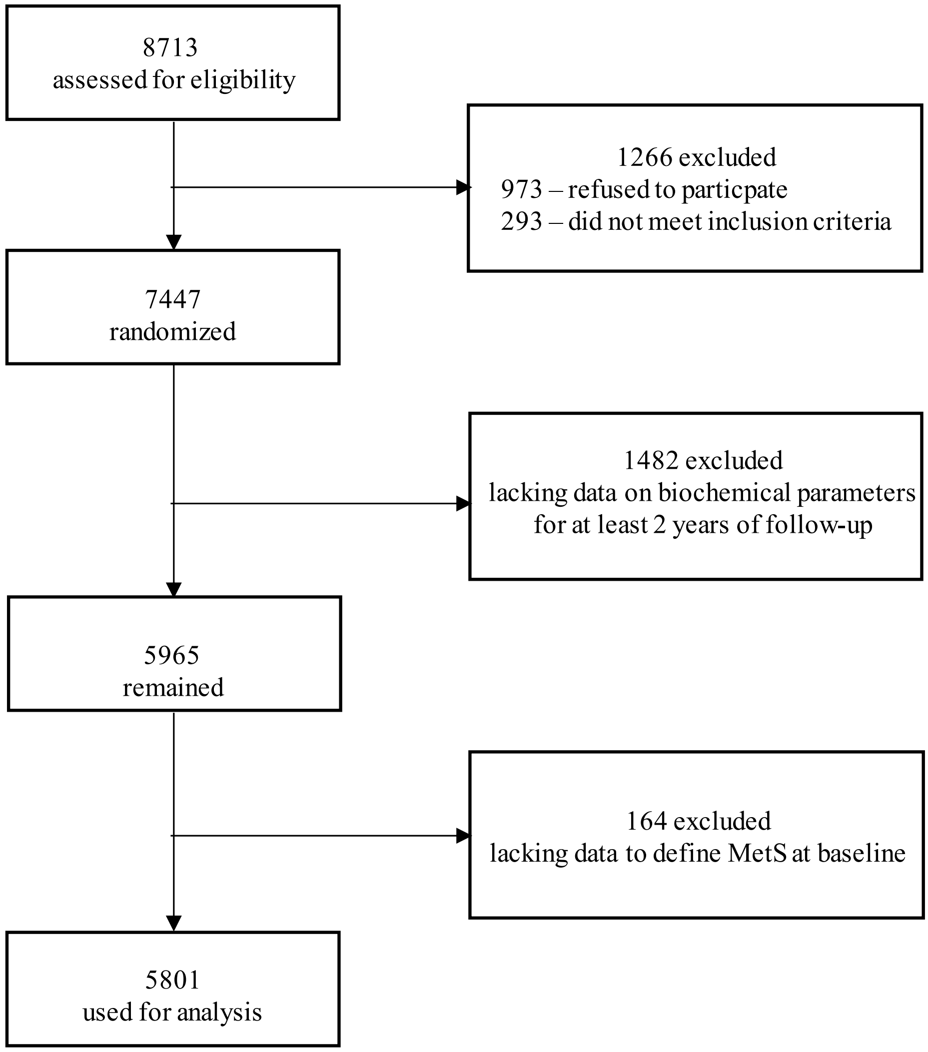


Figure 1.



Flow chart summarizing selection of the PREDIMED participants for obesity phenotypes analyses.

Abbreviations: MedDiet – Mediterranean diet, MetS – metabolic syndrome.

Table 1. Characteristics of the whole study population according to obesity phenotype at baseline.

n=5801	**MAO n=2154 (37%)**	**MHO n=593 (10%)**	**MANO n=1553 (27%)**	**MHNO n=1501 (26%)**	***p*-value**
Age (yrs)	66.9 (6.1)[a]	67.0 (6.0)[a,b]	67.5 (6.3)[b]	66.7 (6.3)[a]	0.002
Sex (% of women)	1357 (63%)[a,c]	397 (67%)[a]	915 (59%)[c]	695 (46%)[b]	<0.001
Diabetes prevalence	1236 (57%)[a]	66 (11%)[b]	949 (61%)[a]	476 (32%)[c]	<0.001
Smoking status					
Current	234 (11%)[a]	78 (13%)[a]	249 (16%)[b]	257 (17%)[b]	<0.001
Former	501 (23%)	114 (19%)	384 (25%)	427 (28%)	
Physical activity (METs. min/day)	191 (215)[a]	207 (198)[a,b]	234 (250)[b]	294 (269)[c]	<0.001
MedDiet score (0 to 14 score)	8.42 (1.98)[a]	8.60 (1.92)[a,b]	8.69 (1.93)[b]	9.00 (1.93)[c]	<0.001
Total energy intake (kcal/day)	2291 (625)[a]	2316 (605)[a,b]	2316 (609)[a]	2379 (593)[b]	<0.001
Protein (% of energy)	16.6 (2.8)[a]	16.2 (2.8)[b,c]	16.5 (2.7)[a,b]	16.1 (2.8)[c]	<0.001
Carbohydrate (% of energy)	41.9 (7.4)	41.9 (6.9)	41.6 (7.4)	42.0 (7.1)	0.533
Fat (% of energy)	39.5 (6.9)	39.7 (6.5)	39.4 (7.2)	38.9 (6.9)	0.025
SFA (% of energy)	10.1 (2.2)[a]	10.0 (2.2)[a]	9.98 (2.34)[a]	9.70 (2.20)[b]	<0.001
MUFA (% of energy)	19.6 (4.8)	19.9 (4.4)	19.6 (4.8)	19.4 (4.5)	0.214
PUFA (% of energy)	6.18 (2.09)	6.20 (2.08)	6.35 (2.09)	6.29 (1.99)	0.080
Alcohol (g/day)	7.36 (13.95)[a]	7.80 (13.78)[a,b]	8.94 (15.64)[b]	11.0 (15.5)[c]	<0.001
Dietary fibre (g/day)	25.6 (9.4)[a]	25.8 (9.7)[a,b]	26.1 (9.4)[a,b]	26.7 (9.1)[b]	0.004
Educational level					
Higher education/Technician	128 (6%)[a]	37 (6%)[a,c]	126 (8%)[c]	168 (11%)[b]	<0.001
Secondary education	270 (13%)	76 (13%)	238 (15%)	295 (20%)	
Primary education/Illiterate	1737 (81%)	477 (80%)	1177 (76%)	1028 (68%)	
Missing data	19 (1%)	3 (0.5%)	12 (1%)	10 (1%)	

Abbreviations: MAO – metabolically abnormal obese, MHO – metabolically healthy obese, MANO – metabolically abnormal non-obese, MHNO – metabolically healthy non-obese, SFA – saturated fatty acids, MUFA – monounsaturated fatty acids, PUFA – polyunsaturated fatty acids.

Data are expressed as means and SDs (continuous variables) or numbers and % (categorical variables). *P*-values were determined using one-way analysis of variance (ANOVA) (continuous variables) and chi-square test (χ^2) (categorical variables), followed by Bonferroni post-hoc test. Data not sharing a common letter (a, b and c) are significantly different ($p<0.05$).

Table 2. Quantitative (14-point) score of compliance with the Mediterranean Diet for the whole study population according to obesity phenotype at baseline.

Foods and frequency of consumption	**Criteria for 1 point***	**MAO**	**MHO**	**MANO**	**MHNO**	***p*-value**
1. Do you use olive oil as main culinary fat?	Yes	1911 (89%)[a]	533 (90%)[a,b]	1393 (90%)[a]	1390 (93%)[b]	0.001
2. How much olive oil do you consume in a given day (including oil used for frying, salads, out of house meals, etc.)?	≥4 tablespoons	1563 (73%)	447 (76%)	1145 (74%)	1115 (74%)	0.443
3. How many vegetable servings do you consume per day? (1 serving = 200g - consider side dishes as 1/2 serving)	≥2 (at least 1 portion raw or as a salad)	886 (41%)	230 (39%)	668 (43%)	653 (44%)	0.161
4. How many fruit units (including natural fruit juices) do you consume per day?	≥3	1111 (52%)	303 (51%)	814 (52%)	817 (54%)	0.335
5. How many servings of red meat, hamburger, or meat products (ham, sausage, etc.) do you consume per day? (1 serving = 100-150 g)	<1	1822 (85%)[a]	518 (88%)[a,b]	1359 (88%)[a,b]	1345 (90%)[b]	<0.001
6. How many servings of butter, margarine, or cream do you consume per day? (1 serving = 12 g)	<1	1947 (90%)	545 (92%)	1380 (89%)	1359 (91%)	0.139
7. How many sweet/carbonated beverages do you drink per day?	<1	1898 (88%)[a]	531 (90%)[a,b]	1378 (89%)[a,b]	1375 (92%)[b]	0.007
8. How much wine do you drink per week?	≥7	525 (24%)[a]	162 (27%)[a,c]	454 (29%)[c]	590 (39%)[b]	<0.001
9. How many servings of legumes do you consume per week? (1 serving = 150 g)	≥3	587 (27%)	155 (26%)	413 (27%)	434 (29%)	0.444
10. How many servings of fish or shellfish do you consume per week? (1 serving: 100-150 g fish, or 4-5 units or 200 g shellfish)	≥3	1172 (54%)[a]	353 (60%)[a,b]	893 (58%)[a,b]	916 (61%)[b]	0.001
11. How many times per week do you consume commercial sweets or pastries (not homemade), such as cakes, cookies, biscuits, or custard?	<3	1478 (69%)[a]	365 (62%)[b]	1096 (71%)[a]	1052 (70%)[a]	0.001
12. How many servings of nuts (including peanuts) do you consume per week? (1 serving = 30 g)	≥3	600 (28%)[a]	184 (31%)[a,c]	548 (35%)[c]	636 (42%)[b]	<0.001
13. Do you preferentially consume chicken, turkey or rabbit meat instead of veal, pork, hamburger or sausage?	Yes	1401 (65%)[a,b]	402 (68%)[a]	1037 (67%)[a]	922 (61%)[b]	0.005
14. How many times per week do you consume vegetables, pasta, rice, or other dishes seasoned with sofrito (sauce made with tomato and onion, leek, or garlic, simmered with olive oil)?	≥2	1238 (57%)	365 (62%)	914 (59%)	908 (60%)	0.159

* 0 points if these criteria are not meet

Abbreviations: MAO – metabolically abnormal obese, MHO – metabolically healthy obese, MANO – metabolically abnormal non-obese, MHNO – metabolically healthy non-obese.

Data are expressed as numbers and percentages (%). *P*-values were determined using chi-square test (χ^2), followed by Bonferroni post-hoc test. Data not sharing a common letter (a, b and c) are significantly different ($p<0.05$).

Table 3. Transition probabilities from MAO, MHO, MANO and MHNO over 1, 3 and 5 years of follow-up time (a-c).

a) **Transition probabilities over 1 year**

Baseline	1 year			
	MAO	**MHO**	**MANO**	**MHNO**
MAO	82.8	8.47	6.51	2.24
MHO	33.5	53.9	3.12	9.56
MANO	9.14	1.33	67.5	22.0
MHNO	2.74	2.82	18.6	75.9
Total	37.4	9.66	25.6	27.4

b) **Transition probabilities over 3 years**

Baseline	3 years			
	MAO	**MHO**	**MANO**	**MHNO**
MAO	84.3	6.36	7.72	1.62
MHO	31.1	56.7	3.36	8.85
MANO	8.82	0.98	71.9	18.3
MHNO	2.33	2.69	19.6	75.3
Total	38.2	8.50	27.7	25.6

c) **Transition probabilities over 5 years**

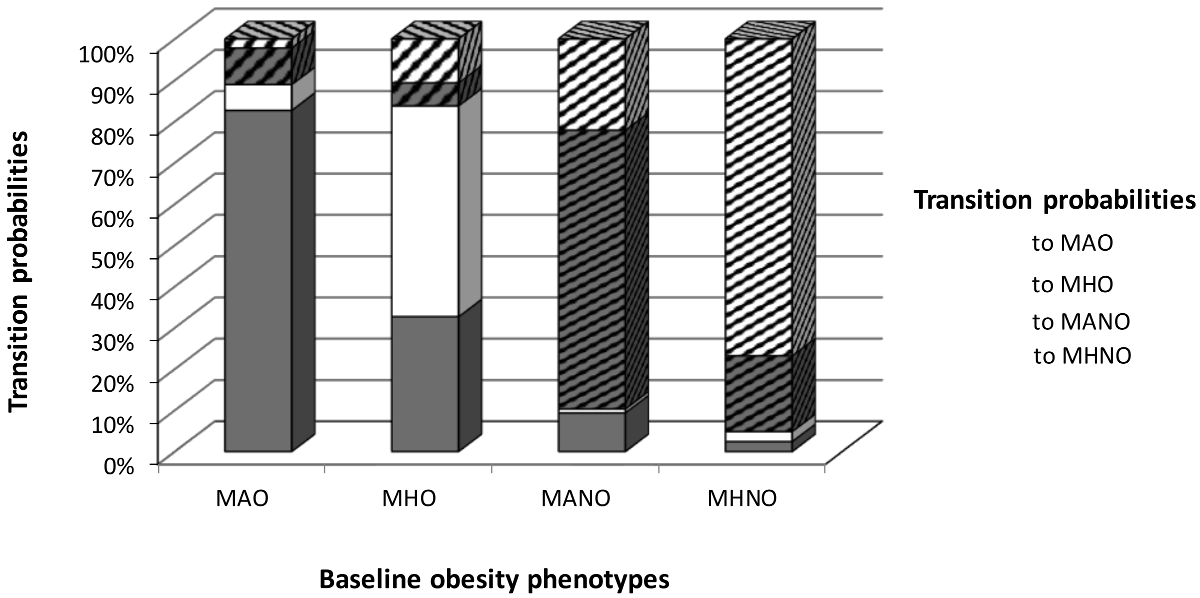
Baseline	5 years			
	MAO	**MHO**	**MANO**	**MHNO**
MAO	84.5	6.01	8.01	1.49
MHO	31.2	56.7	3.59	8.46
MANO	8.94	0.90	73.2	17.0
MHNO	2.33	2.60	19.8	75.3
Total	38.0	7.96	29.0	25.1

Abbreviations: MAO – metabolically abnormal obese, MHO – metabolically healthy obese, MANO – metabolically abnormal non-obese, MHNO – metabolically healthy non-obese

Data are expressed as percentages (%).

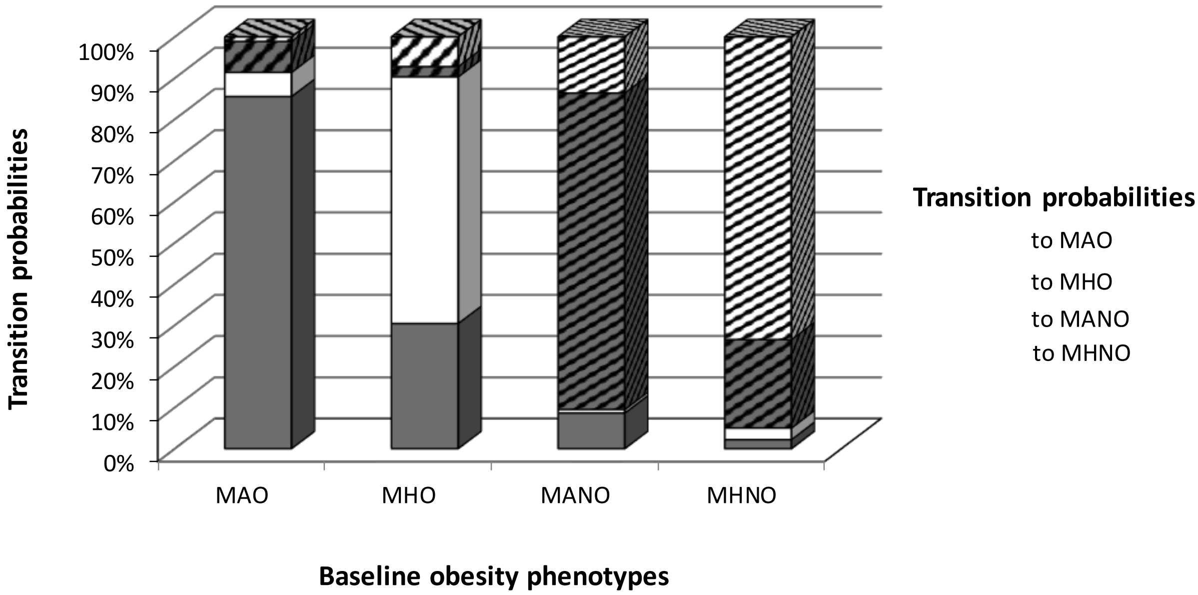
Figure 2.

a) Men



Baseline	5 years			
	MAO	**MHO**	**MANO**	**MHNO**
MAO	82.7	6.25	8.87	2.18
MHO	32.67	51.11	5.56	10.67
MANO	9.38	0.96	67.53	22.13
MHNO	2.42	2.42	18.35	76.8
Total	38.0	7.96	29.0	25.1

b) Women



Baseline	5 years			
	MAO	**MHO**	**MANO**	**MHNO**
MAO	85.51	5.87	7.52	1.10
MHO	30.39	59.9	2.49	7.22
MANO	8.65	0.86	76.85	13.64
MHNO	2.22	2.81	21.46	73.51
Total	38.0	7.96	29.0	25.1

Transition probabilities from MAO, MHO, MANO and MHNO over follow-up time in men (a) and women (b).

Y axis shows transition probabilities and X axis indicates the baseline phenotypes. Each bar represents the sum of unadjusted transition probabilities from each baseline phenotype to any other one over the 5 years of follow-up on a scale of 0-100%.

Abbreviations: MAO – metabolically abnormal obese, MHO – metabolically healthy obese, MANO – metabolically abnormal non-obese, MHNO – metabolically healthy non-obese.