

## **Does the Mediterranean Diet counteract the adverse effects of abdominal adiposity?**

Eguaras S [1,2], Toledo E [2,3,4], Buil-Cosiales P [1,2,3,4], Salas-Salvadó J [3,4,5], Corella D [4,6], Gutierrez-Bedmar M [3,4,7], Santos-Lozano JM [4,8], Arós F [3,4,9], Fiol M [4,10], Fitó M [4,11], Ros E [12], Serra-Majem L [3,4,13], Pintó X [3,4,14], Martínez J A [3,4,15], Sorlí J V [4,6], Muñoz M A [4,11], Basora J [3,4,5], Estruch R [3,4,16], Martínez-González M Á [2,3,4] for the PREDIMED INVESTIGATORS\*

1: Servicio Navarro de Salud-Osasunbidea, Pamplona

2: Department of Preventive Medicine and Public Health, University of Navarra, Pamplona.

3 PREDIMED Research Network (RD 06/0045), Instituto de Salud Carlos III, Madrid.

4 Centro Investigación Biomédica Red Obesidad-Nutrición (CIBERObn), Madrid.

5 Human Nutrition Department, Universitat Rovira i Virgili, Reus.

6 Department of Preventive Medicine, University of Valencia, Valencia.

7 Department of Preventive Medicine, University of Malaga, Malaga.

8 Department of Family Medicine, San Pablo Health Center, Sevilla.

9 Department of Cardiology, University Hospital of Alava, Vitoria.

10 Institute of Health Sciences (IUNICS), Palma de Mallorca.

11 Cardiovascular and Nutrition Research Group, Institut de Recerca Hospital del Mar, Barcelona.

12 Lipid Clinic, Hospital Clinic, Barcelona.

13 Department of Clinical Sciences, University Las Palmas de Gran Canaria, Las Palmas.

14 Lipids and Vascular Risk Unit, Hospital Bellvitge, Barcelona.

15 Department of Nutrition, University of Navarra, Pamplona.

16 Department of Internal Medicine, Hospital Clinic, Barcelona.

\*A complete list of PREDIMED INVESTIGATORS can be found at the appendix.

Correspondence and reprints:

Prof. Miguel Á. Martínez-González. Department of Preventive Medicine, Universidad de Navarra, Irunlarrea 1, 31008-Pamplona (Spain). E-mail: mamartinez@unav.es. Tel: +34 948 42 56 00 Ext: 806463. Fax: + 34 948 42 57 40.

#### FUNDING DISCLOSURE

Supported by the official funding agency for biomedical research of the Spanish government, Instituto de Salud Carlos III (ISCIII), through specific grants (RTIC G03/140; RTIC-RD 06/0045, to Prof. Martínez-González and CIBERobn), and by Fondo de Investigación Sanitaria–ISCIII (PI04-2239, PI05/2584, CP06/00100, PI07/0240, PI07/1138, PI07/0954, PI 07/0473, PI10/01407, PI10/02658, PI11/01647, and P11/02505), Ministerio Ciencia e Innovación (AGL-2009-13906-C02 and AGL2010-22319-C03), Fundación Mapfre 2010, Consejería Salud Junta de Andalucía (PI0105/2007), Health Department of Catalonia, Generalitat Valenciana (ACOMP06109, GVACOMP2010-181, GVACOMP2011-151, CS2010-AP-111, and CS2011-AP-042), and Regional Government of Navarra (P27/2011). ET is supported by a Rio Hortega post-residency fellow of the ISCIII.

**ROLE OF THE FUNDERS:** funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

## **ABSTRACT**

**Background and Aims:** We tested the hypothesis that an intervention with Mediterranean diet (MeDiet) could mitigate the well-known harmful effects of abdominal obesity on cardiovascular health.

**Methods and Results:** We assessed the relationship between baseline waist-to-height ratio (WHtR) and major cardiovascular events during a median follow-up of 4.8 years in the PREDIMED randomized primary prevention trial which tested a MeDiet against a control diet (advice on a low-fat diet). We also examined whether the MeDiet intervention was able to counteract the detrimental cardiovascular effects of increased WHtR. The trial included 7447 participants (55-80 years-old, 57% women) at high cardiovascular risk but free of CVD at enrollment.

An increased risk of CVD events (myocardial infarction, stroke, or cardiovascular death) was apparent for the highest versus the lowest quartile of WHtR (multivariable-adjusted hazard ratio: 1.92 (95% confidence interval: 1.08-3.40, linear trend:  $p=0.023$ ) only in the control diet group, but not in the two groups allocated to intervention with MeDiet ( $p$  for interaction = 0.047). This interaction suggesting that the intervention counterbalanced the detrimental effects of adiposity was also significant for BMI ( $p<0.001$ ) and waist circumference ( $p=0.043$ ).

**Conclusions:** The MeDiet may counteract the harmful effects of increased adiposity on the risk of CVD.

**Keywords:** Waist-to-height ratio, Mediterranean diet, Dietary intervention, Cardiovascular disease.

## **INTRODUCTION**

Excess body weight is likely to be associated with clinical cardiovascular disease (CVD) even at moderate levels of overweight. Sound biological plausibility and recent empirical studies support that the adverse consequences of obesity are mainly attributable to abdominal fat accumulation. [2,3,4,5]. We assessed the association between adiposity indexes and CVD in the PREDIMED study, a randomized nutrition intervention trial comparing a Mediterranean diet (MeDiet) supplemented with extra-virgin olive oil (EVOO) and a MeDiet supplemented with nuts against a control low-fat diet for the primary prevention of CVD in older subjects at high cardiovascular risk [6]. We tested the hypothesis that the MeDiet would counteract or mitigate the detrimental effects of abdominal obesity. Although the final results of the PREDIMED trial [8] supported that a MeDiet was able to prevent CVD, there is scarce information from randomized trials on whether the MeDiet can specifically attenuate the harmful effects of increased abdominal fat.

## **METHODS**

The design, objectives and methods of the PREDIMED trial were previously published. [6]. Briefly, PREDIMED was a randomized, multicenter, cardiovascular primary prevention trial conducted in Spain ([www.predimed.es](http://www.predimed.es)) from October 2003 to December 2010 that compared three dietary interventions: two MeDiets, one supplemented with EVOO and the other supplemented with mixed nuts, versus a control (low-fat) diet.

The Institutional Review Boards at all study locations approved the protocol. The trial was registered at <http://www.controlled-trials.com/ISRCTN35739639>.

### **Subjects**

By study design all participants were at high cardiovascular risk because of the presence of type-2 diabetes or at least three risk factors, but had no CVD at enrolment [6]. Of 7,447 recruited participants, 43% were men 55 to 80 years-old and 57% were women 60 to 80 years-old.

The procedures and specific details of the intervention have been previously described [7, 8]. Of note, energy restriction was not part of the nutritional intervention.

### **Measurements**

Registered nurses previously trained and certified to implement the PREDIMED protocol directly measured weight, height and waist circumference (WC) of participants, as previously described [6,7,9]. Height (m) and weight (kg) were measured with light clothing and no shoes with calibrated scales and a wall-mounted stadiometer, respectively; BMI was calculated as the weight in kilograms divided by the square of the height in meters; WC was measured midway between the lowest rib and the iliac crest using an anthropometric tape; and waist-to-height ratio (WHtR) was calculated as WC divided by height, both in centimetres.

### **Outcome**

The main outcome was a composite primary end-point including myocardial infarction, stroke, or death from cardiovascular causes. Repeated contacts with participants and family physicians, a yearly review of medical records, and consultation (every 6 months) of the National Death Index provided the basic information used by the end-point adjudication committee to classify the events. Members of this committee were blinded to study-group assignments and to the anthropometric indexes of participants.

### **Assessment of confounders**

Medical, socio-demographic, and lifestyle variables were collected in a baseline interview. We used the Minnesota validated physical activity questionnaire to assess leisure-time physical activity [10,11]. Dietary habits were ascertained through a semi-quantitative 137-item food frequency questionnaire previously validated in Spain [12].

### **Statistical analyses**

We used Cox regression models to assess the hazard ratios (HR) and their 95% confidence intervals for total CVD events across quartiles of WHtR (quartile 2 and 3 were merged to simplify the results), BMI (cut-off points: 25 and 30 kg/m<sup>2</sup>) and WC. We adjusted for the following potential confounders measured at baseline: age, sex, smoking, diabetes, hypertension status, dyslipidemia status, intervention group, METs-min/d (adding a quadratic term to account for a non-linear association with

cardiovascular events), and family history of early-onset coronary artery disease. We evaluated the interaction between baseline indexes of adiposity and the intervention using the likelihood ratio test, after merging in a single category the 2 active arms of the trial that received the MeDiet intervention. For WHtR we used the 75<sup>th</sup> percentile as cut-off point to dichotomize the WHtR (1 degree of freedom). To better guarantee comparisons to other studies, we used sex-specific cut-off points for WC according to widely accepted international recommendations (13). We also repeated the analyses using the 90<sup>th</sup> sex-specific percentile of WC as cut-off point, as suggested by our dose-response analysis. For BMI, the commonly accepted cut-off points (those established by the WHO) were used. We evaluated the interaction between WC (dichotomized at the 90<sup>th</sup> sex-specific percentile) and the intervention and between BMI (2 categories, cut-off=30 kg/m<sup>2</sup>) and the intervention (2 categories) on cardiovascular events using the likelihood ratio test (1 degree of freedom). Analyses were performed using STATA version 12.1 (StataCorp, College Station, TX, USA).

## **RESULTS**

We observed 288 incident CVD events during a median follow-up of 4.8 years (the time of follow-up was described by the index person-years). Table 1 shows baseline characteristics of participants by intervention groups. Dietary variables at the beginning and at the end of the trial are presented in table 2. Table 3 shows the relationship between WHtR quartiles and the risk of CVD. The HRs showed an increased risk in the upper (versus the lowest) quartile, but this direct association was only apparent in the control group. A significant linear trend ( $p=0.023$ ) was also apparent only in the control group. No association was not observed in the 2 groups that received MeDiet interventions.

The interaction between baseline WHtR (dichotomized at the 75<sup>th</sup> percentile,  $WHtR \geq 0.67$ ) and the intervention was statistically significant ( $p=0.047$ ), showing that the detrimental effect of a higher baseline WHtR was apparent in the control diet group, but not in the groups randomly allocated to MeDiets.

In table 4 we show the relationship between WC or BMI and CVD. No significant association was found for WC using conventional cut-offs points. However, when we dichotomized WC at the 90<sup>th</sup> sex-specific percentile ( $\geq 112$  cm in females and

$\geq 115$  cm in males), the multiple adjusted HR associated with waist  $> 90$ th percentile was 1.96 (95% CI: 1.15-3.33) in the control group whereas it was only 0.97 (0.59-1.58) in both intervention groups merged (p for interaction = 0.043). The risk of CVD did not significantly change across conventional categories of BMI within any of the three groups. The multivariable-adjusted HR for the highest ( $> 30$ ) versus the lowest ( $< 25$ ) category of BMI was 1.56 (95% CI: 0.64-3.78) in participants allocated to the control group, whereas it was 0.90 (0.54-1.49) in both MeDiet groups merged together. The interaction between a high BMI ( $> 30$  kg/m<sup>2</sup>) and the intervention (Mediet versus control) was highly significant (p for interaction=0.0096).

Figure 1 presents the multivariable-adjusted HRs for the joint cross-classification according to both the values of the WHtR (either below the 75<sup>th</sup> percentile [ $< 0.67$ ] or above it [ $\geq 0.67$ ]) and the intervention groups (the two active arms receiving MeDiets merged together or the control diet group). The reference category was the control diet group with WHtR below the 75<sup>th</sup> percentile.

## DISCUSSION

In this nutritional intervention trial comparing two supplemented MeDiets versus a control diet (advice on a low-fat diet) for incident CVD events, we found that the MeDiets counteracted the harmful effect of abdominal adiposity regarding the risk of CVD events. The MeDiet has been associated with beneficial metabolic effects, regardless of abdominal adiposity in previous studies [14]. But, therewith, we assessed an important benefit of the MeDiet in persons with abdominal adiposity, the acknowledgedly most harmful type of obesity, which is related to higher risk of cardiovascular events. The major strength in our study is that we were able to use the results of an intervention with a randomized design.

Given that recent studies have suggested that the WHtR ratio is one of the best indexes to predict diabetes or CVD, we used this ratio as an anthropometric index of adiposity to assess the relationship of adiposity with cardiovascular events. Because this index has the ability to measure more precisely central obesity than other anthropometrical measurements such as BMI [2,3,4,5, 15]. However, the apparent interaction was also replicated with WC and BMI.

Obesity, specially abdominal obesity contributes to produce a state of low-grade inflammation that increases cardiovascular risk and as a result it could lead to a higher risk of cardiovascular events. The biological mechanism underlying the apparent interaction that we have found is likely to be explained by the known anti-inflammatory properties of the MeDiet, specially when it is supplemented with extra-virgin olive oil as it has been previously reported using circulating inflammatory biomarkers [9, 16]

The main strength and novelty of our research is that the outcomes were ascertained after a long-term (median 4.8 years) dietary intervention in a randomized trial. The significant interactions between the intervention and adiposity suggests that the MeDiet intervention was able to counteract the higher risk of CVD associated with increased adiposity, a finding consistent with the main results of the PREDIMED trial [8], which provided strong evidence for the MeDiet as a preventive strategy against CVD. Previous studies such as the Women's Health Initiative Dietary Modification Trial (WHI-DMT) [17], did not find that an intervention with a low-fat diet could prevent cardiovascular clinical events. The WHI-DMT low-fat diet had no significant effects on incidence of coronary heart disease (HR=0.97; 95% CI: 0.90-1.06), stroke (1.02; 0.90-1.15), or CVD (0.98: 0.92-1.05). We, in contrast, observed a reduction in the incidence of CVD in the two active intervention groups of the PREDIMED trial and furthermore, this intervention with a relatively fat-rich diet nullified the detrimental effects of abdominal adiposity.

We speculate that a longer follow-up (for example, after 10-year) could allow us to observe similar results in the long-term on other end-points (total mortality or cancer) that probably will require a longer induction period.

There were other strengths in our research such as the use of multiple-adjusted models to control for confounding.

On the other hand, we acknowledge some limitations of our study. The elderly population at high cardiovascular risk studied in our cohort limits the generalizability of our findings to younger and/or healthier individuals.

In conclusion, our results are highly supportive of the beneficial role of the MeDiet for the prevention of CVD among subjects with abdominal obesity. Further studies are warranted, particularly to assess whether energy-restricted MeDiets can obtain an

even greater benefit in abdominally obese subjects. In this line, we recently launched the PREDIMED-PLUS study ([www.predimedplus.com](http://www.predimedplus.com)), planning to recruit 6,000 participants with abdominal obesity and will randomly allocate them to 2 diets: a) the control group will receive a traditional MeDiet without energy restriction (as the PREDIMED trial did); b) the intensive intervention group will receive an energy-restricted MeDiet together with physical activity, goals for weight loss and behavioral therapy. Results are expected in 2020.

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