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Does the Mediterranean diet counteract the adverse effects of abdominal adiposity?

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Abstract *Background and aim:* We tested the hypothesis that an intervention with a 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 Prevention with Mediterranean Diet (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 an increased WHtR. The trial included 7447 participants (55–80 years old, 57% women) at high cardiovascular risk but free of cardiovascular disease (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: 1.98) (95% confidence interval: 1.10–3.57; linear trend: $p = 0.019$) only in the control-diet group, but not in the two groups allocated to intervention with MeDiet (p for interaction = 0.034). This apparent interaction suggesting that the intervention counterbalanced the detrimental cardiovascular effects of adiposity was also significant for body mass index (BMI) ($p = 0.01$) and waist circumference ($p = 0.043$).

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

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 [1–5]. We assessed the association between adiposity indexes and CVD in the Primary Prevention of Cardiovascular Disease with a Mediterranean Diet (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) from October 2003 to December 2010, which 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/ISRCTN 35739639.

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 enrollment [6]. Of 7447 recruited participants, 43% were men (aged 55–80 years) and 57% were women (aged 60–80 years).

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; body mass index (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 centimeters.

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 (HRs) and their 95% confidence intervals (CIs) for total CVD events across quartiles of WHtR (quartiles two and three were merged to simplify the results), BMI (cutoff points: 25 and 30 kg/m [2]), and WC. We adjusted for the following potential confounders measured at baseline: age, sex, smoking, diabetes, hypertension status, dyslipidemia status, intervention group, metabolic equivalents (METs)-min/d (adding a quadratic term to account for a nonlinear 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 the two active arms of the trial that received the MeDiet intervention in a single category. For WHtR, we used the 75th percentile as the cutoff point to dichotomize the WHtR (one degree of freedom). To better

guarantee comparisons to other studies, we used sex-specific cutoff points for WC according to the widely accepted international recommendations [13]. We also repeated the analyses using the 90th sex-specific percentile of WC as the cutoff point, as suggested by our dose–response analysis. For BMI, the commonly accepted 25 and 30 kg/m^2 cutoff points were used. We evaluated the interaction between WC (dichotomized at the 90th sex-specific percentile) and the intervention, and between BMI (two categories, cutoff = 30 kg/m^2) and the intervention (two categories) on cardiovascular events using the likelihood ratio test (one 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 the 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 within each intervention group. The HRs showed an increased risk in the upper (vs. the lowest) quartile, but this direct association was only apparent in the control group. A significant linear trend (p = 0.019) was also apparent only in the control group. No association was observed in the two groups that received MeDiet interventions.

The interaction between baseline WHtR (dichotomized at the 75th percentile, WHtR ≥0.67) and the intervention was statistically significant (p = 0.034), 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 cutoff points. However, when we dichotomized WC at the 90th sex-specific percentile (≥112 cm in females and ≥115 cm in males), the multiple adjusted HR associated with waist >90th 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 only 0.90 (0.54–1.49) in both MeDiet groups merged together. The interaction between a high BMI (>30 kg/m^2) and the intervention (MeDiet vs. 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 75th percentile (<0.67) or above it (≥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 75th percentile.

Table 1 Baseline characteristics of PREDIMED participants according to the intervention group.

Characteristic	Group of intervention		
	MeDiet + VOO	MeDiet + nuts	Control group
	N = 2543	N = 2454	N = 2450
Waist-to-height ratio (mean ± SD)	0.63 ± 0.06	0.63 ± 0.06	0.63 ± 0.07
Waist circumference – cm (mean ± SD)	100 ± 10.4	100 ± 10.5	101 ± 10.8
Body mass index (mean ± SD)	29.9 ± 3.7	29.7 ± 3.8	30.2 ± 4.0
Female sex – (%)	58.7	54.0	59.7
Age – year (mean ± SD)	67.0 ± 6.2	66.7 ± 6.1	67.3 ± 6.3
Smoking – (%)			
Never	61.8	59.7	62.3
Former smoker	24.3	25.8	23.8
Current	13.9	14.5	13.8
Overweight (BMI ≥ 25) – (%)	92.4	91.7	93.4
Obesity (BMI ≥ 30) – (%)	47.31	44.5	49.2
Hypertension – (%)	82.1	82.5	83.7
Type-2 diabetes – (%)	50.4	46.6	48.5
Dyslipidemia – (%)	71.6	73.3	72.0
Family history of premature CHD – (%)	22.7	21.7	22.9
Leisure-time physical activity: METs-min/d (mean ± SD)	230.3 ± 229.9	247.0 ± 245.6	214.1 ± 239.4
MeDiet adherence score (mean ± SD)	8.7 ± 2.0	8.7 ± 2.0	8.4 ± 2.1

MeDiet: Mediterranean diet.
EVOO: extra-virgin olive oil.
SD: standard deviation.
BMI: body mass index.
CHD: coronary heart disease.
MET: metabolic equivalent tasks.

Table 2 Intake of energy, nutrients, and supplemental foods at baseline and at the end (3-year follow-up) of the PREDIMED Trial by Study Group.

	MeDiet + extra-virgin olive oil (n = 2364)		MeDiet + nuts (n = 2108)		Control diet (n = 1941)	
	Baseline	3-year follow-up	Baseline	3-year follow-up	Baseline	3-year follow-up
	Mean (SD)		Mean (SD)		Mean (SD)	
Energy (kcal)	2257 ± 550	2172 ± 475	2276 ± 527	2229 ± 477	2186 ± 535	1960 ± 497
Total protein (% E)	16.7 ± 2.8	16.2 ± 2.4	16.6 ± 2.7	16.4 ± 2.5	16.6 ± 2.8	17.1 ± 3.0
Total carbohydrate (%E)	41.7 ± 7.2	40.4 ± 5.9	41.4 ± 7.0	39.7 ± 6.3	42.2 ± 7.1	43.7 ± 7.0
Total fat (%E)	39.2 ± 6.9	41.2 ± 5.4	39.4 ± 6.5	41.5 ± 6.1	39.0 ± 7.0	37.0 ± 7.0
Saturated fatty acids (%E)	10.0 ± 2.2	9.4 ± 2	10.0 ± 2.1	9.3 ± 2.0	10.0 ± 2.3	9.1 ± 2.1
Monounsaturated fatty acids (%E)	19.6 ± 4.6	22.1 ± 3.7	19.6 ± 4.3	20.9 ± 4.1	19.3 ± 4.7	18.8 ± 4.6
Polyunsaturated fatty acids (%E)	6.1 ± 2.1	6.1 ± 1.4	6.4 ± 2.0	7.7 ± 1.8	6.2 ± 2.1	5.5 ± 1.7
Linoleic acid, (g/d)	12.9 ± 6.0	12.2 ± 4.6	13.6 ± 6.1	16.0 ± 5.5	12.6 ± 6.0	10.0 ± 4.8
Alpha-linolenic acid, (g/d)	1.4 ± 0.7	1.3 ± 0.7	1.5 ± 0.7	1.9 ± 0.7	1.3 ± 0.6	1.1 ± 0.5
Marine n-3 fatty acids (g/d)	0.8 ± 0.5	0.9 ± 0.5	0.8 ± 0.5	0.8 ± 0.5	0.8 ± 0.5	0.7 ± 0.4
Fiber (g/d)	25.7 ± 9.1	25.4 ± 7.5	25.7 ± 8.6	27.0 ± 8.0	24.7 ± 8.4	23.7 ± 7.7
Olive oil (%E)	16.3 ± 7.1	22.0 ± 6.0	15.9 ± 6.7	17.6 ± 6.4	15.8 ± 7.4	16.4 ± 6.8
Nuts (% E)	2.5 ± 3.4	2.6 ± 3.1	3.3 ± 3.7	8.2 ± 4.5	2.4 ± 3.2	1.6 ± 2.5
Cholesterol (mg/d)	363 ± 131	339 ± 101	367 ± 117	338 ± 99	356 ± 122	324 ± 106

Note: In the Mediterranean diet with extra-virgin olive oil, Mediterranean diet with nuts, and control diet groups, 42, 57, and 25 participants, respectively, were excluded from calculations of food intake because their total energy intake was outside the prespecified ranges.

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]. However, 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 a 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

Table 3 Hazard Ratios (95% confidence intervals) for cardiovascular major events according to baseline quartiles of the waist-to-height ratio within each of the three intervention groups. The PREDIMED study 2003–2010.

	Quartiles of the Waist-to-height ratio			
	1 (lowest)	2 3	4 (highest)	
Range	0.30 to 0.59	0.59 to 0.67	0.67 to 1.00	
MeDiet with nuts				
Number of events	20	42	21	p for trend
Person-years	2885	5196	2284	
Age-, sex-adjusted HR	1 (ref.)	1.15 (0.68–1.93)	1.32 (0.71–2.43)	0.381
Multivariable adjusted[a]	1 (ref.)	1.21 (0.69–2.12)	1.36 (0.74–2.51)	0.316
MeDiet with EVOO				
Number of events	20	55	21	
Person-years	2946	6116	2790	
Age-, sex-adjusted HR	1 (ref.)	1.25 (0.76–2.08)	1.18 (0.63–2.21)	0.579
Multivariable adjusted[a]	1 (ref.)	1.27 (0.72–2.24)	1.23 (0.65–2.31)	0.514
Control diet				
Number of events	23	46	40	
Person-years	2346	4856	2560	
Age-, sex-adjusted HR	1 (ref.)	0.95 (0.57–1.60)	1.83 (1.07–3.11)	0.023
Multivariable adjusted[a]	1 (ref.)	1.02 (0.60–1.74)	1.98 (1.10–3.57)	0.019

HR, hazard ratio; MeDiet, Mediterranean diet; EVOO, extra-virgin olive oil.
All estimates are stratified for study center.
The interaction term between intervention (both Mediterranean groups merged together) and waist-to-height ratio (dichotomized at ≥0.67) was statistically significant (p = 0.034) in the multivariable-adjusted model.
[a] Adjusted for age, sex, smoking, diabetes, hypertension, dyslipidemia, physical activity, and family history of early-onset coronary artery disease.

Table 4 Hazard ratios of cardiovascular disease according to waist circumference or body mass index and intervention group. The PREDIMED trial.

Waist circumference				
Limits (cm)	Waist: cutoff = harmonized criteria			
Men	<94	94–102	>102	
Women	<80	80–88	>88	
MeDiet (both groups merged)				
Number of events	20	42	117	
Person-year	2247	4720	15249	*P* for trend
Age-adjusted, sex-adjusted HR	1 (ref.)	1.06 (0.62–1.82)	1.08 (0.66–1.79)	0.694
Multivariable adjusted	1 (ref.)	0.93 (0.54–1.60)	0.96 (0.57–1.60)	0.831
Control group				
Number of events	11	21	77	
Person-years	823	2020	6919	
Age-adjusted, sex-adjusted HR	1 (ref.)	0.83 (0.40–1.73)	1.15 (0.60–2.19)	0.250
Multivariable adjusted	1 (ref.)	0.77 (0.36–1.63)	1.03 (0.52–2.04)	0.450
p for interaction[a]			0.475	
Waist circumference				
Limits (cm)	Waist: cutoff = sex-specific 90th percentile			
Men	<115	≥115		
Women	<112	≥112		
MeDiet (both groups merged)				
Number of events	163	16		
Person-year	20219	1997		*p* value
Age-adjusted, sex-adjusted HR	1 (ref.)	0.95 (0.56–1.59)		0.840
Multivariable adjusted	1 (ref.)	0.97 (0.59–1.98)		0.898
Control group				
Number of events	91	18		
Person-year	8806	956		
Age-adjusted, sex- adjusted HR	1 (ref.)	2.03 (1.22–3.39)		0.007
Multivariable adjusted	1 (ref.)	1.96 (1.15–3.33)		0.013
p for interaction[b]		0.0426		
Body mass index				
Limits (kg/m^2)	<25	25–30	>30	
MeDiet (both groups merged)				
Number of events	18	88	73	
Person-year	1801	10244	10172	*P* for trend
Age-adjusted, sex- adjusted HR	1 (ref.)	0.88 (0.54–1.45)	0.82 (0.49–1.37)	0.112
Multivariable adjusted	1 (ref.)	0.98 (0.61–1.60)	0.90 (0.54–1.49)	0.302
Control group				
Number of events	7	37	65	
Person-years	664	4281	4818	
Age-adjusted, sex-adjusted HR	1 (ref.)	0.80 (0.36–1.78)	1.42 (0.66–3.08)	0.570
Multivariable adjusted	1 (ref.)	0.98 (0.41–2.36)	1.56 (0.64–3.78)	0.654
p for interaction[c]		0.0096		

[a] Likelihood-ratio test with one degree of freedom. The cutoff point for waist circumference was 102 cm for males and 88 cm for females.
[b] Likelihood-ratio test with one degree of freedom.
[c] Likelihood-ratio test with one degree of freedom. The cutoff point for body mass index was 30 kg/m^2.

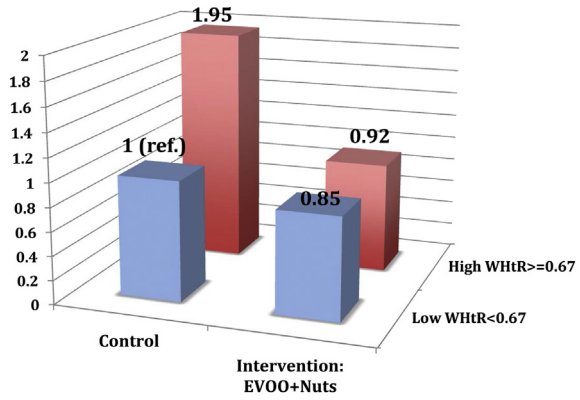

Figure 1 Multivariable-adjusted hazard ratios of cardiovascular disease according to the joint classification by intervention and baseline waist-to-height ratio (WHtR). WHtR: Waist-to-Height Ratio (waist [cm]/height [cm]). EVOO: Extra-Virgin Olive Oil (Intervention with Mediterranean diet and free provision of extra-virgin olive oil). Nuts: Intervention with Mediterranean diet and free provision of mixed nuts (walnuts, hazelnuts and almonds). Adjusted for age, sex, smoking, diabetes, hypertension, physical activity, dyslipidemia, and family history of early-onset coronary artery disease.

to more precisely measure central obesity than other anthropometrical measurements such as BMI [2–5,15]. However, the apparent interaction was also replicated with WC and BMI.

Obesity, especially 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, especially when it is supplemented with EVOO 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 suggest 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 the 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, by 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 baseline abdominal adiposity.

We speculate that a longer follow-up (e.g., after 10 years) 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 number of events was not large, and 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), planning to recruit 6000 participants with abdominal obesity, and we will randomly allocate them to two diets: (a) the control group will receive a traditional MeDiet without energy restriction (as the PREDIMED trial did) and (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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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 this manuscript.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.numecd.2015.03.001.

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