

May the Mediterranean diet attenuate the risk of type 2 diabetes associated with obesity: the Seguimiento Universidad de Navarra (SUN) cohort

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(Submitted 3 February 2017 – Final revision received 4 May 2017 – Accepted 16 May 2017 – First published online 19 June 2017)

Abstract

It is likely that the Mediterranean diet (MedDiet) may mitigate the adverse effects of obesity on the incidence of type 2 diabetes mellitus (T2DM). We assessed this hypothesis in a cohort of 18 225 participants initially free of diabetes (mean age: 38 years, 61 % women). A validated semi-quantitative 136-item FFQ was used to assess dietary intake and to build a 0–9 score of adherence to MedDiet. After a median of 9.5-year follow-up, 136 incident cases of T2DM were confirmed during 173 591 person-years follow-up. When MedDiet adherence was low (≤ 4 points), the multivariable-adjusted hazard ratios (HR) were 4.07 (95 % CI 1.58, 10.50) for participants with BMI 25–29.99 kg/m² and 17.70 (95 % CI 6.29, 49.78) kg/m² for participants with BMI ≥ 30 kg/m², (*v.* < 25 kg/m²). In the group with better adherence to the MedDiet (> 4 points), these multivariable-adjusted HR were 3.13 (95 % CI 1.63, 6.01) and 10.70 (95 % CI 4.98, 22.99) for BMI 25–30 and ≥ 30 kg/m², respectively. The *P* value for the interaction was statistically significant (*P* = 0.002). When we assessed both variables (BMI and MedDiet) as continuous, the *P* value for their interaction product-term was marginally significant (*P* = 0.051) in fully adjusted models. This effect modification was not explained by weight changes during follow-up. Our results suggest that the MedDiet may attenuate the adverse effects of obesity on the risk of T2DM.

Key words: Mediterranean diet: Diabetes: Obesity: BMI: Cohorts

Type 2 diabetes mellitus (T2DM) is considered one of the major epidemics of the twenty-first century. In 2014, WHO estimated that, worldwide, 422 million suffer from diabetes, almost doubling the prevalence in 1980⁽¹⁾. This trend is expected to continue over the coming years, and the International Diabetes Federation estimates that in 2040 there will be 642 million people living with diabetes⁽²⁾. Moreover, T2DM is a leading cause of many severe complications such as CVD, blindness, kidney failure and lower limb amputation⁽³⁾ with the consequent costs to the healthcare system⁽⁴⁾. Therefore, it is essential to assess lifestyle interventions effects on risk factors related to T2DM.

Obesity is a major preventable risk factor for T2DM^(1,2). A new approach in the dietary control of overweight and obesity for the prevention of T2DM should include well known, healthy (cardio-protective), high-quality and palatable dietary patterns. One dietary paradigm that may be beneficial in this

context is a traditional Mediterranean diet (MedDiet), relatively rich in fat from vegetable sources (extra-virgin olive oil, tree nuts) and including an abundance of minimally processed plant-foods (vegetables, fruits, whole grains, legumes), moderate fish consumption, low consumption of meat and meat products, and wine in moderation, usually consumed with meals.

Recent studies support that a better adherence to MedDiet could mitigate the adverse consequences of obesity on CVD even in obese persons at high cardiovascular risk^(5,6). There is strong evidence that modifications in the overall dietary pattern and the adoption of high-quality diets, such as the traditional MedDiet, together with an intervention aimed to promote weight loss may play an important role in decreasing the incidence of T2DM^(7–10). Nevertheless, it is not known whether any dietary change different from weight loss could attenuate the acknowledged adverse effects of obesity on the risk of T2DM.

Abbreviations: HR, hazard ratio; MedDiet, Mediterranean diet; PREDIMED, Prevención con dieta Mediterránea; T2DM, type 2 diabetes mellitus.

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In this study we aimed to assess if only changes in the composition of the food pattern, without any additional weight loss, physical activity or energy restriction can reduce the obesity-associated risk of T2DM. We tested the hypothesis that a higher adherence to a non-energy-restricted MedDiet may mitigate the adverse effect of obesity on the incidence of T2DM.

Methods

Study population

The Seguimiento Universidad de Navarra (SUN) Project is a dynamic multipurpose prospective Spanish cohort of university graduates. This cohort started in 1999 with biennial collection of updated information through self-administered questionnaires and it is permanently open to recruitment of new participants. The aim of this cohort was to assess associations between diet or lifestyles and the incidence of several chronic diseases and mortality. Details of the design, methods and objectives of the SUN Project have been described previously^(11,12).

For the present analyses we assessed 22 476 participants who had answered the baseline questionnaire before December 2015 (Fig. 1). We excluded 406 participants who had prevalent diabetes at baseline and also participants who had not remained in the cohort enough time for being followed-up for at least 2 years (2376). In addition, 1469 participants were excluded because they reported a total daily energy intake out of pre-defined limits (>2092 or <23 012 kJ/d (>500 or

<5500 kcal/d) for female, >3347 or <25 104 kJ/d (>800 or <6000 kcal/d) for male). After exclusions, the final population sample included a total of 18 225 participants.

Ethical approvals

The study protocol was approved by the Institutional Review Board of the University of Navarra. Voluntary completion of the first questionnaire was considered to imply informed consent.

All clinical investigation were conducted according to the guidelines laid down in the Declaration of Helsinki and it was approved by the Human Research Ethical Committee of the University of Navarra.

Anthropometric variables

Information about weight was recorded at baseline and at each follow-up questionnaire. BMI, defined as weight in kilograms divided by the square of height in metres, was calculated in the baseline questionnaire. Reliability of self-reported weight and height to compute BMI was assessed in a subsample of the cohort⁽¹³⁾. A high correlation was found with directly measured weight (r 0.99; 95% CI 0.99, 0.99) and BMI (r 0.94; 95% CI 0.91, 0.97), with mean relative errors of 1.45 and 2.64%, respectively.

Dietary assessment

A validated semi-quantitative 136-item FFQ⁽¹⁴⁾ was used to assess dietary intakes over the previous year. The validity^(14,15) and reproducibility⁽¹⁶⁾ of this FFQ have been repeatedly reported. In order to calculate each nutrient score, nutrient composition of specified portion sizes (using data from food composition tables valid for Spain^(17,18)) was multiplied by the frequency of consumption of each participant. Consumption frequencies were grouped in nine categories (ranging from never/almost never, to >6 times/d) for each food item. A nine-item scale proposed by Trichopoulou *et al.*⁽¹⁹⁾ was used to classify participants according to their baseline adherence to the MedDiet⁽²⁰⁾. One point was assigned to persons whose consumption was above the sex-specific median of components most in line with the traditional MedDiet (vegetables, fruits/nuts, legumes, fish/seafood, cereals and MUFA:SFA lipid ratio). One point was assigned to persons whose consumption was below the sex-specific median of components against the traditional MedDiet (meat/meats products, dairy products). For ethanol, 1 point was assigned to men consuming 10–50 g/d and to women consuming 5–25 g/d, otherwise, no point was assigned.

Outcome assessment

Ascertainment of T2DM in the SUN Project has been reported before⁽²¹⁾. Participants who reported at baseline having been treated with either oral antidiabetic agents or insulin or reported a medical diagnosis of T2DM were considered prevalent cases of diabetes at baseline and were excluded. We considered probable cases of new-onset diabetes to those participants who reported a T2DM clinical diagnosis during any follow-up questionnaire but did not have diabetes at baseline⁽²¹⁾.

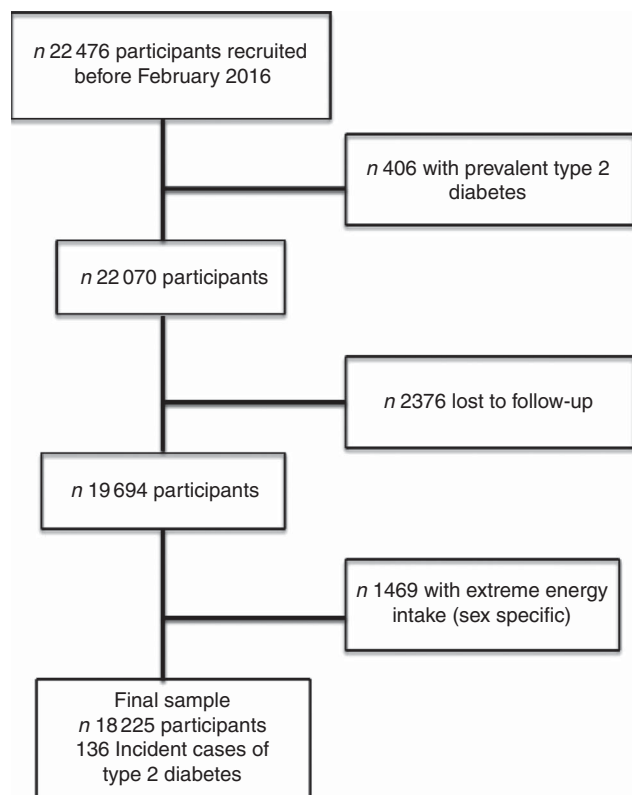


Fig. 1. Flow chart of participants in the Seguimiento Universidad de Navarra Project, 1999–2016.

These participants were asked to confirm their diagnosis with additional-specific confirmation questionnaires where they specified further details (i.e. type of diabetes, date of diagnosis, whether the diagnosis was gestational diabetes, highest fasting glucose value, eventual oral glucose tolerance testing, glycosylated Hb (HbA1c), current use of oral antidiabetic agents or insulin and occurrence of complications) and to provide a copy of their medical reports to ensure a sufficiently high specificity in the classification of incident cases. An endocrinologist, blinded to the dietary variables, revised the information collected with the diabetes-specific questionnaires and the medical records of participants to adjudicate new-onset (incident) cases of T2DM. The American Diabetes Association's criteria were used to classify incident cases of T2DM⁽²²⁾.

Other covariates

At baseline questionnaire, information was gathered about socio-demographic variables (age, marital status, years of university education), health-related habits (smoking status, energy intake, physical activity, sedentary lifestyles, hours of television watching) and clinical variables (medications, personal history of hypertension, diabetes, hypercholesterolaemia, cancer, depression, CVD).

Physical activity was assessed at baseline using a previously validated questionnaire that contained time spent in seventeen different activities⁽²³⁾. Physical activity was expressed in metabolic equivalent tasks-h/week as calculated from the time spent at each activity in h/week multiplied by its typical energy expenditure⁽²⁴⁾. The validity of this questionnaire of physical activity was formally tested in a specific study within a subset of this cohort⁽²³⁾.

Statistical analysis

We estimated statistical power assuming an absolute total cumulative incidence of T2DM=0.8%, sample sizes of 12 000 and 700 in extreme categories of BMI (<25 and >30 kg/m², respectively), with expected relative risks between 6 and 8 (a realistic assumption based on previous literature). Under these assumptions and with a two-tailed α error of 5%, the expected statistical power will range between 0.78 and 0.84. Specifically for interactions, the proposed minimum sample size in each group to obtain a sufficiently high statistical power for assessing interactions was 900/group in the article by Demidenko⁽²⁵⁾ and we had a similar sample size in our groups.

We examined baseline characteristics of participants stratified by their baseline BMI and according to their baseline adherence to MedDiet. Adherence to MedDiet was categorised into two groups (≤ 4 and > 4 points in the Trichopoulou's score).

We used Cox regression models to assess the hazard ratios (HR) and their 95% CI for incident T2DM across categories of BMI (cut off points: 25 and 30 kg/m²). Age was used as the underlying time variable and we stratified all Cox models by broad categories of age (decades). The fully adjusted model included the following potential confounders: sex, year of recruitment (four categories), adherence to the MedDiet (continuous within each strata of poor and good adherence); smoking status (three categories: former smokers, current

smokers and never smokers), physical activity during leisure time (continuous), hours of television watching, hypertension status, hypercholesterolaemia status, depression, cancer, CVD, years of university education, energy intake, marital status, following special diets and between-meal snacking.

In subgroup analyses we stratified the results by baseline adherence to the MedDiet (categorised into two groups: poor adherence (≤ 4 points) and good adherence (> 4 points)). The *P* value for multiplicative interaction was calculated by comparing a full model including a multiplicative interaction term to a reduced model without an interaction term, using a likelihood ratio test. We used both a 2 df product-term (dichotomous MedDiet and three categories for BMI) and a 1 df product-term (both variables as continuous).

To address the possibility that the beneficial effect of the MedDiet on T2DM might be explained only by changes in weight during follow-up we conducted an ancillary analysis where we assessed whether the inverse association between better adherence to the MedDiet and T2DM was attenuated after adjusting for weight changes during follow-up.

To assess non-linear associations we fitted fully adjusted restricted cubic spline models for the association between BMI and incident diabetes stratified by adherence to the MedDiet.

A *P* value <0.05 was considered statistically significant. Analyses were performed using STATA SE version 12.1 (StataCorp LP).

Results

Baseline characteristics of participants stratified by their baseline BMI and according to their baseline adherence to MedDiet are shown in Table 1. Those participants who reported higher levels of adherence to MedDiet were on average older, more likely to be married and more physically active. In the baseline cross-sectional analyses, they also were more likely to have a previous diagnosis of hypercholesterolaemia, hypertension, CVD, cancer or depression, probably because these conditions may have led them to improving their dietary habits. In addition, these participants with better adherence to the MedDiet at baseline were also less likely to be current smokers but more prone to being former smokers. They were also more likely to follow special diets and to consume more alcohol, but were less likely to consume snacks between meals.

After a median of 9.5 years of follow-up we observed 136 incident T2DM cases.

The relationship between categories of BMI and the risk of T2DM according to their baseline adherence to MedDiet (≤ 4 and > 4 points in the Trichopoulou's score) is shown in Table 2. We observed that the HR increased across categories of BMI in both groups built according to conformity with the MedDiet. However, after multivariable adjustment, we observed that in the stratum of low adherence to MedDiet, the obesity-associated HR for T2DM were significantly higher than in the stratum of high adherence to MedDiet. The *P* value for multiplicative interaction between MedDiet and BMI was statistically significant (*P*=0.002). In fully adjusted models, the association between BMI and the risk of diabetes was stronger when the adherence to the MedDiet was poorer (HR=2.50; 95% CI 1.93, 3.24 for each additional standard

Table 1. Baseline characteristics of participants according to their baseline BMI and their adherence to the Mediterranean diet (MedDiet) (Mean values and standard deviations; percentages)

	Low adherence to MedDiet ($\leq 4/9$)				High adherence to MedDiet ($> 4/9$)			
	BMI < 25 kg/m ²	BMI 25–30 kg/m ²	BMI > 30 kg/m ²	<i>P</i> *	BMI < 25 kg/m ²	BMI 25–30 kg/m ²	BMI > 30 kg/m ²	<i>P</i> *
<i>n</i>	7111	2136	401		5921	2265	391	
Age (years)				< 0.001				0.031
Mean	33.4	40.8	42.3		37	45.7	46.0	
SD	9.6	11.5	12.3		11.5	12.0	11.9	
Women (%)	73.3	30.2	30.4	< 0.001	75.2	30.6	30.2	< 0.001
Year of recruitment				0.004				0.08
Mean	2003	2003	2003		2004	2004	2004	
SD	3	3	3		3	3	3	
BMI (kg/m ²)				< 0.001				< 0.001
Mean	21.6	26.9	32.4		21.8	26.9	32.7	
SD	2.0	1.3	2.3		1.9	1.3	3.1	
Energy intake (kJ/d)				< 0.001				0.001
Mean	10 364	9665	9945		11 075	10 770	10 941	
SD	3188	3117	3372		3276	3272	3527	
Energy intake (kcal/d)				< 0.001				0.001
Mean	2447	2310	2377		2647	2574	2615	
SD	762	745	806		783	782	843	
Physical activity (METs)				< 0.001				< 0.001
Mean	20.2	20.3	15.7		25.3	23.4	17.5	
SD	21.7	21.9	18.2		25.6	22.8	17.1	
Marital status (%)								
Single	57.6	35	30.9		49.3	26	27.6	
Married	39.4	61.3	63.3		46.5	69.1	66.5	
Others	3	3.7	5.7	< 0.001	4.2	4.9	5.9	< 0.001
Smoking								
Current smokers (%)	23.4	21.1	20.0		21.6	19.2	18.4	
Former smokers (%)	21.1	32.8	37.9		27.8	41.9	46	
Never smokers (%)	55.5	46.1	42.1	< 0.001	50.7	38.9	35.6	< 0.001
Hypercholesterolaemia (%)	10.7	20.1	30.9	< 0.001	14.7	30	35	< 0.001
Hypertension (%)	2.5	10.3	21.5	< 0.001	3.9	15	27.4	< 0.001
CVD (%)	0.4	1.3	1.3	< 0.001	0.7	2.4	3.1	< 0.001
Cancer (%)	2.4	2.6	4.2	0.069	3.1	3.2	3.3	0.916
Depression (%)	4.8	3.4	2.2	0.002	4.4	3.8	3.6	0.327
Years of university education (%)								
Graduate	23.5	17.6	21.0		26.9	21.2	22.3	
Postgraduate	48.8	52.9	50.9		47.0	49.7	49.4	
Master degree	8.2	8.1	8.7		7.6	7.6	9.2	
Doctoral degree	8.6	12.4	9.5		9.2	13.3	9.5	
Other	10.9	9.2	10.0	< 0.001	9.4	8.2	9.7	< 0.001
Television watching (h/week)								
Mean	1.6	1.7	1.8	0.001	1.6	1.7	1.8	< 0.001
SD	1.2	1.2	1.2		1.2	1.1	1.2	
Number of alcohol intake (g/d)								
Mean	3.5	5.53	6.2	< 0.001	4.7	7.4	9.4	< 0.001
SD	6.3	11.3	12.6		7.2	10.1	14.1	
Between-meal snacking (%)	37.3	36	54.9	< 0.001	30.4	32.2	43.7	< 0.001
Following special diets (%)	4.5	7.9	13.7	< 0.001	8.1	11.3	17.9	< 0.001

* *P* values for the comparison of percentages or means across the three BMI categories, separately within each group of adherence to the MedDiet (≤ 4 or > 4).

deviation in BMI) than when the MedDiet score was higher than 4 points (HR 2.01; 95% CI 1.72, 2.36). The *P* value for interaction between MedDiet and BMI (both as continuous variables) was marginally significant ($P = 0.051$). When the non-confirmed cases were included (in total 169 cases) the results were similar (and the $P_{\text{for interaction}}$ became significant, $P = 0.025$).

We conducted an ancillary analysis after adjusting for weight changes during follow-up. The average yearly weight changes during follow-up were -0.467 and $+0.225$ kg/year among participants who eventually developed and did not develop T2DM during follow-up, respectively. Therefore, there was no indication that weight gain during follow-up may explain the development

of T2DM because weight loss (and not weight gain) during follow-up occurred more likely in cases than in non-cases. After additionally adjusting for weight changes, the HR for each additional standard deviation in BMI were 2.31 (95% CI 1.77, 3.01) kg/m² when adherence to the MedDiet was poor (0–4 points) and 1.95 (95% CI 1.66, 2.30) when it was good (> 4 points), and the interaction remained statistically significant ($P = 0.025$).

We fitted spline models to represent graphically the relationship between baseline BMI and the risk of developing T2DM during the follow-up period according to baseline adherence to the MedDiet (≤ 4 points and > 4 points). We observed that in the group with poor adherence to MedDiet the

Table 2. Relative risks of type 2 diabetes in the Seguimiento Universidad de Navarra project according to baseline BMI and adherence to Mediterranean diet (MedDiet) (Hazard ratios (HR) and 95% confidence intervals)

BMI (kg/m ²)...	Low adherence to MedDiet (0–4)			High adherence to MedDiet (>4–9)			<i>P</i> _{for interaction}
	<25	25–30	>30	<25	25–30	>30	
<i>n</i>	7111	2136	401	5921	2265	391	
Median BMI	21.6	26.6	31.7	21.8	26.6	31.6	
Events	8	27	23	15	37	26	
Person-years	69 817	20 430	3604	55 586	20 817	3336	
Sex-, age-adjusted							0.562
HR	1	4.77	21.16	1	3.52	14.76	
95% CI	Ref.	1.89, 12.03	7.82, 57.26	Ref.	1.87, 6.63	7.21, 30.22	
Multiple adjusted*							0.002
HR	1	4.07	17.70	1	3.13	10.70	
95% CI	Ref.	1.58, 10.50	6.29, 49.78	Ref.	1.63, 6.01	4.98, 22.99	
For each sd in BMI*							0.051†
HR		2.50			2.01		
95% CI		1.93, 3.24			1.72, 2.36		

Ref., referent values.

* Adjusted for age, sex, recruitment year, smoking (three categories: former smokers, current smokers and never smokers), adherence to the Mediterranean diet (continuous), hypercholesterolaemia, hypertension, physical activity, marital status, prevalent CVD, prevalent cancer, prevalent depression, years of university studies, television watching time, snacks intake and special diets. The multiplicative interaction was assessed with a 2 df product-term (dichotomous MedDiet and three categories for BMI).

† Both the nine-item Mediterranean score and BMI were introduced as continuous variables in the product-term used to assess effect modification. 1 df product-term was used to test the *P* value of interaction.

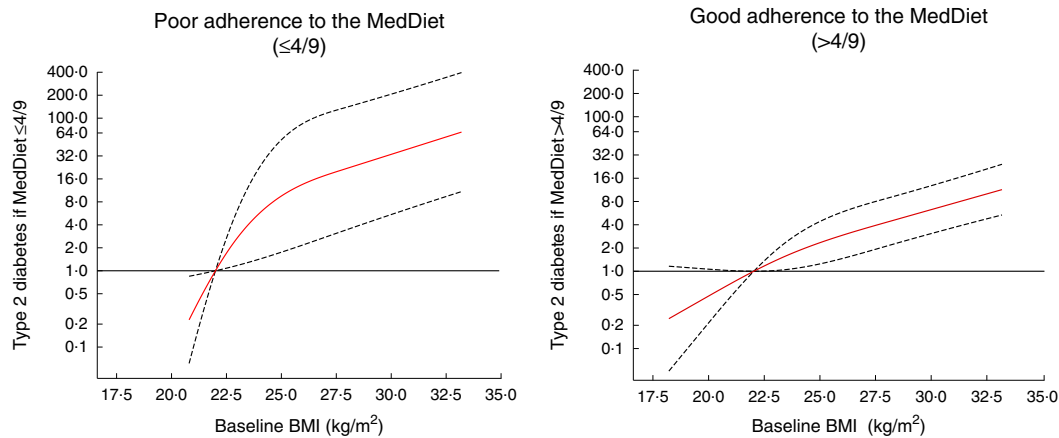


Fig. 2. Dose–response association between baseline BMI and the incidence of type 2 diabetes according to baseline adherence to the Mediterranean diet (MedDiet). The Seguimiento Universidad de Navarra cohort (1999–2015). Values are hazard ratios and 95% CI.

BMI-associated relative risk of T2DM was visibly higher than in the group with better adherence (Fig. 2).

Discussion

In this multipurpose cohort of university graduates we observed an attenuation in the association between high BMI and the risk of developing T2DM in participants with better adherence to MedDiet, after adjusting for other common risk factors in T2DM. This study supports our hypothesis that a higher adherence to MedDiet could mitigate the pernicious effect of obesity on the incidence of T2DM even without inducing loss of weight. In fact, we found a statistically significant interaction (assuming a multiplicative scale for interaction), and our finding is consistent with the inverse association between the MedDiet and the risk of T2DM observed in this cohort⁽²¹⁾ and in other previous studies such as the observational Nurses’s Health Study⁽²⁶⁾,

the EPIC Study⁽²⁷⁾ or the Prevención con dieta Mediterránea (PREDIMED) randomised trial^(8,9). In addition, a recent meta-analysis⁽²⁸⁾ reported a strong association between better adherence to MedDiet and a reduction in the risk of T2DM.

Although at baseline we observed that participants with better adherence to the MedDiet were more likely to have a previous diagnosis of hypercholesterolaemia, hypertension, CVD, cancer or depression, these results could be explained because those differences were based on simple cross-sectional analyses where reverse causality could not be excluded.

It is well known that there is a strong relationship between overweight/obesity and the risk of developing T2DM. In fact, the main measure proposed to prevent T2DM is a weight reduction through an intervention with diet and lifestyle^(29,30–32). Interventions addressing lifestyles, including physical activity, weight reductions and energy-restricted diets, have been successful in achieving a reduction in the incidence of diabetes mellitus in the

long term^(32,33). However, the role of the overall nutritional quality in the prevention of T2DM independent of weight changes, has not been fully addressed by these trials. The paradigm used in most of these trials, including a recent trial for cardiovascular prevention in participants who were already diabetics at baseline (the Look Action for Health in Diabetes (Look AHEAD) trial⁽³⁴⁾), was a low-energy, low-fat diet. In contrast with the low-energy, low-fat diet, the MedDiet represents an updated paradigm of overall dietary quality, with demonstrated effectiveness and sustainability and with the potential to be globally applied^(10,35,36).

The novelty of our research is the suggestion of a reduction in the risk of T2DM by the MedDiet that may attenuate the detrimental effects of increased body weight. We did extra analyses in the multivariable adjustment to take into account the observed yearly average changes in the weight of our participants, and we did not observe any substantial attenuation of our results after adjusting for weight changes during follow-up. This result points to an inherent beneficial effect of a high-quality overall dietary pattern on diabetes risk independent of weight loss. Interestingly, our results are in line with recent studies that assessed a reduction in major CVD events associated with closer conformity with the MedDiet in obese patients with high cardiovascular risk, thereby mitigating the adverse effect of abdominal adiposity^(5,6). In this line, the PREDIMED trial assessed a significant reduction in the risk of T2DM^(9,37). Our results are of particular interest in the context of the current concerns to assess whether interventions with a rationale different from the Look AHEAD trial^(31,32) can provide a better answer to the current epidemics of obesity and T2DM. Specifically, the quality of the diet could be a more important factor for the prevention of T2DM and its cardiovascular complications than the weight loss⁽³⁸⁾. A new large trial focused on MedDiet, weight loss and physical activity (PREDIMED-PLUS) is ongoing (<http://medpreventiva.es/cD5Mp1>). Almost 7000 participants have been already randomised to two equally sized arms in the new PREDIMED-PLUS trial, these two arms are an energy-restricted MedDiet plus physical activity and weight loss in the intensive intervention group, but only MedDiet (without energy restriction or physical activity) in the control group. They will be in the trial for the next 5 years. The primary endpoint is a composite of hard cardiovascular events (myocardial infarction, stroke or CVD death). Results are expected in 2021. An intervention based in an energy-restricted MedDiet together with physical activity in order to obtain weight loss could achieve even greater benefits in obese subjects, than the benefit assessed by the initial PREDIMED study.

Obesity is a well-known risk factor for CVD independent of BMI^(31,39) and the MedDiet could play an important role by reducing the inflammatory mediators involved in the adverse consequences of abdominal adiposity^(7,21,40,41). It is known that all food intake is accompanied by a mild inflammatory oxidative condition that increases plasma levels of inflammatory biomarkers reducing the sensitivity of tissues to insulin that leads to a state of insulin resistance^(42,43). Plant foods typical of the MedDiet are rich in antioxidants and anti-inflammatory elements. Their joint and synergistic effects are likely to be important because the effect of the overall dietary pattern

captures interactions between nutrients and results in a stronger effect⁽⁴⁴⁾. The MedDiet pattern may reduce the risk of T2DM by increasing adiponectin levels⁽⁴⁵⁾, reducing oxidative stress^(45,46) as well as reducing low-grade inflammation^(47,48).

There are several strengths in our research. We used a cohort with a prospective design, including a large number of participants and with a high retention rate. Besides, we used multiple-adjusted models to control for a wide array of potential confounders. Our study shows a strong internal validity due to a high retention rate and sufficiently reliable self-reported measures reported by highly educated participants.

On the other hand, some limitations of our study deserve to be acknowledged. The information on several variables was assessed through self-reporting. However, parameters such as self-reported weight and height or usual diet have been previously validated in sub-samples of this cohort^(13,14). Another possible caveat might be the fact that the cohort is composed of middle-aged, highly educated persons, with a high level of physical activity which could limit the generalisability of our findings to other populations. We acknowledge that the SUN cohort is a relatively young cohort for diabetes research. Previous cohorts have usually included older participants. The advantage of a younger cohort is that it may offer unique characteristics to ascertain the earliest steps in the pathophysiological mechanisms relating dietary exposures to the risk of T2D. Therefore, our findings provide interesting clues with relevance for diabetes prevention research. The disadvantage of assessing these associations in a young cohort is that absolute risks are low, and the statistical power might be limited due to the low number of new cases of T2D. Given that the participants in our study live in a Mediterranean country, they are relatively young (mean baseline age was 38 years) and are, in general, health-conscious subjects, their consumption of products typical of the traditional MedDiet was high, even in participants with lower scores of conformity to the MedDiet. Therefore, under the assumption that the MedDiet plays a protective role against the development of diabetes, in a cohort with these characteristics it is not surprising to find a low incidence of T2DM. However, our findings need to be confirmed in future cohort studies and trials, given the low absolute risks of T2DM in our cohort of young, slim and highly educated adults.

Conclusions

Our prospective study suggests that a high adherence to MedDiet could mitigate the adverse effects of obesity on incidence of T2DM, without specifically requiring a loss of weight. However, due to the low incidence of T2DM further research is needed to confirm our findings.

Acknowledgements

The authors thank the SUN project participants for their enthusiastic collaboration and participation. The authors also thank the other members of the SUN study group: A. Alonso, I. Álvarez, A. Balaguer, I. Barrientos, M. T. Barrio-López, F. J. Basterra-Gortari, P. Bazal, S. Benito, J. J. Beunza, P. Buil-Cosiales, M. Canales, L. Carmona, S. Cervantes,

C. Cristobo, J. de Irala, C. de la Fuente-Arrillaga, M. Delgado-Rodríguez, J. Díaz-Gutiérrez, J. Díez Espino, L. Domínguez, C. Donat-Vargas, M. Donazar, A. Fernández-Montero, U. Fresán, C. Galbete, A. García-Arellano, M. García López, I. Gardeazábal, A. Gea, E. Gómez-Gracia, E. Goñi, F. Guillén, M. Gutiérrez-Bedmar, P. Henríquez, A. Hernández, E. Hu, F. Lahortiga, A. Leone, J. Llorca, C. López del Burgo, A. Marí, I. Marques, A. Martí, N. Martín Calvo, J. A. Martínez, R. Mendonça, P. Molero, J. M. Núñez-Córdoba, P. Pérez de Ciriza, A. Pérez Cornago, A. M. Pimenta, J. Pons, R. Ramallal, C. Razquin, A. Rico, C. Ruano, A. Ruiz Zambrana, E. Salgado, B. San Julián, D. Sánchez, A. Sánchez-Tainta, A. Sánchez-Villegas, S. Santiago, C. Sayón-Orea, E. Toledo, J. Toledo, Z. Vázquez, D. Zarnowiecki and I. Zazpe.

We have received funding from the European Research Council (Advanced Grant (AdG), LS7, ERC-2013-ADG, PREDIMEDPLUS, PI: M. A. M.-G.), the Spanish Government-Instituto de Salud Carlos III, and the European Regional Development Fund (FEDER) (RD 06/0045, CIBER-OBN, grants PI10/02658, PI10/02293, PI13/00615, PI14/01668, PI14/01798, PI14/01764 and G03/140), the Navarra Regional Government (45/2011, 122/2014) and the University of Navarra.

M. A. M.-G. conceived and designed the study; S. E. performed the research; S. E. and M. A. M.-G. analysed data and wrote the paper; all authors critically reviewed the manuscript and approved the final version.

The authors declare that there are no conflicts of interest.

References

1. World Health Organization (2016) Diabetes programme. <http://www.who.int/diabetes/> (accessed September 2016).
2. International Diabetes Federation (2015) IDF Diabetes Atlas, 7th ed. <http://www.idf.org/diabetesatlas> (accessed September 2016).
3. American Diabetes Association (2011) Diagnosis and classification of diabetes mellitus. *Diabetes Care* **34**, Suppl. 1, S62–S69.
4. Zimmet PZ, Magliano DJ, Herman WH, *et al.* (2015) Diabetes: a 21st century challenge. *Lancet Diabetes Endocrinol* **2**, 56–64.
5. Eguaras S, Toledo E, Hernández-Hernández A, *et al.* (2015) Better adherence to the Mediterranean Diet could mitigate the adverse consequences of obesity on cardiovascular disease: the SUN prospective cohort. *Nutrients* **7**, 9154–9162.
6. Eguaras S, Toledo E, Buil-Cosiales P, *et al.* (2015) Does the Mediterranean diet counteract the adverse effects of abdominal adiposity? *Nutr Metab Cardiovasc Dis* **25**, 569–574.
7. Kastorini CM & Panagiotakos DB (2010) Mediterranean diet and diabetes prevention: myth or fact? *World J Diabetes* **1**, 65–67.
8. Salas-Salvadó J, Martínez-González MA, Bulló M, *et al.* (2011) The role of diet in the prevention of type 2 diabetes. *Nutr Metab Cardiovasc Dis* **21**, Suppl. 2, B32–B48.
9. Salas-Salvadó J, Bulló M, Babio N, *et al.* (2011) Reduction in the incidence of type 2 diabetes with the Mediterranean diet: results of the PREDIMED-Reus nutrition intervention randomized trial. *Diabetes Care* **34**, 14–19.
10. Martínez-González MA, Salas-Salvadó J & Estruch R (2013) Intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* **369**, 2357.

11. Martínez-González MA, Sanchez-Villegas A, de Irala J, *et al.* (2002) Mediterranean diet and stroke: Objectives and design of the SUN project. Seguimiento Universidad de Navarra. *Nutr Neurosci* **5**, 65–73.
12. Seguí-Gomez M, de la Fuente C, Vazquez Z, *et al.* (2006) Cohort profile: the ‘Seguimiento Universidad de Navarra’ (SUN) study. *Int J Epidemiol* **35**, 1417–1422.
13. Bes-Rastrollo M, Perez Valdivieso JR, Sanchez-Villegas A, *et al.* (2005) Validation of the self-reported weight and body mass index of the participants in a cohort of university graduates. *Rev Esp Obes* **3**, 352–358.
14. Martín-Moreno JM, Boyle P, Gorgojo L, *et al.* (1993) Development and validation of a food frequency questionnaire in Spain. *Int J Epidemiol* **22**, 512–519.
15. Fernández-Ballart JD, Piñol JL, Zazpe I, *et al.* (2010) Relative validity of a semiquantitative food frequency questionnaire in an elderly Mediterranean population of Spain. *Br J Nutr* **103**, 1808–1816.
16. De la Fuente-Arrillaga C, Vazquez Ruiz Z, Bes-Rastrollo M, *et al.* (2010) Reproducibility of an FFQ validated in Spain. *Public Health Nutr* **13**, 1364–1372.
17. Mataix J (2003) *Tabla de Composición de Alimentos (Food Composition Tables)*, 4th ed. Granada: Universidad de Granada.
18. Moreiras O (2003) *Tablas de Composición de Alimentos (Food Composition Tables)*, 5th ed. Madrid: Ediciones Pirámide.
19. Trichopoulou A, Costacou T, Bamia C, *et al.* (2003) Adherence to a Mediterranean diet and survival in a Greek population. *N Engl J Med* **348**, 2599–2608.
20. Trichopoulou A, Kouris-Blazos A, Wahlqvist ML, *et al.* (1995) Diet and overall survival in elderly people. *BMJ* **311**, 1457–1460.
21. Martínez-González MA, de la Fuente-Arrillaga C, Nunez-Córdoba JM, *et al.* (2008) Adherence to Mediterranean diet and risk of developing diabetes: prospective cohort study. *BMJ* **336**, 1348–1351.
22. American Diabetes Association (2015) Diagnosis and classification of diabetes mellitus. *Diabetes Care* **38**, Suppl. 1, S8–S16.
23. Martínez-González MA, López-Fontana C, Varo JJ, *et al.* (2005) Validation of the Spanish version of the physical activity questionnaire used in the Nurses’ Health Study and the Health Professionals’ Follow-up Study. *Public Health Nutr* **8**, 920–927.
24. Ainsworth BE, Haskell WL, Whitt MC, *et al.* (2000) Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc* **32**, Suppl. 9, S498–S504.
25. Demidenko E (2008) Sample size and optimal design for logistic regression with binary interaction. *Stat Med* **27**, 36–46.
26. Fung TT, Rexrode KM, Mantzoros CS, *et al.* (2009) Mediterranean diet and incidence of and mortality from coronary heart disease and stroke in women. *Circulation* **119**, 1093–1100.
27. InterAct Consortium (2011) Mediterranean diet and type 2 diabetes risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) study: the InterAct project. *Diabetes Care* **34**, 1913–1918.
28. Koloverou E, Esposito K, Giugliano D, *et al.* (2014) The effect of Mediterranean diet on the development of type 2 diabetes mellitus: a meta-analysis of 10 prospective studies and 136,846 participants. *Metabolism* **63**, 903–911.
29. Colditz GA, Willett WC, Rotnitzky A, *et al.* (1995) Weight gain as a risk factor for clinical diabetes mellitus in women. *Ann Intern Med* **122**, 481–486.



30. Scherer PE & Hill JA (2016) Obesity, diabetes, and cardiovascular diseases: a compendium. *Circ Res* **118**, 1703–1705.
31. Alberti KG, Zimmet P & Straw J (2007) International diabetes federation: a consensus on type 2 diabetes prevention. *Diabet Med* **24**, 451–463.
32. Balk EM, Early A, Raman G, *et al.* (2015) Combined diet and physical activity promotion programs to prevent type 2 diabetes among persons at increased risk: a systematic review for the Community Preventive Services Task Force. *Ann Intern Med* **163**, 437–451.
33. Diabetes Prevention Program Research Group (2015) Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study. *Lancet Diabetes Endocrinol* **3**, 866–875.
34. Look AHEAD Research Group, Wing RR, Bolin P, *et al.* (2013) Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* **369**, 145–154.
35. Anand SS, Hawkes C, de Souza RJ, *et al.* (2015) Food consumption and its impact on cardiovascular disease: importance of solutions focused on the globalized food system: a report from the workshop convened by the World Heart Federation. *J Am Coll Cardiol* **66**, 1590–1614.
36. Trichopoulou A, Martínez-González MA, Tong TY, *et al.* (2014) Definitions and potential health benefits of the Mediterranean diet: views from experts around the world. *BMC Med* **12**, 112.
37. Salas-Salvadó J, Bulló M, Estruch R, *et al.* (2014) Prevention of diabetes with Mediterranean diets: a subgroup analysis of a randomized trial. *Ann Intern Med* **160**, 1–10.
38. Després JP & Poirier P (2013) Diabetes: looking back at Look AHEAD-giving lifestyle a chance. *Nat Rev Cardiol* **10**, 184–186.
39. Casanueva FF, Moreno B, Rodríguez-Azaredo R, *et al.* (2010) Relationship of abdominal obesity with cardiovascular disease, diabetes and hyperlipidemia in Spain. *Clin Endocrinol (Oxf)* **73**, 35–40.
40. Esser N, Legrand-Poels S, Piette J, *et al.* (2014) Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. *Diabetes Res Clin Pract* **105**, 141–150.
41. Estruch R, Martínez-González MA, Corella D, *et al.* (2006) Effects of a Mediterranean-style diet on cardiovascular risk factors: a randomized trial. *Ann Intern Med* **145**, 1–11.
42. Vogel RA (2006) Eating vascular biology, and atherosclerosis: a lot to chew on. *Eur Heart J* **27**, 13–14.
43. Hu FB (2007) Diet and cardiovascular disease prevention. The need for a paradigm shift. *J Am Coll Cardiol* **50**, 22–24.
44. De la Rosa J & Luluaga S (2011) La Dieta Mediterránea. Prevención Cardiovascular ‘Al Alcance de la Mano’ (The Mediterranean diet. Cardiovascular prevention in our hands). *Rev Fed Arg Cardiol* **40**, 316–322.
45. Razquin C, Martínez JA, Martínez-González MA, *et al.* (2010) A 3-year Mediterranean-style dietary intervention may modulate the association between adiponectin gene variants and body weight change. *Eur J Nutr* **49**, 311–319.
46. Dai J, Jones DP, Goldberg J, *et al.* (2008) Association between adherence to the Mediterranean diet and oxidative stress. *Am J Clin Nutr* **88**, 1364–1370.
47. Esposito K, Marfella R, Ciotola M, *et al.* (2004) Effect of a Mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. *JAMA* **292**, 1440–1446.
48. Urpi-Sarda M, Casas R, Chiva-Blanch G, *et al.* (2012) Virgin olive oil and nuts as key foods of the Mediterranean diet effects on inflammatory biomarkers related to atherosclerosis. *Pharmacol Res* **65**, 577–583.