

Adherence to Mediterranean diet and risk of developing diabetes: prospective cohort study

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ABSTRACT

Objective To assess the relation between adherence to a Mediterranean diet and the incidence of diabetes among initially healthy participants.

Design Prospective cohort study with estimates of relative risk adjusted for sex, age, years of university education, total energy intake, body mass index, physical activity, sedentary habits, smoking, family history of diabetes, and personal history of hypertension.

Setting Spanish university department.

Participants 13 380 Spanish university graduates without diabetes at baseline followed up for a median of 4.4 years

Main outcome measures Dietary habits assessed at baseline with a validated 136 item food frequency questionnaire and scored on a nine point index. New cases of diabetes confirmed through medical reports and an additional detailed questionnaire posted to those who self reported a new diagnosis of diabetes by a doctor during follow-up. Confirmed cases of type 2 diabetes.

Results Participants who adhered closely to a Mediterranean diet had a lower risk of diabetes. The incidence rate ratios adjusted for sex and age were 0.41 (95% confidence interval 0.19 to 0.87) for those with moderate adherence (score 3-6) and 0.17 (0.04 to 0.75) for those with the highest adherence (score 7-9) compared with those with low adherence (score <3). In the fully adjusted analyses the results were similar. A two point increase in the score was associated with a 35% relative reduction in the risk of diabetes (incidence rate ratio 0.65, 0.44 to 0.95), with a significant inverse linear trend (P=0.04) in the multivariate analysis.

Conclusion Adherence to a Mediterranean diet is associated with a reduced risk of diabetes.

INTRODUCTION

Many studies have shown that a Mediterranean diet has a role in prevention of cardiovascular disease,¹⁻⁵ and some suggest that it could also protect against diabetes. Protective characteristics include a high intake of fibre, a high intake of vegetable fat, a low intake of *trans* fatty acids, a moderate intake of alcohol,⁶⁻⁸ and the abundant use of virgin olive oil,⁹ which is rich in monounsaturated fatty acids. Diets rich in monounsaturated fatty acids improve lipid profiles and glycaemic control in

people with diabetes, suggesting that a high intake improves insulin sensitivity.¹⁰⁻¹³

A prospective follow-up study recently reported an inverse association between adherence to the diet and the incidence of diabetes.¹⁴ All members of that study, however, had survived a previous myocardial infarction, the study used only a short list of food items, and the authors did not attempt to measure the entire diet.

We evaluated the association between adherence to a Mediterranean diet and the incidence of diabetes using a full validated food frequency questionnaire to measure the entire diet.

METHODS

Study population

The objectives, design, and methods of the SUN project have been described elsewhere.^{15,16} After the baseline assessment, we send participants (aged 20-90 years) follow-up questionnaires every two years on diet, lifestyle, risk factors, and medical conditions.¹⁶ Participants who do not reply to the follow-up questionnaires are sent up to five additional mailings. Of 18 700 participants enrolled up to November 2007, we analysed 13 380 (see bmj.com for details).

Dietary assessment

We assessed dietary habits at baseline using a validated semi-quantitative food frequency questionnaire with 136 items. The questionnaire was based on typical portion sizes and had nine options for the frequency of intake in the previous year for each food item (ranging from never or almost never to six or more times a day). Full details on the calculation of daily intake are on bmj.com. Nutrient intake scores were computed with a specifically developed computer program and the latest available information included in food composition tables for Spain. The questionnaire also included questions on use of fats and oils, cooking methods, and dietary supplements.

We appraised adherence to the Mediterranean diet using the score created by Trichopoulou et al.¹⁷ In the scoring index a Mediterranean diet has a high ratio of monounsaturated:saturated fatty acids, moderate intake of alcohol, high intake of legumes, high intake of grains, high intake of fruit and nuts, high intake of vegetables, low intake of meat and meat products,

moderate intake of milk and dairy products, and high intake of fish.⁴¹⁷ The index assigns a score of 0 or 1 according to the daily intake of each of the nine components. The highest score (nine points) reflected maximum adherence.

Assessment of other covariates

At baseline we collected information about the main known risk factors for diabetes, sociodemographic factors, anthropometric measurements, health related habits, and clinical variables. We also used a physical activity questionnaire and assigned a multiple of the resting metabolic rate (MET score) to each activity to quantify the average intensity of physical activity.

Ascertainment of diabetes

Participants reported any medical diagnosis of diabetes at baseline and in each of the follow-up questionnaires. The baseline questionnaire also collected data on use of insulin or oral antidiabetic agents. Follow-up questionnaires recorded the date of any new diagnosis of diabetes (if applicable).

We sent additional questionnaires to participants who reported probable new onset diabetes, requesting further details (see *bmj.com*), including the medical report detailing the diagnosis. A panel of physicians, blinded to the information about dietary habits, confirmed the diagnosis as incident type 2 diabetes or not according to criteria from the American Diabetes Association. We excluded gestational diabetes.

Statistical analysis

We ran Poisson regression models with robust standard errors, controlling simultaneously for known risk factors for diabetes (see *bmj.com*). For all analyses, we considered participants with the lowest level of adherence (score <3) at baseline as the reference category.

We expected an overall rate of new onset type 2 diabetes of three cases for 1000 person years of follow-up. Thus, in the follow-up of 12 000 cohort members for an average 4.4 years we would have expected 158 new cases of type 2 diabetes. Because of the low incidence of confirmed cases of diabetes, we grouped the exposure variable into only three categories: the reference category (score <3), moderate adherence (score 3-6), and high adherence (score 7-9).

Incidence and relative risk of type 2 diabetes (confirmed cases) during follow-up according to adherence (Trichopoulou's score¹⁷) to Mediterranean food pattern at baseline

	No in group	Unadjusted cumulative incidence of type 2 diabetes (%)	Incidence rate ratio* adjusted for age and sex (95% CI)	Multivariate adjusted incidence rate ratio (95% CI)†
Low (score 0-2)	2253	0.40	1 (reference)	1 (reference)
Moderate (score 3-6)	9604	0.23	0.41 (0.19 to 0.87)	0.40 (0.18 to 0.90)
High (score 7-9)	1523	0.13	0.17 (0.04 to 0.75)	0.17 (0.04 to 0.72)

*Poisson regression model with robust standard errors.

†Adjusted for sex, age, years of university education (three categories), body mass index (continuous), family history of diabetes (two categories), hypertension at baseline (two categories), physical activity (three categories), hours/week sitting down (five categories), smoking (three categories), total energy intake (continuous). P=0.04 for trend from likelihood ratio test when Trichopoulou's score was introduced as continuous variable in fully multivariate adjusted model.

RESULTS

During the follow-up period (median 4.4 years), 103 participants initially free of diabetes (according to their baseline questionnaire) self reported a new diagnosis of diabetes. After exclusions (see *bmj.com*) we identified 33 cases of new onset confirmed type 2 diabetes among 58 918 person years of follow-up.

Participants with the highest adherence to the diet (score >6) had a higher level of leisure time physical activity but also exhibited a higher baseline prevalence of most risk factors for diabetes because they were older, had a higher body mass index (BMI), a higher total energy intake, were more likely to have high blood pressure or a family history of diabetes, and more likely to be former smokers.

When we assessed the risk of diabetes according to levels of adherence to the diet we found a significant inverse association after adjustment for age and sex (table). Further multivariate adjustment for total years of university education, BMI, family history of diabetes, hypertension at baseline, physical activity, hours sitting down a week, smoking, and total energy intake did not lead to substantial changes in the estimates, age being the major confounding factor. High adherence to the diet (score >6) was associated with an 83% relative reduction in the risk of developing diabetes (incidence rate ratio 0.17, 95% confidence interval 0.04 to 0.75). With score as a continuous variable an increase of two points in the score was associated with an incidence rate ratio of 0.65 (0.44 to 0.95) in the fully adjusted model, indicating that a two point increase in the score resulted in a 35% relative reduction in the risk of developing diabetes. The multivariate adjusted inverse linear trend was significant (P=0.04).

DISCUSSION

This large prospective study shows that a traditional Mediterranean food pattern is associated with a significant reduction in the risk of developing type 2 diabetes. Among participants with the highest adherence to the diet, there was a high prevalence of important risk factors for diabetes, such as older age, higher BMI, family history of diabetes, and personal history of hypertension and a higher proportion of ex-smokers. Therefore, we would have expected a higher incidence of diabetes among these participants. These higher risk participants with better adherence to the diet, however, had a lower risk of diabetes, suggesting that the diet might have a substantial potential for prevention. This finding is consistent with our previous report of an inverse association between a Mediterranean diet and the metabolic syndrome.¹⁸ In addition, a previous cohort study of survivors of myocardial infarction also reported that a higher adherence to a Mediterranean diet was associated with a reduction in the risk of type 2 diabetes,¹⁴ despite use of a relatively inaccurate tool for the dietary assessment. The inverse graded dose-response pattern and the significant inverse trend that we observed support a causal relation.

WHAT IS ALREADY KNOWN ON THIS TOPIC

A Mediterranean diet protects against coronary mortality and is inversely associated with metabolic syndrome and inflammatory markers

The diet was found to be inversely associated with the incidence of diabetes among patients who survived myocardial infarction

WHAT THIS STUDY ADDS

Higher adherence to a Mediterranean diet rich in olive oil, plant based foods (fruits, vegetables, and legumes), and fibre but low in meats was inversely associated with incidence of type 2 diabetes among initially healthy participants

Diet and disease

There is an analogy between coronary heart disease and diabetes because patients with type 2 diabetes and no coronary heart disease have a risk of coronary heart disease similar to patients without diabetes but with prior coronary heart disease.¹⁹ There is evidence that a Mediterranean diet protects against coronary heart disease, and the analogy between coronary heart disease and diabetes suggests that this diet might also prevent diabetes. Both cohort studies and randomised trials have found that adherence to a Mediterranean diet protects against mortality in patients who already have established coronary heart disease.

The potential mechanisms explaining the protective effect of a Mediterranean diet on diabetes have been reviewed elsewhere.²⁰⁻²³ Two trials have shown that virgin olive oil protects against insulin resistance and the metabolic syndrome.²³ Olive oil is rich in monounsaturated fatty acids, and a diet rich in monounsaturated fatty acids is beneficial among those with diabetes and might lead to improved insulin sensitivity and better lipid profiles than diets rich in carbohydrate.^{10 12 22}

Apart from olive oil, adherence to an overall Mediterranean-type food pattern is related to lower plasma concentrations of inflammatory markers and markers of endothelial dysfunction.^{24 25} These biomarkers are predictive of the future occurrence of type 2 diabetes.²⁶ A large cross sectional study nested in the nurses' health study also found that increased adherence to a Mediterranean diet was associated with higher levels of adiponectin,²⁷ which are associated with a reduced risk of diabetes.

Limitations

The number of new cases of diabetes was small, which is a major drawback and can compromise the statistical power of our study. Nevertheless, our participants had high absolute levels of consumption of the typical food items of the Mediterranean diet, even among those participants classified as poorly compliant (score <3).

Diabetes might have been under-reported in our participants, despite their high educational level and easy access to medical care. The proportions of participants aged over 65 years across increasing categories of adherence to the diet were 0.6% (score <3), 1.7% (3-6), and 3.5% (>6). Therefore, older participants were more compliant with the diet. If selective under-reporting of diabetes was present

among the older participants, this would provide an alternative non-causal explanation for our findings.

All our participants are university graduates and the generalisability of our findings to other groups with less education should be assumed only on biological grounds but not at all on "representativeness" of the general population. Also, the building of the diet score was based on sample specific median cut-off points, and our participants had high absolute levels of consumption of favourable foods and low absolute intakes of detrimental foods. Therefore, it will be difficult to compare our results with those of other non-Mediterranean countries where levels of consumption of favourable foods in the general population are much lower.

Food frequency questionnaires are known to contain a certain degree of measurement error, which might affect results that depend on such questionnaires to assess diet and risk of chronic disease. Total energy intake was included as a covariate in the model to achieve the equivalent of an isocaloric diet and to reduce measurement error in the score. Measurement error, however, would probably have introduced non-differential misclassification, and the implications for the results of this error would have been to bias the estimates towards the null.

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Prolonged conservative care versus early surgery in patients with sciatica from lumbar disc herniation: cost utility analysis alongside a randomised controlled trial

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ABSTRACT

Objective To determine whether the faster recovery after early surgery for sciatica compared with prolonged conservative care is attained at reasonable costs.

Design Cost utility analysis alongside a randomised controlled trial.

Setting Nine Dutch hospitals.

Participants 283 patients with sciatica for 6-12 weeks, caused by lumbar disc herniation.

Interventions Six months of prolonged conservative care compared with early surgery.

Main outcome measures Quality adjusted life years (QALYs) at one year and societal costs, estimated from patient reported utilities (UK and US EuroQol, SF-6D, and visual analogue scale) and diaries on costs (healthcare, patient's costs, and productivity).

Results Compared with prolonged conservative care, early surgery provided faster recovery, with a gain in QALYs according to the UK EuroQol of 0.044 (95% confidence interval 0.005 to 0.083), the US EuroQol of 0.032 (0.005 to 0.059), the SF-6D of 0.024 (0.003 to 0.046), and the visual analogue scale of 0.032 (-0.003 to 0.066). From the healthcare perspective, early surgery resulted in higher

costs (difference €1819 (£1449; \$2832), 95% confidence interval €842 to €2790), with a cost utility ratio per QALY of €41 000 (€14 000 to €430 000). From the societal perspective, savings on productivity costs led to a negligible total difference in cost (€-12, €-4029 to €4006).

Conclusions Faster recovery from sciatica makes early surgery likely to be cost effective compared with prolonged conservative care. The estimated difference in healthcare costs was acceptable and was compensated for by the difference in absenteeism from work. For a willingness to pay of €40 000 or more per QALY, early surgery need not be withheld for economic reasons.

Trial registration Current Controlled Trials ISRCTN 26872154.

INTRODUCTION

In a randomised controlled trial we compared the effectiveness of early surgery for sciatica with six months of prolonged conservative care.¹⁻³ We found faster recovery after early surgery, but no difference after a year.

Early surgery is associated with higher short term healthcare costs than prolonged conservative care. We carried out a cost utility analysis of our randomised