

PREDIMED

A five year Mediterranean and mixed nuts diet study from Spain





WHAT IS THE PREDIMED STUDY?

A long term study undertaken by 16 research groups in seven communities in Spain over 2003-2011 to study the effects of the Mediterranean diet on the primary prevention of cardiovascular disease (CVD) in subjects at high risk of CVD. The acronym PREDIMED stands for PREención con Dieta MEDiterránea (Prevention with Mediterranean Diet). The final results are due for publication in 2012.

Objective

To determine whether a Mediterranean diet supplemented with virgin olive oil or tree nuts, compared to a low-fat diet, can prevent cardiovascular diseases (cardiovascular death, myocardial infarction and stroke). Secondary outcomes are death from all causes, and incidence of heart failure, diabetes mellitus, cancer and dementia; intermediate outcomes include blood pressure, fasting blood glucose, lipid profile, inflammatory markers and other CVD markers.

Subjects

Nearly 7400 older adults at high risk of CVD, but with no symptoms at baseline, followed for five years on average. The age ranges are 55-80 years for men and 60-80 years for women.

Design

Parallel group, multi-centre, single-blind, randomised trial. Nearly 7400 participants, randomised to three groups (n=2400-2500 per group): low-fat control diet, Mediterranean diet supplemented with a free supply of virgin olive oil (1L per family per week or 50ml per participant per day), Mediterranean diet supplemented with nuts (30g mixed nuts per day, made up of 15g walnuts, 7.5g almonds and 7.5g hazelnuts).

Dietetic input^{2,3}

The PREDIMED dietitians received comprehensive training and certification to deliver the PREDIMED dietary protocol.

All subject groups received individual, goal-oriented, motivational consultations and group educational sessions quarterly. The focus for the Mediterranean diets was on changing the dietary pattern, rather than focussing on foods or micronutrients. The dietary fat intake for the Mediterranean diets was ad libitum.

Compliance for the Mediterranean diet in both groups was based on a 14-point score: high in monounsaturates, fish, fruits, vegetables, cereals, legumes and nuts; low in meat and dairy products; wine permitted; soft drinks, cakes and sweets are limited.

The control group participants were given verbal and written instructions on following a low-fat diet and received motivational consultations and group educational sessions with the same intensity as the Mediterranean diet groups. The dietary pattern for this group was to reduce every fat (from animal and vegetable food sources) and increase carbohydrates. Compliance was assessed by a 9-point low-fat score.

Energy was not specifically restricted in any intervention group. Food intake was adapted to the subjects' requirements and advice tailored by the dietitian. Examples of material provided to all groups over the course of the trial are: meal plans, seasonal food lists, shopping lists and recipes. For further information on the dietitians' input refer to reference two.

CARDIOVASCULAR DISEASE (CVD)

CVD biomarkers

A Mediterranean diet supplemented with either virgin olive oil (50ml/day) or mixed nuts (30g/day) has an anti-inflammatory effect on the cardiovascular system. Both diets reduced circulatory and cellular inflammation biomarkers in people at high risk of CVD^{4,5}, making the Mediterranean diet a useful tool against CVD. A Mediterranean diet with nuts has also been found to reduce the level of tissue factor pathway inhibitor (TFPI) which inhibits thrombin needed for blood clotting.⁶

Total polyphenol intake, assessed by urinary excretion, was inversely related to blood pressure and prevalence of hypertension in PREDIMED participants. Those with the highest polyphenol intake (from fruits, vegetables, nuts, coffee and wine) had the lowest blood pressure.⁷

CVD risk factors

At baseline, how well PREDIMED subjects adhered to the Mediterranean diet was assessed and compared to their cardiovascular risk factors. Following the Mediterranean diet was inversely associated with diabetes, hypertension, dyslipidemia and obesity.⁸

CVD risk factors after three months on PREDIMED diets was also assessed.⁹ The Mediterranean diets both produced beneficial changes in most outcomes. In particular, the Mediterranean diet supplemented with nuts reduced mean plasma glucose levels, systolic and diastolic blood pressure and the LDL:HDL cholesterol ratio.

Lipoprotein oxidation

After three months of intervention, the olive oil and nut supplemented Mediterranean diets were associated with reduced levels of oxidized LDL compared to the low-fat diet.¹⁰

Inflammatory markers

At baseline (before the intervention was started), it was demonstrated that the consumption of high amounts of some foods typical of the Mediterranean diet pattern – (including nuts, olive oil, cereals and fruits) were associated with lower concentrations of some inflammatory markers.¹¹

People with the highest consumption of nuts and olive oil had the lowest concentrations of all four inflammatory markers assessed (CRP, VCAM-1, ICAM-1, IL-6). Although only one marker reached statistical significance for each diet, ICAM-1 for nuts (P for trend 0.003) and VCAM-1 for olive oil (P for trend 0.02).

Another analysis of immune cell activation and soluble inflammatory markers in these high-risk subjects found multiple cellular and circulating inflammatory biomarkers were significantly down-regulated by Mediterranean diets supplemented with nuts, and also with olive oil, compared to the low-fat diet.¹²

Nutrients of interest

Resveratrol: One analysis, looking at a marker of the polyphenol resveratrol intake (present in wine and also nuts) found it was correlated with positive changes in a range of cardiovascular risk factors.¹³

Phytosterols: A number of plant foods in the Mediterranean diet contain plant sterols. In a sub-study of the PREDIMED trial, it was found that in the arm of the Mediterranean diet supplemented with nuts, the average intake of phytosterols increased by 158mg/day compared to 76mg/day in the olive oil supplemented group and 15mg/day in the low-fat diet group.¹⁴ The nut supplemented group was the only group where significant changes in outcome variables were observed compared to control. In this group, increases in fibre, polyunsaturated fats and phytosterols were seen, along with significant reductions in LDL cholesterol and the LDL:HDL ratio. Phytosterol intake and absorption correlated to LDL cholesterol changes. This paper concluded that small amounts of phytosterols in natural food can lower cholesterol.¹⁴

WEIGHT MANAGEMENT

Epidemiology

At baseline, the PREDIMED subjects were assessed for four healthy lifestyle behaviours – following a Mediterranean diet; moderate alcohol consumption; a basic level of leisure exercise; and not smoking. When converted to a 'Healthy lifestyle Pattern' score, these four behaviours were inversely associated with obesity and abdominal obesity.¹⁵

The PREDIMED Mediterranean diet supplemented with nuts had a beneficial effect on waist circumference at one-year.¹⁶ This paper also considered new epidemiological results from the SUN cohort and results from the Nurse's Health Study II concluding that consumption of nuts was not associated with a higher risk of weight gain.¹⁶

A cross-sectional analysis of 847 PREDIMED participants looked at the links between food intake and obesity measures (BMI and waist circumference). Nut intake decreased across quintiles of both obesity measures; and, independent of other lifestyle variables, eating nuts was inversely associated with both BMI and waist circumference (P=0.002). BMI and waist circumference decreased by 0.78kg/m² and 2.1cm respectively, for each additional serving of nuts eaten.¹⁷

Genetic components of obesity

Fat accumulation is related to a polymorphism of the gene PPAR gamma, which regulates insulin sensitivity and adipogenesis. A study of PREDIMED subjects showed that a Mediterranean diet (both supplemented with nuts and olive oil) is able to reverse the negative effect on waist circumference of this polymorphism, and this beneficial effect is most marked in people with diabetes, resulting in reduced waist circumference over two years of diet intervention.¹⁸

Variations in the adiponectin gene have been associated with obesity. These were found in PREDIMED participants to be associated with body weight changes over a three year period, with some variants linked to higher body weight gain. Dietary intervention with both Mediterranean diets (olive oil and nuts) appeared to reverse these effects.¹⁹



DIABETES

One PREDIMED analysis in 418 non-diabetic participants recruited at a single centre, showed that following either Mediterranean diet, including nuts or olive oil, resulted in a 50% reduction in diabetes incidence, compared to following the low-fat diet over four years.²⁰ Of note, diabetes incidence was reduced in spite of no body weight changes or physical activity increases. One report found that a sub group of 511 elderly men and women at high cardiovascular risk recruited for PREDIMED with a higher increase in dietary GI or GL showed a greater reduction in leptin and adiponectin plasma levels after one year.²¹ Leptin and adiponectin are involved in slowing the formation of adipose tissue and are implicated in energy balance and cardiometabolic risk.

Not enough evidence was found to support that a Mediterranean Diet is associated with lower levels of HbA1c in subset of 383 patients with T2DM, but PREDIMED results did suggest an inverse trend. Future studies with larger sample size are necessary.²²



“...following a Mediterranean diet, including nuts resulted in a 50% reduction in diabetes incidence.”

METABOLIC SYNDROME

A sub study of over 800 PREDIMED participants found those who best adhered to the traditional Mediterranean diet, allowing for other risk factors such as age, gender, smoking and exercise, also had the lowest prevalence of metabolic syndrome.²³

Another analysis looked specifically at the effect of the PREDIMED diets on metabolic syndrome status after intervention for one year.²⁴ Metabolic syndrome prevalence was significantly reduced, from 61.4% of initial participants meeting the criteria, by 13.7% with the Mediterranean diet supplemented with nuts, non significantly by 6.7% with the Mediterranean diet supplemented with olive oil, and by just 2% for the low-fat control diet.²⁴ Importantly, the main metabolic syndrome component reduced by the nut diet was waist circumference. As there were no body weight changes, this finding suggests fat redistribution with nut consumption.

BRAIN HEALTH

Two studies of the PREDIMED cohort have looked at brain health and the Mediterranean diet. One, focussing on cognitive performance, found that increased consumption of antioxidant rich foods in general, and polyphenols in particular, were associated with better cognitive performance. Some foods were independently related, for example olive oil with immediate verbal memory and walnuts with working memory.²⁵ This study reinforces the theory that the Mediterranean diet might counteract age-related cognitive decline.

The second study in this area looked at the levels of brain-derived neurotrophic factor (BDNF), thought to be of importance in depression. Following a Mediterranean diet supplemented with nuts was found to be significantly associated with improved levels of BDNF in those subjects with depression.²⁶



SUMMARY

Inclusion of 30g of mixed nuts daily in a Mediterranean-style diet provides a range of long term health benefits including: improvements in CVD, weight management and brain health, and reduction in risk of diabetes and metabolic syndrome.

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e admin@nutsforlife.com.au

p 02 9460 0111

w www.nutsforlife.com.au

t [twitter/NutsforLife](https://twitter.com/NutsforLife)

Written by Liz Munn and Lisa Yates APDs Nuts for Life
and reviewed by Prof Jordi Salas Salvado and Dr Emilio Ros from PREDIMED

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