

# PREDIMED

A five year Mediterranean and mixed nuts diet study from Spain

Updated March 2017





## WHAT IS THE PREDIMED STUDY?

A long term study undertaken by 16 research groups in seven communities in Spain over 2003-2011 to examine 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 PREvención con Dieta MEDiterránea (Prevention with Mediterranean Diet).<sup>1,2</sup>

### Objective

To determine whether a Mediterranean diet supplemented with virgin olive oil or tree nuts, compared to a lower-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<sup>2,3</sup>

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; and limited soft drinks, cakes and sweets. Compliance was also assessed by biomarker analysis.

The control group participants were given verbal and written instructions on following a lower-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 were: meal plans, seasonal food lists, shopping lists and recipes. For further information on the dietitians' input refer to reference two.

# Summary of findings

The following summary includes results of the full PREDIMED study with some 7000 participants as well as sub-studies with smaller groups from the 16 study centres in Spain.

## REDUCTION IN TOTAL MORTALITY

Of 7216 older men and women, at high risk of cardiovascular disease, enrolled into the PREDIMED study for nearly five years, those eating a handful of nuts (30g) more than three times a week had a 39% reduction in total mortality compared to non nut consumers (P for trend < 0.05, all).<sup>4</sup> PREDIMED also highlighted the importance of healthy fats in the diet: monounsaturated and short chain (ALA) and long chain (DHA) polyunsaturated fats which both reduce mortality.<sup>5,6</sup>

## PREVENTION OF CVD

The results of the PREDIMED study on the primary prevention of CVD found that for people at high cardiovascular risk, the Mediterranean diet including either nuts or extra-virgin olive oil, reduced cardiovascular events by around 30% (such as myocardial infarction, stroke, and death from cardiovascular causes) after 4.8 years follow up. The hazard ratios, adjusted for multiple variables, were 0.72 for nuts and 0.70 for extra-virgin olive oil, compared to control.<sup>7,8</sup>

## CARDIOVASCULAR DISEASE (CVD)

### CVD risk factors

At baseline, (before the intervention was started), how well PREDIMED subjects adhered to the Mediterranean diet was assessed and compared to their cardiovascular risk factors. Those following the Mediterranean diet had less diabetes, hypertension, dyslipidemia and obesity.<sup>9</sup>

CVD risk factors after three months on PREDIMED diets were also assessed in a sub-study of 772 participants.<sup>10</sup> The Mediterranean diets both produced beneficial changes in most outcomes. In particular, the Mediterranean diet supplemented with nuts reduced average blood glucose levels, systolic and diastolic blood pressure and the LDL:HDL cholesterol ratio.<sup>10</sup> Another sub-study of 106 participants found after one year the Mediterranean diet plus nuts group had significant (P < 0.05) reductions of LDL-cholesterol (0.27 mmol/L or 8.3%) and the LDL/HDL-cholesterol ratio (0.29 mmol/L or 11.5%).<sup>11</sup>

In the total PREDIMED population blood pressure, particularly diastolic blood pressure, remained under better control after four years of follow up with both the nuts and olive oil diets (P < 0.001).<sup>12</sup> Total polyphenol intake, assessed by urinary excretion, was inversely related to blood pressure and prevalence of hypertension in PREDIMED participants.<sup>13,14</sup> Those with the highest polyphenol intake (from fruits, vegetables, nuts, coffee and wine) had the lowest blood pressure.<sup>13</sup> The Mediterranean diets also caused a significant increase in nitric oxide<sup>14,15</sup>, which helps keep blood vessels elastic reducing blood pressure.

### Lipoprotein oxidation and size

After three months of intervention, the olive oil and nut supplemented Mediterranean diets were associated with reduced levels of oxidized LDL compared to the lower-fat control diet.<sup>16</sup> After one year the addition of nuts also reduced small, dense LDL cholesterol and increased large LDL- and HDL- cholesterol<sup>17</sup>, which are less atherogenic.

### CVD biomarkers

A Mediterranean diet supplemented with nuts for three months increased the level of tissue factor pathway inhibitor (TFPI), which inhibits thrombin needed for blood clotting in a sub-study of 49 people.<sup>18</sup> Another sub-study analysis found that 2.4 years on the Mediterranean nuts diet delayed progression of thickening of, and plaque within, the carotid artery.<sup>19</sup> Inflammatory biomarkers related to plaque instability such as C-reactive protein and interleukin-6 were significantly reduced by 95% and 90% in the nuts group respectively (P < 0.05; all) compared to the lower-fat diet group.<sup>20</sup> Plaque stability is important for preventing blocked arteries.

### Inflammatory markers

At baseline consumption of high amounts of some foods typical of the Mediterranean diet pattern (including nuts, olive oil, cereals and fruits) were associated with lower levels of some inflammatory markers.<sup>21</sup>

Several sub-study groups found inflammatory markers were significantly reduced in those consuming nuts and olive oil compared to the lower-fat diet group, even after as little as three months, for example C-reactive protein<sup>21-23</sup>, VCAM-118, ICAM-118,<sup>22</sup> Interleukin-6<sup>21-23</sup>, tumor necrosis factor receptor<sup>22</sup> and, endothelial and monocyte adhesion molecules and chemokines<sup>22,23</sup>.

## Nutrients of interest

**Fatty acids:** After one year of intervention those in the Mediterranean diet plus nuts group showed significant changes in fatty acid composition - increased levels of palmitic, linoleic, and  $\beta$ -inolenic fatty acids, but reduced proportions of myristic, margaric and palmitoleic fatty acids.<sup>24</sup>

**Phytosterols:** A sub-study of the PREDIMED trial found those eating Mediterranean diet with nuts for one year, increased their phytosterol intake by 158mg/day compared to 76mg/day in the olive oil supplemented group and 15mg/day in the lower-fat control diet group.<sup>11</sup> Phytosterols have been shown to reduce cholesterol re-absorption in the intestines.<sup>25</sup>

**Antioxidants:** One analysis, assessing a marker of resveratrol intake (a polyphenol present in wine and nuts) found it was correlated with positive changes in a range of cardiovascular risk factors such as blood lipids, blood glucose and heart rate.<sup>26</sup> Those following the Mediterranean diet plus nuts also had higher blood antioxidant enzyme activity<sup>27</sup> and polyphenol antioxidants reduced markers of inflammation.<sup>28</sup>

**Magnesium:** After a median follow-up of 4.8 years on PREDIMED, higher consumers of dietary magnesium had a 34% reduction in mortality risk compared to lower consumers.<sup>29</sup>

## WEIGHT MANAGEMENT

### Epidemiology and Clinical Trials

The Mediterranean diet supplemented with nuts had a beneficial effect on waist circumference at one year in the first 1224 high-risk participants.<sup>30</sup> This paper also considered new epidemiological results from the SUN cohort and results from the Nurses' Health Study II concluding that consumption of nuts was not associated with a higher risk of weight gain.<sup>30</sup>

After nearly 5 years, those eating the Nut diet did not gain weight but did lose nearly 1cm off their waist circumference ( $P=0.006$ ) compared to those in the low fat diet group. This long term trials supports advice to not restrict healthy fats in a weight management program.<sup>31</sup>

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/m<sup>2</sup> and 2.1cm respectively, for each additional serving of nuts eaten.<sup>32</sup>

Interestingly PREDIMED researchers have found although the energy density of the diets increased there was still no weight gain.<sup>33</sup>

A further cross-sectional analysis of 7210 people recruited into the PREDIMED study, looked at nut consumption at baseline and the overall prevalence of cardiometabolic risk factors, including obesity. Nut consumption was inversely associated with obesity and central obesity, as well as metabolic syndrome and diabetes.<sup>34</sup>

### Genetic components of obesity

Fat accumulation is related to a polymorphism of the gene PPAR gamma, which regulates insulin sensitivity and adipogenesis. A sub-study of 774 PREDIMED subjects showed that a Mediterranean diet (both supplemented with nuts and olive oil) was able to reverse the negative effect on waist circumference of this polymorphism, and this beneficial effect was most marked in people with type 2 diabetes, resulting in reduced waist circumference over two years of diet intervention.<sup>35</sup>

Variations in the adiponectin gene have also been associated with obesity. These variations 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.<sup>36</sup>



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## TYPE 2 DIABETES

Cross-sectional analysis of the diets at baseline of 7210 people in the PREDIMED study, found an inverse relationship with diabetes. Those eating three or more serves of nuts per week, compared to one or fewer serves per week, had a 13% lower risk of diabetes (adjusted odds ratio 0.87).<sup>34</sup> After nearly five years on the Mediterranean Diet plus nuts diet the reduction in risk increased to 18% (odds ratio 0.82).<sup>8</sup>

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 lower-fat diet over four years.<sup>37</sup> Of note, diabetes incidence was reduced in spite of no body weight changes or physical activity increases.

Two sub-studies found a group of 511 older men and women at high cardiovascular risk recruited for PREDIMED, and with a higher increase in dietary Glycemic Index (GI) or Glycemic Load (GL), showed a greater reduction in leptin and adiponectin blood levels after one year on the diet.<sup>38</sup> Leptin and adiponectin are involved in slowing the formation of adipose tissue and are implicated in energy balance and cardiometabolic risk. Similarly another sub-study found both olive oil and nut groups were inversely associated with GI and GL after one year follow up.<sup>39</sup> High dietary GI was found to be positively associated with all-cause mortality in this older population at high cardiovascular risk.<sup>40</sup>

A further study found improvements in insulin resistance with either the nuts or olive oil diet groups.<sup>41</sup> Insulin resistance plays a role in weight gain and diabetes control.

After six years of follow up it was found both olive oil and nut diets group reduced diabetic retinopathy a common eye complication of diabetes<sup>42</sup> and interestingly those eating a high intake of polyphenol antioxidants had a 28% reduced risk of type 2 diabetes (P-trend=0.05).<sup>43</sup>

Not enough evidence was found to support that a Mediterranean Diet is associated with lower levels of glycosylated haemoglobin (HbA1c) in subset of 383 patients with type 2 diabetes, but PREDIMED results did suggest an inverse trend. Future analysis with larger sample size are necessary.<sup>44</sup>

“ ...following a Mediterranean diet, including nuts resulted in a 50% reduction in diabetes incidence<sup>37</sup>. ”



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## METABOLIC SYNDROME

Cross-sectional analysis of the diets of 7210 people recruited into the PREDIMED study, looked at nut consumption at baseline, and found those eating three or more serves of nuts per week had a 26% reduced risk of metabolic syndrome (odds ratio of 0.74), compared with those eating one or fewer serves per week.<sup>34</sup>

A sub-study of over 800 PREDIMED participants at baseline 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.<sup>45</sup>

Another analysis looked specifically at the effect of the PREDIMED diets on metabolic syndrome status after intervention for one year. Metabolic syndrome prevalence was significantly reduced, from 61.4% of initial participants meeting the metabolic syndrome criteria, by 13.7% with the Mediterranean diet supplemented with nuts, by 6.7% with the Mediterranean diet supplemented with olive oil, and by just 2% for the lower-fat control diet.<sup>46</sup> Importantly, the main metabolic syndrome criteria reduced by the nut diet was waist circumference. As there were no body weight changes<sup>34</sup>, this finding suggests fat redistribution with nut consumption.

A further one-year sub-group investigation, found that the Mediterranean diet groups (including nuts or olive oil) reduced the amount of oxidative damage to both body lipids and DNA.<sup>47</sup> An increase in systemic oxidative markers is a non-classic feature of metabolic syndrome.

After nearly five years on the PREDIMED diets a Mediterranean diet supplemented with either extra virgin olive oil or nuts is not associated with the onset of metabolic syndrome, but such diets can help the reversion of metabolic syndrome.<sup>48</sup>

During nearly 5 years of follow up a higher glycemic index of the diet was related to a great risk of developing high fasting blood glucose and Metabolic Syndrome - steps towards type 2 diabetes.<sup>49</sup>

## BRAIN HEALTH

Four sub-studies from 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, was associated with better cognitive performance.<sup>50</sup> Some foods were independently related, for example olive oil with immediate verbal memory and walnuts with working memory.<sup>50</sup> This study reinforced the theory the Mediterranean diet might counteract age-related cognitive decline. Further sub-studies also supported the idea the Mediterranean diet in general improved cognitive performance after 4-6 years.<sup>50-53</sup>

An additional 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.<sup>54</sup>

After three years of PREDIMED it was found those eating the Mediterranean diet supplements with mixed nuts had a 22% lower risk of developing depression compared to the low fat diet group and in those with type 2 diabetes there was a 41% reduced risk.<sup>55</sup>



## 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 and risk factors, weight management, cognition, and a reduction in the risk of type 2 diabetes, metabolic syndrome and possibly depression.



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Nuts for Life is a nutrition communication initiative to educate the health benefits of regular nut consumption in the Australian diet. It is staffed by accredited practising dietitians and funded by the Australian Tree Nut Industry with matching funds for R&D activities from the Australian Government through Horticulture Innovation Australia (HIA).

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