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## THE PREDIMED-PLUS STUDY: A NEW CHALLENGE IN RESEARCH

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After the important results obtained in the PREDIMED trial, which have demonstrated that a long-term adherence to an energy unrestricted Mediterranean Diet (MedDiet) supplemented with extra-virgin olive oil (EVOO) or mixed nuts reduced incidence cardiovascular disease (CVD), by about 30% compared to a low fat control diet, in older subjects at high cardiovascular risk<sup>1</sup>, the PREDIMED study investigators think that it would be important to further investigate if this type of dietary pattern could be also useful in the primary prevention of CVD in the context of weight loss.

The escalating global epidemic of overweight and obesity is already affecting more than 50% of adult population and represents a global public health crisis. In fact, the prevalence of obesity has duplicated between 1980 and 2008<sup>2</sup>.

People with overweight and obesity are treated in order to lose weight. This is associated to a better metabolic profile; a decrease in the number of medications; less risk of diabetes or other complications, and a better quality of life. However it is very important to investigate if body weight loss and maintenance reduces the risk of chronic diseases and mortality.

Expert panels set up by the National Institutes of Health and the World Health Organization advice that overweight and obese adults with comorbid conditions should lose 10% of their initial weight, with lifestyle intervention as primary treatment: an energy-restricted diet, physical activity and behavioral therapy.

Recently, scientific societies and institutional reviews have recommended low-fat-diets as the most suitable approach to promote both health and weight loss. However long-term adherence to low-fat diets is limited and, for those who lost

weight, weight gain relapses usually occur after 6-12 months. In addition, with low-fat diets, long-term vegetable intake is reduced in parallel with the associated restriction in the use of plant-derived oils usually recommended for achieving the low-fat content of the diet

Alternate classical approaches for weight loss are those restricting carbohydrates. Low-carbohydrate, high-protein, high-fat diets (referred to as low-carbohydrate diets) have been compared with low-fat, energy-restricted diets. A meta-analysis of five trials with 447 participants suggested that a low-carbohydrate diet is a feasible alternative to a low-fat diet for achieving weight loss, and may have also favorable metabolic effects after a 6-month follow-up. However, the weight loss capacity of low-carbohydrate diets, as well as the improvements they induce in blood pressure, glucose metabolism and the lipid profile were lost after 12-months.

Only one randomized controlled trial has compared weight loss and metabolic outcomes after a 2-year follow-up, with a low-carbohydrate diet or a low-fat diet, and no between-group differences in weight, body composition or bone mineral density were found.

The relative success of a dietary pattern to induce loss of body weight has been more frequently ascribed to participant's compliance with the prescribed energy-restricted diet than to the relative proportions of macronutrients. On the other hand, extreme weight reduction diets differing from the usual diet in the proportion of macronutrient contents are difficult to follow in the long term, and their safety has not been well documented

The only randomized trial that has addressed the long-term effect of an intensive weight-loss lifestyle program in obese

adults on CVD and mortality was the *Look AHEAD* trial<sup>3</sup>, including only diabetic subjects and using a low-fat diet (<30% of total energy intake with <10% from saturated fat) and increased physical activity. The trial was stopped prematurely due to futility, namely the lack of association between the loss of weight in the intervention group (5% of initial body weight on average), and cardiovascular events<sup>4</sup>.

A new approach in the dietary control of overweight and obesity for CVD prevention should include well known, healthy, and palatable dietary patterns.

One dietary paradigm that may be beneficial when implemented within an intensive weight-loss intervention is a traditional MedDiet, relatively rich in fat from vegetable sources (EVOO and 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.

No clinical trial has assessed the impact of weight loss with an energy-restricted MedDiet on CVD risk<sup>5</sup>. The PREDIMED trial did not include energy restriction or increased physical activity and did not aim at weight loss. By implementing such lifestyle changes within the context of a MedDiet among overweight or obese subjects with metabolic syndrome, we seek to provide a new, affordable and sustainable approach to reduce excess cardiovascular morbidity and mortality beyond the results of the PREDIMED trial, such is the rationale of the PREDIMED-PLUS study.

The PREDIMED-PLUS study is a randomized clinical trial for the primary prevention of CVD with an energy-restricted MedDiet and intensive lifestyle intervention directed to lose weight in older subjects with overweight or obesity and metabolic syndrome.

The primary aim of this trial is to evaluate the effects of 6-years intervention with an energy-restricted MedDiet combined with a comprehensive lifestyle modification program or usual care for weight loss on incident of CVD, weight loss

and maintenance of weight loss, quality of life, incidence of other chronic diseases and reversion of metabolic syndrome. The final goal regarding adiposity is to obtain a between-group average absolute difference in weight loss and waist circumference reduction >5%.

Twenty recruiting centers located in university hospitals and specialized primary care facilities throughout Spain will recruit 6,000 participants (3,000 at control group and 3,000 at intervention group) without prior CVD, aged between 55 and 75 years, with overweight or obesity and metabolic syndrome.

Participants in the active treatment group will attend individual and group sessions with a frequency of 3 per month during the first year, 2 per month in the second year, and 1 group monthly session and individual sessions every 3 months from the third year on. The intervention will be based on detailed dietary recommendations for an energy-restricted MedDiet, together with promotion of physical activity and psychological help to achieve planned goals.

Participants in the usual care (control) group will attend group sessions with recommendations to follow the MedDiet (similar to those imparted in the PREDIMED trial) every six months for the duration of the study. To promote compliance with the MedDiet, participants in the 2 groups will be provided at no cost with EVOO (1 liter per month) and mixed nuts (500 g per month: 125 g walnuts, 125 g almonds, 125 g hazelnuts and 125 g pistachios).

Recruitment will take place from fall 2013 to the end of 2015. At this moment, the pilot study has started in two centers (Reus and Pamplona) and it is expected to start in another 18 centers by February 2014.

PREDIMED has changed dietary recommendations to prevent CVD, and we hope this new clinical trial will demonstrate that a MedDiet in the context of weight loss is an effective tool in cardiovascular primary prevention.

We thank the food industries who have believed in the importance of the PREDIMED-PLUS study, and will make it possible.



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