



Invited Commentary

Olive oil and CVD: accruing evidence of a protective effect

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CHD is a leading cause of death and disability worldwide. Remarkably, CHD is largely preventable, as unhealthy lifestyles (smoking, lack of exercise and poor dietary habits) contribute to nearly 80% of population-attributable risk^(1,2). Among these lifestyle components, diet has been well studied. After decades of epidemiological, clinical and experimental research, an impressive body of scientific evidence has been built on the profound influence that nutrients, foods and dietary patterns have on health outcomes, including CHD^(3,4). The present paradigm in nutritional epidemiology is to use diet-pattern analysis instead of isolated food or nutrient analysis, because it can assess the cumulative effects of the overall diet^(5,6). In this sense, there is accumulating scientific evidence that, among widely followed dietary patterns, the Mediterranean diet (MeDiet) might be the healthiest one. For instance, a recent meta-analysis of eighteen prospective cohort studies showed that adherence to the MeDiet confers a significant and consistent protection in relation to the occurrence of major chronic degenerative diseases, including CVD incidence and mortality⁽⁷⁾. Additionally, a systematic review of the effects of thirty-two candidate dietary factors on CHD risk ranked the MeDiet first as the most likely dietary model to provide causal protection⁽⁴⁾.

The MeDiet is identified as the traditional dietary pattern found in Crete, Greece, Italy and Spain in the early 1960s, and is characterised by a high intake of cereals, vegetables, fruits, nuts and olive oil; a moderate intake of fish and alcohol, mostly wine; and a low intake of dairy products, meat and meat products and sweets⁽⁸⁾. Most foods consumed in the MeDiet are also present in other healthy dietary models. However, in opposition to all other healthy diets, the MeDiet has a high fat content as a distinguishing feature. This is because of the customarily high intake of olive oil, which is used abundantly as culinary fat and for dressing dishes, which facilitates intake of substantial quantities of vegetables.

Olive oil is a flavoursome, tasty and nutritious edible fat that is usually obtained directly from pressing ripe olives; thus, it can be considered as an olive juice. When produced by mechanically pressing olives, olive oil is called 'virgin' and contains both the fat, made up mostly of the MUFA oleic acid (*cis*-18:1*n*-9), and minor components from the fruit, many of which are bioactive phytochemicals⁽⁹⁾. The minor constituents are both lipid molecules such as squalene, tocopherols, fatty alcohols, triterpenic alcohols, 4-methylsterols, plant sterols and polar pigments and hydrophilic compounds, mainly polyphenols. While the virgin variety of olive oil has a

unique composition of beneficial compounds, ordinary or refined olive oil loses minor components, particularly the polyphenols, during the refining process. Nevertheless, whether virgin or refined, the high MUFA content confers olive oil a high resistance to elevated temperatures, a reason why it can be reutilised more than once for frying, unlike polyunsaturated-rich oils⁽¹⁰⁾.

Many small randomised clinical trials have shown that consumption of olive oil, particularly the virgin variety, is associated with beneficial effects on intermediate cardiovascular biomarkers, such as blood lipids, blood pressure, inflammation and thrombosis (reviewed in López-Miranda *et al.*⁽⁹⁾). It is widely assumed that olive oil, particularly virgin olive oil due to its antioxidant potential, is the main component of the MeDiet that makes it cardioprotective⁽⁹⁾. However, given the consistent evidence on the cardiovascular benefit of the MeDiet^(4,7), there has been a surprising paucity of epidemiological data on olive oil consumption and CVD. One reason is the difficulty of disentangling olive oil from the other components of the MeDiet, mainly because most observational studies have used scores of adherence where the item MUFA:SFA ratio replaced olive oil proper, as initially described by Trichopoulou *et al.*⁽¹¹⁾. Besides, epidemiological studies centred on olive oil consumption and CHD have provided contradictory results. Thus, case-control studies have reported that increased olive oil use was unrelated to CHD in Italy^(12,13), while it was associated with a 47% lower risk in a Greek study⁽¹⁴⁾ and an inordinately high 82% protection in a small study in Spain⁽¹⁵⁾. The only published large observational study focused on olive oil exposure and incident CHD is the EPICOR study⁽¹⁶⁾, in which nearly 30 000 women from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Italy cohort were followed for 7.85 years. A strong CHD risk reduction was reported among participants in the highest quartile of olive oil consumption (>31.2 g/d), with a multivariate-adjusted hazard ratio (HR) of 0.56 (95% CI 0.31, 0.99; *P*=0.04). No distinction was made among different varieties of olive oil in this study.

In the present issue, Buckland *et al.*⁽¹⁷⁾ present the results of the entire Spanish EPIC cohort of 40 142 participants (62% women), relating olive oil consumption to CHD risk after follow-up for 10.4 years. Olive oil consumption was negatively associated with CHD risk after adjustment for possible confounders (HR 0.93; 95% CI 0.87, 1.00 for each 10 g/d per 8368 kJ (2000 kcal) and HR 0.78; 95% CI 0.59, 1.03 for the top *v.* the bottom quartile of intake (≥ 28.9 *v.*

<10 g/d, respectively)). Interestingly, there was an effect modification by alcohol intake and smoking, in such a way that the inverse association between olive oil consumption and CHD was more pronounced in never smokers and in never/low alcohol drinkers, which the authors rightly interpret as the protective effect of olive oil being masked in higher-risk smokers and obscured in already protected moderate alcohol drinkers, respectively. Buckland *et al.*⁽¹⁷⁾ must be commended for differentiating the effects of refined and virgin olive oil. The results suggested a greater decreased CHD risk for consumption of virgin compared to refined olive oil (HR 0.86; 95% CI 0.72, 1.01 and HR 0.97; 95% CI 0.91, 1.03, respectively, for each 10 g/d per 8368 kJ (2000 kcal) increment).

In a recent report of the same EPIC-Spain cohort, olive consumption was inversely related to total and CVD mortality after 13.4 years of follow-up⁽¹⁸⁾. In comparison with no consumption (15% of the sample), the top quartile of olive oil consumption was associated with a 26 (95% CI 13, 36)% reduction in risk of overall mortality and a 44 (95% CI 21, 60)% reduction in CVD mortality after multivariate adjustment. The authors separately assessed the effect of virgin and ordinary olive oil, but observed no differences in their association with overall mortality.

A further important report on olive oil consumption and CVD stems from the Three-City study from France, whereby the association between olive oil consumption and incident stroke was evaluated in 7625 aged men and women after follow-up for 5.25 years⁽¹⁹⁾. Compared to subjects who never used olive oil (23% of the sample), those who used it for both cooking and dressing (37% of the sample) had a 41 (95% CI 6, 63)% lower risk of stroke after adjustment for various confounders. No distinction between virgin and refined olive oil was made in this study.

The two EPIC-Spain reports^(17,18) and the Three-City study⁽¹⁹⁾ make up a significant addition to the literature on olive oil and CVD. The observational evidence suggesting a beneficial effect of olive oil on cardiovascular health is consistent in these three large Mediterranean cohort studies. However, in each of them, subjects who consumed more olive oil were more educated, had less adiposity and, when reported, had a healthier overall diet than low or no consumers. Adjustment for these and other factors in risk analyses still does not allow inferring causality, because of the possibility of residual confounding, a common limitation of epidemiological studies. To prove causality and provide a compelling argument to increase olive oil use for CVD prevention, randomised controlled trials with cardiovascular endpoints are needed. A large randomised clinical trial in high-risk subjects, the PREDIMED (PREvención con Dieta MEDiterránea) study⁽²⁰⁾, is examining the effects of two MedDiets supplemented with virgin olive oil or mixed nuts against a low-fat diet for primary prevention of CVD. The final results of the PREDIMED study are expected soon and might eventually provide the level of scientific evidence required to definitively answer the question whether olive oil consumption protects from CVD.

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