

Diet and Nutrition after the PURE study

Dietary modification on a global scale has the potential of reducing cardiovascular disease (CVD) by 50%. There is unequivocal evidence that consumption of industrialized trans unsaturated fats is associated with increased cardiovascular mortality. Despite contrary evidence from short-term meta-analyses, saturated fats are also partly condemned as a potential macronutrient enemy for cardiovascular health.¹ There is a general consensus among the scientific community that lowering saturated fat is beneficial in reducing the risk of CVD.

The 2016 European Society of Cardiology (ESC) guidelines recommend a total fat intake of $\leq 30\%$ of which $\leq 10\%$ should consist of saturated fats. The guidelines also suggest decreasing saturated fat intake by substitution with polyunsaturated fatty acids.² In June 2017, the American Heart Association's (AHA) presidential advisory on dietary fats summarized that replacing saturated fat with polyunsaturated vegetable oil reduced CVD by 30%.³

The PREDIMED study, a multicentre randomized controlled trial with 7447 participants demonstrated that addition of five tablespoons of olive oil or 30 g unsalted nuts to the conventional Mediterranean diet was associated with a 30% relative reduction in risk of cardiovascular mortality compared with simply lowering saturated fat intake.⁴ Contrary to the international dietary recommendations for preventing CVD, data from the Prospective Urban Rural Epidemiology (PURE) study has challenged the guidance relating to fat consumption.⁵

PURE study

In the largest epidemiological study of its type, over 135 000 patients were enrolled from 18 different countries (3 high-income countries, 5 low-income countries, and 10 middle-income countries) in five continents. Patients completed food frequency questionnaires and were followed up for a median of 7.4 years. Outcomes included total mortality and major CVDs (cardiovascular deaths, non-fatal myocardial infarction, stroke, and heart failure). During the period of the study there were 4784 cardiovascular events and a total of 5796 deaths. The investigators reported that higher intake of fats, was associated with lower total mortality.

There was increasing total mortality benefit as fat consumption increased from 11% (lowest quintile) to 35% (highest quintile) total nutritional intake [hazard ratio (HR) 0.77, 95% confidence interval (CI) 0.67–0.87; $P < 0.0001$]. The relative reduction in mortality with fats was maintained irrespective of saturated fat (HR 0.86, 95% CI 0.76–0.99; $P = 0.0088$), monounsaturated fat (HR 0.81, 95% CI 0.71–0.92; $P < 0.0001$), or polyunsaturated fat intake (HR 0.80, 95% CI 0.71–0.89; $P < 0.0001$). Indeed, saturated fat intake of $< 7\%$ was deemed harmful. In contrast, a progressive increase in carbohydrate intake was associated with increased total mortality from lowest quintile to highest quintile (HR 1.28, 95% CI 1.12–1.46; $P < 0.0001$); specifically,

carbohydrate intake exceeding 60% of total energy consumption was associated with increased mortality (Table 1).

Potential implication and explanations

Most studies assessing the dietary impact on CVD are conducted in North America and Europe where the percentage of saturated fat intake is higher than the rest of the world. Over the past couple of decades, however, there has been an exponential rise in CVD in low-income countries where the impact of dietary intake has not been explored in detail. The major strengths of the PURE study are its sheer size and global representation, providing an incredible resource to inform future nutritional recommendations. Pooled data from 18 countries of which 15 were low- or middle-income reveals that high carbohydrate rather than fat intake (barring trans unsaturated fats) is the dietary enemy!

Theoretically, replacement of fat with carbohydrates may increase triglyceride concentrations, reduce high density lipoprotein, and create smaller apoproteins thereby, increasing the risk of heart disease. In the PURE study however, neither an increased carbohydrate intake nor increasing fat intake was associated with an impact on major CVD or cardiovascular mortality. Indeed, most deaths were from non-CVDs.

Replacement of 5% isocaloric carbohydrates with polyunsaturated fats had no impact of CVD mortality but improved non-CVD mortality by 16%. Although replacement of carbohydrates with saturated fat reduced risk of stroke by 20%, there was no effect on CVD mortality. Therefore, another possible explanation for reduced mortality with higher fat levels could be the replacement of micronutrients from fat and meat that are essential for general well-being and, possibly protective against infectious diseases or malignancy. Given that the diet from

Table 1 Main findings from the PURE study

Higher intake of fat (saturated and unsaturated) is associated with a lower risk of mortality.
Higher carbohydrate intake ($> 60\%$ of diet) is associated with a higher risk of mortality.
No association between total fat or types of fat and cardiovascular mortality.
Current guidelines restricting total fat to $< 30\%$ or saturated fat to $< 10\%$ total fat are NOT SUPPORTED by this study.

participants from low-income countries mainly consisted of high (and mainly refined) carbohydrates it is also possible that a diet that was low in fat was a proxy for poverty and its own complications.

Limitations

As with all nutritional studies, the main source of patient dietary information was from questionnaires and hence recall bias cannot be excluded. In addition, when reporting carbohydrates in dietary questionnaire, the researchers would not have been able to accurately differentiate between refined carbohydrates and whole grain carbohydrates. As with all observational studies, there is concern regarding confounding factors in the PURE study, in particular income, education, culture and conscientiousness, which may



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all contribute to adverse outcomes. It is arguable that with attentive multivariable adjustment some of these potential confounders may have been accounted for however, the scope for confounding variables in a trial of this magnitude and diversity cannot be underestimated.

Conclusion

The PURE study provides an interesting and thought-provoking view on the impact of macronutrients on total mortality. Whether the study calls for a radical change in the current ESC recommendations is debatable. The PURE diet supports previous observations that mortality is increased when saturated fat is replaced with refined carbohydrates as was probably the case in low-income countries. Consistent with current recommendations, the study also reveals that the mortality benefit is greatest when refined carbohydrates are replaced largely by polyunsaturated fat.⁶

With respect to relaxing the current recommendations for saturated fat intake, the scientific community should be encouraged to explore more precise reasons for the findings of the study before changing current, well considered, recommendations.

Conflict of interest: none declared.

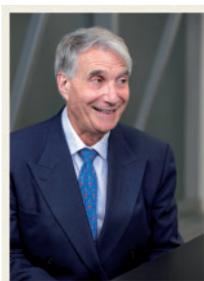
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References are available as [supplementary material](#) at *European Heart Journal* online.

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Peter Libby MD and CANTOS

Peter Libby MD, reflects on CANTOS and a new era of personalised medicine



For many basic science labs around the world the hotly-anticipated findings of the CANTOS trial delivered at the ESC Congress in 2017 were welcomed as an affirmation of years, if not decades of work on inflammation. It was an important moment for Peter Libby MD, Mallinckrodt Professor of Medicine at Harvard Medical School and long-time Chief of Cardiovascular Medicine at Brigham and Women's Hospital in Boston, Massachusetts, USA. Investigators in his own

lab have been engaged in inflammation research for many years after he helped to pioneer the concept that inflammation had a role in relation to atherosclerosis in the modern era (*Figure 1*).

Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) was set up by researchers at the Brigham and Women's Hospital and Harvard Medical School to test the inflammatory hypothesis of atherosclerosis and investigate whether blocking pro-inflammatory cytokine, interleukin-1 β (IL-1 β), can reduce rates of recurrent heart attack and stroke. Libby explains 'We used the IL-1 β antibody which neutralizes the protein cytokine in a large-scale trial

(conducted in nearly 40 countries around the world), of men and women who were stable post myocardial infarction, but at risk and on 'a very rigorous end of care regimen', with an indication of inflammation. We measured the overall amount of inflammatory burden by gauging the level of high-sensitivity C-reactive protein. The trial randomized 10 061 people to either a placebo or one of three doses of canakinumab. Patients were followed up until investigators had over 1400 events and analysis showed that the middle dose used of 150 mg, subcutaneously every 3 months, four times a year, could reduce cardiovascular events to about 15% of primary endpoint or 17% on a broader endpoint.



Libby's first serious effort to pinpoint the role of interleukin-1 in atherosclerosis dates to 1986 when he published a paper in the *American Journal of Pathology* (at the time cardiology journals showed little interest in inflammation.) He wrote in that paper that the results indicated a strong possibility that IL-1 β promoted atherosclerosis. He then laboured for over 30 years to prove this