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Macronutrients and cardiovascular risk in a global context

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The evidence base and guidance on the consumption of dietary macronutrients for health has come a long way. This evolution includes a shift from a historically almost exclusive focus on restriction of total and saturated fat intake for reducing concentrations of the bad LDL cholesterol for cardiovascular risk prevention, to recognition of the importance of the different types of fat (saturated, polyunsaturated, monounsaturated, or trans-fatty acids), and to the relevance of the replacement nutrient (unsaturated fat or carbohydrates) when intake of saturated fat is reduced.[1,2] However, our understanding of these issues is by no means complete. For example, are saturated fats or carbohydrates equally bad, or is one worse than the other for cardiovascular health? Questions remain, and these issues are still hotly debated, leaving many lost in the fog of the of the fat-versus-carbohydrate war. Meanwhile, the global relevance of dietary research mostly done in North American and European countries is unclear.

In *The Lancet Diabetes & Endocrinology*, investigators of the Prospective Urban–Rural Epidemiology (PURE) study weigh in on these issues, reporting the results of a cross-sectional analysis with a focus on intermediate cardiovascular risk markers: lipids and blood pressure.[3] With 125 287 participants enrolled from 18 countries across five continents, spanning a range of economic development, the findings suggest that a wider consideration of lipids—beyond LDL cholesterol—is important to capture the net effect of macronutrient substitutions. Together with an accompanying PURE study Article in *The Lancet* reporting on the link between macronutrients, mortality, and incident cardiovascular disease,[4] the findings lead to two broad conclusions: unsaturated fat is more favourable than saturated fat, and saturated fat is more favourable than carbohydrates. However, several nuances of the study design restrict the causal inferences that can be made. Not only are the risk-factor analyses cross-sectional, but the study also raises a previously undescribed possibility of an interaction whereby changes in lipid concentrations related to macronutrient substitutions vary according to level of total and saturated fat intake. Therefore, because diet varied substantially between world regions (eg, the estimated mean saturated fat intake in China is 5·6% of total energy *vs* about 11% in North America and Europe[3]), pooling data across regions might be problematic. The notion that saturated fat is more favourable than carbohydrates is broadly in line with summary evidence from high-income countries showing that replacing saturated fat with carbohydrate is unlikely to help to reduce cardiovascular disease risk.[1,2] Carbohydrate quality was not assessed in the PURE study, yet refined carbohydrate intake was likely to predominate in PURE populations, and to do so differentially across regions.[3]

Taken together across the two reports,[3,4] the conclusions are provocative: first that the focus on a single lipid biomarker, LDL cholesterol, is misplaced, and second that the key dietary priority should be to reduce intake of carbohydrate, rather than total fat or saturated fat, worldwide.

So what are the public health implications of these findings? The appraisal of whether a change in dietary guidance is warranted rests broadly on a body of evidence informed by different study designs within the so-called hierarchy-of-evidence framework, and with replication and consistency of findings. Against these criteria, strengths of the PURE study lie in its important and timely investigation across diverse global populations with varying diets, and bold attempts to standardise dietary assessment and a comprehensive range of lipid measurements. Limitations, in addition to those previously mentioned, include the inability to measure trans-fat intake and, with respect to the lipid and blood pressure analyses in particular, the cross-sectional design and the potential for residual confounding from an absence of adjustment for BMI or alcohol intake. The consideration of non-traditional lipid parameters is noteworthy, but their causal or meaningful predictive value over traditional lipid measures[5,6] needs to be determined in different ethnic groups.

Notable heterogeneity in nutrient and lipid associations also remains unexplained, thereby limiting the inference based on the averaged associations in the total study population. For example, the estimated effect of replacing saturated fat with polyunsaturated fat (by 3% energy) on the ratio of total cholesterol to HDL cholesterol was –0·38 in North America and Europe, 0·16 in South America, –0·07 in the Middle East, 0·13 in south Asia, 0·06 in China, –0·15 in Malaysia, and 0·09 in Africa.[3] The authors' overall estimate was

0·059 (95% CI 0·041 to 0·078; p<0·0001). However, we calculated that the summary estimate could be –0·010 (95% CI –0·127 to 0·108; I^2=93·0%) via random-effects modelling, and thus the presented estimates are unstable. The authors appropriately attributed variation to different food sources, varying distributions of dietary consumption, and related dose responses,[3,4] but other sources deserve consideration, including untested interactions by population characteristics (eg, obesity status[7]), and varying degrees of validity of dietary questionnaires and food-composition tables that were partly based on US databases.[3] Possible confounding due to varying dietary patterns is also relevant. For example, refined carbohydrates could be consumed from white rice associated with salty fish consumption in some regions in Asia, but in North America and Europe they could be consumed from white bread, soft drinks, or confectionary, which are associated with an unhealthy lifestyle. Finally, diverse risk patterns of cardiovascular disease are likely to cause heterogeneous findings between populations—eg, higher haemorrhagic stroke risk than ischaemic stroke risk in low-income countries and vice versa in high-income countries.[8]

The PURE study offers a global perspective that fills an important research gap, for which the study investigators should be applauded. However, their cross-sectional evidence[3] should be considered hypothesis generating, and their prospective findings[4] need to be replicated. The work should therefore act as a stimulus for further systematic appraisal of existing and new evidence, including randomised trials in low-income and middle-income countries. Acknowledging that nutritional trials for hard endpoints are especially challenging to undertake, prospective evidence combined with trials of intermediate risk markers could help with public health decision making to extend nutrient-based evidence to future dietary recommendations based on local foods, meals, and dietary patterns, and embracing the sociocultural environment. For now, despite some caveats, the PURE study's findings broadly support the notion that reducing total fat intake may be unwarranted and that replacing saturated fat intake with (refined) carbohydrates is not a good recipe for cardiovascular health.

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