Association of dietary nutrients with blood lipids and blood pressure in 18 countries: a cross-sectional analysis from the PURE study

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Summary

Background The relation between dietary nutrients and cardiovascular disease risk markers in many regions worldwide is unknown. In this study, we investigated the effect of dietary nutrients on blood lipids and blood pressure, two of the most important risk factors for cardiovascular disease, in low-income, middle-income, and high-income countries.

Methods We studied 125 287 participants from 18 countries in North America, South America, Europe, Africa, and Asia in the Prospective Urban Rural Epidemiology (PURE) study. Habitual food intake was measured with validated food frequency questionnaires. We assessed the associations between nutrients (total fats, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, carbohydrates, protein, and dietary cholesterol) and cardiovascular disease risk markers using multilevel modelling. The effect of isocaloric replacement of saturated fatty acids with other fats and carbohydrates was determined overall and by levels of intakes by use of nutrient density models. We did simulation modelling in which we assumed that the effects of saturated fatty acids on cardiovascular disease events was solely related to their association through an individual risk marker, and then compared these simulated risk marker-based estimates with directly observed associations of saturated fatty acids with cardiovascular disease events.

Findings Participants were enrolled into the study from Jan 1, 2003, to March 31, 2013. Intake of total fat and each type of fat was associated with higher concentrations of total cholesterol and LDL cholesterol, but also with higher HDL cholesterol and apolipoprotein A1 (ApoA1), and lower triglycerides, ratio of total cholesterol to HDL cholesterol, ratio of triglycerides to HDL cholesterol, and ratio of apolipoprotein B (ApoB) to ApoA1 (all $p_{trend}<0·0001$). Higher carbohydrate intake was associated with lower total cholesterol, LDL cholesterol, and ApoB, but also with lower HDL cholesterol and ApoA1, and higher triglycerides, ratio of total cholesterol to HDL cholesterol, ratio of triglycerides to HDL cholesterol, and ApoB-to-ApoA1 ratio (all $p_{trend}<0·0001$, apart from ApoB [$p_{trend}=0·0014$]). Higher intakes of total fat, saturated fatty acids, and carbohydrates were associated with higher blood pressure, whereas higher protein intake was associated with lower blood pressure. Replacement of saturated fatty acids with carbohydrates was associated with the most adverse effects on lipids, whereas replacement of saturated fatty acids with unsaturated fats improved some risk markers (LDL cholesterol and blood pressure), but seemed to worsen others (HDL cholesterol and triglycerides). The observed associations between saturated fatty acids and cardiovascular disease events were approximated by the simulated associations mediated through the effects on the ApoB-to-ApoA1 ratio, but not with other lipid markers including LDL cholesterol.

Interpretation Our data are at odds with current recommendations to reduce total fat and saturated fats. Reducing saturated fatty acid intake and replacing it with carbohydrate has an adverse effect on blood lipids. Substituting saturated fatty acids with unsaturated fats might improve some risk markers, but might worsen others. Simulations suggest that ApoB-to-ApoA1 ratio probably provides the best overall indication of the effect of saturated fatty acids on cardiovascular disease risk among the markers tested. Focusing on a single lipid marker such as LDL cholesterol alone does not capture the net clinical effects of nutrients on cardiovascular risk.

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Introduction

Cardiovascular disease is a global epidemic with 80% of the burden in low-income and middle-income countries.[1] For decades, blood total cholesterol was assumed to be a robust marker for predicting the risk of cardiovascular disease.[2] The focus later shifted to LDL cholesterol, which has been the basis of dietary recommendations to reduce the risk of cardiovascular disease in populations. A diet low in saturated fatty acids has been widely recommended to reduce LDL cholesterol concentrations and presumably to reduce the risk of cardiovascular disease.[3–6] However, this approach assumes that the net clinical benefit of

Research in context

Evidence before this study

We searched PubMed for relevant research published between Jan 1, 1960, and May 1, 2017, using the terms "carbohydrate" or "total fat" or "saturated fat" or "monounsaturated fatty acid" or "polyunsaturated fatty acid" and "lipids" or "cholesterol" or "apolipoprotein" or "blood pressure" or "hypertension", restricted to studies in the English language. We screened papers by title and abstract to identify full-text reports that were relevant to our study aims. We also screened citation lists from these full-text reports to identify other relevant research. We considered papers relevant if they contained an evaluation of the relation between macronutrient intake and at least one of the outcomes of interest (blood lipids and blood pressure). The papers cited in this report were selected to be representative of the existing evidence base, but are not an exhaustive list of relevant research. Dietary guidelines focus on reducing total fat and saturated fatty acid intake to reduce total cholesterol concentrations, which in turn is presumed to reduce cardiovascular disease. However, this recommendation has recently been challenged because the effect of reducing saturated fatty acids depends on what nutrients replace them in the diet. Furthermore, there are no relevant data from low-income and middle-income countries, where 80% of premature cardiovascular deaths occur.

Added value of this study

In this large, international, epidemiological study of 125 287 people in diverse regions of the world, we investigated the effect of dietary nutrients on blood lipids and blood pressure, two of the most important risk factors for cardiovascular disease. We also aimed to examine the association of isocaloric replacement of saturated fatty acid with other nutrients on these cardiovascular disease risk markers, and to assess whether the changes in risk markers with changes in total fat and saturated fatty acid vary significantly by level of intake. We also compared whether the associations observed between saturated fatty acid and carbohydrate intake and cardiovascular disease could be explained by their associations with specific lipid markers. To our knowledge, this is the largest study relating macronutrient intake to cardiovascular disease risk markers.

Implication of all the available evidence

Our findings suggest that reducing saturated fatty acid intake and replacing it with carbohydrate has an adverse effect on blood lipids. Substituting saturated fatty acids with unsaturated fats might be beneficial for some risk markers (LDL cholesterol and blood pressure), but might worsen others (HDL cholesterol and triglycerides). The effect of nutrient substitution on lipid markers varies significantly by the level of total fat and saturated fatty acid intake, suggesting that the effects of different diets could be dissimilar in populations that are undernourished compared with those that are adequately nourished or overnourished. The observed association between saturated fatty acids and cardiovascular disease events was explained by the association of this nutrient with the ratio of apolipoprotein B (ApoB) to apolipoprotein A1 (ApoA1), but not by associations with other lipid markers including LDL cholesterol (which has been the basis of many guidelines). This finding suggests that ApoB-to-ApoA1 ratio probably provides the best overall indication of effect of saturated fatty acids on cardiovascular disease risk among the markers tested. Focusing on a single lipid marker such as LDL cholesterol alone does not capture the net clinical effect of nutrients on cardiovascular risk. The current recommendation to reduce total fat and saturated fatty acids, which leads to a de facto increase in carbohydrate intake, is not supported by our data.

saturated fatty acid reduction can be accurately predicted from its effect on a single risk factor (LDL cholesterol) alone without considering its overall effect on other common risk markers of cardiovascular disease, including triglycerides, HDL cholesterol, ratio of total cholesterol to HDL cholesterol, ratio of apolipoprotein B (ApoB) to apolipoprotein A1 (ApoA1), and blood pressure. Furthermore, the recommendation that total fat should be reduced does not take into account the types of fats or the net effect of replacing one type of fat with another or with carbohydrates on cardiovascular disease risk factors.

Most existing observational cohort studies investigating the effects of nutrients on risk factors for cardiovascular disease have been done in Europe and North America, and it is not known whether their findings can be extrapolated to other regions of the world, where dietary patterns vary. Furthermore, most studies from Europe and North America have been concerned with the effect of overnutrition, but do not address the consequences of inadequate intake of fats or other nutrients.

The Prospective Urban Rural Epidemiology (PURE) study[1,7–9] is a large international epidemiological study undertaken in diverse regions of the world. In some regions, overnutrition is common and in other regions undernutrition is common. Therefore, PURE presents an opportunity to study the effects of both nutritional excess and inadequacy and therefore to reliably characterise the relation between dietary nutrients and cardiovascular disease risk factors across a broad range of nutrient intakes that is not possible in studies done solely in high-income countries.

In the present analysis from the PURE study, we aimed to assess the association of nutrients (total fats, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, carbohydrates, protein, and dietary cholesterol) with cardiovascular disease risk markers (ie, blood lipid measures and blood pressure). We also aimed to examine the association of isocaloric replacement of saturated fatty acid with other nutrients on these cardiovascular disease risk markers, and to assess whether the changes in risk

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See Online for appendix

markers with changes in total fat and saturated fatty acid vary significantly by level of intake. Finally, we aimed to compare the observed magnitude and patterns of associations between saturated fatty acid and carbohydrate intake and cardiovascular disease events (as assessed in a separate analysis[9]) with the predicted hazard ratio (HR) modelled on the assumption that the association between saturated fatty acid and carbohydrate intake on cardiovascular disease was mediated by the effects on specific lipid markers.

Methods

Study design and participants

The design of the PURE study has been described previously.[1,7–8] Briefly, the study is a large-scale prospective cohort study of 157 543 men and women enrolled from 667 communities in 18 low-income, middle-income, and high-income countries. We considered the heterogeneity of socioeconomic factors and the feasibility of carrying out long-term follow-up when selecting the participating countries. The study included three high-income countries (Canada, Sweden, and United Arab Emirates), 11 middle-income countries (Argentina, Brazil, Chile, China, Colombia, Iran, Malaysia, occupied Palestinian territory, Poland, South Africa, and Turkey), and four low-income countries (Bangladesh, India, Pakistan, and Zimbabwe). Selection of the participants is described in the appendix (p 2). Recruitment began on Jan 1, 2003, and was completed by March 31, 2013. To ensure standardised methods of data collection, research assistants were trained with comprehensive operation manuals, videos, and workshops. Data were transferred electronically to the project office and coordinating centre at the Population Health Research Institute (PHRI; Hamilton, ON, Canada), where quality-control checks were undertaken. All participants provided written informed consent. The study was coordinated by the PHRI. The protocol was approved by the Hamilton Health Sciences Research Ethics Board and by the local ethics committee at each site.

Procedures

Participants' habitual food intake was recorded using country-specific (region-specific in India) validated food frequency questionnaires (FFQs; appendix p 5). For almost all countries where a validated FFQ was not available, we developed and validated FFQs using a standard method (appendix p 5). The FFQ was undertaken by interview together with other questionnaires at the PURE study baseline.

Information on personal medical history, use of prescription medications, education level, and smoking status was recorded using a standardised questionnaire.[7–9] Two recordings of blood pressure after 5 min of rest in a sitting position with the use of an Omron automatic digital monitor (Omron HEM-757; Omron Corp, Tokyo, Japan) were recorded in all participants. A fasting blood sample was collected from each participant and frozen at between –20°C and –70°C. All blood samples were shipped in ambient packaging with the use of STP-250 shipping boxes (Saf-T-Pak, AnInmark Company, Edmonton, AB, Canada) to the Clinical Research and Clinical Trials Laboratory at Hamilton General Hospital (Hamilton, ON, Canada) or the regional laboratories in Beijing (China), Bangalore (India), or Kocaeli (Turkey), for analyses with the use of validated and standardised methods. Fasting blood samples were analysed for total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, ApoA1, and ApoB at the PHRI.[10]

148 723 participants completed the FFQ, of which 143 342 people had plausible energy intake (500–5000 kcal per day)[11] and had no missing values on age and sex. Of this sample, 135 335 individuals had no history of cardiovascular disease. The final study sample consisted of 125 287 participants with baseline blood pressure recorded, 104 486 with baseline measures of total cholesterol, LDL cholesterol, and HDL cholesterol, and 18 330 with baseline measures of ApoB and ApoA1.

Statistical analysis

Means (SDs) were calculated to summarise continuous variables. Mean (95% CI) intake of each nutrient was calculated overall and by income region (with tests for trend) and by geographic region, while adjusting for age, sex, and centre.[11] Participants were categorised into quintiles of nutrient intake, based on percentage of energy intake provided by specific nutrients. The primary outcomes of this report are concentrations of blood lipids (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, total cholesterol-to-HDL cholesterol ratio, triglycerides-to-HDL cholesterol ratio, ApoB, ApoA, and ApoB-to-ApoA1 ratio) and blood pressure. Multilevel linear regression, with random-effect models to account for community-level clustering, was used to assess the effect of percentage of energy intake provided by various nutrients and dietary cholesterol with blood lipid concentrations and blood pressure. All models were adjusted for covariates of age, sex, urban or rural location, education, smoking status, and treatment with statins (for lipids analyses) or use of antihypertensive drugs (for blood pressure analyses). The median value for each quintile group was used for tests for trend, modelled as a continuous variable. To help compare the strength of association between the various nutrients and risk markers in common units, we calculated standardised coefficients that represented the number of SDs a risk marker changed per 1 SD increase in nutrient intake. Sensitivity analyses were done excluding individuals who were taking statins or those who were taking antihypertensive drugs. We also did sensitivity analyses excluding Malaysia and Zimbabwe, since we were not able to estimate different fatty acids for a few foods consumed in these countries. Since overnutrition is generally represented by European and North American countries and undernutrition by countries in other

continents, and given that dietary recommendations focus on reducing total fat and saturated fatty acid intake, we further evaluated the effects of fats on risk markers at different levels of fat intake. For this analysis, moderate was defined as a 5% interval closest to the average level of intake (25–30% of energy for total fat and 5–10% of energy for saturated fat). Individuals with intakes below or above these values were categorised as low intake or high intake, respectively. We did tests for interaction to assess the effect of different levels of intake on the slope of association between total fat (and saturated fatty acid) intake and the risk markers.

We estimated the effect of isocaloric replacement of saturated fatty acids with carbohydrates and other fatty acids using a multivariable nutrient density model.[11] In this modelling, the percentage of energy intake from carbohydrates, different fatty acids, and protein were included as exposure, and total energy as a covariate. The coefficients in this model indicate the change in a risk marker for a 3% of energy intake isocaloric replacement of saturated fatty acids with other nutrients.

We did simulation modelling of the effect of changes in saturated fatty acids and carbohydrate intake on risk of incident cardiovascular disease events (fatal cardiovascular disease, non-fatal myocardial infarction, stroke, and heart failure), based on the assumption that the observed associations between saturated fatty acid and carbohydrate intake and cardiovascular disease events could be explained by the effects of these nutrients on risk markers (appendix p 7). We compared these simulated risk marker-based estimates with directly observed HRs of cardiovascular disease events associated with intake of saturated fatty acids and carbohydrates, which are reported in a separate analysis.[9] We quantified the degree to which the modelled HR estimates differed from the observed HR estimates of cardiovascular disease events using the I^2 statistic (ranging from 0% to 100%). All statistical analyses were done with SAS, version 9.3 and Comprehensive Meta Analysis software, version 2.2 (Biostat, Englewood, NJ, USA).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding (AM) and senior (SSA and SYu) authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Data collection for the study was done between Jan 1, 2003, and March 31, 2013. The characteristics of the participants are shown in the appendix (pp 8–10). Across the study population, mean daily carbohydrate intake was 61·3% (SD 11·6) of total energy intake, total fat was 23·4% (9·3) of total energy intake, and protein was 15·2% (3·5) of total energy intake (figure 1, appendix pp 8–10). Total fat consisted of 7·7% (SD 4·2) from saturated fatty acids, 7·7% (3·5) from monounsaturated fatty acids, 5·0% (2·9) from polyunsaturated fatty acids, and 3·0% (2·6) from glucose, glycerol, and other aldehydes.

Intake of total fat, saturated fatty acids, monounsaturated fatty acids, and total protein decreased as country income level decreased, whereas carbohydrate and polyunsaturated fatty acid intake was highest in low-income countries, intermediate in middle-income countries, and lowest in high-income countries (p_{trend}<0·0001 for each measure; figure 1A). Consumption of total fat (mainly from saturated fatty acids and monounsaturated fatty acids) was highest in North America, Europe, and the Middle East, whereas carbohydrate intake was highest in south Asia,

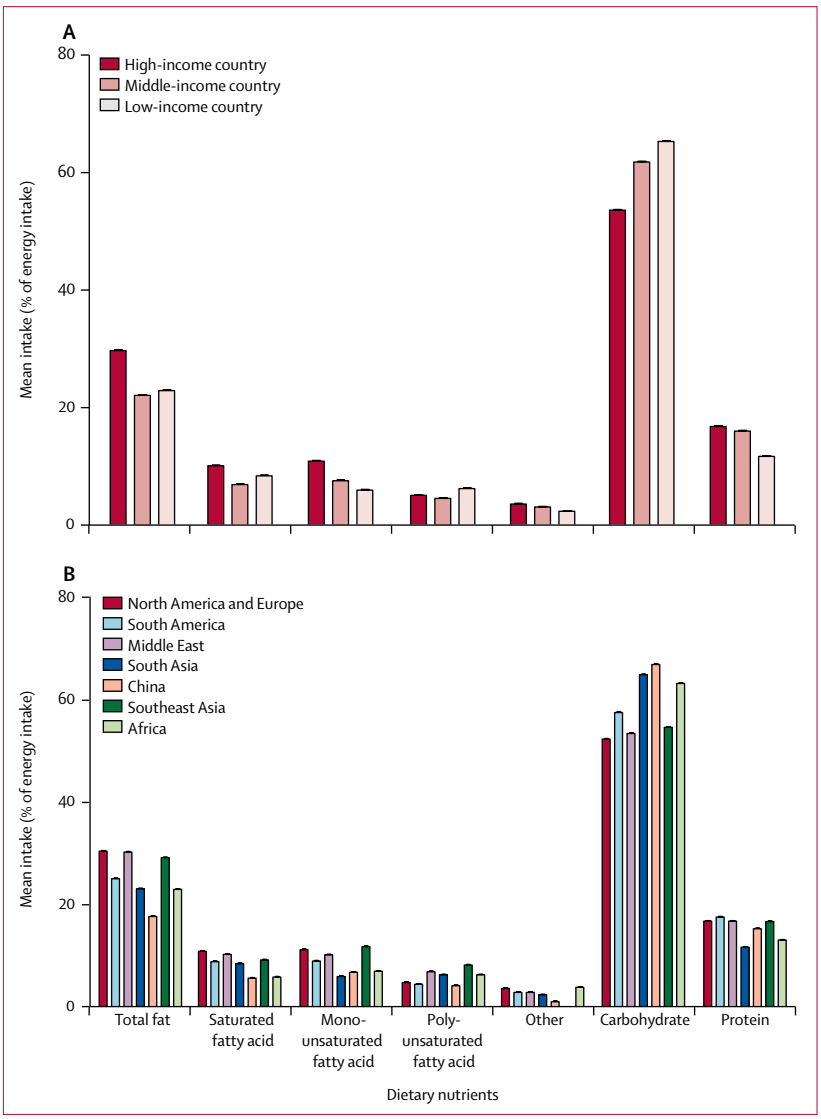
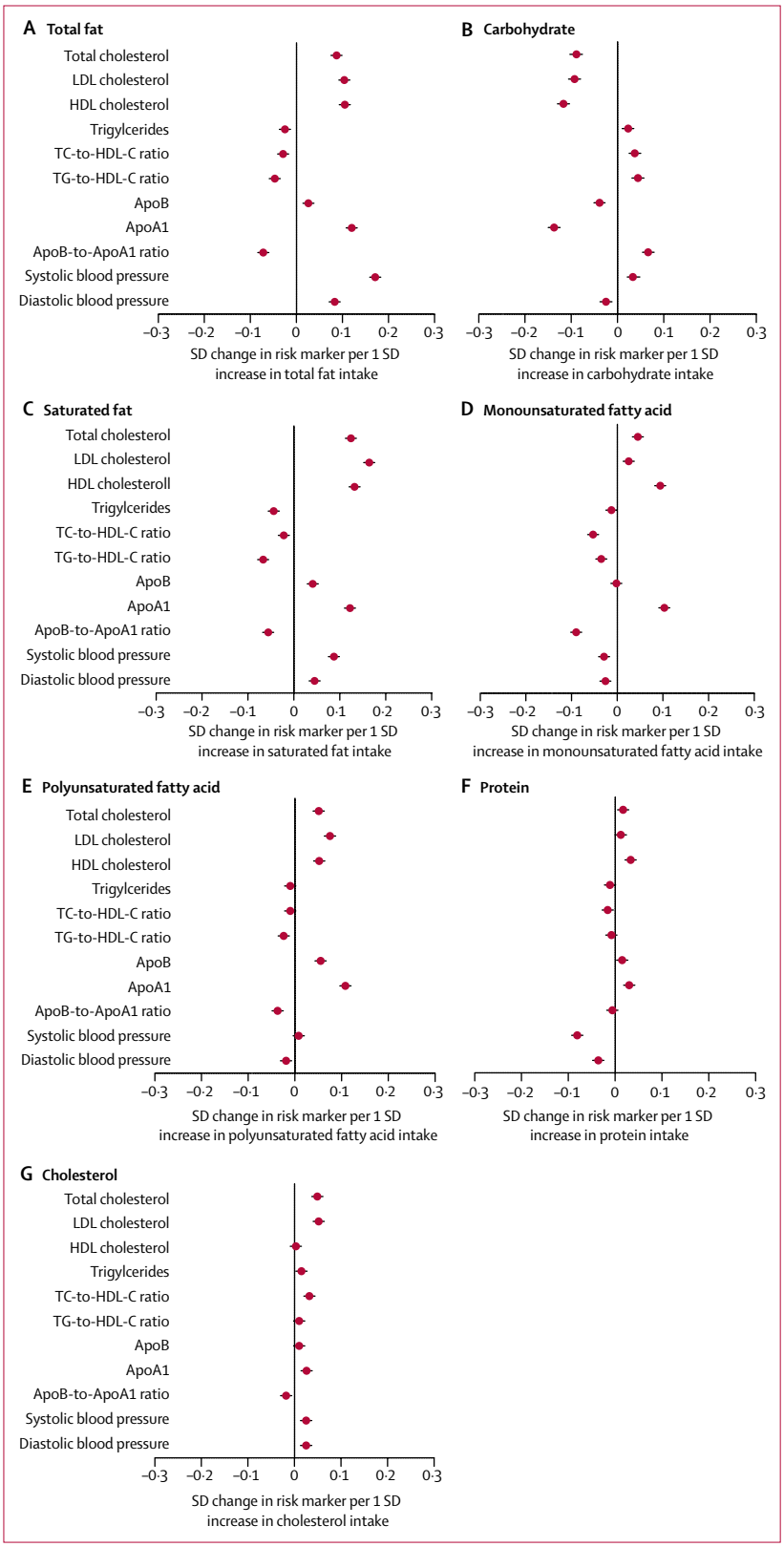


Figure 1: **Mean intake of nutrients by country income group (A) and geographical region (B); n=125 287**
Means are adjusted for age, sex, and centre (as a random effect). Other consists of glucose, glycerol, and other aldehydes. Bars are 95% CIs.



China, and Africa. Protein intake was lower in south Asia than in other regions (figure 1B).

Standardised coefficients (with 95% CIs) showing the number of SDs change in risk markers per 1 SD increase in nutrient intake are shown in figure 2 and the appendix (pp 11–15). Generally, carbohydrates and fats had stronger associations with risk markers, in comparison with the associations of protein and dietary cholesterol with risk markers. In sensitivity analyses, the exclusion of 3759 participants who were taking statins or 16 537 who were taking antihypertensive drugs or 7976 individuals from Malaysia or Zimbabwe (where we were not able to estimate different fatty acids for a few foods), did not materially affect the regression coefficients (data not shown).

After adjustment for covariates, we found that total fat intake was associated with higher total cholesterol and LDL cholesterol, but also with higher HDL cholesterol and ApoA1, and with lower ratio of total cholesterol to HDL cholesterol, triglycerides, ratio of triglycerides to HDL cholesterol, and ApoB-to-ApoA1 ratio (all p_{trend}<0·0001; figure 3, appendix pp 16–19). Intake of each type of fat (saturated fatty acids, monounsaturated fatty acids, and polyunsaturated fatty acids) was associated with higher concentrations of total cholesterol and LDL cholesterol, but also with higher HDL cholesterol and ApoA1, and lower triglycerides, ratio of total cholesterol to HDL cholesterol, ratio of triglycerides to HDL cholesterol, and ApoB-to-ApoA1 ratio (all p_{trend}<0·0001). Intakes of saturated fatty acids and polyunsaturated fatty acids were also associated with higher ApoB concentration (p_{trend}=0·0016 for saturated fatty acids and p_{trend}<0·0001 for polyunsaturated fatty acids; appendix pp 16–22).

Conversely, higher carbohydrate intake was associated with lower total cholesterol, LDL cholesterol, and ApoB, but also with lower HDL cholesterol, ApoA1, and with higher triglycerides, ratio of total cholesterol to HDL cholesterol, ratio of triglycerides to HDL cholesterol, and ApoB-to-ApoA1 ratio (all p_{trend}<0·0001, apart from ApoB [p_{trend}=0·0014]; figure 4, appendix pp 16–19). Higher protein intake was associated with higher total cholesterol and LDL cholesterol, but also with higher HDL cholesterol and ApoA1 (all p_{trend} <0·0001; appendix pp 16, 23). Dietary cholesterol intake was associated with higher total cholesterol, LDL cholesterol, triglycerides, and ratio of total cholesterol to HDL cholesterol, but also with higher HDL cholesterol and ApoA1, and with lower

Figure 2: **Standardised coefficients for the association between nutrient intake and risk markers (A–G)**

Bars are 95% CIs. The coefficients represent the number of SDs a risk marker changes per 1 SD increase in nutrient intake. Data are adjusted for age, sex, urban or rural location, education, current smoking, and treatment with statins (for lipids analyses) or use of antihypertensive drugs (for blood pressure analyses); centre was also included as a random effect. ApoB=apolipoprotein B. ApoA1=apolipoprotein A1. TC-to-HDL-C ratio=ratio of total cholesterol to HDL cholesterol. TG-to-HDL-C ratio=ratio of triglycerides to HDL cholesterol.

ApoB-to-ApoA1 ratio (all $p_{trend}<0·0001$, apart from ApoB-to-ApoA1 ratio [$p_{trend}=0·0045$]; appendix pp 16, 24).

Intakes of both total fat and carbohydrates were associated with higher systolic blood pressure ($p_{trend}<0·0001$; figure 5, appendix p 25). Higher saturated fatty acid and dietary cholesterol intakes were associated with higher systolic and diastolic blood pressures, whereas higher polyunsaturated fatty acid intake was associated with lower diastolic blood pressures (all $p_{trend}<0·0001$). We found no significant association between monounsaturated fatty acid intake and blood pressure. Conversely, higher protein intake was associated with lower systolic and diastolic blood pressure (all $p_{trend}<0·0001$).

The slopes of the association between fat intake and risk markers were generally steeper among people with lower fat intake (<25% of energy) than in those with

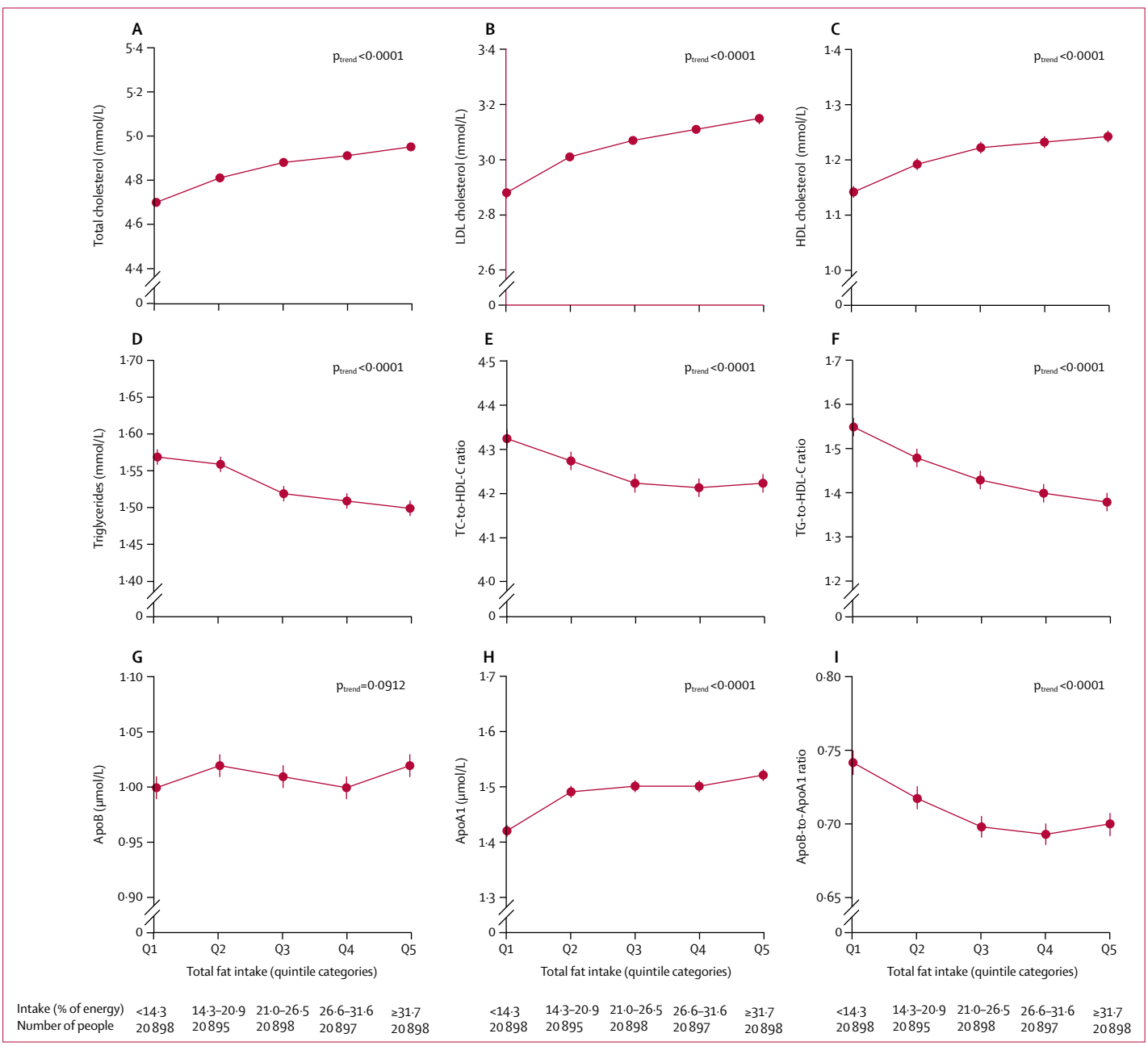


Figure 3: **Mean blood lipid concentrations by fat intake (n=104 486)**

Bars are 95% CIs. Data are adjusted for age, sex, urban or rural location, education, current smoking, and statin use; centre was also included as a random effect. A subset of 18 330 participants had measures of apolipoprotein B (ApoB) to apolipoprotein A1 (ApoA1). Data are shown for total cholesterol (A), LDL cholesterol (B), HDL cholesterol (C), triglycerides (D), TC-to-HDL-C ratio (E), TG-to-HDL-C ratio (F), ApoB (G), ApoA1 (H), and ApoB-to-ApoA1 ratio (I). TC-to-HDL-C ratio=ratio of total cholesterol to HDL cholesterol. TG-to-HDL-C ratio=ratio of triglycerides to HDL cholesterol.

moderate (25–30% of energy) or higher (>30% of energy) fat intake (figure 6, appendix p 29). Similar results were found for saturated fatty acid intake, with steeper slopes of association between saturated fatty acid intake and risk markers among persons with lower saturated fatty acid intake (<5% of energy) than in those with moderate (5–10% of energy) or higher (>10% of energy) saturated fatty acid intake (figure 6, appendix p 29).

In the nutrient replacement analyses, replacement of 3% of energy from saturated fatty acid with an equal percentage from carbohydrates was associated with a decrease in total cholesterol, LDL cholesterol, and ApoB, but also with a decrease in HDL cholesterol and ApoA1, and an increase in triglycerides, ratio of total cholesterol to HDL cholesterol, and ratio of triglycerides to HDL cholesterol (all p<0·0001, apart from ratio of total

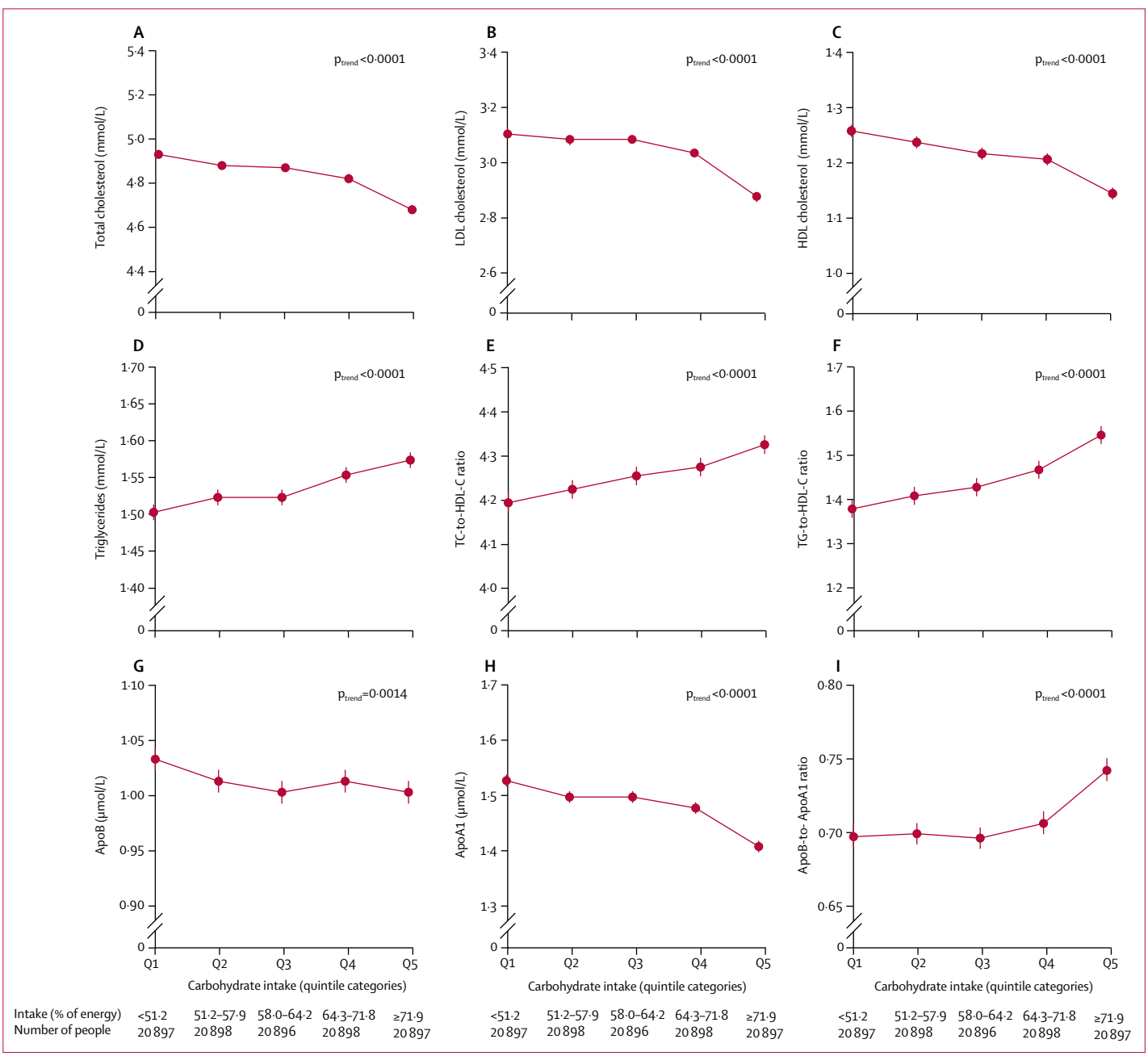
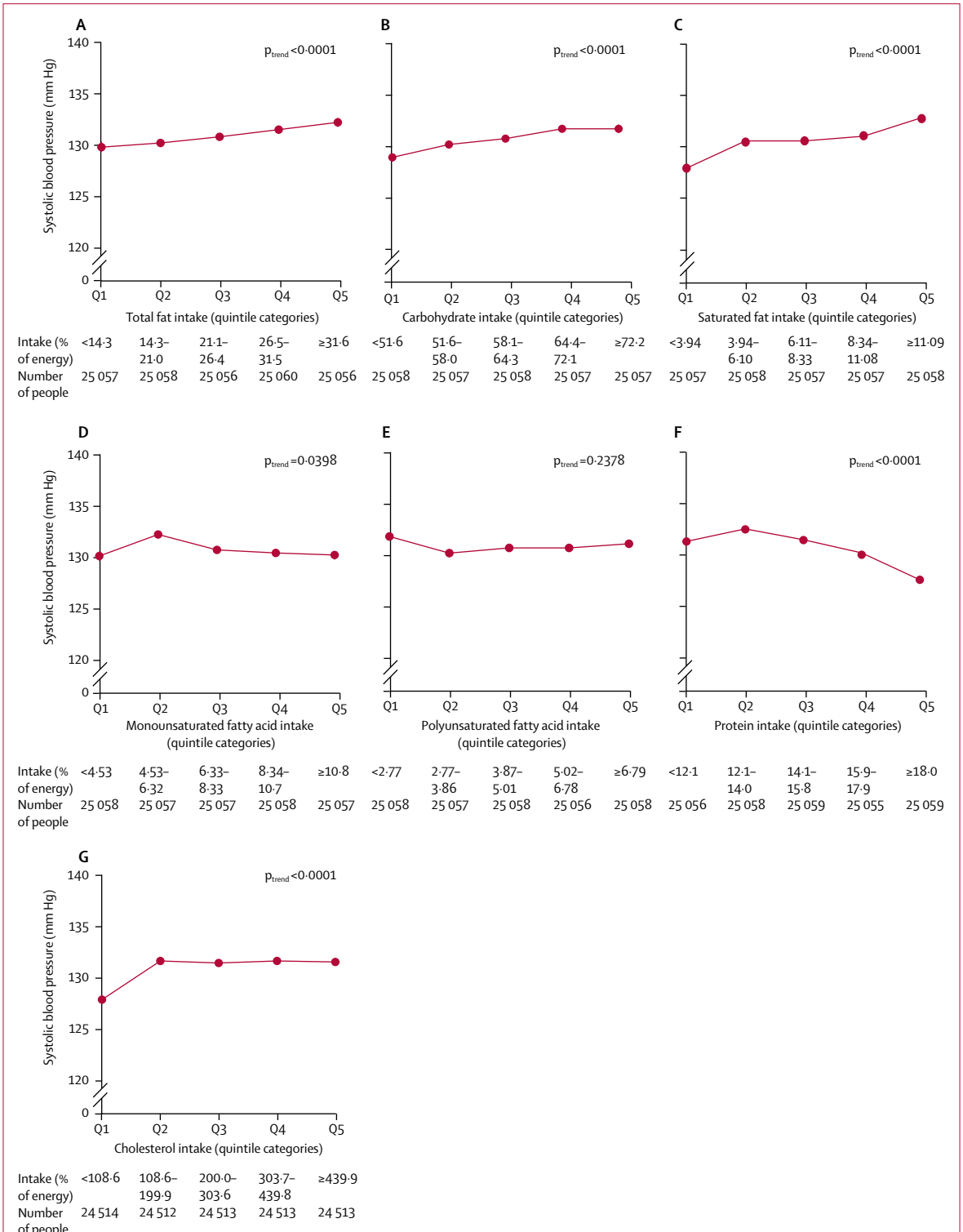


Figure 4: **Mean blood lipid concentrations by carbohydrate intake (n=104 486)**
Bars are 95% CIs. Data are adjusted for age, sex, urban or rural location, education, current smoking, and statin use; centre was also included as a random effect. A subset of 18 330 participants had measures of apolipoprotein B (ApoB) to apolipoprotein A1 (ApoA1). Data are shown for total cholesterol (A), LDL cholesterol (B), HDL cholesterol (C), triglycerides (D), TC-to-HDL-C ratio (E), TG-to-HDL-C ratio (F), ApoB (G), ApoA1 (H), and ApoB-to-ApoA1 ratio (I). TC-to-HDL-C ratio=ratio of total cholesterol to HDL cholesterol. TG-to-HDL-C ratio=ratio of triglycerides to HDL cholesterol.



Intake (% of energy)	<14·3	14·3–21·0	21·1–26·4	26·5–31·5	≥31·6	<51·6	51·6–58·0	58·1–64·3	64·4–72·1	≥72·2	<3·94	3·94–6·10	6·11–8·33	8·34–11·08	≥11·09
Number of people	25 057	25 058	25 056	25 060	25 056	25 058	25 057	25 058	25 057	25 057	25 057	25 058	25 057	25 057	25 058

Intake (% of energy)	<4·53	4·53–6·32	6·33–8·33	8·34–10·7	≥10·8	<2·77	2·77–3·86	3·87–5·01	5·02–6·78	≥6·79	<12·1	12·1–14·0	14·1–15·8	15·9–17·9	≥18·0
Number of people	25 058	25 057	25 057	25 058	25 057	25 058	25 057	25 058	25 056	25 058	25 056	25 058	25 059	25 055	25 059

Intake (% of energy)	<108·6	108·6–199·9	200·0–303·6	303·7–439·8	≥439·9
Number of people	24 514	24 512	24 513	24 513	24 513

Figure 5: **Mean systolic blood pressure by total fat (A), carbohydrate (B), saturated fat (C), monounsaturated fatty acid (D), polyunsaturated fatty acid (E), protein (F), and cholesterol (G) intake (n=125 287)**

Bars are 95% CIs. Data are adjusted for age, sex, urban or rural location, education, current smoking, and use of antihypertensive drugs (for blood pressure analyses) or statins (for lipids analyses); centre was also included as a random effect.

cholesterol to HDL cholesterol [p=0·0354]; figure 7, appendix p 32). We did not identify any significant change in ApoB-to-ApoA1 ratio with replacement of 3% of energy from saturated fatty acid with an equal percentage from carbohydrates (p=0·2283).

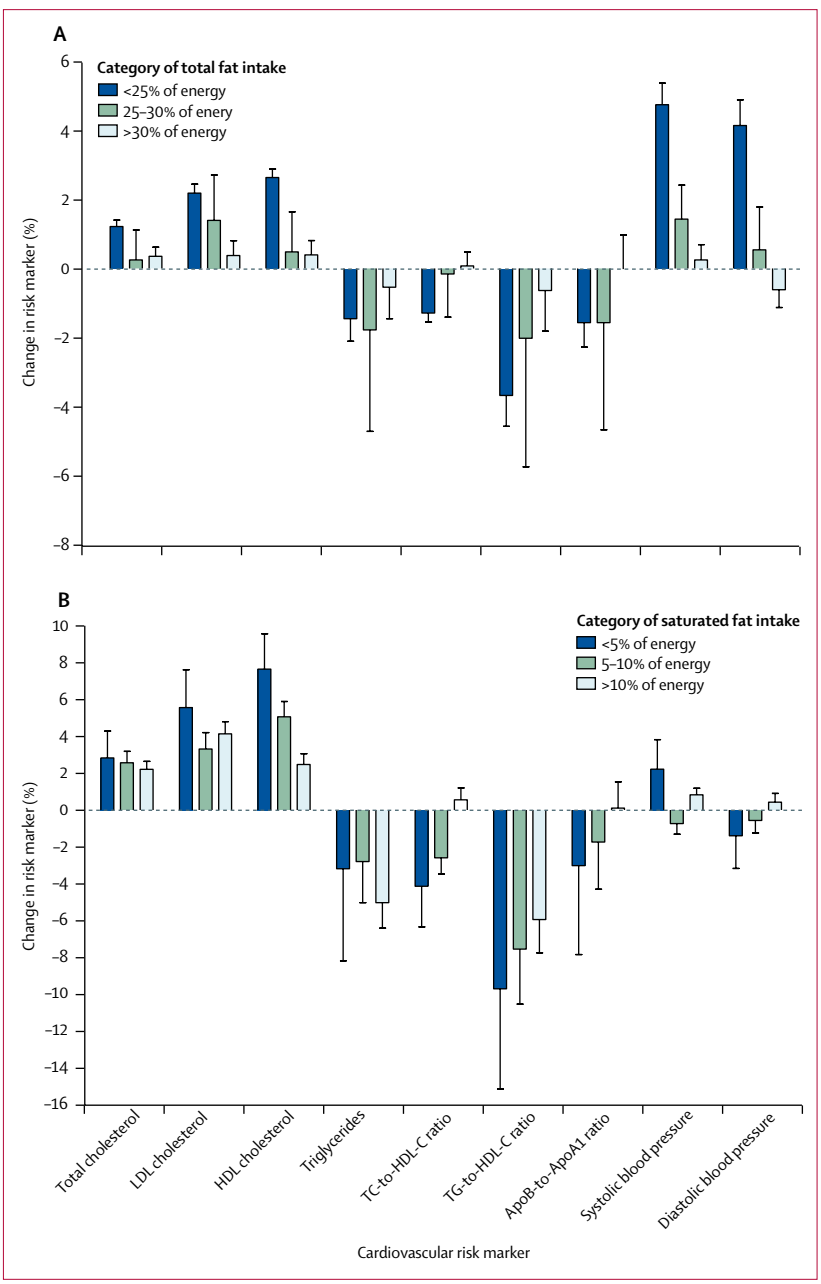


Figure 6: **Percentage change in cardiovascular risk markers for every 5% of energy intake increase in total fat (A) and saturated fat (B), stratified by intake level**

Bars are 95% CIs. Data are adjusted for age, sex, urban or rural location, education, current smoking, and use of antihypertensive drugs (for blood pressure analyses) or statins (for lipids analyses); centre was also included as a random effect. For total fat, all $p_{interaction}$<0·0001, apart from triglycerides ($p_{interaction}$=0·0142). For saturated fat, all $p_{interaction}$<0·0001, apart from TG-to-HDL-C ratio ($p_{interaction}$=0·0450), systolic blood pressure ($p_{interaction}$=0·0029), diastolic blood pressure ($p_{interaction}$=0·0057), and triglycerides ($p_{interaction}$=0·1891). ApoB=apolipoprotein B. ApoA1=apolipoprotein A1. TC-to-HDL-C ratio=ratio of total cholesterol to HDL cholesterol. TG-to-HDL-C ratio=ratio of triglycerides to HDL cholesterol.

By contrast, replacing saturated fatty acid with monounsaturated fatty acids or polyunsaturated fatty acids resulted in a decrease in total cholesterol and LDL cholesterol. However, this replacement was also associated with a decrease in HDL cholesterol, and an increase in triglycerides and ratio of triglycerides to HDL cholesterol ratio (all p<0·0001, apart from the effect of polyunsaturated fat on triglycerides [p=0·0012]; figure 7, appendix p 32).

Replacing saturated fatty acids with monounsaturated fatty acids was associated with a decrease in ratio of total cholesterol to HDL cholesterol and ApoB, a decrease in ApoA1, and a decrease in ApoB-to-ApoA1 ratio. Conversely, replacing saturated fatty acids with polyunsaturated fatty acids was associated with an increase in the ratio of total cholesterol to HDL cholesterol and ApoB (all p<0·0001), although no significant increase in ApoB-to-ApoA1 ratio was identified (p=0·0601; figure 7, appendix p 32).

Replacing saturated fatty acids with carbohydrates was associated with a decrease in systolic and diastolic blood pressures. Similarly, replacing saturated fatty acid with monounsaturated fats or polyunsaturated fats was associated with a decrease in systolic and diastolic blood pressures (all p<0·0001; figure 7, appendix p 32).

In the simulation models, in which we assumed that the effect of saturated fatty acid intake on cardiovascular disease events was solely related to its association through an individual risk marker, different risk markers produced different projections (figure 8, appendix p 37). When LDL cholesterol was used to make projections, the modelled HR of major cardiovascular disease events increased modestly in a graded fashion with higher saturated fatty acid intake, but this effect was not seen for the directly observed association of saturated fatty acids with cardiovascular disease risk. This discordance was substantial at higher levels of saturated fatty acid intake (ie, greater than 9·8% of energy; figure 8, appendix pp 37, 40). The simulation model shows higher HR estimates with higher saturated fatty acid intake, whereas the observed HR estimates show a lower risk of events with higher saturated fatty acid intake.

For HDL cholesterol, triglycerides, and ratio of total cholesterol to HDL cholesterol, the modelled HR estimates of cardiovascular disease events were neutral or modestly protective (ie, since saturated fatty acid generally shows beneficial associations with these markers). However, for the ApoB-to-ApoA1 ratio, the modelled HR estimates of cardiovascular disease events showed a decreased risk with higher saturated fatty acid intake (ie, given that saturated fatty acid intake is inversely associated with this risk marker). The use of ApoB-to-ApoA1 ratio produced the most consistent associations between the modelled versus observed HR estimates of risks of cardiovascular disease events, whereas LDL cholesterol produced the greatest divergence in modelled versus observed HR estimates (figure 8, appendix pp 37, 40).

For carbohydrate intake, no single risk marker emerged as the best predictor of the effects of carbohydrate intake on cardiovascular disease events (appendix pp 41–45).

Discussion

In this large international observational study from 18 countries, higher total fat intake (and intake of each type of fat) was associated with potentially beneficial effects on most lipid parameters, apart from total cholesterol and LDL cholesterol. Conversely, higher carbohydrate intake was associated with potentially harmful effects on most lipid parameters. Both total fat (mainly saturated fatty acids) and carbohydrates were associated with higher systolic blood pressure. Protein and dietary cholesterol showed both beneficial and harmful associations with lipids, but protein was associated with lower blood pressure. Replacement of saturated fatty acids with carbohydrates was associated with the most adverse effects on lipids, whereas replacement of saturated fatty acids with unsaturated fats showed improvements in some risk markers (LDL cholesterol and blood pressure), but not others (HDL cholesterol and triglycerides).

In our simulation models, LDL cholesterol and blood pressure produced the least similarity between modelled versus observed HR estimates of cardiovascular disease events, whereas ApoB-to-ApoA1 ratio produced the most similar modelled and observed estimates. Our findings suggest that focusing on a single risk marker might misinform the net clinical effect of nutrients on cardiovascular disease risk. Furthermore, the effect of nutrient intake on lipid markers varied significantly by the level of the nutrient, suggesting that the effects of different diets might be dissimilar in populations that are undernourished and those that are adequately nourished or overnourished.

The current recommendations to reduce total fat and saturated fatty acids, which de facto increases carbohydrate intake, are not supported by our data. For decades, dietary guidelines have largely focused on reducing total fat and saturated fatty acid intake, on the basis of the idea that replacing saturated fatty acids with carbohydrates and unsaturated fats can lower LDL cholesterol and therefore should reduce the risk of cardiovascular disease. This perspective continues to influence health policy today and is based mostly on data from Europe and North America with relatively high intakes of total fat (>40% of energy) and saturated fats (>20% of energy).[12] Apart from studies from Japan,[13] there is little information about populations with lower amounts of fat intake. Importantly, current guidelines focus on the effect of diet on LDL cholesterol, but effects of diet on other important markers (eg, ratio of total cholesterol to HDL cholesterol, ApoB, and triglycerides) have not been considered in dietary recommendations,[3–6] even though a global risk marker such as the ratio of total cholesterol to HDL cholesterol[14] (or ApoB-to-ApoA1 ratio)[15,16] is likely to provide the best overall indication of the effect of an intervention such as diet on cardiovascular disease risk.

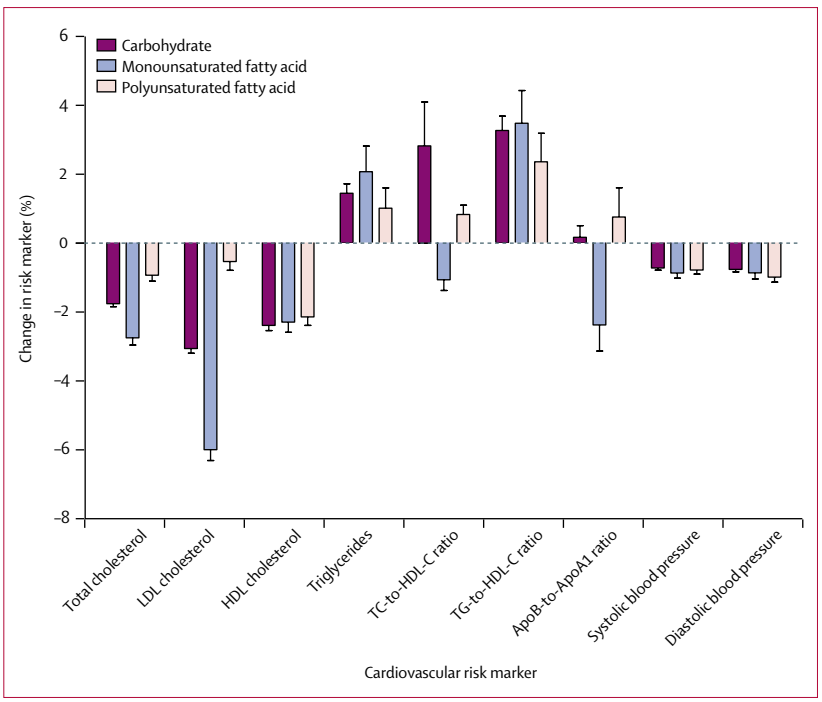


Figure 7: **Percentage change in cardiovascular risk markers for a 3% of energy intake isocaloric replacement of saturated fats with other nutrients**

Bars are 95% CIs. Data are adjusted for age, sex, urban or rural location, education, current smoking, and use of antihypertensive drugs (for blood pressure analyses) or statins (for lipids analyses); centre was also included as a random effect. All p<0·0001, apart from polyunsaturated fatty acids in relation to triglycerides (p=0·0012), carbohydrates in relation to TC-to-HDL-C ratio (p=0·0354), carbohydrates in relation to ApoB-to-ApoA1 ratio (p=0·2283), and polyunsaturated fatty acids in relation to ApoB-to-ApoA1 ratio (p=0·0601). ApoB=apolipoprotein B. ApoA1=apolipoprotein A1. TC-to-HDL-C ratio=ratio of total cholesterol to HDL cholesterol. TG-to-HDL-C ratio=ratio of triglycerides to HDL cholesterol.

In this analysis from the PURE study, total fat intake was associated with modestly higher total cholesterol and LDL cholesterol (0·25 and 0·27 mmol/L change, respectively), for a very large (20% of energy) increment in fat intake. By contrast, there were beneficial effects on other lipid measures (eg, higher HDL cholesterol and ApoA1, and lower triglycerides, ratio of total cholesterol to HDL cholesterol, ratio of triglycerides to HDL cholesterol, and ApoB-to-ApoA1 ratio). Our findings are compatible with findings from ecological and cross-sectional studies and several small trials (involving ten to 50 participants) showing that higher fat intake increases total cholesterol and LDL cholesterol,[17–20] but also increases HDL cholesterol, thereby lowering the ratio of total to HDL cholesterol. Similarly, in the large Women's Health Initiative trial,[21] substantial reductions in total fat intake (28·8% *vs* 37·0% of energy) led to only a very slight lowering of total cholesterol (difference –0·08 mmol/L) and LDL cholesterol (difference –0·09 mmol/L). Contrary to previous studies,[18,19] in PURE, 55% of participants had a fat intake of less than 25% of energy, so our study provides new information at the lower range of fat intake (figure 8).

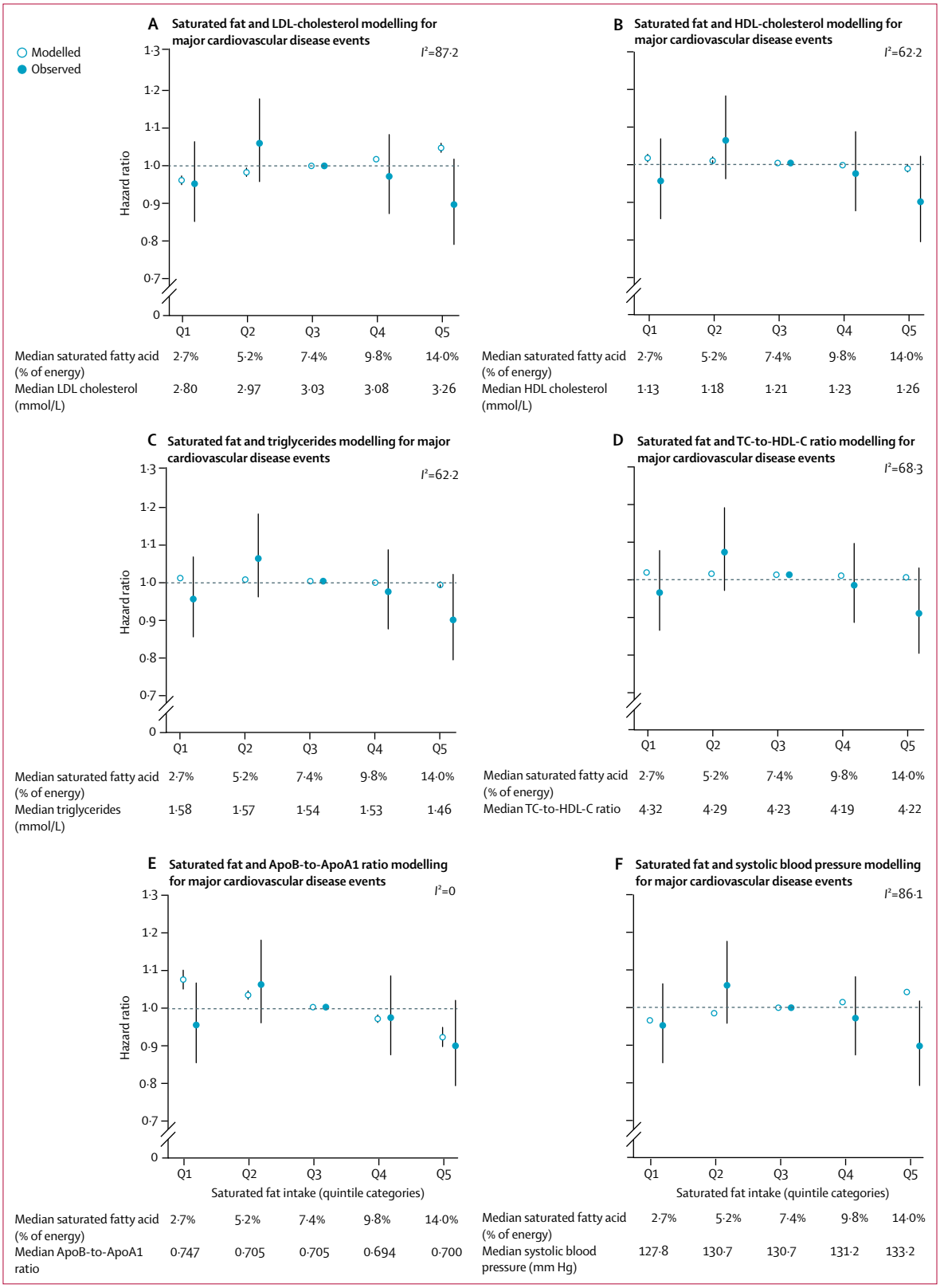


Figure 8: **Simulation modelled versus observed hazard ratio estimates of the association between saturated fat intake versus major cardiovascular disease events (A–F)**

Bars are 95% CIs. The observed associations between saturated fatty acid intake and cardiovascular disease events are approximated by the simulated associations mediated through the effects on ApoB-to-ApoA1 ratio, but not with other lipid markers, including LDL cholesterol, which suggests that the ApoB-to-ApoA1 ratio provides the best overall indication of effect of saturated fatty acids on cardiovascular disease risk. ApoB=apolipoprotein B. ApoA1=apolipoprotein A1. TC-to-HDL-C ratio=ratio of total cholesterol to HDL cholesterol.

Saturated fatty acid intake in our study was associated with higher LDL cholesterol, but also with higher HDL cholesterol, and with lower triglycerides, ratio of total cholesterol to HDL cholesterol, ratio of triglycerides to HDL cholesterol, and ApoB-to-ApoA1 ratio, which is consistent with the findings from a recent meta-analysis of randomised controlled trials.[22] Our study provides new data from global populations that are under-represented in previous studies (but which constitute the majority of the world's population) and information about new lipid parameters across a wider range of dietary intakes. Collectively, our data do not support reducing saturated fatty acid intake below 10% of energy intake as a means of improving the overall blood lipid profile.

Our finding of a benefit on total cholesterol and LDL cholesterol with replacement of saturated fatty acids with polyunsaturated fatty acids is in keeping with the results of clinical trials.[23–25] However, these trials showed that improvement in blood lipids (including ratio of total to HDL cholesterol) is greater with polyunsaturated fatty acids than with monounsaturated fatty acids as the replacement nutrient for saturated fatty acids,[23,24] which differs from our data (in which saturated fatty acids replaced with polyunsaturated fatty acids was associated with a higher ratio of total to HDL cholesterol and a higher concentration of ApoB). Furthermore, unlike data from previous observational studies and trials,[11,23,24] our results suggest that replacing saturated fatty acids with monounsaturated fatty acids or polyunsaturated fatty acids is associated with higher triglycerides and ratio of triglycerides to HDL cholesterol, and lower HDL cholesterol. However, previous studies were done mainly in Europe and North America, and diets, cooking oils, and cooking methods vary in different parts of the world. Therefore, findings from European and North American populations might not be applicable to Asia, South America, or Africa—regions that are included in PURE, but not in most previous studies. For example, deep-fried or stir-fried cooking is common in south Asia and China, and is known to increase the oxidation of polyunsaturated fatty acids. This process might produce trans-fats and promote inflammation and nullify the possible benefits of polyunsaturated fatty acids on blood lipids.[26] Overall, our findings, based on multiple lipid measures, suggest that increased consumption of monounsaturated fatty acids might be more favourable than polyunsaturated fatty acids. Nevertheless, in our separate analyses of clinical events,[9] the associations of monounsaturated fatty acids and polyunsaturated fatty acids with cardiovascular disease events were generally similar.

Our finding that higher carbohydrate intake is associated with the least favourable lipid profile is consistent with data from previous observational studies.[27] Furthermore, results from randomised trials have shown that reducing carbohydrate intake improves blood lipid concentrations (lower triglycerides, ApoB, and ratio of total to HDL cholesterol, and higher HDL cholesterol) relative to a higher carbohydrate and a low-fat diet.[20,28,29] Our findings have implications for global dietary recommendations, especially in low-income populations in which refined carbohydrates are the main source of energy intake (>60% of energy). These populations are likely to benefit from a reduction in carbohydrate intake rather than a reduction in fat intake.

Our study shows a positive association between intake of saturated fatty acids and higher blood pressure in a global population, consistent with findings from previous observational studies and clinical trials.[20,30] Data from small observational studies have shown no association or an inverse association between dietary protein and blood pressure,[31] whereas randomised trials have shown that higher protein intake lowers blood pressure,[31] consistent with our results.

Dietary guidelines for intake of saturated fatty acids (<10% of energy or lower) are based on the assumption that the LDL cholesterol-lowering effects of saturated fatty acid reduction will translate into reductions in cardiovascular disease. This belief assumes that dietary effects on LDL cholesterol can be used to predict the net clinical effect on cardiovascular events, the effects of changes in diet have similar effects on LDL cholesterol at all levels of nutrient (eg, saturated fatty acid) intake, and the effects on other cardiovascular disease risk markers (ratio of total to HDL cholesterol, ApoB-to-ApoA1 ratio), which are also affected by saturated fatty acid intake, are not of major influence.[4–6] Our data show that even with large changes in saturated fatty acids in the diet, the change in LDL cholesterol is modest, varies significantly by the levels of saturated fatty acid intake, and produces estimates of effects on cardiovascular disease events in the simulation models that differ from the direct observations of the associations between saturated fatty acid intake and cardiovascular disease events and mortality. Using LDL cholesterol or systolic blood pressure in the simulation models produced the least similarity between modelled versus observed HR estimates of cardiovascular disease events, whereas the greatest similarity between the simulated model and the observed model occurred when the effects on ApoB-to-ApoA1 ratio were considered. ApoB-to-ApoA1 ratio reflects the presence of small dense LDL particles, which are thought to be more atherogenic than larger LDL particles, providing a possible explanation of why in the INTERHEART and INTERSTROKE studies, ApoB-to-ApoA1 ratio was the strongest predictor of myocardial infarction and ischaemic stroke risk.[15,16] For carbohydrate intake, no single risk marker was superior in predicting the effects of carbohydrate intake on cardiovascular disease events, which raises questions as to the value of emphasising one risk marker over another to make recommendations on carbohydrate intake.

In the accompanying paper by Dehghan and colleagues,[9] we relate the intake of total fat, types of fat, and carbohydrate to clinical events and observe that an

increased consumption of total fat and individual types of fat are all associated with lower risk of death, but have a neutral (or modestly beneficial) association with cardiovascular disease events. By contrast, a diet high in carbohydrate is associated with a higher risk of death, but not with risk of cardiovascular disease. These findings are compatible with the potentially beneficial effects of higher total fat intake (and intake of each type of fat) on most lipid parameters, particularly on the ApoB-to-ApoA1 ratio as noted in our simulation modelling above and might provide a mechanistic explanation for the modest but generally lower risk of cardiovascular disease events with greater consumption of dietary fats.

Our study has some limitations. First, the FFQs used in our study are not measures of absolute intake, but are suited for classifying individuals into categories of nutrient intake. Second, diet was self-reported and variations in reporting might lead to random errors that could dilute real associations between nutrients and cardiovascular disease risk markers. Third, we were not able to estimate different fatty acids for a few foods consumed in Malaysia and Zimbabwe, and so the intake of these nutrients might have been underestimated. However, the direction of association between specific nutrients and blood lipids was similar in analyses that included or excluded these countries. Fourth, we were unable to measure trans-fat intake, which might affect our results, especially our replacement analyses. Fifth, our FFQs assessed intake of monounsaturated fatty acids and polyunsaturated fatty acids from foods or mixed dishes, rather than from vegetable oils, which might have different health effects than shown in our study. Lastly, the nutrient replacement (ie, substitution) analyses are based on modelling, which is less robust than direct observations of the effects of interventions in randomised controlled trials.[25] The substitution modelling assumes linearity of associations, but our data suggest that the assumption of linearity might not be appropriate when populations with low intakes of fats are studied.

In conclusion, high carbohydrate intake has the most adverse impact on cardiovascular disease risk factors, whereas monounsaturated fatty acids seem to be beneficial and saturated fatty acids are not harmful. Reducing saturated fatty acids and replacing them with carbohydrates might have an adverse effect on cardiovascular disease risk. Therefore, determining the net clinical effects of nutrients on cardiovascular disease risk requires information from large studies on clinical outcomes. Current recommendations to reduce total fat and saturated fatty acids in all populations, which de facto increases carbohydrate intake, are not supported by our data.

Contributors

AM contributed to the design of the present study, did the statistical analysis, and wrote the first draft of the report. SYu contributed to the design of the study, conceived and initiated the Prospective Urban Rural Epidemiology (PURE) study, supervised its conduct and data analysis, and provided critical comments on all drafts of the report. MD and SSA reviewed and provided critical comments on drafts of the report. SR coordinated the worldwide PURE study and reviewed and commented on drafts of the report. SYu was the principal investigator and KT the co-principal investigator of the PURE study. KT reviewed and commented on drafts of the report. All other authors coordinated the study and collected the data in their respective countries and provided comments on drafts of the report.

Declaration of interests

We declare no competing interests.

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