THE LANCET
Diabetes & Endocrinology

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Mente A, Dehghan M, Rangarajan S, et al, on behalf of the Prospective Urban Rural Epidemiology (PURE) study investigators. Association of dietary nutrients with blood lipids and blood pressure in 18 countries: a cross-sectional analysis from the PURE study. *Lancet Diabetes Endocrinol* 2017; published online Aug 29. http://dx.doi.org/10.1016/S2213-8587(17)30283-8.

Table of Contents

Appendix 1: The Prospective Urban Rural Epidemiological Study (PURE Study) Design

The Prospective Urban Rural Epidemiological Study (PURE Study) enrolled 157,543 individuals between 35 and 70 years of age from 18 low, middle and high-income countries (1,2). The study includes population samples from 667 communities from 18 countries from 5 continents representing a broad range of economic and social circumstances (1,2). PURE includes countries in four income strata based on World Bank classification in 2006: four low-income countries (Bangladesh, India, Pakistan, and Zimbabwe), four lower middle-income countries (China, Colombia, Iran, and Occupied Palestinian Territory), seven upper middle-income countries (Argentina, Brazil, Chile, Malaysia, Poland, South Africa, and Turkey), and three high-income countries (Canada, Sweden, and United Arab Emirates). The study is coordinated by the Population Health Research Institute, Hamilton Health Sciences and McMaster University, Canada.

Participant Selection Methodology as Excerpted from Teo et al. (1)

Selection of Countries

The choice and number of countries selected in PURE reflects a balance between involving a large number of communities in countries at different economic levels, with substantial heterogeneity in social and economic circumstances and policies, and the feasibility of centers to successfully achieve long-term follow-up. Thus, PURE included sites in which investigators are committed to collecting good-quality data for a low-budget study over the planned 10-year follow-up period and did not aim for a strict proportionate sampling of the entire world.

Selection of Communities

Within each country, urban and rural communities were selected based on broad guidelines. A common definition for "community" that is applicable globally is difficult to establish (3). In PURE, a community was defined as a group of people who have common characteristics and reside in a defined geographic area. A city or large town was not usually considered to be a single community, rather communities from low-, middle-, and high-income areas were selected from sections of the city and the community area defined according to a geographical measure (eg, a set of contiguous postal code areas or a group of streets or a village). The primary sampling unit for rural areas in many countries was the village. The reason for inclusion of both urban and rural communities is that for many countries, urban and rural environments exhibit distinct characteristics in social and physical environment, and hence, by sampling both, we ensured considerable variation in societal factors across PURE communities. The number of communities selected in each country varied, with the aim to recruit communities with substantial heterogeneity in social and economic circumstances balanced against the capacity of local investigators to maintain follow-up. In some countries (eg, India, China, Canada, and Colombia), communities from several states/provinces were included to capture regional diversity, in policy, socioeconomic status, culture, and physical environment. In other countries (eg, Iran, Poland, Sweden, and Zimbabwe), fewer communities were selected.

Selections of Households and Individuals

Within each community, sampling was designed to achieve a broadly representative sample of that community of adults aged between 35 and 70 years. The choice of sampling frame within each center was based on both "representativeness" and feasibility of long-term follow-up, following broad study guidelines. Once a community was identified, where possible, common and standardized approaches were applied to the enumeration of households, identification of individuals, recruitment procedures, and data collection. The method of approaching households differed between regions. For example, in rural areas of India and China, a community announcement was made to the village through contact of a community leader, followed by in-person door-to-door visits of all households. In contrast in Canada, initial contact was by mail followed by telephone inviting members of the households to a central clinic. For each approach, at least 3 attempts at contact were made. Households were eligible if at least 1 member of the household was between the ages of 35 and 70 years and the household members intended to continue living in their current home for a further 4 years. All individuals within these households between 35 and 70 years providing written informed consent were enrolled. When a household refused to participate, demographics and simple self-report risk factor data were recorded in a non-responder form.

Appendix 2: Dietary Assessment Methods

Participants' food intake was measured using country specific food frequency questionnaire. For almost all countries where a validated FFQ was not available, we developed and validated FFQs using a standard method (4-14). Multiple 24-hour dietary recalls were used as the reference method to validate the FFQs and 60-250 participants from each country participated in the FFQ validation study (4-14). The number of food items in the FFQs varied from 95-250 items. Participants were asked "during the past year, on average, how often have you consumed the following foods or drinks" and the list of food items was given. For almost all countries, FFQs had the same format and frequencies of consumption ranging from never to more than 6 times/day. Seasonal variation of fruit and vegetable consumption was captured by most FFQs.

To compute daily nutrient intake, country-specific food databases listing nutrient values (including carbohydrates, fats and protein) for each food item listed in the FFQ were constructed. Since the tools were designed for use in an international study, a food composition database containing nutrient estimates was developed allowing comparisons among the PURE countries (15). Briefly, the nutrient database was constructed based on the United States Department of Agriculture (USDA) food composition database and was modified appropriately with reference to the country's food composition tables. For seven out of 19 countries (Canada, China, India, Malaysia, South Africa, Sweden, and Turkey), country specific food composition tables were used to estimate daily energy and nutrient intake. The nutrient database has information on 43 macro and micro-nutrients.

To compute the daily nutrient intake, the reported frequency of consumption for each food item was converted to daily intake and then was multiplied by the portion size. Daily food intake was converted to nutrient intake based on the food nutrient profile. All food items reported in the

FFQs were used to develop main food groups. Daily intake of fruits and vegetables (excluding potatoes) was estimated based on all types consumed (raw, cooked, dried, and canned). Starchy foods included all types of bread, rice, porridge, cereal, and potatoes. Meats included all types of red meat, fish, sea-foods, and poultry. Processed foods included all types of packaged and formulated foods and beverages that contained food additives, artificial flavorings or other chemical ingredients. Mixed dishes were disaggregated into their constituent food groups, and a proportional weight was assigned to each component part. Each component was then included in the corresponding food group.

Appendix 3: Simulation modelling of the association between saturated fat and carbohydrate intake and future CVD events

We conducted simulation modeling of the effect of changes in SFA and carbohydrate intake on risk of future CVD events in the 125,287 individuals in the current study, based on the assumption that the observed associations between SFA (and carbohydrates) on CVD could be explained by the effects of these nutrients on risk markers. Using the change in risk marker per 1% of energy increment in SFA (and carbohydrate) intake (shown in Appendix 6, per 5% of energy), and from the HR of CVD events per 1 unit change in the risk marker in the same participants in PURE, we computed the effect of each quintile incremental change in SFA and carbohydrate intake on the HR of CVD events (16). We then projected the HR estimates of CVD events, when SFA and carbohydrate intake changes from average levels in quintile 3 (reference) to the average in quintile 1, 2, 4 and 5, representing a broad range of SFA intake (3.0, 5.6, 7.7, 9.8 and 13.3% of energy intake) and carbohydrate intake (44.4, 52.2, 58.0, 64.2 and 74.7% of energy intake). The observed HRs of CVD events associated with these same nutrients are presented in the accompanying paper by Dehghan et al (16). In that study, Cox frailty models with random intercepts to account for center clustering were used to calculate HRs, adjusting for covariates (16). We compared the simulated risk marker-based estimates from the current paper with directly observed HR of CVD associated with intake of SFA and carbohydrates, which are reported in Dehghan et al (16). We quantified the degree to which the modeled HR estimates differed from the observed HR estimates of CVD events using the I^2 statistic (ranging from 0 to 100 %).

Appendix 4. Comparison of participants in the current study with the entire PURE cohort. Study participants and non-participants were generally similar on all baseline characteristics. †			
	Study participants with blood lipid measures	**Study participants with blood pressure measures**	**Overall PURE study**
Participants	104,486	125,287	157,543
Age, y	50.3 ± 9.7	50.2 ± 9.8	50.6 ± 9.9
% women	60628 (58.0%)	73101 (58.4%)	90783 (57.7%)
Education			
<high school	41859 (40.2%)	52955 (42.4%)	66994 (42.8%)
High school completed	40778 (39.1%)	47789 (38.2%)	59705 (38.1%)
Post-secondary or higher	21586 (20.7%)	24257 (19.4%)	29848 (19.1%)
Body mass index, kg/m^2	25.8 ± 5.1	25.6 ± 5.2	25.8 ± 5.2
Waist to hip ratio	0.871 ± 0.08	0.871 ± 0.09	0.872 ± 0.09
Smoking status			
Never	68890 (66.3%)	83919 (67.3%)	105040 (67.4%)
Former	12854 (12.4%)	14336 (11.5%)	18198 (11.7%)
Current	22160 (21.3%)	26394 (21.2%)	32733 (21.0%)
Physical activity			
Low	15600 (16.0%)	19533 (16.8%)	23003 (16.2%)
Medium	37269 (38.2%)	44115 (37.9%)	55194 (38.9%)
High	44824 (45.9%)	52896 (45.4%)	63638 (44.9%)
Alcohol			
Never	69072 (66.3%)	86313 (69.1%)	110662 (70.8%)
Former	4500 (4.3%)	5152 (4.1%)	6867 (4.4%)
Current	30562 (29.4%)	33476 (26.8%)	38875 (24.9%)
Diabetes	6762 (6.5%)	8340 (6.7%)	12782 (8.1%)
Systolic BP, mm Hg	131.3 ± 21.3	130.8 ± 21.3	131.4 ± 21.5
Diastolic BP, mm Hg	81.7 ± 12.1	81.6 ± 12.1	81.7 ± 12.2
Hypertension, self-reported or	40968 (39.4%)	48607 (38.8%)	63750 (40.5%)

>=140/90 mm Hg			
Blood pressure medication	12927 (12.4%)	14795 (11.8%)	19465 (12.4%)
Statin medication	2363 (2.3%)	2662 (2.1%)	4386 (2.8%)

† Values are mean ± SD or N (%).

Appendix 5. Mean (SD) intake of nutrients by country income and geographic regions (n=125,287).†								
		% of total energy from nutrients						
	N	**Carbohydrate**	**Protein**	**Total fat**	**SFA**	**MUFA**	**PUFA**	**Other ‡**
Overall	125,287	61.3±11.6	15.1±3.5	23.4±9.3	7.71±4.2	7.67± 3.5	5.01±2.9	2.99±2.6
Income countries								
HIC	17,950	53.6±8.2	16.8±2.8	29.7±6.1	10.1±3.7	10.9±2.7	5.08±1.5	3.59±1.3
MIC	78,625	61.8±11.5	16.0±3.3	22.1±9.0	6.9±3.6	7.56±3.4	4.55±2.5	3.08±3.4
LIC	28,712	65.3±11.2	11.7±2.0	22.9±10.3	8.4±5.1	5.97±3.1	6.23±4.0	2.36±1.6
P for trend across HIC, MIC, and LIC		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Geographic regions								
North America/ Europe	14,185	52.4±8.1	16.8±2.7	30.5±6.0	10.9±3.7	11.2±2.6	4.78±1.3	3.65±1.2
South America	20,946	57.6±11.5	17.6±3.8	25.1±7.7	8.86±3.4	8.99±3.3	4.44±1.6	2.85±0.7
Middle East	10,374	53.5±7.5	16.8±2.6	30.3±6.1	10.3±2.9	10.2±3.1	6.90±1.8	2.85±1.0
South Asia	28,030	65.0±11.1	11.7±1.9	23.1±10.3	8.47±5.1	5.95±3.1	6.29±4.0	2.37±1.6
China	41,253	67.0±9.8	15.3±2.8	17.7±7.8	5.65±2.7	6.81±2.9	4.16±2.8	1.04±1.1
Southeast Asia	6,994	54.7±8.2	16.7±3.4	29.2±5.9	9.2±2.1	11.8±3.9	8.2±2.0	Not derived
Africa	3,505	63.3±11.4	13.1±2.9	23.0±8.5	5.85±2.9	7.01±3.3	6.29±3.0	3.86±1.6

† Means are adjusted for age, sex, and community level clustering.

‡ "Other" is comprised of glucose, glycerol and other aldehydes. In Southeast Asia, "Other" was not included in the nutrition database.

Abbreviations: HIC, high income-countries; MIC, middle-income countries; LIC, low-income countries.

Appendix 6. Regression coefficient (95% CI) † and standardized coefficients ‡ for the association between nutrient intake and risk markers. §				
	LDL-C, mmol/l	TC/HDL-C	ApoB/ApoA1	Systolic BP, mmHg
Carbohydrates				
Overall	-0.039 (-0.041 to -0.036); -0.093	0.021 (0.017 to 0.024); 0.037	0.006 (0.005 to 0.008); 0.066	0.316 (0.199 to 0.432); 0.033
N America/ Europe	-0.042 (-0.050 to -0.035); -0.089	0.001 (-0.009 to 0.012); 0.002	0.002 (-0.002 to 0.006); 0.019	-0.322 (-0.670 to 0.027); -0.029
S America	0.003 (-0.003 to 0.010); 0.008	0.067 (0.058 to 0.076); 0.106	0.010 (0.007 to 0.013); 0.078	-0.852 (-1.122 to -0.581); -0.079
Middle East	-0.041 (-0.052 to -0.029); -0.07064	-0.024 (-0.044 to -0.005); -0.02535	0.000 (-0.007 to 0.008); 0.00308	-2.297 (-2.821 to -1.773); -0.17182
South Asia	-0.149 (-0.157 to -0.141); -0.28167	-0.002 (-0.012 to 0.007); -0.00362	0.026 (0.022 to 0.031); 0.23467	-2.683 (-3.058 to -2.309); -0.28493
China	-0.005 (-0.008 to -0.001); -0.01429	0.034 (0.029 to 0.038); 0.07958	-0.001 (-0.003 to 0.002); -0.00753	2.171 (1.971 to 2.370); 0.2375
SE Asia	-0.027 (-0.046 to -0.008); -0.04368	-0.017 (-0.046 to 0.011); -0.0187	-0.010 (-0.023 to 0.004); -0.07597	-0.231 (-0.601 to 0.139); -0.01638
Africa	0.001 (-0.015 to 0.017); 0.002	0.033 (0.006 to 0.061); 0.052	0.005 (-0.001 to 0.010); 0.051	-0.313 (-0.867 to 0.242); -0.025
Total fat				
Overall	0.056 (0.053 to 0.059); 0.104	-0.021 (-0.026 to -0.016); -0.029	-0.009 (-0.011 to -0.007); -0.072	2.137 (1.779 to 2.495); 0.171
N America/ Europe	0.050 (0.040 to 0.061); 0.076	0.023 (0.009 to 0.038); 0.026	-0.003 (-0.007 to 0.002); -0.018	-1.085 (-2.732 to 0.563); -0.071
S America	-0.013 (-0.022 to -0.004); -0.021	-0.079 (-0.092 to -0.067); -0.090	-0.014 (-0.019 to -0.009); -0.080	-0.444 (-3.605 to 2.717); -0.029
Middle East	0.026 (0.012 to 0.041); 0.03715	0.007 (-0.016 to 0.031); 0.00617	-0.002 (-0.011 to 0.006); -0.01444	9.608 (7.794 to 11.422); 0.58404
South Asia	0.160 (0.151 to 0.169);	-0.007 (-0.017 to 0.004);	-0.032 (-0.037 to -0.027);	4.803 (4.018 to 5.589);

	0.28135	-0.0107	-0.25504	0.47425
China	0.012 (0.007 to 0.016); 0.02631	-0.047 (-0.053 to -0.041); -0.07995	0.003 (-0.001 to 0.006); 0.02665	-1.333 (-1.706 to -0.961); -0.10509
SE Asia	0.035 (0.008 to 0.062); 0.04095	0.020 (-0.020 to 0.060); 0.01556	0.016 (-0.003 to 0.035); 0.08956	0.514 (0.020 to 1.009); 0.02616
Africa	0.037 (0.016 to 0.059); 0.073	0.057 (0.022 to 0.093); 0.068	0.004 (-0.005 to 0.012); 0.026	-2.719 (-5.604 to 0.166); -0.167
Saturated fat				
Overall	0.190 (0.182 to 0.198); 0.164	-0.035 (-0.045 to -0.024); -0.022	-0.015 (-0.020 to -0.010); -0.056	2.256 (2.007 to 2.506); 0.087
N America/ Europe	0.119 (0.100 to 0.138); 0.101	0.079 (0.053 to 0.105); 0.049	-0.002 (-0.010 to 0.006); -0.009	2.404 (1.628 to 3.180); 0.089
S America	-0.043 (-0.063 to -0.024); -0.033	-0.189 (-0.217 to -0.162); -0.097	-0.027 (-0.037 to -0.017); -0.072	-0.856 (-1.603 to -0.109); -0.025
Middle East	0.117 (0.087 to 0.147); 0.07892	0.077 (0.027 to 0.127); 0.03123	0.000 (-0.018 to 0.018); -0.00070316	-4.061 (-5.120 to -3.002); -0.11679
South Asia	0.433 0.416 to 0.450); 0.3698	0.005 (-0.015 to 0.026); 0.00392	-0.075 (-0.088 to -0.061); -0.19743	-0.368 (-0.883 to 0.147); -0.01811
China	0.045 (0.033 to 0.057); 0.03743	-0.131 (-0.147 to -0.114); -0.08173	0.005 (-0.006 to 0.015); 0.01713	0.115 (-0.921 to 1.152); 0.00332
SE Asia				
Africa	0.096 (0.033 to 0.159); 0.064	0.194 (0.088 to 0.299); 0.078	0.010 (-0.015 to 0.036); 0.025	-2.428 (-5.256 to 0.401); -0.051
Mono-unsaturated fat				
Overall	0.031 (0.023 to 0.040); 0.025	-0.090 (-0.102 to -0.078); -0.053	-0.027 (-0.031 to -0.022); -0.090	-0.842 (-1.141 to -0.543); -0.029
N America/ Europe	0.104 (0.076 to 0.132); 0.061	0.028 (-0.010 to 0.066); 0.012	-0.003 (-0.016 to 0.010); -0.008	-4.688 (-6.270 to -3.106); -0.116
S America	-0.022 (-0.043 to -0.001); -0.015	-0.166 (-0.196 to -0.136); -0.080	-0.030 (-0.041 to -0.019); -0.073	-0.808 (-1.830 to 0.214); -0.023
Middle East	0.009	0.019	-0.001	-0.751

	(-0.021 to 0.038); 0.00593	(-0.030 to 0.067); 0.00777	(-0.020 to 0.017); -0.00351	(-1.654 to 0.153); -0.02263
South Asia	-0.045 (-0.075 to -0.015); -0.02335	-0.188 (-0.222 to -0.154); -0.08855	-0.079 (-0.089 to -0.070); -0.29379	-3.767 (-4.413 to -3.121); -0.10919
China	0.035 (0.025 to 0.046); 0.03269	-0.117 (-0.132 to -0.103); -0.08131	0.003 (-0.006 to 0.011); 0.01053	3.887 (2.839 to 4.934); 0.1238
SE Asia				
Africa	0.032 (-0.022 to 0.086); 0.025	0.123 (0.033 to 0.214); 0.059	-0.005 (-0.025 to 0.015); -0.015	3.101 (0.873 to 5.330); 0.077
Poly-unsaturated fat				
Overall	0.116 (0.106 to 0.126); 0.075	-0.021 (-0.034 to -0.007); -0.010	-0.018 (-0.026 to -0.011); -0.037	0.287 (0.031 to 0.543); 0.008
N America/ Europe	0.087 (0.037 to 0.138); 0.028	-0.093 (-0.162 to -0.025); -0.022	-0.029 (-0.053 to -0.006); -0.041	6.898 (4.930 to 8.866); 0.093
S America	0.012 (-0.028 to 0.051); 0.004	-0.132 (-0.189 to -0.076); -0.034	-0.033 (-0.054 to -0.012); -0.041;	2.452 (1.159 to 3.745); 0.036
Middle East	-0.014 (-0.062 to 0.034); -0.00566	-0.082 (-0.162 to -0.003); -0.0206	-0.030 (-0.061 to 0.000); -0.04986	-2.982 (-4.130 to -1.833); -0.05415
South Asia	0.321 (0.297 to 0.344); 0.21031	0.022 (-0.005 to 0.049); 0.01289	-0.093 (-0.111 to -0.075); -0.18154	-2.576 (-3.060 to -2.092); -0.09909
China	-0.003 (-0.015 to 0.009); -0.00278	-0.067 (-0.083 to -0.051); -0.04207	0.012 (0.002 to 0.022); 0.04213	1.025 (0.595 to 1.454); 0.02988
SE Asia				
Africa	0.087 (0.031 to 0.100); 0.061	0.074 (-0.020 to 0.168); 0.031	0.024 (-0.003 to 0.052); 0.053	-3.562 (-5.348 to -1.775); -0.077
Protein				
Overall	0.011 (0.005 to 0.018); 0.012	-0.020 (-0.030 to -0.011); -0.016	-0.002 (-0.006 to 0.003); -0.006	-1.826 (-1.981 to -1.671); -0.081
N America/ Europe	0.029 (0.005 to 0.054); 0.019	0.038 (0.004 to 0.072); 0.018	0.019 (0.007 to 0.030); 0.053	-1.042 (-1.635 to -0.449); -0.029
S America	-0.036 (-0.055 to -0.018);	-0.041 (-0.068 to -0.014);	-0.004 (-0.013 to 0.005);	-0.882 (-1.315 to -0.449);

	-0.028	-0.022	-0.012	-0.027
Middle East	0.052 (0.018 to 0.086); 0.03089	0.073 (0.017 to 0.130); 0.02618	0.028 (0.007 to 0.049); 0.06601	0.859 (0.192 to 1.525); 0.02221
South Asia	0.240 (0.195 to 0.285); 0.07741	0.170 (0.119 to 0.221); 0.04945	-0.061 (-0.081 to -0.042); -0.12308	2.690 (1.974 to 3.405); 0.04842
China	-0.007 (-0.014 to 0.000); -0.00978	-0.043 (-0.053 to -0.034); -0.04595	-0.004 (-0.010 to 0.002); -0.02465	-2.171 (-2.370 to -1.971); -0.10658
SE Asia	0.050 (0.004 to 0.095); 0.03426	0.039 (-0.029 to 0.106); 0.0176	0.009 (-0.023 to 0.041); 0.03112	-0.376 (-1.229 to 0.476); -0.01099
Africa	0.036 (-0.025 to 0.097); 0.023	0.023 (-0.078 to 0.124); 0.009	-0.010 (-0.031 to 0.012); -0.026	0.429 (-1.275 to 2.133); 0.009
Cholesterol				
Overall	0.022 (0.019 to 0.024); 0.052	0.018 (0.014 to 0.022); 0.032	-0.002 (-0.004 to 0.000); -0.018	0.218 (0.169 to 0.268); 0.025
N America/ Europe	0.052 (0.044 to 0.061); 0.099	0.039 (0.027 to 0.051); 0.054	-0.006 (-0.010 to -0.003); -0.058	1.590 (1.404 to 1.776); 0.132
S America	0.002 (-0.005 to 0.009); 0.004	-0.002 (-0.012 to 0.008); -0.003	0.000 (-0.004 to 0.004); 0.000	0.066 (-0.080 to 0.212); 0.006
Middle East	0.013 (0.004 to 0.022); 0.02797	0.007 (-0.008 to 0.023); 0.00934	-0.005 (-0.011 to 0.001); -0.04046	0.196 (0.011 to 0.380); 0.01826
South Asia	0.038 (0.021 to 0.055); 0.03562	0.010 (-0.009 to 0.030); 0.00861	-0.022 (-0.027 to -0.016); -0.13744	0.320 (0.243 to 0.396); 0.04865
China	0.015 (0.011 to 0.018); 0.04253	0.017 (0.012 to 0.022); 0.03692	0.001 (-0.002 to 0.004); 0.01266	0.139 (0.047 to 0.231); 0.01382
SE Asia	0.001 (0.000 to 0.001); 0.02818	0.000 (-0.001 to 0.002); 0.01268	0.000 (0.000 to 0.001); 0.05993	-0.020 (-0.032 to -0.008); -0.03449
Africa	0.012 (-0.010 to 0.034); 0.021	-0.020 (-0.057 to 0.017); -0.022	0.000 (-0.008 to 0.008); 0.002	0.637 (0.110 to 1.164); 0.039

† Regression coefficients represent change in risk marker per 5%E increment in carbohydrate, fats, and protein protein, and per 100 mg increment in dietary cholesterol.

‡ Standardized coefficients represent the SD change in the risk marker per 1 SD increase in nutrient intake.

§ Adjusted for age, sex, urban/rural location, education, current smoking, and antihypertensive or statin medication use. Center was also included as a random effect.

Appendix 7. Mean (95% CI) blood lipid levels (total cholesterol, LDL-C, HDL-C, TC/HDL-C ratio, triglycerides, triglycerides/HDL-C ratio, Apo B, Apo A1, and Apo B/Apo A1 ratio) by nutrient (carbohydrates, total fat, saturated fat, monounsaturated fat, polyunsaturated fat, protein, and cholesterol) intake (n=104,486).†‡

		TC, mmol/l	LDL-C, mmol/l	HDL-C, mmol/l	TC/HDL-C	TG, mmol/l	TG/HDL-C	Apo B, µmol/l	Apo A1, µmol/l	ApoB/ApoA1
%E from Carbohydrate										
Quintile category (N)	**Mean ±SE**									
<51.2 (N=20897)	45.1± 0.03	4.94 (4.93 to 4.96)	3.11 (3.10 to 3.13)	1.25 (1.25 to 1.26)	4.19 (4.17 to 4.20)	1.50 (1.49 to 1.51)	1.38 (1.36 to 1.40)	1.03 (1.02 to 1.03)	1.53 (1.52 to 1.54)	0.697 (0.690 to 0.705)
51.2 to 57.9 (N=20898)	54.7± 0.01	4.89 (4.88 to 4.90)	3.09 (3.07 to 3.10)	1.23 (1.22 to 1.23)	4.22 (4.20 to 4.23)	1.52 (1.51 to 1.53)	1.41 (1.39 to 1.43)	1.01 (1.00 to 1.02)	1.50 (1.49 to 1.51)	0.699 (0.692 to 0.706)
58.0 to 64.2 (N=20896)	61.0± 0.01	4.88 (4.87 to 4.89)	3.09 (3.08 to 3.10)	1.21 (1.21 to 1.22)	4.25 (4.23 to 4.26)	1.52 (1.51 to 1.54)	1.43 (1.42 to 1.45)	1.00 (1.00 to 1.01)	1.50 (1.49 to 1.51)	0.696 (0.689 to 0.703)
64.3 to 71.8 (N=20898)	67.9± 0.01	4.83 (4.82 to 4.85)	3.04 (3.03 to 3.05)	1.20 (1.19 to 1.20)	4.27 (4.25 to 4.29)	1.55 (1.54 to 1.57)	1.47 (1.46 to 1.49)	1.01 (1.00 to 1.02)	1.48 (1.47 to 1.49)	0.706 (0.699 to 0.714)
≥71.9 (N=20897)	77.6± 0.03	4.69 (4.68 to 4.71)	2.88 (2.86 to 2.89)	1.14 (1.14 to 1.14)	4.32 (4.30 to 4.34)	1.57 (1.56 to 1.59)	1.55 (1.53 to 1.57)	1.00 (0.99 to 1.01)	1.41 (1.40 to 1.42)	0.742 (0.735 to 0.750)
P for trend		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0014	<0.0001	<0.0001
%E from total fat										
Quintile category (N)	**Mean ±SE**									
<14.3 (N=20898)	10.2± 0.02	4.70 (4.69 to 4.71)	2.88 (2.86 to 2.89)	1.14 (1.14 to 1.15)	4.32 (4.31 to 4.34)	1.57 (1.56 to 1.59)	1.55 (1.53 to 1.57)	1.00 (0.99 to 1.01)	1.42 (1.41 to 1.43)	0.740 (0.732 to 0.748)
14.3 to 20.9 (N=20895)	17.7± 0.01	4.81 (4.80 to 4.82)	3.01 (3.00 to 3.02)	1.19 (1.18 to 1.19)	4.27 (4.25 to 4.28)	1.56 (1.54 to 1.57)	1.48 (1.47 to 1.50)	1.02 (1.01 to 1.03)	1.49 (1.48 to 1.50)	0.716 (0.709 to 0.724)
21.0 to 26.5	23.8±	4.88	3.07	1.22	4.22	1.52	1.43	1.01	1.50	0.697

(N=20898)	0.01	(4.87 to 4.89)	(3.06 to 3.08)	(1.22 to 1.23)	(4.20 to 4.24)	(1.51 to 1.54)	(1.41 to 1.44)	(1.00 to 1.01)	(1.49 to 1.51)	(0.690 to 0.704)
26.6 to 31.6 (N=20897)	29.0± 0.01	4.91 (4.90 to 4.92)	3.11 (3.10 to 3.12)	1.23 (1.23 to 1.24)	4.21 (4.19 to 4.23)	1.51 (1.49 to 1.52)	1.40 (1.38 to 1.42)	1.00 (0.99 to 1.01)	1.50 (1.49 to 1.51)	0.692 (0.685 to 0.699)
≥31.7 (N=20898)	36.2± 0.03	4.95 (4.94 to 4.96)	3.15 (3.13 to 3.16)	1.24 (1.24 to 1.25)	4.22 (4.20 to 4.23)	1.50 (1.49 to 1.52)	1.38 (1.36 to 1.40)	1.02 (1.01 to 1.03)	1.52 (1.51 to 1.53)	0.699 (0.691 to 0.706)
P for trend		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0912	<0.0001	<0.0001
%E from saturated fats										
Quintile category (N)	**Mean ±SE**									
<4.03 (N=20897)	2.73± 0.01	4.64 (4.63 to 4.66)	2.80 (2.78 to 2.81)	1.13 (1.12 to 1.13)	4.32 (4.30 to 4.34)	1.58 (1.56 to 1.60)	1.58 (1.56 to 1.60)	0.99 (0.98 to 1.00)	1.40 (1.39 to 1.41)	0.747 (0.738 to 0.756)
4.03 to 6.28 (N=20898)	5.17± 0.01	4.78 (4.77 to 4.79)	2.97 (2.96 to 2.99)	1.18 (1.17 to 1.18)	4.29 (4.27 to 4.31)	1.57 (1.55 to 1.58)	1.51 (1.49 to 1.53)	1.01 (1.00 to 1.02)	1.48 (1.47 to 1.49)	0.705 (0.697 to 0.713)
6.29 to 8.50 (N=20896)	7.38± 0.01	4.84 (4.83 to 4.85)	3.03 (3.01 to 3.04)	1.21 (1.20 to 1.21)	4.23 (4.22 to 4.25)	1.54 (1.53 to 1.56)	1.46 (1.44 to 1.47)	1.01 (1.01 to 1.02)	1.49 (1.48 to 1.50)	0.705 (0.698 to 0.712)
8.51 to 11.22 (N=20897)	9.80± 0.01	4.89 (4.88 to 4.91)	3.08 (3.07 to 3.09)	1.23 (1.23 to 1.24)	4.19 (4.17 to 4.21)	1.53 (1.51 to 1.54)	1.41 (1.40 to 1.43)	1.01 (1.00 to 1.02)	1.51 (1.50 to 1.52)	0.694 (0.687 to 0.701)
≥11.23 (N=20898)	14.0± 0.02	5.02 (5.01 to 5.04)	3.26 (3.25 to 3.27)	1.26 (1.26 to 1.27)	4.22 (4.21 to 4.24)	1.46 (1.45 to 1.47)	1.32 (1.31 to 1.34)	1.02 (1.01 to 1.03)	1.52 (1.51 to 1.53)	0.700 (0.692 to 0.707)
P for trend		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0016	<0.0001	<0.0001
%E from monounsaturated fats										
Quintile category (N)	**Mean ±SE**									
<4.66 (N=20898)	3.29± 0.01	4.75 (4.73 to 4.77)	2.94 (2.93 to 2.96)	1.15 (1.15 to 1.16)	4.34 (4.31 to 4.36)	1.55 (1.53 to 1.57)	1.54 (1.52 to 1.56)	1.02 (1.01 to 1.03)	1.41 (1.40 to 1.42)	0.762 (0.752 to 0.771)
4.66 to 6.51 (N=20897)	5.58± 0.01	4.87 (4.86 to 4.88)	3.11 (3.09 to 3.12)	1.20 (1.19 to 1.20)	4.31 (4.30 to 4.33)	1.53 (1.52 to 1.55)	1.46 (1.45 to 1.48)	1.02 (1.01 to 1.03)	1.48 (1.47 to 1.49)	0.721 (0.712 to 0.730)
6.52 to 8.56	7.51±	4.84	3.04	1.20	4.26	1.54	1.45	1.01	1.49	0.703

(N=20897)	0.01	(4.82 to 4.85)	(3.03 to 3.06)	(1.19 to 1.20)	(4.24 to 4.27)	(1.53 to 1.56)	(1.44 to 1.47)	(1.00 to 1.02)	(1.48 to 1.50)	(0.696 to 0.711)
8.57 to 10.98 (N=20897)	9.71± 0.01	4.86 (4.85 to 4.88)	3.04 (3.03 to 3.06)	1.22 (1.22 to 1.23)	4.19 (4.18 to 4.21)	1.52 (1.51 to 1.54)	1.42 (1.40 to 1.43)	1.00 (0.99 to 1.01)	1.50 (1.49 to 1.51)	0.688 (0.681 to 0.694)
≥10.99 (N=20897)	13.1± 0.01	4.90 (4.89 to 4.92)	3.06 (3.05 to 3.07)	1.24 (1.24 to 1.25)	4.17 (4.15 to 4.19)	1.52 (1.50 to 1.53)	1.40 (1.38 to 1.41)	1.01 (1.00 to 1.02)	1.51 (1.51 to 1.52)	0.692 (0.685 to 0.698)
P for trend		<0.0001	<0.0001	<0.0001	<0.0001	0.0049	<0.0001	0.0609	<0.0001	<0.0001
%E from polyunsaturated fats										
Quintile category (N)	**Mean ±SE**									
<2.80 (N=20897)	2.02± 0.005	4.76 (4.74 to 4.77)	2.92 (2.91 to 2.94)	1.15 (1.15 to 1.16)	4.35 (4.32 to 4.37)	1.59 (1.58 to 1.61)	1.56 (1.53 to 1.58)	0.99 (0.98 to 1.00)	1.41 (1.40 to 1.42)	0.742 (0.734 to 0.750)
2.80 to 3.88 (N=20898)	3.35± 0.002	4.81 (4.79 to 4.82)	3.00 (2.99 to 3.01)	1.19 (1.18 to 1.19)	4.26 (4.25 to 4.28)	1.55 (1.53 to 1.56)	1.47 (1.46 to 1.49)	1.01 (1.00 to 1.02)	1.48 (1.47 to 1.49)	0.712 (0.706 to 0.718)
3.89 to 5.03 (N=20897)	4.44± 0.002	4.85 (4.84 to 4.86)	3.03 (3.02 to 3.04)	1.22 (1.21 to 1.22)	4.21 (4.19 to 4.22)	1.52 (1.51 to 1.53)	1.43 (1.42 to 1.45)	1.01 (1.00 to 1.01)	1.50 (1.49 to 1.51)	0.692 (0.686 to 0.698)
5.04 to 6.80 (N=20896)	5.81± 0.003	4.88 (4.87 to 4.89)	3.07 (3.06 to 3.09)	1.23 (1.23 to 1.24)	4.18 (4.17 to 4.20)	1.49 (1.48 to 1.51)	1.39 (1.37 to 1.41)	1.02 (1.01 to 1.02)	1.51 (1.50 to 1.52)	0.699 (0.692 to 0.706)
≥6.81 (N=20898)	9.39± 0.018	4.94 (4.93 to 4.95)	3.16 (3.15 to 3.18)	1.23 (1.22 to 1.23)	4.26 (4.24 to 4.28)	1.52 (1.51 to 1.53)	1.41 (1.39 to 1.43)	1.04 (1.03 to 1.05)	1.53 (1.52 to 1.55)	0.705 (0.695 to 0.715)
P for trend		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
%E from protein										
Quintile category (N)	**Mean ±SE**									
<12.3 (N=20898)	10.8± 0.01	4.74 (4.73 to 4.76)	2.95 (2.94 to 2.97)	1.19 (1.19 to 1.20)	4.19 (4.16 to 4.21)	1.49 (1.48 to 1.51)	1.42 (1.40 to 1.45)	1.01 (1.00 to 1.02)	1.47 (1.46 to 1.48)	0.722 (0.713 to 0.731)
12.3 to 14.2 (N=20895)	13.3± 0.01	4.86 (4.85 to 4.87)	3.06 (3.04 to 3.07)	1.21 (1.20 to 1.21)	4.25 (4.24 to 4.27)	1.54 (1.52 to 1.55)	1.45 (1.43 to 1.46)	1.00 (0.99 to 1.01)	1.49 (1.48 to 1.49)	0.698 (0.692 to 0.705)
14.3 to 15.9	15.1±	4.86	3.06	1.19	4.31	1.55	1.48	1.00	1.48	0.707

(N=20897)	0.01	(4.85 to 4.88)	(3.05 to 3.07)	(1.19 to 1.20)	(4.29 to 4.32)	(1.54 to 1.57)	(1.46 to 1.49)	(1.00 to 1.01)	(1.47 to 1.49)	(0.701 to 0.714)
16.0 to 18.0 (N=20898)	16.9± 0.01	4.89 (4.88 to 4.90)	3.08 (3.06 to 3.09)	1.20 (1.20 to 1.21)	4.30 (4.28 to 4.31)	1.57 (1.56 to 1.58)	1.49 (1.47 to 1.51)	1.01 (1.01 to 1.02)	1.48 (1.47 to 1.49)	0.712 (0.705 to 0.719)
≥18.1 (N=20898)	20.5± 0.02	4.88 (4.86 to 4.89)	3.06 (3.04 to 3.07)	1.23 (1.23 to 1.24)	4.18 (4.17 to 4.20)	1.50 (1.49 to 1.52)	1.41 (1.39 to 1.43)	1.02 (1.01 to 1.03)	1.50 (1.49 to 1.52)	0.709 (0.700 to 0.717)
P for trend		<0.0001	<0.0001	<0.0001	0.2911	0.1239	0.6649	0.0464	0.0007	0.3830
Dietary cholesterol, mg.day										
Quintile category (N)	**Mean ±SE**									
<120.3 (N=20352)	64.4 ±0.24	4.68 (4.66 to 4.69)	2.87 (2.86 to 2.89)	1.18 (1.17 to 1.18)	4.19 (4.17 to 4.21)	1.51 (1.49 to 1.52)	1.45 (1.43 to 1.47)	1.010 (1.001 to 1.020)	1.466 (1.454 to 1.477)	0.719 (0.711 to 0.728)
120.3 to 214.2 (N=20351)	167.5 ±0.19	4.88 (4.86 to 4.89)	3.04 (3.03 to 3.05)	1.22 (1.21 to 1.22)	4.24 (4.22 to 4.26)	1.56 (1.55 to 1.58)	1.47 (1.45 to 1.49)	1.007 (0.999 to 1.015)	1.479 (1.469 to 1.489)	0.712 (0.705 to 0.720)
214.3 to 316.8 (N=20351)	264.1± 0.21	4.87 (4.86 to 4.88)	3.04 (3.03 to 3.05)	1.22 (1.21 to 1.22)	4.22 (4.20 to 4.24)	1.54 (1.52 to 1.55)	1.44 (1.42 to 1.46)	1.007 (1.000 to 1.014)	1.483 (1.474 to 1.492)	0.708 (0.702 to 0.715)
316.9 to 450.9 (N=20354)	378.2 ±0.27	4.88 (4.87 to 4.89)	3.05 (3.04 to 3.06)	1.21 (1.20 to 1.21)	4.25 (4.24 to 4.27)	1.55 (1.53 to 1.56)	1.46 (1.44 to 1.47)	1.010 (1.002 to 1.017)	1.492 (1.483 to 1.501)	0.704 (0.697 to 0.710)
≥451.0 (N=20351)	622.6 ±1.22	4.91 (4.90 to 4.93)	3.08 (3.07 to 3.10)	1.20 (1.20 to 1.21)	4.31 (4.29 to 4.33)	1.56 (1.55 to 1.58)	1.48 (1.46 to 1.50)	1.013 (1.004 to 1.022)	1.495 (1.484 to 1.505)	0.704 (0.697 to 0.712)
P for trend		<0.0001	<0.0001	<0.0001	<0.0001	0.0004	0.1610	0.5897	<0.0001	0.0045

† Adjusted for age, sex, urban/rural location, education, current smoking, and statin medication use. Center was also included as a random effect.

‡ A subset of 18,330 participants had measures of ApoB and ApoA1.

Appendix Fig. 8A

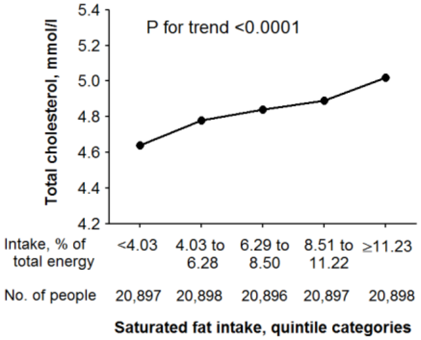


Fig. 8B

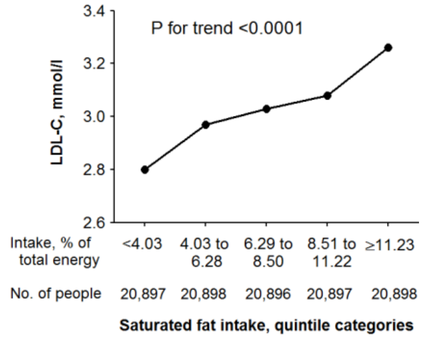


Fig. 8C

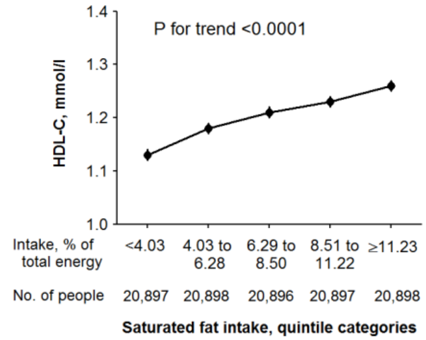


Fig. 8D

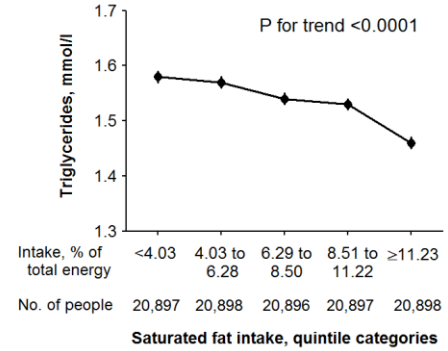


Fig. 8E

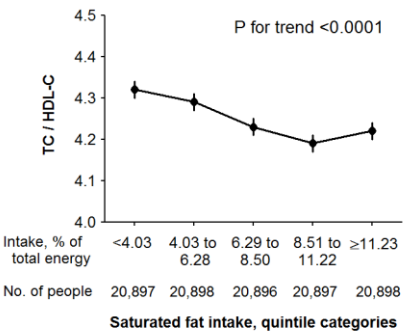


Fig. 8F

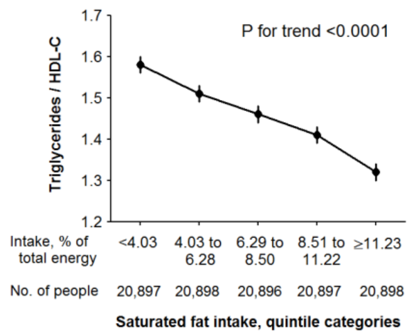


Fig. 8G

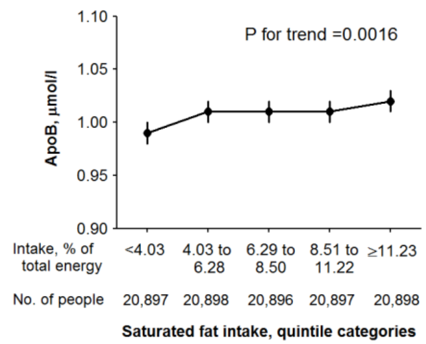


Fig. 8H

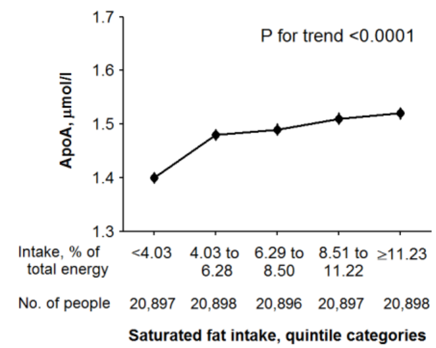
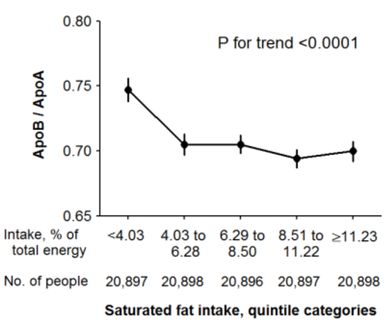


Fig. 8I



Appendix 8. Mean (95% CI) blood lipid concentrations (n=104,486) by saturated fat intake.†‡

† Adjusted for age, sex, urban/rural location, education, current smoking, and statin medication use. Center was also included as a random effect.

‡ A subset of 18,330 participants had measures of ApoB and ApoA.

Appendix Fig. 9A

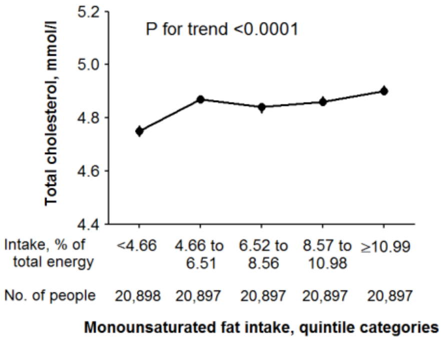


Fig. 9B

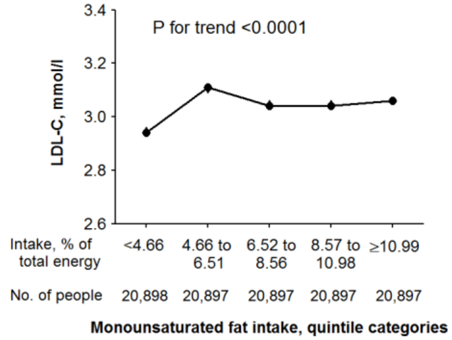


Fig. 9C

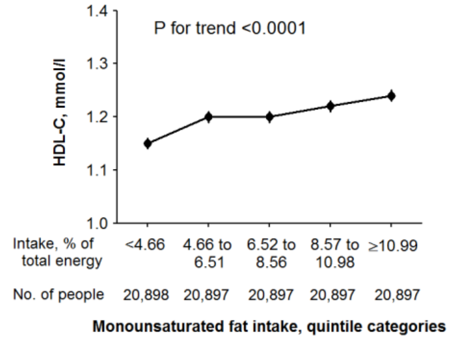


Fig. 9D

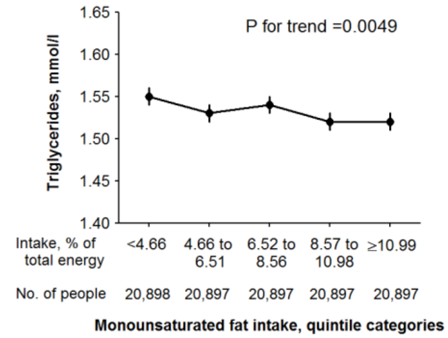


Fig. 9E

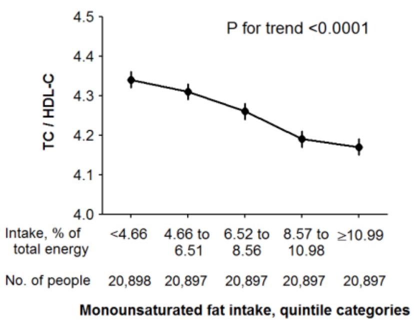


Fig. 9F

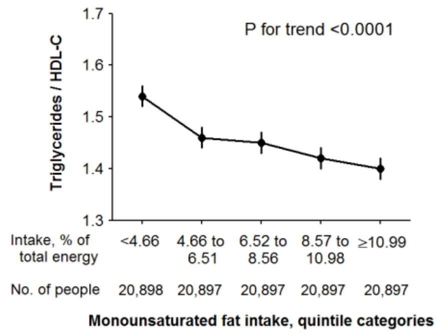


Fig. 9G

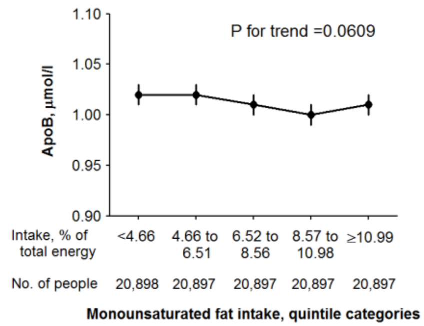


Fig. 9H

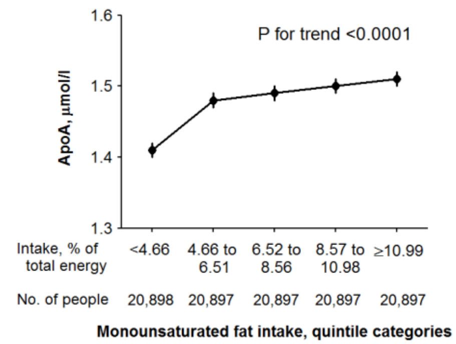
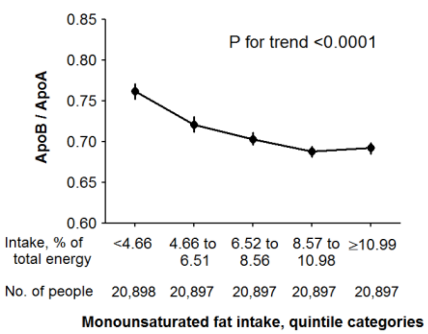


Fig. 9I



Appendix 9. Mean (95% CI) blood lipid concentrations (n=104,486) by monounsaturated fat intake.†‡

† Adjusted for age, sex, urban/rural location, education, current smoking, and statin medication use. Center was also included as a random effect.

‡ A subset of 18,330 participants had measures of ApoB and ApoA.

Appendix Fig. 10A

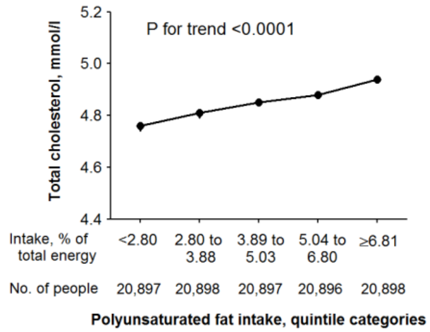


Fig. 10B

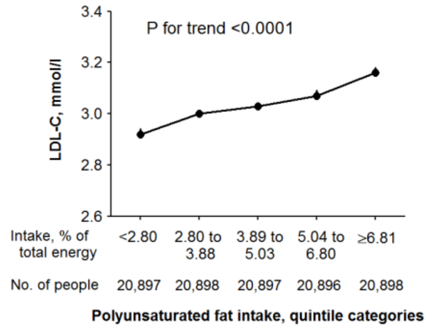


Fig. 10C

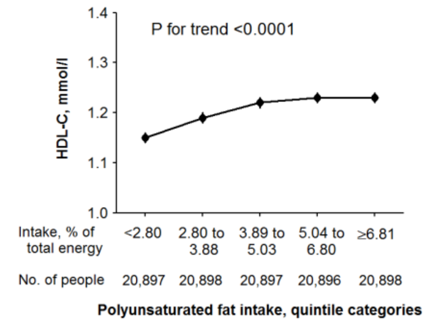


Fig. 10D

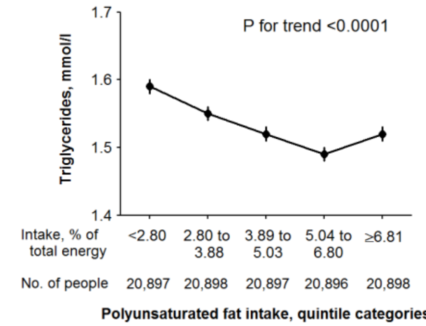


Fig. 10E

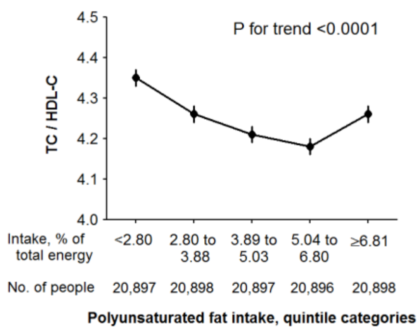


Fig. 10F

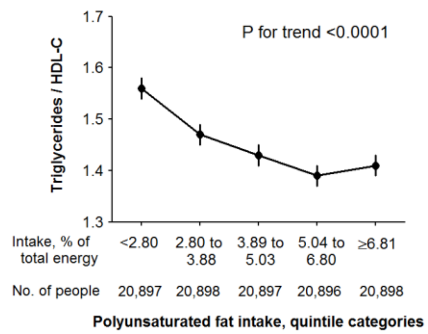


Fig. 10G

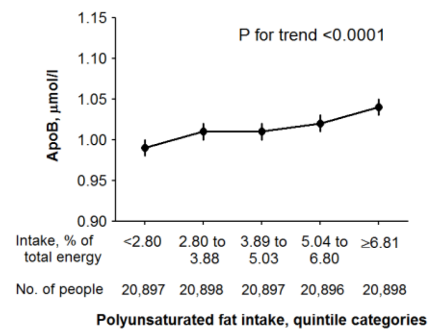


Fig. 10H

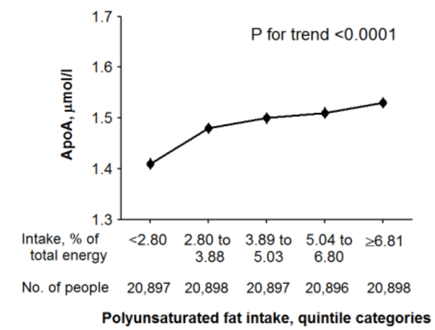
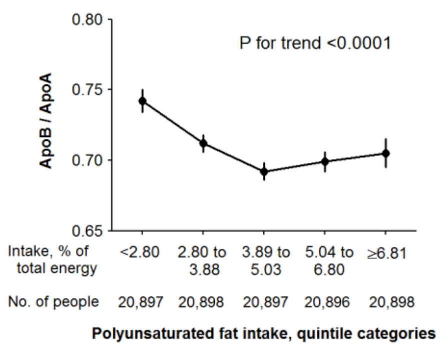


Fig. 10I



Appendix 10. Mean (95% CI) blood lipid concentrations (n=104,486) by polyunsaturated fat intake.†‡

† Adjusted for age, sex, urban/rural location, education, current smoking, and statin medication use. Center was also included as a random effect.

‡ A subset of 18,330 participants had measures of ApoB and ApoA.

Appendix 11 **Fig. 11A**

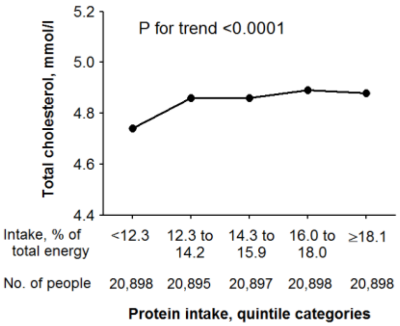


Fig. 11B

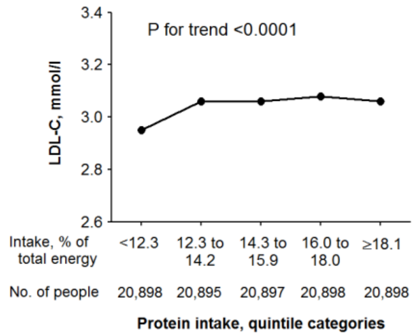


Fig. 11C

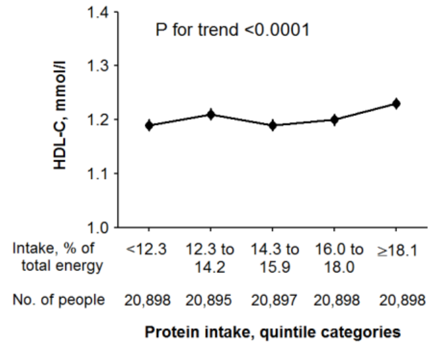


Fig. 11D

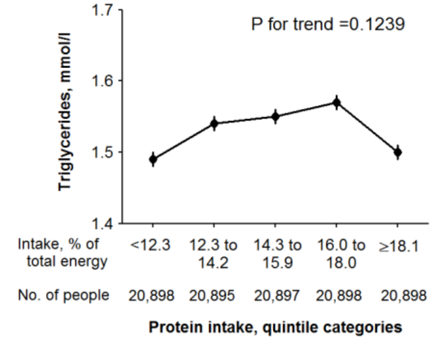


Fig. 11E

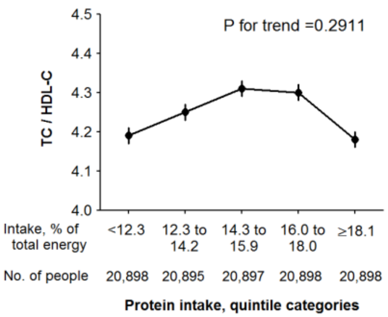


Fig. 11F

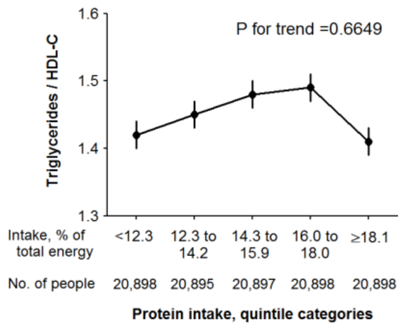


Fig. 11G

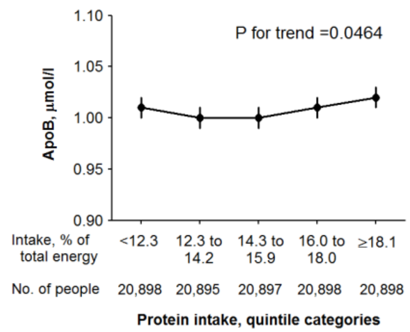


Fig. 11H

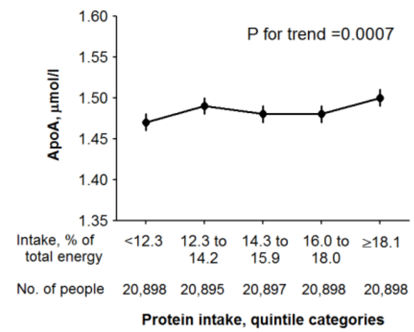
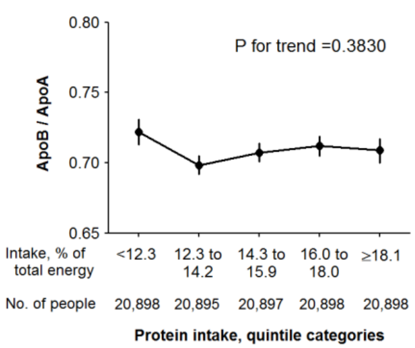


Fig. 11I



Appendix 11. Mean (95% CI) blood lipid concentrations (n=104,486) by protein intake.†‡

† Adjusted for age, sex, urban/rural location, education, current smoking, and statin medication use. Center was also included as a random effect.

‡ A subset of 18,330 participants had measures of ApoB and ApoA.

Appendix 12 Fig. 12A

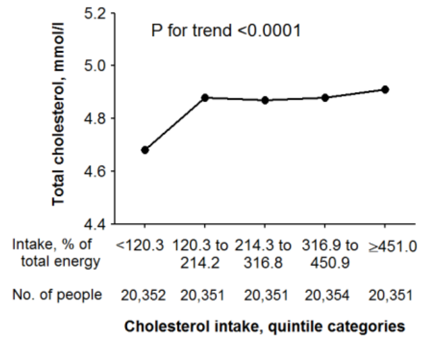


Fig. 12B

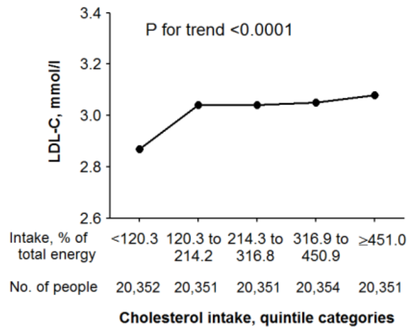


Fig. 12C

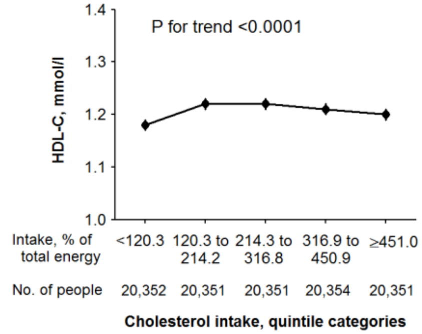


Fig. 12D

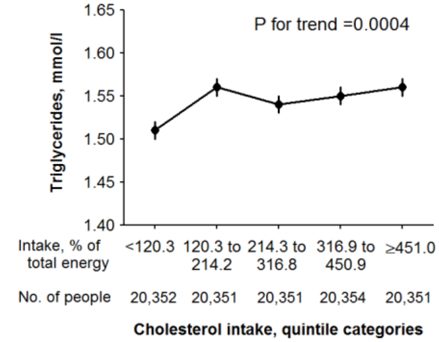


Fig. 12E

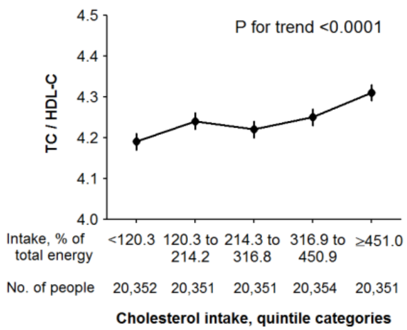


Fig. 12F

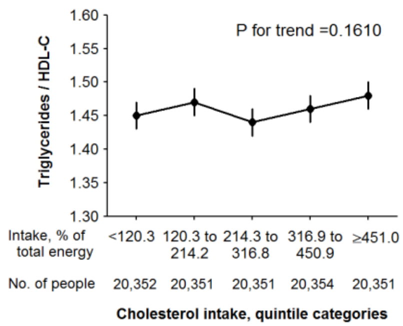


Fig. 12G

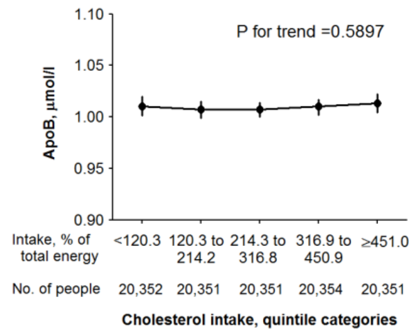


Fig. 12H

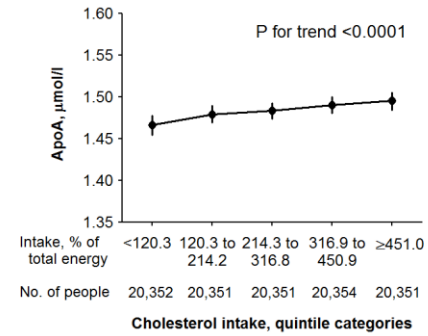
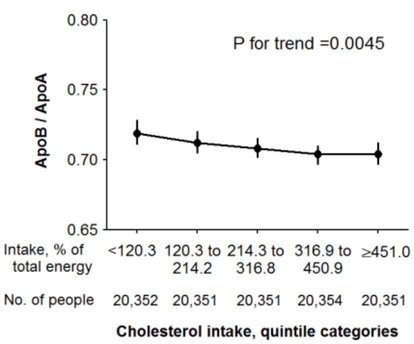


Fig. 12I



Appendix 12. Mean (95% CI) blood lipid concentrations (n=104,486) by cholesterol intake.†‡

† Adjusted for age, sex, urban/rural location, education, current smoking, and statin medication use. Center was also included as a random effect.

‡ A subset of 18,330 participants had measures of ApoB and ApoA.

Appendix 13. Mean (95% CI) blood pressure by nutrient intake (n=125,287).†			
		Systolic BP, mmHg	**Diastolic BP, mmHg**
%E from Carbohydrate			
Quintile category (N)	**Mean±SE**		
<51.6 (N=25058)	45.3±0.03	129.0 (128.6 to 129.3)	82.0 (81.8 to 82.3)
51.6 to 58.0 (N=25057)	54.9±0.01	130.3 (130.0 to 130.6)	81.9 (81.7 to 82.1)
58.1 to 64.3 (N=25058)	61.1±0.01	130.9 (130.7 to 131.2)	81.9 (81.7 to 82.1)
64.4 to 72.1 (N=25057)	68.0±0.01	131.9 (131.7 to 132.2)	81.9 (81.7 to 82.1)
≥72.2 (N=25057)	77.8±0.03	131.9 (131.5 to 132.3)	81.5 (81.2 to 81.8)
P for trend		<0.0001	0.0708
%E from total fat			
Quintile category (N)	**Mean±SE**		
<14.3 (N=25057)	10.1±0.02	129.7 (129.3 to 130.2)	82.0 (81.7 to 82.3)
14.3 to 21.0 (N=25058)	17.7±0.01	130.1 (129.8 to 130.4)	81.6 (81.4 to 81.8)

21.1 to 26.4 (N=25056)	23.9±0.01	130.7 (130.5 to 131.0)	81.8 (81.6 to 82.0)
26.5 to 31.5 (N=25060)	29.0±0.01	131.4 (131.1 to 131.7)	81.9 (81.7 to 82.1)
≥31.6 (N=25056)	36.2±0.03	132.1 (131.7 to 132.5)	82.0 (81.7 to 82.3)
P for trend		<0.0001	0.6874
%E from saturated fatty acids			
Quintile category (N)	**Mean±SE**		
<3.94 (N=25057)	2.67±0.01	127.8 (127.4 to 128.2)	81.3 (81.0 to 81.6)
3.94 to 6.10 (N=25058)	5.02±0.01	130.7 (130.4 to 131.0)	81.7 (81.5 to 81.9)
6.11 to 8.33 (N=25057)	7.21±0.01	130.7 (130.4 to 130.9)	81.7 (81.6 to 81.9)
8.34 to 11.08 (N=25057)	9.64±0.01	131.2 (130.9 to 131.5)	81.8 (81.6 to 82.0)
≥11.09 (N=25058)	14.0±0.02	133.2 (132.9 to 133.6)	82.7 (82.4 to 82.9)
P for trend		<0.0001	<0.0001
%E from monounsaturated fatty acids			
Quintile category (N)	**Mean±SE**		
<4.53 (N=25058)	3.17±0.01	130.2 (129.8 to 130.6)	81.8 (81.5 to 82.1)

4.53 to 6.32 (N=25057)	5.43±0.01	132.3 (132.0 to 132.5)	82.2 (82.0 to 82.4)
6.33 to 8.33 (N=25057)	7.30±0.01	130.8 (130.6 to 131.1)	81.9 (81.7 to 82.1)
8.34 to 10.7 (N=25058)	9.49±0.01	130.5 (130.2 to 130.8)	81.9 (81.7 to 82.1)
≥10.8 (N=25057)	13.0±0.01	130.3 (129.9 to 130.6)	81.5 (81.3 to 81.8)
P for trend		0.0398	0.1806
%E from polyunsaturated fatty acids			
Quintile category (N)	**Mean±SE**		
<2.77 (N=25058)	1.99±0.005	131.7 (131.4 to 132.0)	82.9 (82.6 to 83.1)
2.77 to 3.86 (N=25057)	3.33±0.002	130.1 (129.8 to 130.3)	81.8 (81.6 to 82.0)
3.87 to 5.01 (N=25058)	4.42±0.002	130.6 (130.4 to 130.9)	82.0 (81.8 to 82.2)
5.02 to 6.78 (N=25056)	5.80±0.003	130.6 (130.4 to 130.9)	81.4 (81.2 to 81.6)
≥6.79 (N=25058)	9.53±0.018	131.0 (130.7 to 131.3)	81.3 (81.1 to 81.5)
P for trend		0. 2378	<0.0001
%E from protein			
Quintile category (N)	**Mean±SE**		
<12.1	10.6±0.01	131.8	81.6

(N=25056)		(131.4 to 132.2)	(81.4 to 81.9)
12.1 to 14.0 (N=25058)	13.1±0.01	133.5 (133.3 to 133.8)	83.0 (82.8 to 83.2)
14.1 to 15.8 (N=25059)	14.9±0.01	132.0 (131.8 to 132.3)	82.5 (82.3 to 82.7)
15.9 to 17.9 (N=25055)	16.8±0.01	130.2 (129.9 to 130.4)	82.0 (81.8 to 82.2)
≥18.0 (N=25059)	20.4±0.02	126.5 (126.2 to 126.8)	80.2 (80.0 to 80.5)
P for trend		<0.0001	<0.0001
Dietary cholesterol, mg.day			
Quintile category (N)	**Mean±SE**		
<108.6 (N=24514)	57.9 ±0.16	127.8 (127.4 to 128.1)	79.6 (79.4 to 79.9)
108.6 to 199.9 (N=24512)	154.3 ±0.18	131.6 (131.4 to 131.9)	82.3 (82.1 to 82.5)
200.0 to 303.6 (N=24513)	249.6 ±0.19	131.4 (131.2 to 131.7)	82.6 (82.4 to 82.8)
303.7 to 439.8 (N=24513)	365.8 ±0.25	131.6 (131.4 to 131.9)	82.6 (82.4 to 82.8)
≥439.9 (N=24513)	641.6 ±1.82	131.5 (131.2 to 131.8)	82.2 (82.0 to 82.4)
P for trend		<0.0001	p<0.0001

† Adjusted for age, sex, urban/rural location, education, current smoking, and antihypertensive or statin medication use. Center was also included as a random effect.

Appendix 14. Beta coefficient (95% CI) for change in risk marker for every 5% of energy intake increase in total fat and saturated fat, stratified by intake level.†‡

	Total fat intake level			P for interaction
	<25% of energy	**25 to 30% of energy**	**>30% of energy**	
Total cholesterol, mmol/l	0.060 (0.051 to 0.069)	0.013 (-0.030 to 0.055)	0.018 (0.006 to 0.031)	<0.0001
LDL cholesterol, mmol/l	0.067 (0.059 to 0.075)	0.043 (0.003 to 0.083)	0.012 (0.000 to 0.025)	<0.0001
HDL cholesterol, mmol/l	0.032 (0.029 to 0.035)	0.006 (-0.008 to 0.020)	0.005 (0.001 to 0.010)	<0.0001
Total cholesterol / HDL cholesterol ratio	-0.054 (-0.065 to -0.043)	-0.006 (-0.059 to 0.047)	0.004 (-0.014 to 0.021)	<0.0001
Triglycerides, mmol/l	-0.022 (-0.032 to -0.013)	-0.027 (-0.072 to 0.018)	-0.008 (-0.022 to 0.005)	0.0142
Triglycerides / HDL cholesterol ratio	-0.053 (-0.066 to -0.041)	-0.029 (-0.083 to 0.026)	-0.009 (-0.026 to 0.009)	<0.0001
ApoB, ummol/l	0.013 (0.008 to 0.018)	0.001 (-0.023 to 0.026)	0.012 (0.004 to 0.020)	0.0006
ApoA1, ummol/l	0.039 (0.033 to 0.046)	0.017 (-0.013 to 0.047)	0.016 (0.007 to 0.025)	<0.0001
ApoB / ApoA1 ratio	-0.011 (-0.016 to -0.006)	-0.011 (-0.033 to 0.011)	0.000 (-0.006 to 0.007)	<0.0001
Systolic blood pressure,	6.230	1.894	0.349	<0.0001

mmHg	(5.409 to 7.051)	(0.603 to 3.186)	(-0.231 to 0.928)	
Diastolic blood pressure, mmHg	3.408 (2.799 to 4.017)	0.458 (-0.559 to 1.476)	-0.488 (-0.909 to -0.067)	<0.0001
	Saturated fat intake level			**P for interaction**
	<5% of energy	**5 to 10% of energy**	**>10% of energy**	
Total cholesterol, mmol/l	0.138 (0.067 to 0.208)	0.125 (0.094 to 0.155)	0.108 (0.088 to 0.129)	<0.0001
LDL cholesterol, mmol/l	0.169 (0.106 to 0.231)	0.101 (0.074 to 0.128)	0.126 (0.106 to 0.146)	<0.0001
HDL cholesterol, mmol/l	0.092 (0.069 to 0.115)	0.061 (0.051 to 0.071)	0.030 (0.023 to 0.037)	<0.0001
Total cholesterol / HDL cholesterol ratio	-0.173 (-0.266 to -0.081)	-0.108 (-0.145 to -0.070)	0.025 (-0.002 to 0.052)	<0.0001
Triglycerides, mmol/l	-0.048 (-0.124 to 0.027)	-0.042 (-0.076 to -0.008)	-0.076 (-0.097 to -0.055)	0.1891
Triglycerides / HDL cholesterol ratio	-0.139 (-0.239 to -0.040)	-0.108 (-0.151 to -0.065)	-0.085 (-0.111 to -0.058)	0.0450
ApoB, ummol/l	0.089 (0.051 to 0.126)	0.003 (-0.017 to 0.023)	0.015 (0.003 to 0.026)	0.0555
ApoA1, ummol/l	0.178 (0.135 to 0.222)	0.022 (-0.002 to 0.047)	0.020 (0.006 to 0.034)	<0.0001
ApoB / ApoA1 ratio	-0.021 (-0.055 to 0.013)	-0.012 (-0.030 to 0.006)	0.001 (-0.009 to 0.011)	<0.0001

Systolic blood pressure, mmHg	2.924 (0.838 to 5.009)	-0.907 (-1.660 to -0.154)	1.115 (0.649 to 1.581)	0.0029
Diastolic blood pressure, mmHg	-1.111 (-2.546 to 0.325)	-0.434 (-0.982 to 0.114)	0.374 (-0.012 to 0.760)	0.0057

† Beta coefficients represent change in risk marker per 5%E increment in fats.

‡ Adjusted for age, sex, urban/rural location, education, current smoking, and antihypertensive medication use. Center was also included as a random effect.

Appendix 15. Change (95% CI) in cardiovascular risk factor for a 5% of energy intake isocaloric replacement of saturated fat with other nutrients.								
	Total Cholesterol, change (95% CI)							
Saturated fat replaced with	**Overall**	**North America/ Europe**	**South America**	**Middle East**	**South Asia**	**China**	**Malaysia**	**Africa**
Carbohydrates	-0.085 (-0.089 to -0.081); P<0.0001	-0.192 (-0.079 to -0.058); P<0.0001	-0.029 (-0.038 to -0.020); P<0.0001	-0.137 (-0.155 to -0.120); P<0.0001	-0.141 (-0.150 to -0.132); P<0.0001	-0.034 (-0.062 to -0.007); P=0.015	-0.148 (-0.253 to -0.043): P=0.0058	-0.017 (-0.031 to -0.002); P=0.0243
Monounsaturated fat	-0.133 (-0.143 to -0.124); P<0.0001	-0.074 (-0.120 to -0.028); P=0.0016	-0.071 (-0.103 to -0.039); P<0.0001	-0.229 (-0.268 to -0.190); P<0.0001	-0.288 (-0.307 to -0.268); P<0.0001	0.003 (-0.050 to 0.056); P=0.9129	-0.303 (-0.483 to -0.123); P=0.0010	-0.059 (-0.109 to -0.008); P=0.0216
Polyunsaturated fat	-0.045 (-0.053 to -0.036); P<0.0001	0.003 (-0.052 to 0.058); P=0.9083	0.008 (-0.031 to 0.047); P=0.692	-0.064 (-0.102 to -0.026); P=0.0010	-0.075 (-0.094 to -0.056); P<0.0001	-0.048 (-0.075 to -0.021); P=0.0004	-0.052 (-0.197 to 0.094); P=0.4884	0.049 (-0.002 to 0.100); P=0.0592
	LDL cholesterol, change (95% CI)							
Saturated fat replaced with	**Overall**	**North America/ Europe**	**South America**	**Middle East**	**South Asia**	**China**	**Malaysia**	**Africa**
Carbohydrates	-0.093 (-0.097 to -0.089); P<0.0001	-0.037 (-0.046 to -0.027); P<0.0001	-0.014 (-0.023 to -0.007); P=0.0004	-0.086 (-0.101 to -0.072); P<0.0001	-0.212 (-0.222 to -0.201); P<0.0001	-0.025 (-0.049 to -0.001); P=0.0467	-0.113 (-0.209 to -0.018); P=0.0197	0.014 (0.002 to 0.026); P=0.0199
Monounsaturated fat	-0.182 (-0.192 to -0.173); P<0.0001	-0.004 (-0.045 to 0.037); P=0.8370	-0.061 (-0.089 to -0.034); P<0.0001	-0.150 (-0.182 to -0.118); P<0.0001	-0.432 (-0.454 to -0.410); P<0.0001	-0.010 (-0.056 to 0.036); P=0.6685	-0.246 (-0.409 to -0.083); P=0.0032	0.010 (-0.032 to 0.051); P=0.6487
Polyunsaturated fat	-0.016 (-0.024 to -0.008); P<0.0001	-0.044 (-0.092 to 0.005); P=0.0770	0.036 (0.002 to 0.070); P=0.0381	-0.051 (-0.083 to -0.018); P=0.0022	-0.064 (-0.086 to -0.043); P<0.0001	-0.040 (-0.063 to -0.016); P=0.0010	-0.010 (-0.141 to 0.122); P=0.8895	0.055 (0.022 to 0.097); P=0.0096
	HDL cholesterol, change (95% CI)							
Saturated fat	**Overall**	**North America/**	**South America**	**Middle East**	**South Asia**	**China**	**Malaysia**	**Africa**

replaced with		**Europe**						
Carbohydrates	-0.029 (-0.031 to -0.028); P<0.0001	-0.034 (-0.038 to -0.030); P<0.0001	-0.027 (-0.029 to -0.025); P<0.0001	-0.027 (-0.032 to -0.022); P<0.0001	-0.047 (-0.051 to -0.044); P<0.0001	-0.020 (-0.030 to -0.010); P<0.0001	0.002 (-0.025 to 0.029); P=0.8666	-0.026 (-0.033 to -0.020); P<0.0001
Monounsaturated fat	-0.028 (-0.031 to -0.024); P<0.0001	-0.098 (-0.115 to -0.082); P<0.0001	-0.020 (-0.029 to -0.011); P<0.0001	-0.044 (-0.055 to -0.033); P<0.0001	-0.037 (-0.043 to -0.029); P<0.0001	0.001 (-0.019 to 0.020); P=0.9691	0.003 (-0.044 to 0.050); P=0.9057	-0.071 (-0.092 to -0.051); P<0.0001
Polyunsaturated fat	-0.026 (-0.029 to -0.023); P<0.0001	0.088 (0.068 to 0.108); P<0.0001	-0.011 (-0.022 to -0.001); P=0.0357	-0.013 (-0.024 to -0.002); P=0.0179	-0.056 (-0.063 to -0.050); P<0.0001	-0.025 (-0.034 to -0.015); P<0.0001	0.006 (-0.032 to 0.044); P=0.7543	0.010 (-0.011 to 0.031); P=0.3652
	Total cholesterol / HDL ratio, change (95% CI)							
Saturated fat replaced with	**Overall**	**North America/ Europe**	**South America**	**Middle East**	**South Asia**	**China**	**Malaysia**	**Africa**
Carbohydrates	0.120 (0.066 to 0.174); P=0.0354	0.038 (0.025 to 0.052); P<0.0001	0.073 (0.061 to 0.085); P<0.0001	-0.039 (-0.064 to -0.014); P=0.0021	0.008 (-0.005 to 0.020); P=0.241	0.037 (0.004 to 0.070); P=0.0283	-0.193 (-0.336 to -0.051); P=0.0079	0.050 (0.030 to 0.071); P<0.0001
Monounsaturated fat	-0.045 (-0.058 to -0.032); P<0.0001	0.209 (0.153 to 0.264); P<0.0001	0.009 (-0.030 to 0.049); P=0.6483	-0.049 (-0.104 to 0.006); P=0.0791	-0.198 (-0.225 to -0.171); P<0.0001	0.004 (-0.059 to 0.067); P=0.8908	-0.363 (-0.608 to -0.119); P=0.0036	0.129 (0.061 to 0.198); P=0.0002
Polyunsaturated fat	0.035 (0.025 to 0.047); P<0.0001	-0.228 (-0.295 to -0.162); P<0.0001	0.097 (0.049 to 0.146); P<0.0001	-0.043 (-0.097 to 0.012); P=0.1248	0.076 (0.049 to 0.103); P<0.0001	0.034 (0.002 to 0.066); P=0.0373	-0.089 (-0.287 to 0.108); P=0.3751	0.052 (-0.017 to 0.122); P=0.1424
	Triglycerides, change (95% CI)							
Saturated fat replaced with	**Overall**	**North America/ Europe**	**South America**	**Middle East**	**South Asia**	**China**	**Malaysia**	**Africa**
Carbohydrates	0.022 (0.017 to 0.026); P<0.0001	0.016 (0.007 to 0.026); P=0.0012	0.020 (0.008 to 0.032); P=0.0015	0.010 (-0.006 to 0.027); P=0.2163	0.061 (0.053 to 0.070); P<0.0001	0.053 (0.020 to 0.085); P=0.0017	-0.056 (-0.153 to 0.041); P=0.2620	0.001 (-0.010 to 0.011); P=0.9482

Monounsaturated fat	0.032 (0.021 to 0.043); P<0.0001	0.090 (0.049 to 0.131); P<0.0001	-0.036 (-0.077 to 0.005); P=0.085	0.012 (-0.025 to 0.049); P=0.5169	0.068 (0.050 to 0.087); P<.0001	0.094 (0.031 to 0.158); P=0.0034	-0.095 (-0.262 to 0.071); P=0.2623	0.050 (0.014 to 0.086); P=0.0058
Polyunsaturated fat	0.016 (0.006 to 0.025); P=0.0012	-0.098 (-0.148 to -0.049); P<0.0001	-0.035 (-0.085 to 0.016); P=0.1807	0.008 (-0.029 to 0.045); P=0.677	0.028 (0.010 to 0.046); P=0.0028	0.064 (0.032 to 0.096); P<.0001	-0.040 (-0.175 to 0.095); P=0.5610	-0.019 (-0.055 to 0.017); P=0.3161
	Triglycerides / HDL ratio, change (95% CI)							
Saturated fat replaced with	**Overall**	**North America/ Europe**	**South America**	**Middle East**	**South Asia**	**China**	**Malaysia**	**Africa**
Carbohydrates	0.047 (0.041 to 0.053); P<0.0001	0.032 (0.022 to 0.043); P<0.0001	0.052 (0.037 to 0.067); P<0.0001	0.046 (0.022 to 0.071); P=0.0002	0.100 (0.088 to 0.111); P<0.0001	0.067 (0.026 to 0.109); P=0.0014	-0.063 (-0.200 to 0.074); P=0.3668	0.015 (-0.003 to 0.032); P=0.1033
Monounsaturated fat	0.050 (0.036 to 0.064); P<0.0001	0.130 (0.084 to 0.175); P<0.0001	-0.014 (-0.064 to 0.035); P=0.5687	0.070 (0.015 to 0.124); P=0.0126	0.062 (0.037 to 0.086); P<0.0001	0.085 (0.005 to 0.164); P=0.0367	-0.098 (-0.334 to 0.137); P=0.4139	0.130 (0.070 to 0.190); P<0.0001
Polyunsaturated fat	0.034 (0.022 to 0.046); P<0.0001	-0.121 (-0.175 to -0.067); P<0.0001	0.014 (-0.046 to 0.074); P=0.6461	0.009 (-0.045 to 0.063); P=0.7396	0.058 (0.034 to 0.082); P<0.0001	0.082 (0.042 to 0.122); P<0.0001	-0.040 (-0.230 to 0.151); P=0.6857	-0.020 (-0.081 to 0.041); P=0.5209
	ApoB, change (95% CI)							
Saturated fat replaced with	**Overall**	**North America/ Europe**	**South America**	**Middle East**	**South Asia**	**China**	**Malaysia**	**Africa**
Carbohydrates	-0.010 (-0.013 to -0.007)	-0.002 (-0.008 to 0.004); P=0.4663	-0.003 (-0.008 to 0.003); P=0.3682	-0.014 (-0.025 to -0.003); P=0.0129	-0.014 (-0.022 to -0.007); P=0.0007	-0.026 (-0.052 to -0.001); P=0.0396	-0.049 (-0.133 to 0.034); P=0.2479	0.001 (-0.004 to 0.008); P=0.6313
Monounsaturated fat	-0.028 (-0.034 to -0.022)	0.010 (-0.012 to 0.032); P=0.3704	-0.019 (-0.036 to -0.003); P=0.0224	-0.004 (-0.029 to 0.022); P=0.777	-0.083 (-0.010 to -0.070); P<.0001	-0.035 (-0.083 to 0.013); P=0.1572	-0.076 (-0.201 to 0.050); P=0.2370	-0.009 (-0.025 to 0.007); P=0.271

Polyunsaturated fat	0.018 (0.012 to 0.025)	-0.025 (-0.049 to -0.001); P=0.0459	0.014 (-0.005 to 0.032); P=0.1548	-0.038 (-0.060 to -0.013); P=0.0027	0.079 (0.060 to 0.097); P<.0001	-0.016 (-0.040 to 0.009); P=0.2139	-0.018 (-0.140 to 0.105); P=0.7695	0.030 (0.010 to 0.050); P=0.0043
	ApoA1, change (95% CI)							
Saturated fat replaced with	**Overall**	**North America/ Europe**	**South America**	**Middle East**	**South Asia**	**China**	**Malaysia**	**Africa**
Carbohydrates	-0.021 (-0.024 to -0.018)	-0.026 (-0.033 to -0.020); P<.0001	-0.026 (-0.033 to -0.021); P<.0001	-0.030 (-0.041 to -0.020); P<.0001	-0.006 (-0.014 to 0.003); P=0.1754	0.007 (-0.023 to 0.038); P=0.6544	0.120 (0.013 to 0.228); P=0.0287	-0.024 (-0.031 to -0.017); P<.0001
Monounsaturated fat	-0.022 (-0.029 to -0.015)	-0.068 (-0.092 to -0.044); P<.0001	-0.036 (-0.058 to -0.014); P=0.0011	-0.033 (-0.058 to -0.008); P=0.0101	-0.017 (-0.031 to -0.002); P=0.0228	0.037 (-0.025 to 0.100); P=0.2081	0.163 (0.001 to 0.326); P=0.0489	-0.036 (-0.052 to -0.016); P=0.0005
Polyunsaturated fat	0.014 (0.006 to 0.022)	0.040 (0.012 to 0.065); P=0.0046	0.006 (-0.019 to 0.031); P=0.6294	-0.020 (-0.044 to 0.003); P=0.0901	0.137 (0.118 to 0.157); P<.0001	-0.004 (-0.034 to 0.026); P=0.7883	0.110 (-0.050 to 0.270); P=0.1781	-0.013 (-0.040 to 0.014); P=0.3544
	ApoB / ApoA1 ratio, change (95% CI)							
Saturated fat replaced with	**Overall**	**North America/ Europe**	**South America**	**Middle East**	**South Asia**	**China**	**Malaysia**	**Africa**
Carbohydrates	0.001 (-0.001 to 0.004); P=0.2283	0.010 (0.005 to 0.014); P<0.0001	0.011 (0.006 to 0.016); P<0.0001	0.008 (-0.002 to 0.017); P=0.1158	-0.008 (-0.016 to 0.000); P=0.0495	-0.016 (-0.036 to 0.004); P=0.117	-0.088 (-0.156 to -0.019); P=0.0129	0.008 (0.004 to 0.014); P=0.0015
Monounsaturated fat	-0.017 (-0.022 to -0.011); P<0.0001	0.034 (0.016 to 0.051); P=0.0002	0.005 (-0.011 to 0.020); P=0.5743	0.017 (-0.005 to 0.039); P=0.1322	-0.062 (-0.075 to -0.049); P<0.0001	-0.030 (-0.068 to 0.008); P=0.1247	-0.125 (-0.229 to -0.021); P=0.0185	0.002 (-0.013 to 0.017); P=0.7878
Polyunsaturated fat	0.005 (0.000 to 0.011); P=0.0601	-0.034 (-0.053 to -0.014); P=0.0009	0.002 (-0.016 to 0.020); P=0.831	-0.014 (-0.035 to 0.007); P=0.1728	-0.011 (-0.029 to 0.006); P=0.2026	-0.006 (-0.025 to 0.014); P=0.5559	-0.056 (-0.159 to 0.046); P=0.2803	0.032 (0.012 to 0.052); P=0.0019
	Systolic blood pressure, change (95% CI)							

Saturated fat replaced with	**Overall**	**North America/ Europe**	**South America**	**Middle East**	**South Asia**	**China**	**Malaysia**	**Africa**
Carbohydrates	-0.943 (-1.022 to -0.862); P<0.0001	-0.821 (-1.032 to -0.610); P<0.0001	-0.898 (-1.077 to -0.720); P<0.0001	-0.482 (-0.773 to -0.191); P=0.0012	-1.300 (-1.438 to -1.160); P<0.0001	1.234 (0.612 to 1.856); P=0.0001	-0.392 (-1.866 to 1.086); P=0.6028	-0.111 (-0.432 to 0.210); P=0.4983
Monounsaturated fat	-1.135 (-1.328 to -0.941); P<0.0001	-1.735 (-2.620 to -0.850); P=0.0001	-1.286 (-1.885 to -0.688); P<0.0001	-0.314 (-0.955 to 0.327); P=0.3374	-2.011 (-2.356 to -1.666); P<0.0001	2.264 (1.069 to 3.460); P=0.0002	-0.834 (-2.742 to 1.080); P=0.3931	0.934 (-0.169 to 2.036); P=0.0970
Polyunsaturated fat	-1.016 (-1.173 to -0.858); P<0.0001	2.129 (1.076 to 3.182); P<0.0001	1.094 (0.360 to 1.829); P=0.0035	-1.469 (-2.108 to -0.830); P<0.0001	-1.298 (-1.573 to -1.022); P<0.0001	0.546 (-0.061 to 1.153); P=0.0779	1.344 (-0.930 to 3.624); P=0.2461	-1.988 (-3.097 to -0.880); P=0.0004
	Diastolic blood pressure, change (95% CI)							
Saturated fat replaced with	**Overall**	**North America/ Europe**	**South America**	**Middle East**	**South Asia**	**China**	**Malaysia**	**Africa**
Carbohydrates	-0.621 (-0.681 to -0.561); P<0.0001	-1.076 (-1.210 to -0.943); P<0.0001	-0.379 (-0.581 to -0.176); P=0.0002	-0.780 (-0.967 to -0.593); P<0.0001	-0.476 (-0.565 to -0.387); P<0.0001	-0.289 (-0.688 to 0.110); P=0.1558	1.770 (0.774 to 2.760); P=0.0005	-0.350 (-0.539 to -0.161); P=0.0003
Monounsaturated fat	-0.706 (-0.851 to -0.561); P<0.0001	-1.739 (-2.298 to -1.181); P<0.0001	0.088 (-0.590 to 0.766); P=0.7992	-1.333 (-1.745 to -0.922); P<0.0001	-0.794 (-1.014 to -0.573); P<0.0001	-0.564 (-1.331 to 0.203); P=0.1493	2.514 (1.230 to 3.798); P=0.0001	0.130 (-0.519 to 0.778); P=0.6956
Polyunsaturated fat	-0.806 (-0.923 to -0.688); P<0.0001	1.205 (0.541 to 1.870); P=0.0004	-0.653 (-1.484 to 0.178); P=0.1236	-1.283 (-1.694 to -0.873); P<0.0001	-0.958 (-1.133 to -0.781); P<0.0001	-0.215 (-0.604 to 0.174); P=0.2788	2.952 (1.422 to 4.482); P=0.0002	-1.042 (-1.694 to -0.390); P=0.0017

Adjusted for age, sex, urban/rural location, education, current smoking, and antihypertensive or statin medication use. Center was also included as a random effect.

Appendix 16. Modeled † and observed ‡ hazard ratios (95% CI) of association between saturated fat intake and CVD events. The observed associations between SFA and CVD events are approximated by the simulated associations mediated through the effects on Apo B/Apo A1 ratio but not with other lipid markers including LDL-C, which suggests that Apo B/Apo A1 ratio provides the best overall indication of effect of SFA on CVD risk.

	Saturated fat intake, quintile category (% of energy intake)				
	Quintile 1	**Quintile 2**	**Quintile 3**	**Quintile 4**	**Quintile 5**
	2.7%	**5.2%**	**7.4%**	**9.8%**	**14.0%**
LDL cholesterol					
Major CVD events					
Modeled †	0.962 (0.960 to 0.963)	0.983 (0.982 to 0.984)	1.0 (ref)	1.018 (1.017 to 1.019)	1.048 (1.046 to 1.050)
Observed ‡	0.952 (0.852 to 1.064)	1.070 (0.968 to 1.188)	1.0 (ref)	0.972 (0.873 to 1.083)	0.897 (0.791 to 1.018)
CVD deaths					
Modeled †	0.969 (0.968 to 0.971)	0.986 (0.985 to 0.987)	1.0 (ref)	1.014 (1.013 to 1.015)	1.038 (1.036 to 1.040)
Observed ‡	1.097 (0.923 to 1.303)	1.187 (1.014 to 1.393)	1.0 (ref)	1.067 (0.869 to 1.309)	0.906 (0.724 to 1.134)
HDL cholesterol					
Major CVD events					
Modeled †	1.013 (1.012 to 1.014)	1.006 (1.005 to 1.007)	1.0 (ref)	0.994 (0.993 to 0.995)	0.985 (0.984 to 0.986)
Observed ‡	0.952 (0.852 to 1.064)	1.070 (0.968 to 1.188)	1.0 (ref)	0.972 (0.873 to 1.083)	0.897 (0.791 to 1.018)
CVD deaths					
Modeled †	1.005 (1.004 to 1.006)	1.002 (1.001 to 1.003)	1.0 (ref)	0.998 (0.997 to 0.999)	0.995 (0.994 to 0.996)
Observed ‡	1.097 (0.923 to 1.303)	1.187 (1.014 to 1.393)	1.0 (ref)	1.067 (0.869 to 1.309)	0.906 (0.724 to 1.134)
Triglycerides					

Major CVD events					
Modeled †	1.008 (1.010 to 1.007)	1.004 (1.005 to 1.003)	1.0 (ref)	0.996 (0.995 to 0.997)	0.990 (0.988 to 0.991)
Observed ‡	0.952 (0.852 to 1.064)	1.070 (0.968 to 1.188)	1.0 (ref)	0.972 (0.873 to 1.083)	0.897 (0.791 to 1.018)
CVD deaths					
Modeled †	1.009 (1.011 to 1.008)	1.004 (1.003 to 1.004)	1.0 (ref)	0.996 (0.995 to 0.997)	0.990 (0.988 to 0.991)
Observed ‡	1.097 (0.923 to 1.303)	1.187 (1.014 to 1.393)	1.0 (ref)	1.067 (0.869 to 1.309)	0.906 (0.724 to 1.134)
Total cholesterol / HDL cholesterol ratio					
Major CVD events					
Modeled †	1.006 (1.004 to 1.008)	1.003 (1.002 to 1.004)	1.0 (ref)	0.997 (0.996 to 0.998)	0.993 (0.991 to 0.995)
Observed ‡	0.952 (0.852 to 1.064)	1.070 (0.968 to 1.188)	1.0 (ref)	0.972 (0.873 to 1.083)	0.897 (0.791 to 1.018)
CVD deaths					
Modeled †	1.004 (1.003 to 1.005)	1.002 (1.001 to 1.003)	1.0 (ref)	0.998 (0.997 to 0.999)	0.995 (0.994 to 0.997)
Observed ‡	1.097 (0.923 to 1.303)	1.187 (1.014 to 1.393)	1.0 (ref)	1.067 (0.869 to 1.309)	0.906 (0.724 to 1.134)
ApoB/ApoA1 ratio					
Major CVD events					
Modeled †	1.073 (1.048 to 1.098)	1.032 (1.021 to 1.043)	1.0 (ref)	0.969 (0.959 to 0.979)	0.920 (0.895 to 0.946)
Observed ‡	0.952 (0.852 to 1.064)	1.070 (0.968 to 1.188)	1.0 (ref)	0.972 (0.873 to 1.083)	0.897 (0.791 to 1.018)
CVD deaths					
Modeled †	1.071 (1.046 to 1.095)	1.031 (1.021 to 1.041)	1.0 (ref)	0.970 (0.960 to 0.980)	0.922 (0.898 to 0.947)

Observed ‡	1.097 (0.923 to 1.303)	1.187 (1.014 to 1.393)	1.0 (ref)	1.067 (0.869 to 1.309)	0.906 (0.724 to 1.134)
Systolic blood pressure					
Major CVD events					
Modeled †	0.966 (0.963 to 0.970)	0.985 (0.983 to 0.987)	1.0 (ref)	1.015 (1.014 to 1.017)	1.042 (1.037 to 1.046)
Observed ‡	0.952 (0.852 to 1.064)	1.070 (0.968 to 1.188)	1.0 (ref)	0.972 (0.873 to 1.083)	0.897 (0.791 to 1.018)
CVD deaths					
Modeled †	0.971 (0.967 to 0.974)	0.987 (0.985 to 0.988)	1.0 (ref)	1.013 (1.012 to 1.015)	1.036 (1.032 to 1.040)
Observed ‡	1.097 (0.923 to 1.303)	1.187 (1.014 to 1.393)	1.0 (ref)	1.067 (0.869 to 1.309)	0.906 (0.724 to 1.134)

† Extrapolated hazard ratio (95% CI) of clinical events when changing saturated fat intake from the average level in Quintile 3 (reference) to the average in Quintiles 1, 2, 4 and 5.

‡ Observed hazard ratio (95% CI) of clinical events for Quintiles 1, 2, 4 and 5 of saturated fat intake compared to Quintile 3 (reference).

Assumptions: Change in LDL-C per 1% of energy increment in saturated fat intake is 0.038 (95% CI: 0.036 to 0.040) mmol/l, adjusting for covariates. The corresponding change in the other risk markers is 0.011 (95% CI: 0.010 to 0.012) mmol/l for HDL-C, -0.011 (95% CI: -0.013 to -0.010) mmol/l for triglycerides, -0.007 (95% CI: -0.009 to -0.005) for TC/LDL-C, -0.003 (95% CI: -0.004 to -0.002) for ApoB/ApoA1 ratio, and 0.451 (95% CI: 0.401 to 0.501) mmHg for systolic blood pressure.

Appendix 17: Association between macronutrients and major CVD events in the PURE study (n=135,335)

	Incidence (person/1000yr)					HR (95% CI)				
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	**Q2 vs· Q1**	**Q3 vs· Q1**	**Q4 vs· Q1**	**Q5 vs· Q1**	**P for trend**
Carbohydrate, % of energy										
Median (IQR)	46·4 (6·4)	54·6 (3·3)	60·8 (3·0)	67·7 (4·0)	77·2 (6·3)					
Major CVD*	3·8(3·5-4·1)	4·1(3·8-4·4)	4·1(3·8-4·4)	4·4(4·2-4·7)	5·0(4·7-5·3)	1·00(0·90-1·12)	1·02(0·91-1·14)	1·08(0·96-1·22)	1·01(0·88-1·15)	0·6165
Total fat, % of energy										
Median (IQR)	10·6 (4·6)	18·0 (3·4)	24·2 (2·7)	29·1 (2·4)	35·3 (4·9)					
Major CVD	5·2(4·9-5·5)	4·2(3·9-4·5)	4·0(3·8-4·3)	3·9(3·7-4·2)	4·0 (3·7-4·3)	1·01(0·92-1·11)	1·01(0·90-1·13)	0·95(0·84-1·07)	0·95(0·83-1·08)	0·3284
Saturated fatty acids, % of energy										
Median (IQR)	3·0 (1·6)	5·6 (1·2)	7·7 (1·0)	9·8 (1·2)	13·3 (3·1)					
Major CVD	5·0(4·7-5·3)	4·6(4·3-4·9)	4·0(3·7-4·3)	3·8(3·5-4·1)	4·0(3·8-4·3)	1·13(1·02-1·25)	1·06(0·95-1·18)	1·03(0·91-1·17)	0·95(0·83-1·10)	0·49
Mono-unsaturated fatty acids, % of energy										
Median (IQR)	3·6 (1·7)	5·8 (1·0)	7·8 (1·0)	10·0 (1·2)	13·0 (2·4)					
Major CVD	5·1(4·7-5·4)	4·5(4·3-4·8)	4·4(4·1-4·7)	3·8(3·5-4·0)	3·7(3·5-4·0)	1·04(0·94-1·15)	1·06(0·95-1·18)	1·02(0·90-1·15)	0·95(0·84-1·09)	0·5414
Poly-unsaturated fatty acids, % of energy										
Median (IQR)	2·2 (0·9)	3·5 (0·6)	4·7 (0·6)	6·3 (1·0)	9·1 (2·7)					
*Major CVD	5.3(5.0-5.6)	3.8(3.5-4.1)	3.9(3.6-4.1)	4.0(3.7-4.3)	4.5(4.2-4.8)	1·01(0·91-1·11)	0·99(0·89-1·10)	0·97(0·87-1·09)	1·01(0·90-1·14)	0·94
Protein, % of energy										
Median (IQR)	10·8(1·5)	13·1(1·0)	15·0(1·1)	16·9(1·1)	19·7(3·0)					
*Major CVD	5·0(4·7-5·3)	4·6(4·3-4·9)	4·4(4·1-4·7)	4·2(3·9-4·5)	3·7(3·5-4·0)	1·02(0·91-1·13)	1·08(0·96-1·22)	1·09(0·97-1·24)	0·96(0·84-1·10)	0·86

Hazard ratios and 95% CI are adjusted for age, sex, education, waist hip ratio, smoking, physical activity, diabetes, urban/rural, and energy intake. Center was also included as random effect and frailty models were used. CVD=Cardiovascular Disease * Major CVD= Fatal CVD + MI+ Stroke + Heart Failure

Appendix 18. Modeled † and observed ‡ hazard ratios (95% CI) of association between carbohydrate intake and CVD events. No single risk marker was superior in predicting the effects of carbohydrate intake on CVD events, which raises questions as to the value of emphasizing one risk marker over another to make recommendations on carbohydrate intake.					
	Carbohydrate intake, quintile category (% of energy intake)				
	Quintile 1	**Quintile 2**	**Quintile 3**	**Quintile 4**	**Quintile 5**
	45.1%	**54.7%**	**61.0%**	**67.9%**	**77.6%**
LDL cholesterol					
Major CVD events					
Modeled †	1.023 (1.022 to 1.025)	1.010 (1.009 to 1.011)	1.0 (ref)	0.990 (0.989 to 0.991)	0.972 (0.971 to 0.974)
Observed ‡	0.981 (0.874 to 1.102)	0.987 (0.887 to 1.097)	1.0 (ref)	1.070 (0.967 to 1.185)	1.000 (0.895 to 1.117)
CVD deaths					
Modeled †	1.019 (1.017 to 1.020)	1.008 (1.007 to 1.009)	1.0 (ref)	0.992 (0.991 to 0.993)	0.978 (0.976 to 0.979)
Observed ‡	0.973 (0.789 to 1.199)	1.147 (0.955 to 1.379)	1.0 (ref)	1.084 (0.902 to 1.304)	1.113 (0.910 to 1.361)
HDL cholesterol					
Major CVD events					
Modeled †	0.988 (0.987 to 0.989)	0.995 (0.994 to 0.996)	1.0 (ref)	1.006 (1.005 to 1.007)	1.015 (1.014 to 1.016)
Observed ‡	0.981 (0.874 to 1.102)	0.987 (0.887 to 1.097)	1.0 (ref)	1.070 (0.967 to 1.185)	1.000 (0.895 to 1.117)
CVD deaths					
Modeled †	0.996 (0.995 to 0.997)	0.998 (0.997 to 0.999)	1.0 (ref)	1.002 (1.001 to 1.003)	1.005 (1.004 to 1.006)
Observed ‡	0.973 (0.789 to 1.199)	1.147 (0.955 to 1.379)	1.0 (ref)	1.084 (0.902 to 1.304)	1.113 (0.910 to 1.361)
Triglycerides					
Major CVD events					

Modeled †	0.995 (0.994 to 0.997)	0.998 (0.997 to 0.999)	1.0 (ref)	1.002 (1.001 to 1.003)	1.006 (1.004 to 1.007)
Observed ‡	0.981 (0.874 to 1.102)	0.987 (0.887 to 1.097)	1.0 (ref)	1.070 (0.967 to 1.185)	1.000 (0.895 to 1.117)
CVD deaths					
Modeled †	0.995 (0.994 to 0.997)	0.998 (0.997 to 0.999)	1.0 (ref)	1.002 (1.001 to 1.003)	1.006 (1.005 to 1.008)
Observed ‡	0.973 (0.789 to 1.199)	1.147 (0.955 to 1.379)	1.0 (ref)	1.084 (0.902 to 1.304)	1.113 (0.910 to 1.361)
Total cholesterol / HDL cholesterol ratio					
Major CVD events					
Modeled †	0.990 (0.989 to 0.991)	0.996 (0.995 to 0.997)	1.0 (ref)	1.005 (1.004 to 1.006)	1.013 (1.010 to 1.015)
Observed ‡	0.981 (0.874 to 1.102)	0.987 (0.887 to 1.097)	1.0 (ref)	1.070 (0.967 to 1.185)	1.000 (0.895 to 1.117)
CVD deaths					
Modeled †	0.993 (0.992 to 0.995)	0.997 (0.996 to 0.998)	1.0 (ref)	1.003 (1.002 to 1.004)	1.008 (1.007 to 1.010)
Observed ‡	0.973 (0.789 to 1.199)	1.147 (0.955 to 1.379)	1.0 (ref)	1.084 (0.902 to 1.304)	1.113 (0.910 to 1.361)
ApoB/ApoA1 ratio					
Major CVD events					
Modeled †	0.922 (0.898 to 0.935)	0.966 (0.955 to 0.972)	1.0 (ref)	1.038 (1.031 to 1.051)	1.105 (1.086 to 1.142)
Observed ‡	0.981 (0.874 to 1.102)	0.987 (0.887 to 1.097)	1.0 (ref)	1.070 (0.967 to 1.185)	1.000 (0.895 to 1.117)
CVD deaths					
Modeled †	0.924 (0.900 to 0.936)	0.967 (0.956 to 0.972)	1.0 (ref)	1.037 (1.030 to 1.049)	1.102 (1.084 to 1.138)

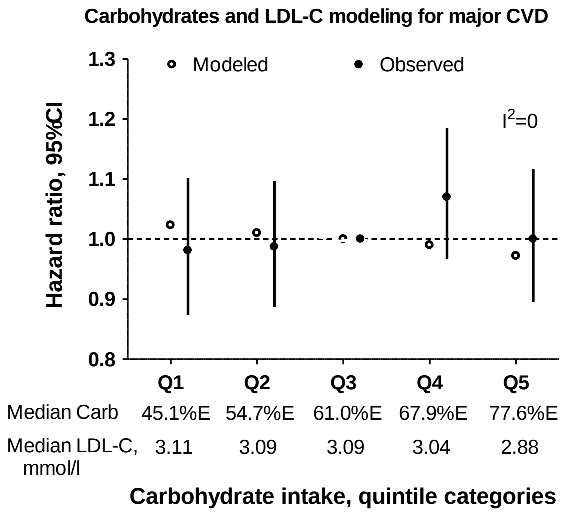
Observed ‡	0.973 (0.789 to 1.199)	1.147 (0.955 to 1.379)	1.0 (ref)	1.084 (0.902 to 1.304)	1.113 (0.910 to 1.361)
Systolic blood pressure					
Major CVD events					
Modeled †	0.986 (0.981 to 0.991)	0.994 (0.992 to 0.996)	1.0 (ref)	1.006 (1.004 to 1.009)	1.017 (1.011 to 1.024)
Observed ‡	0.981 (0.874 to 1.102)	0.987 (0.887 to 1.097)	1.0 (ref)	1.070 (0.967 to 1.185)	1.000 (0.895 to 1.117)
CVD deaths					
Modeled †	0.988 (0.984 to 0.992)	0.995 (0.993 to 0.997)	1.0 (ref)	1.006 (1.004 to 1.008)	1.015 (1.009 to 1.021)
Observed ‡	0.973 (0.789 to 1.199)	1.147 (0.955 to 1.379)	1.0 (ref)	1.084 (0.902 to 1.304)	1.113 (0.910 to 1.361)

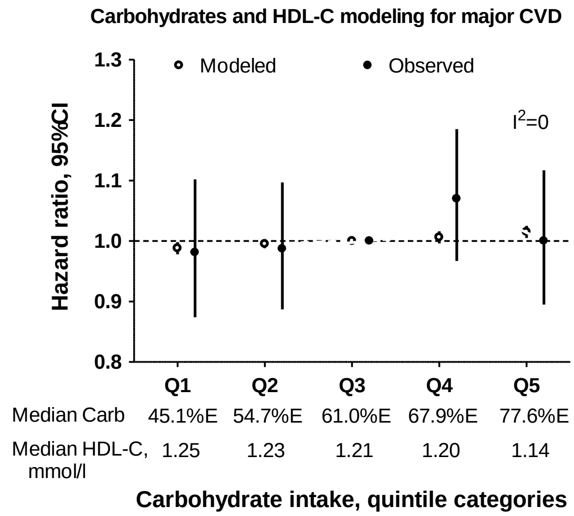
† Extrapolated hazard ratio (95% CI) of clinical events when changing carbohydrate intake from the average level in Quintile 3 (reference) to the average in Quintiles 1, 2, 4 and 5.

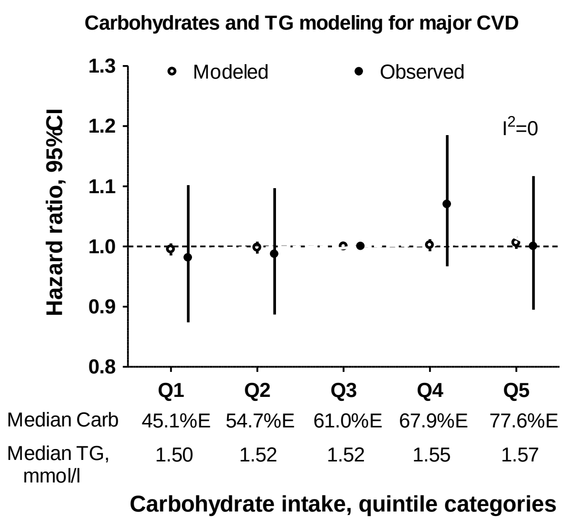
‡ Observed hazard ratio (95% CI) of clinical events for Quintiles 1, 2, 4 and 5 of carbohydrate intake compared to Quintile 3 (reference).

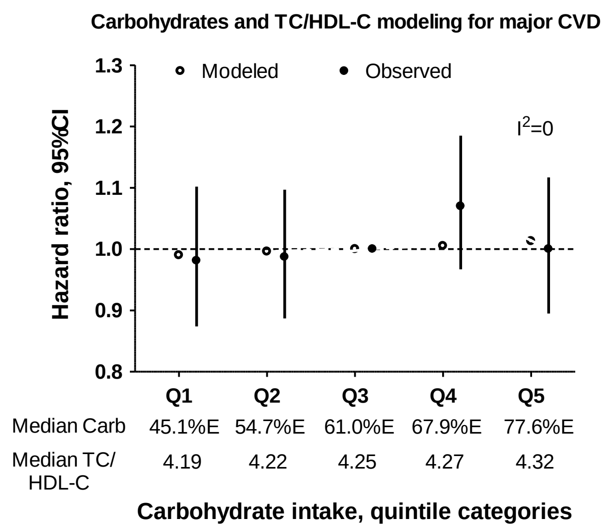
Assumptions: Change in LDL-C per 1% of energy increment in carbohydrate intake is -0.0078 (95% CI: (-0.0082 to-0.0072) mmol/l, adjusting for covariates. The corresponding change in the other risk markers is -0.0036 (95% CI: -0.0038 to -0.0034) mmol/l for HDL-C, 0.0022 (95% CI: 0.0016 to 0.0028) mmol/l for triglycerides, 0.0042 (95% CI: 0.0034 to0.0048) for TC/LDL-C, 0.0012 (95% CI: 0.0010 to 0.0016) for ApoB/ApoA1 ratio, and 0.0632 (95% CI: 0.0398 to 0.0864) mmHg for systolic blood pressure.

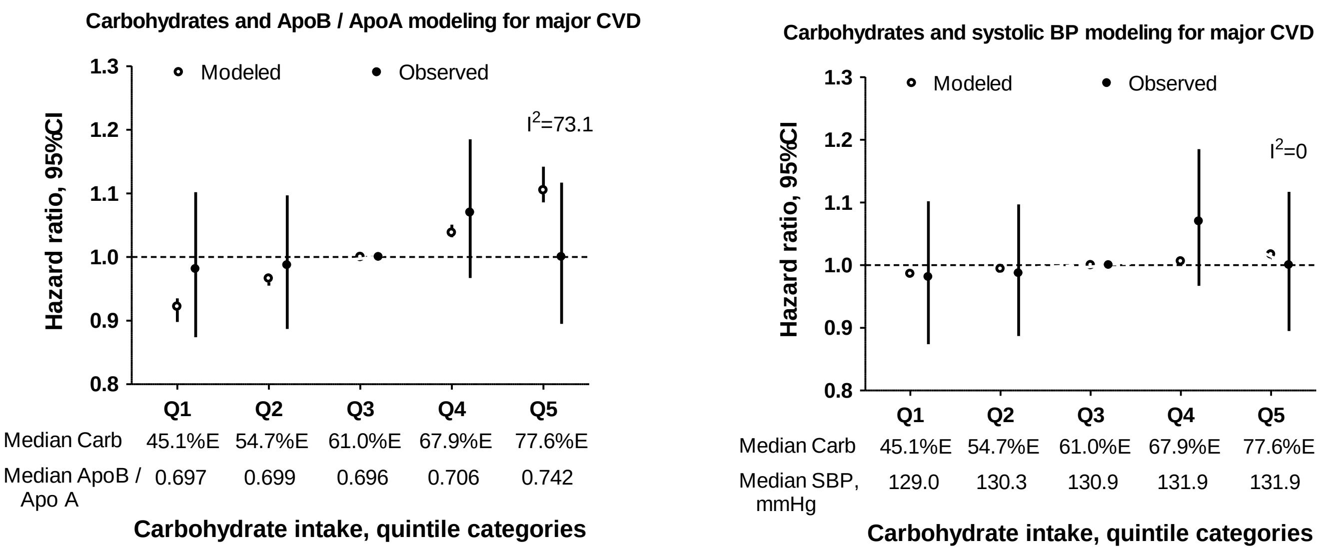
Appendix 19. Carbohydrate intake and risk markers modeling for major CVD events.











Appendix 18. Simulation modelled versus observed hazard ratio (HR) estimates of the association between carbohydrate intake versus major CVD events. No single risk marker was superior in predicting the effects of carbohydrate intake on CVD events, which raises questions as to the value of emphasizing one risk marker over another to make recommendations on carbohydrate intake.

Appendix 20: Cohesive information from three PURE papers published in the Lancet and Lancet Diabetes and Endocrinology which inform global dietary policies

This week three papers (16,17,18) from the large prospective international Prospective Urban Rural Epidemiology (PURE) study of 135,335 individuals are being simultaneously published in the Lancet and Lancet Diabetes and Endocrinology. PURE is unique as it provides information from urban and rural populations from 18 countries in 5 continents of the world. The paper by Mente et al (The Lancet Diabetes and Endocrinology) together with the accompanying paper by Dehghan et al (17) (The Lancet) provide a cohesive message on the association of carbohydrates and fats on mortality, CVD events, and CVD risk markers. The PURE study is the only study that has information on the association of diet, CVD and mortality from multiple regions in the world (five continents). This is relevant because in some parts of the world nutritional inadequacy is a problem, whereas in other parts of the world nutritional excesses may be the problem. Therefore recommendations based solely on studies from North America and Europe may or may not be applicable to other regions of the world.

<u>Nutrients versus CVD and mortality</u>: For decades, dietary guidelines have largely focused on reducing total fat and saturated fat intake based on the idea that reducing saturated fat should reduce the risk of CVD. But this did not take into account how saturated fat is replaced. Given that carbohydrates are relatively inexpensive in most countries, reducing fats (especially saturated fat) was associated with an accompanying increase in carbohydrate consumption. This approach continues to influence health policy today. Further, the current recommendations are based on findings from North America and Europe where nutrition excess is of concern. The guidelines were developed some 4 decades back using data from some Western countries (such as Finland) where fat and saturated fat intakes were very high (eg total fat intake was >40% of caloric intake and saturated fats was >20% of caloric intake) (19). It is not clear whether the harms seen at such high levels applies to current global intakes or countries outside North America and

Europe where fat intakes are much lower. Apart from studies from Japan (20) there was little information on populations with lower amounts of fat intake. Importantly, dietary recommendations are based on the assumption of a linear association between saturated fat intake and LDL-C, and then the association between LDL-C and CVD events. However, this assumption does not consider the effect of SFA on other lipoproteins (e.g. high density lipoprotein), total cholesterol/HDL-C ratio or on apolipoproteins (which could be a better marker of CVD risk) (21,22) and blood pressure which also affect the risk of CVD (23).

The paper by Dehghan et al (17) shows that contrary to popular belief, increased consumption of fats (including saturated fat, monounsaturated fat and polyunsaturated fat) are all associated with lower risk of death, but have a neutral association with cardiovascular diseases. By contrast, a diet high in carbohydrate is associated with a higher risk of death, but not with risk of cardiovascular disease. The study also shows that those with a high fat intake (about 35% of daily energy intake) had a 23% lower risk of mortality, and an 18% lower risk of stroke. All types of fats (saturated, polyunsaturated and monounsaturated) are associated with lower risks of death. Total fat and individual types of fat are not associated with risk of myocardial infarction or death due to cardiovascular disease.

These results are consistent with several meta-analyses of observational studies and randomized controlled trials conducted in North America and Europe in the last 2 decades, where the mean fat intake was higher than levels represented in the PURE study (eg, ~30% of energy compared to 23% of energy in PURE). Despite these studies several guidelines (e.g. WHO or AHA) continue to emphasize reductions in fats (especially saturated fat) consumption, irrespective of their levels of intake. This has automatically led to increases in carbohydrate consumption. Currently, total fat and saturated fat intake in North America and Europe is markedly lower than the amount consumed during the time of the earlier studies more than 4 decades ago, closer to around 30% for total fats and about 12% saturated fats of daily energy intake. The new results from PURE show a similar level of intake in North America and Europe (total fat intake is 31% and saturated fat intake is 11% of daily caloric intake). The study also showed that total fat consumption is highest in North America/Europe and the Middle East, and lowest in South Asia, China, and Africa (below 25% of total caloric intake). In the context of today's diets, this would suggest that there is little need to further lower average fat intake today for most populations, unlike the case 20 or 30 years ago. This paper also shows that increased carbohydrate consumption (above 60% of energy, which about half the population consumes) is associated with increased mortality. This may explain why certain populations such as South Asians, who do not consume much fat but consume a lot of carbohydrates, have higher mortality rates. Therefore, PURE, along with a large body of evidence, questions the conventional beliefs regarding dietary fats and clinical outcomes. Relaxing current restrictions on fat intake but limiting carbohydrate intake (when high) could improve longevity for most populations.

<u>Nutrients versus lipids and blood pressure</u>: The paper by Mente et al (16) examines the effects of different nutrients on a range of surrogate endpoints, including different lipid markers and blood pressure. It shows that the effects of fats and carbohydrates in the PURE study are consistent with what has been reported for North America and Europe on total cholesterol, LDL, HDL, their ratios, as well as triglycerides. For instance, while LDL increases with higher intakes of saturated fat, HDL also increases so that the net effect is a decrease in the ratio of total cholesterol/HDL. For decades, dietary guidelines have largely focused on the effect of diet on LDL. This assumes, however, that the net clinical benefit of saturated fat reduction can be accurately predicted from its impact on a single risk factor (LDL) alone without considering its collective impact on other common cardiovascular risk markers including triglycerides, HDL, total cholesterol/HDL-C ratio, or blood pressure. This study also provides new data on the effects of diet on Apolipoprotein B (ApoB), Apolipoprotein A1 (ApoA1) and their ratio (ApoB/ApoA1). Apo B/Apo A1 reflects the presence of small dense LDL particles, which is thought to be more atherogenic than larger LDL particles and is the strongest predictor of myocardial infarction in the INTERHEART

study and ischemic stroke risk in the INTERSTROKE study. The study shows that total fat intake (and each type of fat) is generally beneficial toward most cardiovascular blood markers (eg a reduction in Apo B and its ratio with ApoA1), except for total cholesterol and LDL. Conversely, carbohydrate intake is associated with potentially harmful effects on most lipid parameters (eg an increase in Apo B/Apo A1). Importantly, using LDL-C (the basis of many dietary guidelines) to predict the risks of CVD in the simulation models produces the least similarity between modeled compared to the actual risks of CVD observed in the study with saturated fat intake. Instead, ApoB/ApoA1 provides the best overall indication of effect of saturated fat on cardiovascular risk among the markers tested. For carbohydrate intake, no single risk marker could explain the effects of carbohydrate intake on CVD events. These data suggest that focusing on a single lipid marker such as LDL-C alone does not capture the net clinical impact of nutrients on cardiovascular risk.

<u>Fruits and vegetables versus CVD and mortality</u>: The paper by Miller et al (18) shows that with minimal adjustment for confounding variables, higher fruit, vegetable and legume intake is associated with a strong protective effect against mortality risk. However, with full adjustment for known confounders, the strength of the association is attenuated by about 50%. This suggests that without extensive adjustment for confounders, the degree of benefit associated with higher fruit and vegetable consumption in populations may be exaggerated. Second, our study showed that three daily servings of fruit, vegetables and legumes are related to lower mortality, with little additional benefit for intake beyond that range. Current fruit, vegetable and legume intake globally is between three to four servings per day, but most dietary guidelines recommend a minimum of five daily servings, a level of intake that few people in many regions of the world (South Asia, China, Southeast Asia and Africa) can afford and do not reach. Therefore, guidelines should emphasize the intakes of at least 3 to 4 servings of fruits and vegetables per day (which is more affordable) (24) and higher levels may only provide little incremental benefit.

Additionally, fruit and legume intake was more strongly associated with benefit than vegetables. Lastly, raw vegetable intake was more strongly associated with a lower risk of cardiovascular disease and death compared to cooked vegetable intake. However, raw vegetables are rarely eaten in South Asia, Africa and Southeast Asia. Dietary guidelines do not differentiate between the benefits of raw versus cooked vegetables---our results indicate that recommendations should emphasize raw vegetable intake over cooked. In short, the findings indicate that consuming three servings per day (375 grams) is sufficient for reducing the risk of death, a target that is likely more affordable and achievable especially in low and middle income countries where the costs of fruits and vegetables are relatively high and make them unaffordable as we described in a paper published earlier (24).

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