Saturated and unsaturated dietary fats and cardiometabolic risk in the Framingham Offspring Study

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Abstract

Background. The association between dietary fats and the risk of cardiovascular disease (CVD) and type 2 diabetes (T2DM), leading causes of death in the developed world, is controversial. More data are needed to determine how dietary fats may impact a wide range of cardiometabolic risk factors. We assessed the association between dietary fats and CVD, T2DM, all-cause mortality, and several types of cardiometabolic risk factors in the prospective Framingham Offspring Study.

Methods. We included participants ≥30 years of age with dietary data from 3-day diet records. Weight-adjusted dietary fats included saturated, monounsaturated, and polyunsaturated fats (omega-3 and omega-6). Cox-proportional hazards models were used to estimate hazard ratios (HR) for disease outcomes and death, while analysis of covariance models were used to estimate adjusted mean levels of body fat, inflammation, fasting glucose, lipid levels, and lipid particle sizes and concentrations associated with categories of dietary fat intakes.

Findings. Participants were followed for up to 18 years; 536 CVD cases, 288 T2DM cases, and 764 deaths were recorded. Neither saturated nor polyunsaturated fats, including omega-3 and omega-6, were associated with CVD or T2DM risks, but both were inversely associated with all-cause mortality. Monounsaturated fat intake was associated with a 55% increased risk of CVD in men only. Higher intakes of all dietary fats were associated with less body fat, higher HDL, and lower triglycerides (TG) and TG:HDL ratio. Further, all dietary fats tended to be associated with less atherogenic lipid particle profiles.

Interpretation. We found no indication that saturated or polyunsaturated fats increase CVD or T2DM risk, and both were linked with lower all-cause mortality. In general, all types of dietary fat were associated with less body fat and a more favorable lipoprotein profile. This study found no evidence that saturated fat has an adverse impact on cardiometabolic health.

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Research in context

Evidence before this study

Previous evidence has shown that diets with high levels of saturated fat can adversely affect LDL cholesterol. At the same time, some additional evidence suggests that it may have other beneficial effects, such as those on lipid ratios and particle sizes and concentrations. The sources of dietary fats are typically energy-dense foods, thus leading to concerns about excess weight gain, the promotion of inflammation, and glucose dysregulation. Taken together, saturated fats have long been believed to raise the risk of cardiovascular disease, diabetes, and even premature death. We conducted a PubMed search for relevant papers published from August 2001 to August 2022 using the following search terms: "dietary fat", "saturated fat", "monounsaturated fat", "polyunsaturated fat", "all-cause mortality", "cardiovascular disease", "diabetes", "lipoprotein profile", “adiposity”, “obesity”, “cardiometabolic risk”, “lipids”, “lipid particles”, “body fat”, and “inflammation”. We also searched the reference lists from recent meta-analyses and other publications.

Added value of this study

The current *Dietary Guidelines* in the United States continue to recommend limiting saturated fat intake to less than 10% of energy. In the United Kingdom, males and females from 19-64 years of age are counseled to restrict their intakes of saturated fat to less than 30 grams and 20 grams, respectively. Despite the belief that this will lower the long-term risk of cardiovascular disease, diabetes, and total mortality, recent meta-analyses have failed to find beneficial effects of fat restriction on any of these outcomes. The current analyses also failed to find an adverse effect of saturated or unsaturated fats on incident CVD, type 2 diabetes, or total mortality. Instead, these analyses suggest several ways in which saturated fat intake may benefit long-term cardiometabolic health.

Implications of all the available evidence

The evidence presented in this research will be beneficial to the development of future dietary guidance. Saturated fats in these analyses were associated with apparent beneficial effects on body fat, selected lipids (i.e., HDL, triglycerides, and the triglyceride to HDL ratio), as well as lipid particle sizes and concentrations. In contrast, there was no association between dietary fats of any type and LDL cholesterol. This research provides important evidence to inform dietary advice and the design of future mechanistic studies and clinical trials.

Introduction

For decades, the *Dietary Guidelines for Americans* (DGA) have recommended restricting intakes of total and saturated fats and replacing saturated with unsaturated fat to prevent cardiovascular disease (CVD).[1] The basis for these recommendations is the long-standing "diet-heart" hypothesis which proposed that higher saturated fat intakes would increase serum low-density lipoprotein cholesterol (LDL-C) levels, thereby increasing CVD risk.[2] In recent years, more attention has been focused on the importance of lipid ratios, lipid particles, and other cardiometabolic outcomes such as inflammation.

Saturated fat intakes have been linked with higher LDL-C levels but also with higher HDL-C levels and by some, with lower triglyceride (TG) levels[3], although evidence on the latter is inconsistent.[4] The ratio of triglycerides-to-high density lipoprotein-cholesterol (TG:HDL) levels has been shown to more strongly predict CVD risk than individual lipids.[5] In addition, a preponderance of small, dense lipid particles has been shown to be more pro-atherogenic than large buoyant particles,[6] and, in some studies, higher saturated fat intakes have been associated with larger LDL particle sizes.[4] The particular food sources of saturated fat and other dietary macronutrients may also have important effects on particle sizes and concentrations.[7]

Since CVD and type 2 diabetes mellitus (T2DM) constitute leading causes of death in the US, dietary factors that impact these outcomes are likely to affect total mortality as well. However, data from the PURE study found that various dietary fats were associated with lower total mortality but not cardiovascular death[8]. Despite inconclusive evidence, current guidelines still recommend replacing saturated with polyunsaturated fat. More research on the effects of polyunsaturated fats, including omega-3 and omega-6 PUFAs, on cardiometabolic risk, is needed.

This study aimed to evaluate the association between dietary intakes of saturated, monounsaturated, polyunsaturated (total, omega-3 and omega-6) fats, and cardiometabolic risk among adults in the Framingham Offspring Study. Specifically, we examined associations between dietary fats and biomarkers of inflammation, body fat, fasting glucose, lipids, and lipid particles, as well as risks of CVD, T2DM, and all-cause mortality.

Methods

Study design and participants

The Framingham Offspring Study enrolled 5124 adults in 1971 who were the offspring of participants in the original Framingham Heart Study. Approximately every four years, participants were asked to complete questionnaires on health status, lifestyle, and demographic information and to undergo anthropometric measurements and blood tests. Dietary information from food records was collected at exams three to five, so we considered exam five to be the baseline exam for these analyses. The Boston University Medical Center Institutional Review Board approved the analysis protocol, and all participants provided written informed consent.

Figure 1 provides inclusion and exclusion details for the current analyses. Of the 5124 participants at the first examination visit, 3095 survived, aged ≥30 years and provided dietary record data. We excluded subjects with missing BMI, baseline BMI <18·5 kg/m^2, prevalent cancers, alcohol consumption >20% kcal daily, or extreme intakes of total energy, dietary fats, or red meat, poultry,

or fish. This left 2586 participants for all-cause mortality analyses. For the CVD and T2DM risk analyses, we excluded prevalent cases for each outcome, yielding 2340 participants for the analysis of incident CVD and 2286 for incident T2DM. Lastly, for the analyses of other cardiometabolic outcomes, we first excluded 63 who were missing potential confounding variables and 132 who were missing all other cardiometabolic outcome measures (i.e., body fat, lipids, lipid particles, glucose, and inflammatory biomarkers), leaving a maximum of 2391 participants for these analyses. Sample sizes for individual cardiometabolic risk factors are shown in Figure 1.

Dietary Assessment

Approximately 16,000 days of diet records were collected, with each set including two weekdays and one weekend day with instructions from a trained nutritionist. Participants used two-dimensional food models to estimate portion sizes. Nutrient composition of the diet was derived by entering the diet records into the Nutrition Data System (NDS) of the University of Minnesota, version 23.[9] Intakes in each USDA food group were derived by linking NDS food code data with USDA food codes using the MyPyramid Equivalents Database, version 06A (https://www.rs.usda.gov/ARSUserFiles/80400530/pdf/mped/mped2_doc.pdf) (accessed March 2022). Mean intakes of foods and nutrients were estimated from all days of diet records. Exposure variables for these analyses included saturated, monounsaturated, and polyunsaturated fat, including omega-3 and omega-6 PUFAs. The omega-3 PUFAs available through the NDS system are 18:3 (linolenic acid), 18:4 (stearidonic acid), 20:5 (eicosapentaenoic acid), 22:5 (docosapentaenoic acid), and 22:6 (docosahexaenoic acid). The available omega-6 PUFAs include 18:2 (linoleic acid) and 20:4 (arachidonic acid).

Outcomes

Cardiovascular outcomes in Framingham are adjudicated by a panel of physicians and include incident cases of coronary heart disease, peripheral vascular disease, heart failure, and stroke. Follow-up for CVD endpoints continued through 2016. Diabetes was diagnosed using the following criteria: (a) non-fasting glucose ≥200 mg/dL; (b) taking oral hypoglycemics or insulin; (c) 10-hour fasting glucose ≥126 mg/dL; (d) history of diabetes combined with a non-fasting glucose 126-200 mg/dL; or (e) self-reported diagnosis of diabetes at one visit with a subsequent diagnosis of definite diabetes at the next visit without extreme weight gain (≥7% of body weight) between exam visits. Death certificates were used to determine all-cause mortality through 2016.

Other cardiometabolic outcomes were assessed at exam six, four years after baseline. Mean height (from all measures prior to age 60) was used together with weight from exam six to calculate body mass index (BMI, kg/m^2). Percent body fat at exam six was estimated using bioelectrical impedance analysis (BIA) data.

Routine laboratory assessments for inflammatory markers, glucose, and lipids at exam six were conducted following a 12-hour fast. IL-6 and fibrinogen were measured with commercially-available enzyme-linked immunoassay kits. Plasma lipid levels (LDL-C, HDL-C, TG) were determined in the Framingham lipoprotein cholesterol laboratory following Centers for Disease Control guidelines[10] for measured or estimated cholesterol content. Lipoprotein particle sizes and concentrations for HDL, LDL, and VLDL were measured by Nuclear Magnetic Resonance (NMR) spectroscopic assay. The average weighted lipoprotein particle size (nm diameter) was computed

as the sum of the size of each subclass multiplied by the percent of its relative mass as estimated by the amplitude of its NMR signal. Particle concentrations are expressed as nanomoles of each particle per liter (nmol/L). Since lipid particles were only measured at exam four, they were analyzed cross-sectionally.

Potential confounding

Potential confounding factors were assessed initially during the dietary assessment period and then updated during follow-up. Education level and physical activity was self-reported. A physical activity index was created by multiplying daily hours of moderate and vigorous activity by an appropriate weight based on oxygen consumption required for that level of exercise.[11] Cigarette smoking status and amount smoked were assessed by interview, and pack-years of cigarette smoking were updated at each exam. The following dietary factors were explored as potential confounding variables: (a) energy-adjusted (and weight-adjusted) intakes of monounsaturated fat, polyunsaturated fat, carbohydrates, protein, and dietary fiber; (b) servings per day of foods such as fruits and non-starchy vegetables or dairy products, (c) energy intake (kilocalories per day); and (d) Healthy Eating Index (HEI) 2015[12] and Dietary Approaches to Stop Hypertension (DASH)[13] scores. Finally, we explored co-morbidities, including prevalent hypertension, baseline diabetes status (except models for T2DM), and lipid-lowering and antihypertensive medications use.

Statistical analysis

Each dietary fat intake was adjusted for the participant's body weight by adding the residuals from linear regression models to the overall median intake values. The weight-adjusted intakes were compared with energy-adjusted intakes among a subset of participants who were determined to have plausible energy intakes (within 20% of the predicted intake level). There were strong correlations between energy-adjusted intakes and weight-adjusted intakes among those with plausible intakes but weaker correlations among those with implausible energy intakes. Thus, we chose to adjust dietary fat intake for body weight rather than energy intake to minimize the impact of biased reporting of energy intake.

We used sensitivity analyses and power considerations to classify each subject's intake of weight-adjusted dietary fats. Categories of saturated fat intake were as follows: <20, 20–<30, and ≥30 g/day. Monounsaturated fat intakes were classified as <25, 25–<35, and ≥35 g/day, while polyunsaturated fat intakes were classified as <12, 12–<20, and ≥20 g/day. Intake of omega-3 PUFA was classified as <1, 1–<2, and ≥2 g/day, while omega-6, the predominant PUFA, was categorized as <10, 10–<15, and ≥15 g/day.

Person-years of follow-up to CVD occurrence were calculated as the time from baseline (end of the dietary exposure period) to the first of the following events: (1) date of diagnosis of incident CVD; (2) loss to follow-up; (3) death; or (4) end of study follow-up. Follow-up for T2DM and all-cause mortality was determined similarly. Cox proportional hazard models were used to estimate the adjusted hazards ratio (HR) and 95% confidence interval (CI) for risks of CVD, T2DM, and all-cause mortality.

For continuous outcome variables, we used analysis of covariance (ANCOVA) modeling to estimate adjusted mean levels of adiposity (BMI, % body fat), fasting glucose, inflammatory

markers (IL-6 and fibrinogen), lipid levels (HDL-C, LDL-C, TG, and the TG:HDL ratio), and lipoprotein particle sizes and concentrations (HDL, LDL, and VLDL). Non-normally distributed variables were log-transformed, including TG, IL-6, fibrinogen, and VLDL particle concentrations.

Confounding was assessed by adding each factor one at a time to the age- and sex-adjusted models, then building the model forward by adding each individual confounder singly to the model and avoiding collinearity. The final models included age, sex (except in sex-specific models), weight-adjusted carbohydrate intakes, HEI 2015 scores, use of lipid-lowering medications, pack-years of cigarette smoking, baseline BMI, and prevalent diabetes (except in T2DM models). Mortality analyses were also adjusted for prevalent hypertension. Energy intake, education level, use of antihypertensive drugs, and other factors did not alter the effect estimates and were dropped from the final models. The proportional hazards assumption was tested in all models, and no assumption violations were found. Statistical Analysis Systems software, version 9·4 (SAS Institute, Cary, NC), was used to perform all analyses.

Role of the funding sources

The funders had no role in the study design, data collection, analysis, interpretation of the data, preparation, review, or approval of the manuscript.

Results

Participant characteristics according to categories of saturated fat intake are shown in Table 1. Participants with higher intakes were somewhat younger, less frequently female, more likely to be smokers, and had a lower BMI and lower HEI scores. Higher saturated fat intake was also associated with higher energy intake and higher intakes of dairy, nuts and seeds, red meats, and fiber, but slightly lower intakes of fruits and vegetables. Supplementary Table 1 shows participant characteristics associated with monounsaturated and polyunsaturated fat intakes. Those with higher intakes of polyunsaturated fat were less likely to be smokers and had higher mean HEI scores, while those with higher monounsaturated fat intakes had lower HEI scores.

Figure 2 shows the adjusted HRs and 95% CIs for CVD, T2DM, and all-cause mortality associated with dietary fat intakes. Overall, after adjusting for confounding, there was no association between intake of different dietary fats and risk of CVD or T2DM over this long-term follow-up. However, in sex-specific analyses (Supplementary Figure 2), moderate and higher intakes of monounsaturated fat were associated with at least a 50% higher risk of CVD in men. Overall, Figure 2 shows a tendency for both saturated fat and polyunsaturated fats (including omega-3 and omega-6 PUFAs) to be inversely associated with lower total mortality risk.

In Table 2, participants with the lowest intake of dietary fats, regardless of type, had the highest body fat levels. Sex-specific analyses in Supplementary Table 2 indicate that saturated and monounsaturated fat intakes were inversely associated with one or both measures of body fat in both men and women. Both omega-3 and omega-6 PUFAs were also inversely associated with body fat measures in women, while omega-6 PUFAs were inversely associated only with BMI in men. Table 2 also shows that both saturated and monounsaturated fats were inversely associated

with fibrinogen levels but not with IL-6, while omega-3 PUFAs were inversely associated with IL-6. There were no associations between any of these dietary fats and fasting glucose.

Table 3 shows the adjusted mean levels of plasma lipids associated with intake categories of dietary fats. Higher intakes of saturated, monounsaturated, and polyunsaturated fats were associated with higher adjusted mean levels of HDL-C, lower mean TG levels, and a lower TG:HDL ratio. There was no indication that dietary fat of any type was associated with increases in LDL-C levels. Sex-specific analyses in Supplementary Figure 2 were generally similar.

Figure 3 shows the association between dietary fats and adjusted mean lipoprotein particle sizes (Panel A) and concentrations (Panel B). Overall, higher intakes of dietary fats were positively associated with HDL particle size and concentration. Further, higher intakes of saturated and monounsaturated fats were associated with beneficial increases in LDL particle size and decreases in LDL particle concentration. Higher intakes of polyunsaturated fat were also associated with reduced LDL particle concentrations. Similarly, higher fat intakes were associated with reductions in VLDL particle concentration but not size. Results stratified by sex are shown in Supplementary Figure 3.

Discussion

In this large prospective cohort study with a long follow-up period, we found no evidence that higher intakes of saturated and polyunsaturated fats were associated with an increased risk of CVD or T2DM. Monounsaturated fat intake was associated with a higher risk of CVD in men only. Saturated and polyunsaturated fats (total, omega-3, and omega-6) tended to be associated with a lower all-cause mortality risk. In general, dietary fats also tended to be associated with favorable cardiometabolic risk profiles, including lower BMI and percent body fat, higher HDL-C and lower TG levels and TG:HDL ratio, and higher concentrations of larger, more buoyant lipid particles. In addition, both saturated and monounsaturated fat intakes were inversely associated with the inflammatory marker fibrinogen, while polyunsaturated fat was inversely associated with IL-6.

While some studies find a positive association between saturated fat and CVD risk,[14–16] current and previous analyses that did not account for replacement nutrients showed no adverse association between saturated fat intake and CVD or T2DM risk.[8,17–19] Recent meta-analyses of prospective cohort studies also contradict the long-held belief that higher saturated fat intake increases the risk of T2DM[20] or CVD.[21] In these analyses, both saturated fat and polyunsaturated fat intakes tended to be associated with lower all-cause mortality after adjusting for key risk factors such as diet quality, carbohydrate intakes, BMI, smoking, lipid-lowering medications, and prevalent T2DM and hypertension. Although the evidence on saturated fat intake and total mortality has been inconsistent[8,22–24], two meta-analyses of prospective studies found no association.[25,26] The discrepancies in results between studies could be because saturated fat intakes are associated with underlying dietary patterns that differ across populations. For example, three major US-based cohort studies found a positive association between higher saturated fat and all-cause mortality risk,[22,25,27] while studies conducted in the Mediterranean and other multiethnic populations showed a null or even an inverse association.[28,8]

Monounsaturated fat intake in this study was not associated with T2DM or all-cause mortality but was associated with a 50% or higher risk of CVD in men only. Once again, the evidence regarding

monounsaturated fat associated with the aforementioned outcomes is very inconsistent. Previous prospective cohort studies and meta-analyses found no association of monounsaturated fat intake overall with CVD,[8,29–31] mortality,[8,22,24,25], or T2DM risks.[16,17,19,20,28,32] These studies did not find the same association with CVD risk in men that we found in the current study.[33,34] The major food source of monounsaturated fat in a typical Westernized diet, particularly for men, is red meat. In populations consuming mainly plant-based food sources of monounsaturated fat, higher monounsaturated fat intake (vs. lower) was found to reduce CVD[28] or mortality risk[22,27,28], while higher animal-based monounsaturated fat intakes increased mortality risk.[22] In this study, monounsaturated fat intake was highly correlated with saturated fat (Pearson r=0.87), which might limit our ability to assess the independent contribution of monounsaturated fat.

Both omega-3 and omega-6 are essential fatty acids involved in several cardiometabolic pathways, including lipids, inflammation, vascular function, and cardiac rhythm, and thereby may exert protective effects on cardiometabolic diseases and mortality via different mechanisms.[35] In this study, total polyunsaturated fat and omega-3 intakes were associated with lower mortality risk in men, while omega-6 intakes were mainly protective in women. Previous epidemiologic studies that modeled independent associations between polyunsaturated fat intakes and all-cause mortality had mixed findings.[8,22–25] Those who used substitution analyses found that replacing carbohydrates with polyunsaturated fat intake was associated with lower all-cause mortality.[11,34,38,39,45] Rich sources of long-chain omega-3s, docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA), which promote anti-lipid and anti-aggregatory effects, are oily fishes.[35] In this study population, the consumption of fish rich in omega-3s is relatively low, which may explain the absence of association between omega-3s and CVD or T2DM risk.

Dietary fats are associated with consuming energy-dense foods and, as a result, have been hypothesized to increase body fat. However, this hypothesis fails to consider the importance of mechanisms involved in fuel partitioning[36] and satiety signals and the divergent effects of different types of fat on lipid metabolism[2] and the gut microbiome.[37] In this study, we found that both BMI and percent body fat declined with higher levels of fat intake. These results differ from those of three prospective US cohorts showing that a 5% increase in energy from saturated fat at the expense of carbohydrates was associated with 0.61 kg weight gain over 4 years.[38] They also found that a 5% increase in energy from polyunsaturated fat (mainly plant-based) was associated with weight loss, a finding consistent with ours. The relevance of our findings on the effects of unsaturated fat on mitigating obesity is confirmed at least by three controlled trials showing that monounsaturated and polyunsaturated fat-enriched diets or meals may increase fat oxidation and energy expenditure while suppressing appetite and visceral fat deposition.[39–42]

In the current study, saturated and monounsaturated fat intakes were inversely associated with fibrinogen levels, while omega-3 PUFAs were inversely associated with IL-6 levels. Previous research has suggested that meals rich in dietary fats may stimulate the innate immune response, thereby promoting inflammation.[43] In a randomized cross-over study, investigators failed to find any effect of saturated or other fats on circulating inflammatory biomarkers.[44] The variable effects of dietary fats on inflammation across studies could also be due to dissimilar effects of different dietary fats and their food sources, which could differently impact pathways such as the gut microbiome.[43] Lastly, concerns have been raised that an excess of linoleic acid, an essential omega-6 PUFA, might promote inflammation and LDL oxidation; however, there is still no

consensus around these effects.[45] The American Heart Association concluded that there is little direct evidence to support a pro-inflammatory role of linoleic acid.[46]

A considerable amount of evidence shows that the changes in lipoprotein profile, including particle size and concentration, are stronger risk factors for atherosclerosis than serum LDL concentrations.[4,47] We found no evidence that higher saturated fat intake or any other type of fat increased fasting LDL-C levels; instead, saturated and monounsaturated fats and omega-3s led to substantial reductions in the TG:HDL ratio, an important predictor of cardiometabolic risk.[5] Further, our results extend beyond serum lipids and show that a higher intake of dietary fats was cross-sectionally associated with more and larger protective HDL particles and lower concentrations in LDL and VLDL particles. Further, higher saturated and monounsaturated fat intakes also led to larger LDL particles that are less atherogenic than the small dense particles that are more prone to oxidation.[2,4] Previous analyses from the PURE study with >100,000 participants showed that diets rich in saturated fat were associated with higher LDL levels but also with higher levels of HDL, lower TGs, and a lower apolipoprotein B: apolipoprotein A ratio.[48] In addition, clinical trials have shown that monounsaturated fat-rich meals could lead to the formation of larger chylomicrons, thus increasing the clearance of TGs.[4]

Strengths of the present study include its prospective longitudinal design with up to 16 years of follow-up. In addition, longer-term dietary intakes were determined by averaging 3-day food diaries over 8 years. Dietary records are also generally considered a more accurate assessment to estimate individual intakes.[49,50] Despite adjusting for several carefully-collected risk factors, we cannot rule out residual confounding, particularly with respect to inter-correlated dietary factors. Further, the Framingham Offspring Study is a historical cohort that is almost exclusively Caucasian, thus limiting the extrapolation of these results to a multiethnic population.

In summary, we found no evidence supporting a long-term adverse association between saturated or polyunsaturated fat intakes and risks of CVD or T2DM. Instead, higher intakes of saturated and polyunsaturated fats, including omega-3 and omega-6 PUFAs, were associated with a lower risk of all-cause mortality. Further, dietary fats were associated with substantial reductions in body fat and the TG:HDL ratio. Notably, our results extend beyond serum lipids and show that saturated and monounsaturated fats were associated with larger LDL particle sizes. Further, higher intakes of all dietary fats were associated with higher concentrations of larger protective HDL particles and lower concentrations of LDL and VLDL particles.

Contributors

LLM designed and supervised the analyses for this study. LLM and IY interpreted the results and wrote the manuscript. MRS and MY carried out the analyses, participated in interpreting the results, and reviewed and commented on all drafts of the manuscript. XZ reviewed and edited all drafts of the manuscript. All authors read and approved the final manuscript.

Declaration of interests

The authors have declared that no conflicts of interest exist.

Data sharing statement

Much of the de-identified Framingham data is available through the BIOLINCC repository: https://biolincc.nhlbi.nih.gov/studies/framoffspring/. Use of other data requires submission and approval of a research proposal to the Framingham executive committee.

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Table 1. Subject characteristics according to categories of weight-adjusted intakes of saturated fat

	Saturated fat intake (g/day)			
	<20 n=851 Mean (SE)	**20–<30** n=1014 Mean (SE)	**≥30** n=721 Mean (SE)	*P-value* †
Subject characteristics				
Age	58·4 (0·3)	55·9 (0·3)	53·2 (0·4)	<0·0001
Sex (N, % female)*	549 (64·5%)	587 (57·9%)	264 (36·6%)	<0·0001
Education (N, % >high school)*	510 (59·9%)	620 (61·1%)	478 (66·3%)	0·0236
Smoking (N, % current)*	113 (13·3%)	165 (16·3%)	136 (18·9%)	0·0390
Smoking (pack-years)	24·8 (0·9)	26·2 (0·9)	28·5 (1·0)	0·0326
BMI (kg/m^2)	28·4 (0·2)	26·5 (0·1)	26·3 (0·2)	<0·0001
Physical activity index (METs/hour)	14·6 (0·3)	14·9 (0·3)	14·4 (0·3)	0·52
HEI-2015 score	62·6 (0·4)	55·7 (0·3)	50·6 (0·4)	<0·0001
Alcohol (gram-eq/day, current)	9·2 (0·5)	9·5 (0·4)	9·2 (0·5)	0·85
Dietary composition				
Energy intake (kcals/day)	1553 (11·8)	1867 (10·6)	2322 (12·9)	<0·0001
Dairy (cup-eq/day)	1·0 (0·03)	1·3 (0·03)	1·8 (0·03)	<0·0001
Nuts & seeds (oz-eq/day)	0·3 (0·03)	0·5 (0·02)	0·7 (0·03)	<0·0001
Red meats (oz-eq/day)	1·7 (0·05)	2·3 (0·04)	3·0 (0·05)	<0·0001
High omega-3 fish (oz-eq/day)	0·3 (0·02)	0·2 (0·02)	0·2 (0·02)	0·0270
Fruit/vegetables (cup-eq/day)	3·2 (0·05)	3·1 (0·04)	3·0 (0·05)	0·0355
Fiber (g/day)	15·6 (0·2)	16·0 (0·2)	16·6 (0·2)	0·0042
Saturated fat (g/day)	15·5 (0·2)	24·8 (0·1)	37·8 (0·2)	<0·0001

All means are adjusted for age and sex. BMI=body mass index. Gram-eq=gram-equivalents. METs=metabolic equivalents. HEI=healthy eating index. *Column %. †P-values for continuous variables were generated from a generalized linear regression model and p-values for categorical variables from chi-square tests.

Table 2. Means of adiposity, inflammatory and glucose measures associated with weight-adjusted intakes of dietary fats

	Adiposity			Inflammation			Glucose	
		BMI (kg/m^2)	% Body Fat		Log(Interleukin 6) (pg/ml)	Log(Fibrinogen) (mg/dL)		Fasting Levels (mmol/L)
Fat intake	N	Mean (SE)	Mean (SE)	N	Mean (SE)	Mean (SE)	N	Mean (SE)
Saturated (g/day)								
<20	730	28·0 (0·18)	34·2 (0·27)	640	1·32 (0·02)	5·80 (0·01)	676	96·3 (0·39)
20–<30	888	26·5 (0·14)	32·3 (0·22)	803	1·33 (0·01)	5·79 (0·01)	869	96·4 (0·30)
≥30	604	26·5 (0·20)	32·3 (0·30)	578	1·31 (0·02)	5·77 (0·01)	603	96·8 (0·41)
P_{trend}		<0·0001	<0·0001		0·76	0·0235		0·44
Monounsaturated (g/day)								
<25	980	27·5 (0·15)	33·5 (0·23)	865	1·35 (0·01)	5·80 (0·01)	923	96·0 (0·31)
25–<35	777	26·6 (0·16)	32·5 (0·23)	712	1·30 (0·02)	5·79 (0·01)	760	96·9 (0·32)
≥35	465	26·7 (0·22)	32·5 (0·33)	444	1·32 (0·02)	5·77 (0·01)	465	96·8 (0·45)
P_{trend}		0·0013	0·0056		0·17	0·0439		0·13
Polyunsaturated (g/day)								
<12	714	27·5 (0·17)	33·6 (0·25)	627	1·35 (0·02)	5·78 (0·01)	665	96·6 (0·35)
12–<20	1080	26·7 (0·13)	32·6 (0·20)	997	1·31 (0·01)	5·79 (0·01)	1061	96·3 (0·27)
≥20	428	26·9 (0·22)	32·8 (0·33)	397	1·32 (0·02)	5·78 (0·01)	422	96·9 (0·44)
P_{trend}		0·0069	0·0375		0·11	0·98		0·82
Omega-3 PUFAs (g/day)								
<1·0	444	27·8 (0·21)	33·9 (0·32)	379	1·36 (0·02)	5·78 (0·01)	401	96·1 (0·45)
1·0–<2·0	1324	26·8 (0·12)	32·6 (0·18)	1216	1·32 (0·01)	5·79 (0·00)	1304	96·6 (0·24)
≥2·0	454	26·9 (0·21)	32·9 (0·31)	426	1·29 (0·02)	5·78 (0·01)	443	96·7 (0·42)
P_{trend}		0·0053	0·0271		0·0266	0·72		0·35
Omega-6 PUFAs (g/day)								
<10	605	27·6 (0·18)	33·7 (0·27)	527	1·36 (0·02)	5·79 (0·01)	561	96·4 (0·38)
10–<15	851	26·7 (0·15)	32·6 (0·22)	790	1·30 (0·01)	5·79 (0·01)	839	96·1 (0·30)
≥15	766	26·8 (0·16)	32·8 (0·24)	704	1·32 (0·02)	5·78 (0·01)	748	96·9 (0·33)
P_{trend}		0·0024	0·0374		0·22	0·30		0·29

Models were adjusted for age, sex, weight-adjusted carbohydrate intake, HEI 2015 scores, use of lipid-lowering medications, pack-years of cigarette smoking, and prevalent diabetes. Inflammatory biomarker models were additionally adjusted for baseline BMI. BMI=body mass index. PUFA=polyunsaturated fat. HEI=healthy eating index.

Table 3. Mean lipid levels according to weight-adjusted intakes of dietary fats

		HDL-C (mg/dL)	LDL-C (mg/dL)	Log (TG) (mg/dL)		TG:HDL ratio
Fat intake	N	Mean (SE)	Mean (SE)	Mean (SE)	N	Mean (SE)
Saturated (g/day)						
<20	626	49·8 (0·64)	128·2 (1·49)	4·81 (0·02)	619	3·14 (0·10)
20–<30	834	53·1 (0·48)	127·3 (1·12)	4·72 (0·02)	831	2·88 (0·07)
≥30	606	55·3 (0·65)	126·8 (1·50)	4·67 (0·02)	601	2·55 (0·10)
P_{trend}		<0·0001	0·57	0·0001		0·0001
Monounsaturated (g/day)						
<25	872	50·6 (0·52)	128·4 (1·19)	4·77 (0·02)	863	3·09 (0·08)
25–<35	728	53·2 (0·52)	126·8 (1·20)	4·73 (0·02)	726	2·86 (0·08)
≥35	466	56·1 (0·71)	126·8 (1·65)	4·65 (0·03)	462	2·43 (0·11)
P_{trend}		<0·0001	0·42	0·0003		<0·0001
Polyunsaturated (g/day)						
<12	643	51·6 (0·58)	128·6 (1·33)	4·77 (0·02)	635	2·95 (0·09)
12–<20	1014	52·7 (0·44)	126·6 (1·01)	4·73 (0·02)	1009	2·88 (0·07)
≥20	409	54·6 (0·72)	127·9 (1·66)	4·68 (0·03)	407	2·67 (0·11)
P_{trend}		0·0022	0·63	0·0105		0·08
Omega-3 PUFAs (g/day)						
<1·0	397	50·0 (0·72)	128·1 (1·67)	4·78 (0·03)	392	3·10 (0·11)
1·0–<2·0	1238	52·9 (0·40)	126·7 (0·92)	4·73 (0·01)	1230	2·85 (0·06)
≥2·0	431	54·8 (0·69)	128·9 (1·59)	4·69 (0·02)	429	2·67 (0·10)
P_{trend}		<0·0001	0·68	0·0153		0·0058
Omega-6 PUFAs (g/day)						
<10	544	51·7 (0·63)	128·1 (1·44)	4·77 (0·02)	538	2·93 (0·10)
10–<15	804	52·2 (0·49)	126·3 (1·14)	4·74 (0·02)	797	2·94 (0·08)
≥15	718	54·1 (0·54)	128·2 (1·25)	4·70 (0·02)	716	2·72 (0·08)
P_{trend}		0·0041	0·89	0·0160		0·09

Models were adjusted for age, sex, weight-adjusted carbohydrate intake, HEI 2015 scores, pack-years of cigarette smoking, and prevalent diabetes. TG=triglycerides. PUFA=polyunsaturated fats. HEI=Healthy Eating Index.

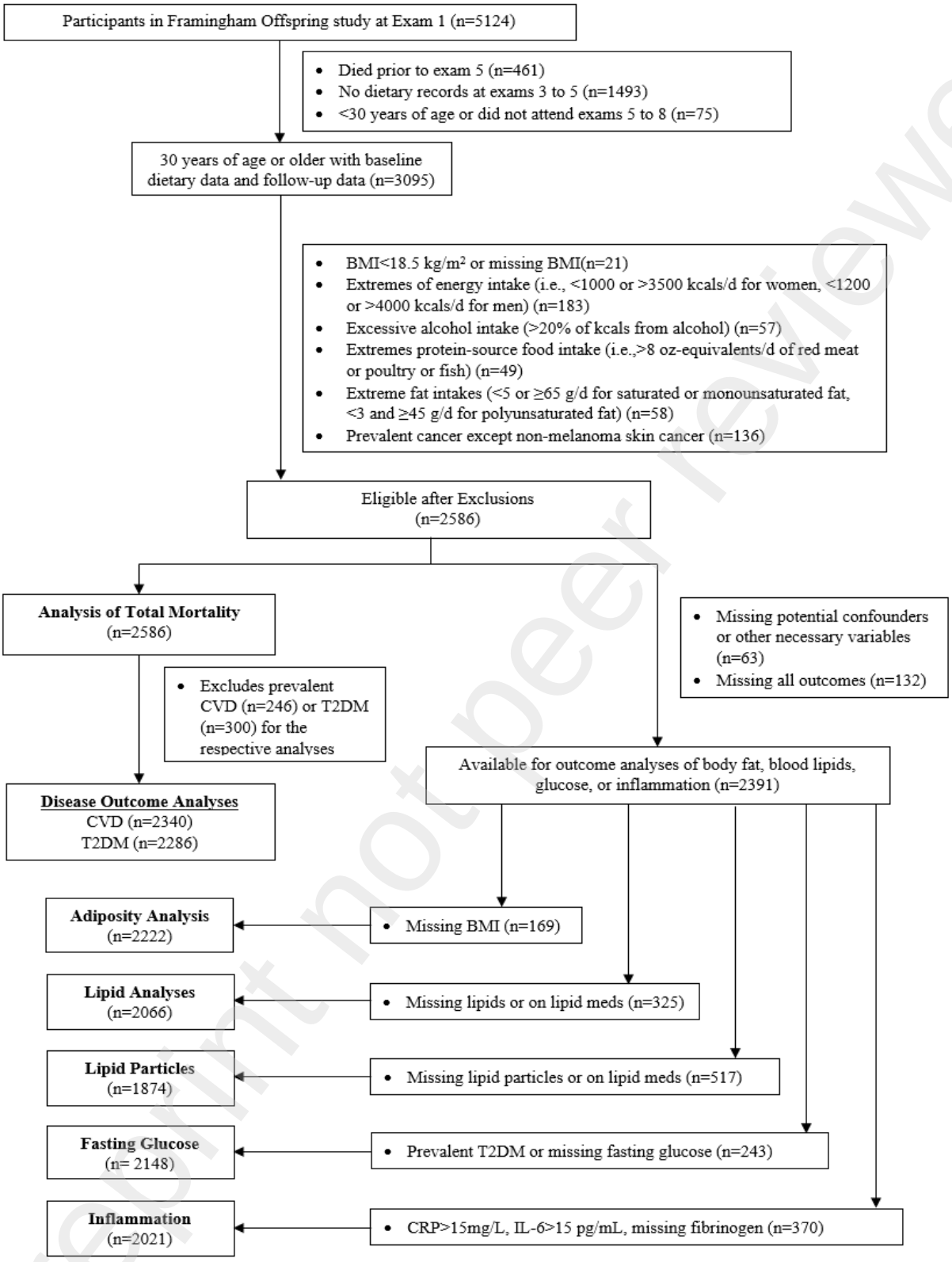

Figure 1. Flowchart of study participants

CVD=cardiovascular disease. BMI=body mass index. CRP=c-reactive protein. IL-6=interleukin-6.

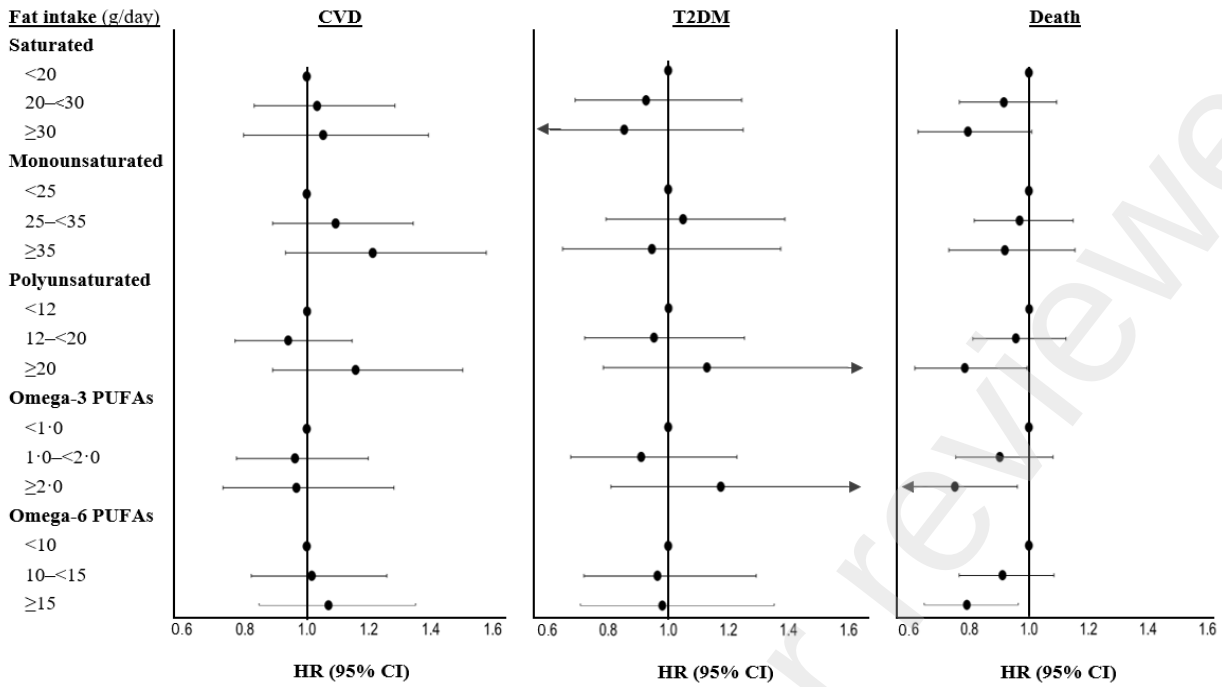

Figure 2. Hazard ratios (HR) for CVD, type 2 diabetes, and total mortality associated with weight-adjusted intakes of dietary fats
All models adjusted for age, sex, weight-adjusted carbohydrate intakes, HEI 2015 scores, use of lipid-lowering medications, pack years of cigarette smoking, and baseline BMI. CVD also adjusted for prevalent diabetes. Mortality also adjusted for prevalent diabetes and prevalent hypertension. CVD=cardiovascular disease. T2DM=type 2 diabetes mellitus. PUFA=polyunsaturated fat. HEI, healthy eating index. BMI=body mass index.

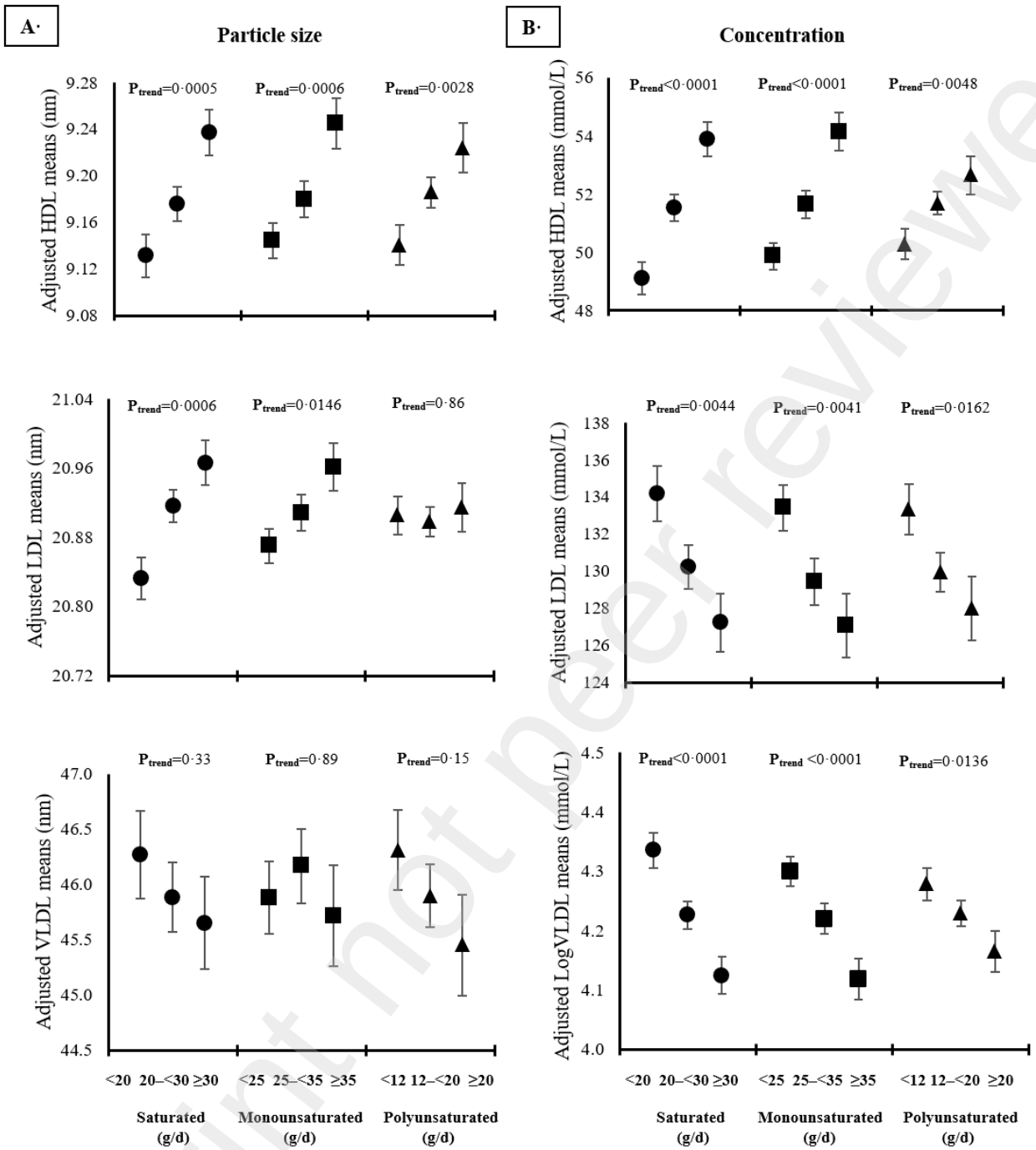

Figure 3. Cross-sectional associations between dietary fat intakes, lipid particle size (Panel A) and lipid concentrations (Panel B)
All models were adjusted for age, sex, weight-adjusted carbohydrate intakes, HEI 2015 scores, use of lipid-lowering medications, pack years of cigarette smoking, baseline BMI, and prevalent diabetes. The circle markers represent the intake categories of SFA, square markers represent the intake categories of MUFA, and triangle markers represent the PUFA intake categories. VLDL=very low density lipoprotein. Log=logarithmic transformed. TG=triglycerides. SFA=saturated fat intake. MUFA=monounsaturated fat. PUFA=polyunsaturated fat. HEI=healthy eating index. BMI=body mass index.