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Associations of Monounsaturated Fatty Acids from Plant and Animal Sources with Total and Cause-Specific Mortality in Two U.S. Prospective Cohort Studies

Marta Guasch-Ferré[1,2,*], **Geng Zong**[1,3,*], **Walter C. Willett**[1,2,4], **Peter L. Zock**[5], **Anne J Wanders**[5], **Frank B. Hu**[1,2,4], and **Qi Sun**[1,2]

[1]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA; [2]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA; [3]CAS Key Laboratory of Nutrition, Metabolism and Food Safety, Institute of Nutrition and Health, Shanghai Institutes for Biological Sciences, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai, 200031, China; [4]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA; [5]Unilever Research and Development, Vlaardingen, The Netherlands.

Abstract

Rationale: Dietary monounsaturated fatty acids (MUFAs) can come from both plant and animal sources with divergent nutrient profiles that may potentially obscure the associations of total MUFAs with chronic diseases.

Objective: To investigate the associations of *cis*-MUFA intake from plant (MUFA-P) and animal (MUFA-A) sources with total and cause-specific mortality.

Methods and Results: We followed 63,412 women from the Nurses' Health Study (1990–2012) and 29,966 men from the Health Professionals Follow-Up Study (1990–2012). MUFA-Ps and MUFA-As were calculated based on data collected through validated food frequency questionnaires administered every 4-years and updated food composition databases. During 1,896,864 person-years of follow-up, 20,672 deaths occurred. Total MUFAs and MUFA-Ps were inversely associated with total mortality after adjusting for potential confounders, whereas MUFA-

Address correspondence to: Dr. Qi Sun, Department of Nutrition, Harvard T.H. Chan School of Public Health, 665 Huntington Ave., Boston, MA 02115, USA, Tel: (617) 432-7490, qisun@hsph.harvard.edu.

*M.G-F. and G.Z. equally contributed to this work.

AUTHOR CONTRIBUTIONS

FBH and QS designed the study. MG and GZ analyzed data. MG and GZ wrote the first draft of the manuscript. All authors contributed to the interpretation of data, critical revision of the manuscript, and had final approval of the submitted and published version. MG, GZ and QS had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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DISCLOSURES

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As were associated with higher mortality. When MUFA-Ps were modeled to iso-calorically replace other macronutrients, hazard ratios [HRs, 95% confidence intervals (95%CIs)] of total mortality were 0.84 (0.77, 0.92;*P*<0.001) for replacing saturated fatty acids (SFAs; 5% of energy); 0.86 (0.82, 0.91;*P*<0.001) for replacing refined carbohydrates (5% energy); 0.91 (0.85, 0.97;*P*<0.001) for replacing *trans* fats (2% energy), and 0.77 (0.71, 0.82; *P*<0.001) for replacing MUFA-As (5% energy). For iso-calorically replacing MUFA-As with MUFA-Ps, HRs (95% CIs) were 0.74 (0.64, 0.86; *P*<0.001) for cardiovascular mortality; 0.73 (0.65, 0.82; *P*<0.001) for cancer mortality, and 0.82 (0.73, 0.91; *P*<0.001) for mortality due to other causes.

Conclusions: Higher intake of MUFA-Ps was associated with lower total mortality, and MUFA-As intake was associated with higher mortality. Significantly lower mortality risk was observed when SFAs, refined carbohydrates, or *trans* fats were replaced by MUFA-Ps, but not MUFA-As. These data suggest that other constituents in animal foods, such as SFAs, may confound the associations for MUFAs when they are primarily derived from animal products. More evidence is needed to elucidate the differential associations of MUFA-Ps and MUFA-As with mortality.

Subject Terms:

Cardiovascular Disease; Diabetes; Type 2; Diet and Nutrition; Epidemiology; Mortality/Survival

Keywords

Monounsaturated fatty acid; plant fat; animal fat; total mortality; cause-specific mortality; cardiovascular disease prevention; nutrition; epidemiology; diet

INTRODUCTION

According to the World Health Organization, of the 56.4 million deaths worldwide in 2015, more than half (54%) were due to 10 top causes.[1] Ischemic heart disease, stroke and cancer remain leading causes of deaths in the U.S. and several other developed countries.[1] Many premature deaths are preventable by adopting a healthy lifestyle, including smoking cessation, increasing physical activity, and improving diet quality.[1]

Recommendations by international organizations and the 2015 USDA Dietary Guidelines for Americans have emphasized the importance of the quality of dietary fat rather than the quantity of fat for the primary prevention of chronic diseases.[2] Specifically, the intake of plant oils and other fats from plant sources is encouraged while the intake of animal fats, and particularly those from red and processed meat and butter, is discouraged. Of the fatty acids rich in plant-based food sources, polyunsaturated fatty acids (PUFAs) were consistently associated with lower risk of cardiovascular disease (CVD) and mortality across observational studies and clinical trial,[3–6] but the impact of monounsaturated fatty acids (MUFAs) on chronic disease risk and especially mortality is less clear.[7,8]

Existing studies regarding MUFA intake and mortality risk have largely reported inconsistent findings.[3,5,9] One possible reason is that dietary MUFAs come from both plant and animal sources with divergent dietary components that may potentially obscure the associations for MUFAs and health outcomes. In a recent analysis, we found that MUFAs

from plant-based foods (MUFA-Ps) were associated with a lower risk of coronary heart disease (CHD), whereas the opposite was observed for MUFAs from animal products (MUFA-As), suggesting that food sources may play an important role in the relation between MUFAs and human health.[8] To our knowledge, potentially divergent associations of long-term intake of MUFA-Ps and MUFA-As with total and cause-specific mortality have never been evaluated. Moreover, no large cohort studies have examined the associations with cause-specific mortality when other nutrients are replaced by MUFAs from different sources.

In two large prospective cohorts of U.S. men and women, we examined the hypothesis that the intake of MUFA-Ps is associated with lower total and cause-specific mortality whereas MUFA-A intake is not. In addition, we estimated the risk of total and cause-specific mortality when substituting MUFAs for SFAs, refined carbohydrates, and *trans* fats, based on the current dietary guidelines that recommend replacing these nutrients with healthier alternatives.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study design and population.

The Nurses' Health Study (NHS) is a prospective cohort study of 121,700 female registered nurses aged 30–55 years at enrollment in 1976. The Health Professionals Follow-up Study (HPFS) is a prospective cohort study of 51,529 male health professionals aged 40–75 years at enrollment in 1986. In both cohorts, information about medical history, lifestyle, and health conditions has been collected by self-administered biennial questionnaires since baseline. Detailed information on the cohorts has been described in previous publications.[10–12]

For this analysis, we used 1990 as study baseline when olive oil consumption was first asked as part of a validated food frequency questionnaire (FFQ) administered in the cohorts. At baseline, 80,332 women and 38,842 men completed the FFQ. Participants were excluded if: they reported physician-diagnosed cancer, diabetes, or CVD at study baseline; reported implausible energy intake (<600 or >3,500 kcal/day in NHS, and <800 or >4,200 kcal/day in HPFS); had missing values for age; or they answered the baseline questionnaire only. The final analyses included 63,412 women and 29,966 men. The institutional review boards of Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health approved the study protocol. The return of a completed questionnaire was considered as informed consent.

Dietary assessment.

Dietary intake was measured using the FFQ with >130 items administered every 4 years to assess and update habitual diet. The questionnaire inquires how often, on average, participants had consumed specific foods, as well as the types of fats, oils, and brand or type of margarines used for cooking and added at the table in the preceding year. Nutrient intakes

were calculated based on the U.S. Department of Agriculture and Harvard University Food Composition Database, which is updated over time to reflect potential changes in the nutrient profile of food items and to incorporate new items[13]. We periodically analyzed the fatty acid composition of commonly consumed foods using gas chromatography during the follow-up period to account for changes in food processing. The nutrient database separated *trans* fats with one double bond from *cis* MUFAs, which are the main exposures of the present study. MUFA-As were the sum of MUFAs from animal foods, such as animal fats for cooking, dairy products, eggs, poultry, processed and unprocessed red meats, and fish; MUFA-Ps were calculated based on plant-based foods, such as plant-based cooking oils, salad dressing, margarines, bread and cereals, fruits, vegetables, legumes, nuts and seeds. For mixed food items, ingredients were identified according to manufacturer product labels or cookbooks for home-prepared items. We derived refined carbohydrates as the sum of added sugar and carbohydrates from refined grains (such as pasta, bread, white rice, pizza, and English muffins, among others).

The cumulative average of food intake from all available FFQs was calculated to better represent long-term diet and to minimize within-person variation.[14] To minimize the possibility of reverse causation bias, we stopped updating diet information after participants reported a diagnosis of stroke, heart disease, angina, diabetes, or cancer. We replaced missing values of MUFAs during follow-up with valid cumulative averages of prior assessments. Intakes of different dietary fats estimated by FFQs were validated at baseline and during follow-up.[12,15,16] In the most recent validation study of the NHS, de-attenuated Spearman rank correlation coefficients (r_s) of energy-adjusted nutrient data from FFQ and multiple 7-day dietary records were between 0.58 and 0.65 (both P<0.001) for total MUFAs and oleic acid, respectively.[17]

Ascertainment of deaths.

Deaths were identified through search of the vital records of states and of the National Death Index. This search was supplemented by reports from next of kin and postal authorities. Using these methods, we were able to ascertain >98% of the deaths in the cohorts.[18] A physician who was blinded to data on food consumption data and other risk factors reviewed death certificates, medical records, or autopsy reports to classify the cause of deaths according to the eighth and ninth revisions of the *International Classification of Diseases*. Deaths were grouped into 5 major groups (CVD, cancer, respiratory disease, neurodegenerative disease and all other causes, including suicide, injury, infections, diabetes, kidney disease, and etc.) (Online Table I).

Statistical analysis.

Because the consumption of MUFA-Ps and MUFA-As changed during follow-up,[8] we presented participants' characteristics according to MUFA quintiles and the correlations among dietary fats at the mid-point of follow-up in 2002. Macronutrients were analyzed as percentages of energy by dividing the energy from specific macronutrients by total energy intake. We calculated each individual's person-time from the return date of baseline questionnaire to the date of death, or the end of follow-up (June 2012 in NHS and January 2012 in HPFS), whichever came first. We used Cox proportional hazards regression models

to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs) of total and cause-specific mortality in each cohort with follow-up duration as the timescale. Multivariate models were stratified jointly by age in months and calendar year to better control for confounding by age, calendar time, and any possible two-way interactions between them. Multivariate models were adjusted for covariates that were updated in follow-up questionnaires. The following covariates were considered: ethnicity, smoking status, alcohol intake, family history of myocardial infarction, family history of diabetes, family history of cancer, menopausal status and post-menopausal hormone use (NHS only), physical activity, current aspirin use, multivitamin use, baseline hypertension, baseline hypercholesterolemia, body mass index (BMI), calorie intake, energy from *trans* fats, energy from SFAs, fruit and vegetables, and coffee intake (in quintiles). When modeling MUFA-Ps, we further included MUFA-As as a covariate, and vice versa. We calculated *P* values for trend with the use of the Wald test of a score variable based on the median of MUFAs in each category as a continuous variable. The proportional hazards assumption was tested by fitting a model that included interaction terms between MUFAs and duration of follow-up and by using a likelihood ratio test to examine the significance of the interaction terms. The assumption was unlikely to be violated ($P > 0.05$ for all tests).

We estimated the risk of total and cause-specific mortality when energy from SFAs was replaced by MUFA-Ps in an isocaloric energy density model that included total energy, energy from carbohydrates, energy from protein and energy from other fats (PUFAs, *trans* fats and MUFA-As). By leaving SFAs out of the model, regression coefficients for MUFA-Ps can be interpreted as the estimated effect of iso-calorically substituting MUFA-Ps for SFAs while holding other fats and total energy constant. Similar isocaloric substitution analyses were conducted for MUFA-As and for substituting MUFA fractions for *trans* fats and refined carbohydrates. In light of strong correlations of SFAs and MUFA-As and of PUFAs and MUFA-Ps, we further conducted substitution analyses replacing SFAs+MUFA-As with PUFAs+MUFA-Ps.

We performed sensitivity analyses to examine the robustness of findings by: 1) continuing updating diet after the diagnosis of intermediate outcomes; and 2) further adjusting for modified Alternate Healthy Eating Index (AHEI), to explore whether findings may be explained by underlying dietary pattern. Analyses were conducted in the two cohorts separately, and then results were pooled with the use of an inverse variance–weighted meta-analysis using a fixed-effect model. Analyses were performed with the SAS statistical package (version 9.4, SAS Institute). Statistical tests were 2 sided, and *P* values of <0.05 were considered to indicate statistical significance.

RESULTS

During 22 years of follow-up, we documented 20,672 deaths (12,774 in NHS and 7,898 in HPFS) in 1,896,864 person-years. Participants' characteristics according to MUFA-P and MUFA-A quintiles at the midpoint of follow-up (2002) are shown in Table 1. Compared with participants with lower MUFA-P intake, those in the highest quintile were younger, less likely to have hypertension, more likely to take aspirin and multivitamins, and had a higher AHEI score. Participants with higher MUFA-A intake, were younger, more likely to smoke,

and less likely to exercise. They also had higher BMI, a lower intake of fruits and vegetables, and a lower AHEI score (Table 1).

Major MUFA-P sources included olive oil, nuts, salad dressing, fried foods, baked products (chocolate chip cookies and homemade/ready-made pie), margarine, milk chocolate, and avocado.[8] MUFA-As came mainly from red (beef and pork) and processed meats (41–42%), dairy products, butter, poultry, eggs, and fish. In both cohorts, mean percentage of energy from MUFA-Ps increased from 5.8–6.3% to 7.9% during the follow-up, whereas MUFA-As decreased from 5.4–5.5% to 4.2–4.4%[8].

Intakes of MUFA-Ps and MUFA-As were weakly, inversely correlated (r =−0.07 for NHS and −0.10 HPFS). MUFA-Ps were positively correlated with total PUFAs and n-6 PUFAs (r≥0.59, P<0.001). MUFA-As were weakly correlated with total PUFAs and n-6 PUFAs (r≤0.16, P<0.001). SFA intake was strongly correlated with MUFA-As (r≥0.82, P<0.001) (Online Table II).

Age-adjusted and multivariate-adjusted analyses showed a consistent, significant, inverse association between MUFA-Ps and total mortality, and a positive association between MUFA-As and total mortality (Table 2). The pooled multivariate-adjusted HRs (95% CIs) for participants in the highest quintile of MUFA-Ps and MUFA-As, as compared with those in the lowest quintile, were: 0.84 [0.80, 0.89; P_{trend} < 0.001] and 1.16 [1.08, 1.24; P_{trend} < 0.001], respectively (Table 2). In the model without SFAs, total MUFAs were not associated with total mortality. After adjustment for SFAs, which were highly correlated with MUFA-As, the HR (95%CI) of total mortality comparing extreme quintiles of total MUFAs was significant at 0.84 (0.79, 0.89; P_{trend}<0.001).

MUFA-Ps were associated with significantly lower cardiovascular and cancer mortality after multivariate adjustments of covariates, although these associations were attenuated to non-significant when further adjusting for intake of MUFA-As and SFAs. In contrast, MUFA-As were associated with 16% and 29% higher risk of cardiovascular and cancer mortality, respectively, after adjustment for covariates and MUFA-Ps (Table 2). MUFA-Ps were inversely associated with mortality due to other causes while MUFA-As were not associated to these deaths after mutual adjustments. Cohort-specific HRs and 95% CIs of total and cause-specific mortality according to MUFA intake are presented in Online Table III. Furthermore, we observed inverse associations between MUFA-Ps and neurodegenerative and respiratory deaths (Online Table IV). After adjusting for potential confounders including MUFA-As, the HRs (95% CIs) comparing extreme quintiles of MUFA-Ps were 0.75 (0.63, 0.89, P_{trend} <0.001) for neurodegenerative disease mortality and 0.65 (0.54, 0.78, P_{trend} <0.001) for respiratory disease mortality.

Figure 1 shows the pooled substitution analyses for total, CVD, cancer and non-CVD and non-cancer deaths. For MUFA-Ps, pooled HRs (95% CIs) of total mortality were 0.84 (0.77, 0.92; P_{trend} <0.001) when replacing 5% energy of SFAs; 0.86 (0.82, 0.91; P_{trend} <0.01) when replacing 5% energy of refined carbohydrates; and 0.91 (0.85, 0.97; P_{trend} =0.003) when replacing 2% energy of *trans* fats. The relative risk of total mortality was 20% lower when 5% energy from MUFA-Ps iso-calorically replaced SFAs and MUFA-As (0.80 [0.77, 0.84];

P_{trend} <0.001). A 15% to 27% lower risk of CVD, cancer and other deaths was observed when replacing MUFA-As or SFAs+MUFA-As with MUFA-Ps. Substituting MUFA-Ps for other nutrients was not significantly associated with CVD and cancer mortality. Cohort-specific and pooled HRs and 95% CIs for substitution analysis are shown in Online Table V.

The results for the substitution models remained largely unchanged when we continuously updated the diet regardless of the development of intermediate outcomes **(**Online Table VI) or when the models were adjusted for the AHEI score (Online Table VII).

DISCUSSION

In the present prospective investigation among men and women in two large U.S. cohorts, we observed that the association of MUFA intake with mortality was determined by food sources of these fatty acids. Higher intake of MUFA-Ps was associated with lower total mortality, whereas the opposite was true for higher intake of MUFA-As. Moreover, total mortality was 14–28% lower when SFAs, refined carbohydrates, or *trans* fats were isocalorically replaced by MUFA-Ps. Substituting MUFA-Ps for MUFA-As and SFAs combined was also associated with lower total and cause-specific mortality. To our knowledge, this is the first prospective study that examined MUFAs from plant and animal sources separately in relation to total and cause-specific mortality.

Previous data on the association between MUFA intake and mortality have been inconsistent. In some studies, non-significant associations were observed, while others showed positive associations.[3,9,19] In a recent meta-analysis of 17 prospective cohort studies, *Schwingshackl et al.* found that MUFA intake was associated with 11% lower risk of all-cause mortality and 12% lower risk of CVD mortality.[9] However, substantial between-study heterogeneity was observed, partly due to the inconsistent adjustment of covariates among individual studies.[9] The other possible reason might be that MUFAs have diverse food sources, some of which may contain high amounts of unhealthful nutrients, such as SFAs or cholesterol in meats, dairy products, and partially hydrogenated oils, that may confound the associations for total MUFAs. In the NHS and HPFS, in the earlier FFQ, total MUFAs were strongly correlated with SFAs (r=0.8), which have been associated with higher mortality in previous analyses.[5] Strong correlations of MUFAs with SFAs could likely explain the lack of associations observed between MUFAs and all-cause mortality when SFAs were not included in the model.

Our study findings generated novel evidence suggesting that MUFAs from plant and animal sources are differentially associated with total and cause-specific mortality. Existing studies that addressed MUFAs from different food sources in relation to mortality are sparse. In an ecological study from the Seven Countries Study, all-cause mortality rates were inversely correlated with the ratios of MUFAs/SFAs and (MUFAs + PUFAs)/(SFAs + trans fats), as well as vegetable oils,[20] but this study did not explicitly examined MUFA-As and MUFA-Ps. In contrast, evidence is abundant for some major food sources of MUFAs. In our cohorts, olive oil, nuts, salad dressing, and fried foods were major sources of MUFA-Ps, while red and processed meats, dairy products, butter and poultry were leading contributors of MUFA-As.[8] The meta-analysis by *Schwingshackl et al.* showed that higher intake of olive oil was

associated with a 23% lower risk of all-cause mortality.[9] In addition, higher intake of nuts was associated with a lower risk of all-cause and cause specific mortality in the NHS and HPFS cohorts[21] and in a meta-analysis that included twenty prospective cohort studies.[22] Specifically, this meta-analysis showed that per 28 g increase in nut consumption was associated with 22% (95% CI: 16%−28%) lower risk of all-cause mortality risk. In contrast, higher intake of red meat and processed meat has been associated with higher risk of mortality in prospective cohort studies.[23,24]

Specification of an explicit comparison is the cornerstone of isocaloric nutritional substitution analysis, which evaluates the effects of adding or subtracting a calorie-bearing macronutrient by changing intake of other macronutrients correspondingly while holding the total energy intake constant. In the NHS and HPFS cohorts, we previously reported that replacing 5% of energy from SFAs with equivalent energy from PUFAs and MUFAs was associated with 27% and 13% lower total mortality, respectively.[5] In addition, the risk of CHD was significantly lower when SFAs, refined carbohydrates, or *trans* fats were isocalorically replaced by MUFA-Ps but not MUFA-As in our recent analysis.[8] Findings from the present analysis also showed significantly lower CVD mortality when MUFA-Ps replaced MUFA-As and MUFA-As+SFAs, but not SFAs or refined carbohydrates.

Moreover, we also observed lower mortality of cancer, and non-CVD and non-cancer causes when MUFA-Ps replaced MUFA-As and MUFA-As+SFAs. Existing data on specific types of dietary fats and non-CVD mortality are sparse. One prospective study showed an inverse association between MUFAs and breast cancer incidence in women aged 50 years or more, while other studies reported non-significant associations.[25] Some studies have suggested that olive oil could be beneficial in the prevention of certain cancers, such as breast cancer.[26] The consumption of nuts, an important source of MUFAs, has also been inversely related with the incidence of colorectal cancer, endometrial cancer, pancreatic cancer, and total cancer.[27] Nut consumption was not associated with a lower risk of prostate cancer incidence and mortality,[27,28] although frequent nut consumption was associated with better survival among prostate cancer patients.[28] In addition, several lines of evidence suggested that high intakes of MUFAs and PUFAs were associated with slower cognitive decline.[29] An analysis in the Rotterdam Study that prospectively followed 5289 participants ≥55 years old showed that the intakes of total fats, *cis*-MUFAs and PUFAs were significantly associated with a lower risk of Parkinson disease.[30]

The cardiovascular effects of different fatty acids have been extensively examined. Results from clinical trials showed that higher MUFA intake improves blood lipid profile,[31] decreases blood pressure,[32] and modulates insulin resistance and glycemic control.[33] In a meta-analysis of RCTs comparing high- versus low-MUFA diets in patients with abnormal glucose metabolism, high MUFA intake was associated with lower HbA1c but other parameters of insulin resistance were unaffected.[32] However, whether these effects can be entirely ascribed to MUFA-Ps deserves further investigations. Nevertheless, controlled feeding studies that examined vegetable oils rich in MUFAs, including olive oil, high-oleic-acid sunflower oil, high-oleic acid canola oil and nuts, have consistently demonstrated beneficial effects of higher intake of these oils on reducing cardiovascular risk.[6,33,34] These findings may underlie the associations that we observed between MUFA-P intake and

mortality risk. The observed inverse associations between plant food sources of MUFAs and mortality can also be explained by the potential synergic effects with other bioactive components such as polyphenols, dietary fiber, vitamins and minerals.[35,36] Meanwhile, recent clinical trials comparing vegetable oils that differed in the composition of fatty acids only showed that MUFAs significantly improved blood lipid profile and reduced central obesity, independent of the other components in the vegetable oils.[37–39]

Observational studies have suggested that higher consumption of red meat and processed meat, sources of MUFA-As and SFAs, is associated with a higher risk of developing type 2 diabetes,[40] CVD,[41] and certain cancers.[42,43] In addition, many controlled feeding studies have shown that dietary cholesterol and SFAs increase total and LDL concentrations, especially when compared with unsaturated fatty acids.[34] Because dietary *cis*-MUFAs, including those from animal sources, are mostly oleic acid, the positive associations of MUFA-As with total and CVD mortality are likely explained by confounding of other components in animal foods, especially SFAs. Importantly, our results indicated that replacement of the combination of MUFA-As and SFAs by MUFA-Ps was significantly associated with lower risk of total, CVD, cancer and non-CVD and non-cancer mortality. Given that MUFA-As and SFAs cannot be easily separated in the diet, they shall be replaced together by MUFAs from plant foods as a preferable source of fats.

Even though the intake of *cis*-MUFAs has been associated with beneficial effects on health, there are still no consistent dietary recommendations regarding MUFAs. However, most dietary guidelines recommend higher intake of healthy plant foods, including mainly unsaturated vegetable oils, nuts and seeds, which are high in MUFAs and PUFAs, and lower intake of animal foods to prevent chronic diseases[2]. Our results provide further epidemiological evidence supporting the recommendation of increasing the intake of unsaturated fats from plant-based food sources instead of fats from animal food sources, as well as replacing SFAs with unsaturated fatty acids. This evidence may also assist individuals in identifying healthy dietary choices for reducing animal fat intake.

The present study has several strengths including using data from two large, longitudinal cohorts with long follow-up and repeated measurements of diet. As in any observational study, the possibility of residual or unmeasured confounding cannot be excluded. Although we adjusted for many dietary factors in our analysis, confounding by other dietary components in the same food sources of MUFAs cannot be fully ruled out. In addition, synergistic effects of MUFAs with other nutrients are also possible,[8] although a larger sample size is needed to examine such interactions. Our study population was relatively homogeneous (predominantly Caucasian health professionals), and thus caution shall be exercised when extrapolating our findings to other populations with different demographic characteristics. However, there is no reason to believe that the biological mechanisms would differ in other populations. We cannot entirely rule out reverse causation bias, because people with chronic diseases might change their habitual diet. However, we excluded participants with known major chronic diseases at baseline, used cumulative averages of diet to reduce short-term variability, and stopped updating diet after the development of certain major chronic diseases.

In conclusion, we found divergent associations between MUFA-Ps and MUFA-As with total and cause-specific mortality. Higher MUFA-P intake was associated with lower mortality whereas MUFA-A intake was associated with higher mortality. Significantly lower mortality was observed when SFAs, *trans* fats, or refined carbohydrates were replaced by MUFA-Ps. Overall, these data support current dietary recommendations to replace animal fats with unsaturated plant oils for the prevention of chronic diseases and premature deaths.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Nonstandard Abbreviations and Acronyms:

AHEI	Alternate Healthy Eating Index
CHD	coronary heart disease
CI	confidence interval
CVD	cardiovascular disease
FFQ	food frequency questionnaire
HPFS	Health Professionals Follow-up Study
HR	hazard ratio
MUFA	monounsaturated fatty acids
MUFA-As	monounsaturated fatty acids from animal sources
MUFA-Ps	monounsaturated fatty acids from plant sources
NHS	Nurses' Health Study
PUFA	polyunsaturated fatty acids
SFA	saturated fatty acids

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NOVELTY AND SIGNIFICANCE

What Is Known?

- Existing studies regarding monounsaturated fatty acid (MUFA) intake and mortality risk have reported inconsistent findings.
- MUFAs share animal foods as major dietary sources with saturated fatty acids (SFAs), cholesterol and other constituents, therefore the expected benefits of MUFAs could be masked in observational studies.

What New Information Does This Article Contribute?

- Total and plant MUFAs were associated with lower mortality risk, whereas MUFA-As were associated with higher risk.
- Replacing saturated fats, refined carbohydrates, trans fats, or MUFA-As with MUFA-Ps was associated with lower mortaltity risk.

In this study we report that MUFAs from animal and plant sources are largely different with respect to their associations with the risk of mortality. These data support current dietary recommendations to replace animal fats with unsaturated plant oils for the prevention of chronic diseases and premature deaths.

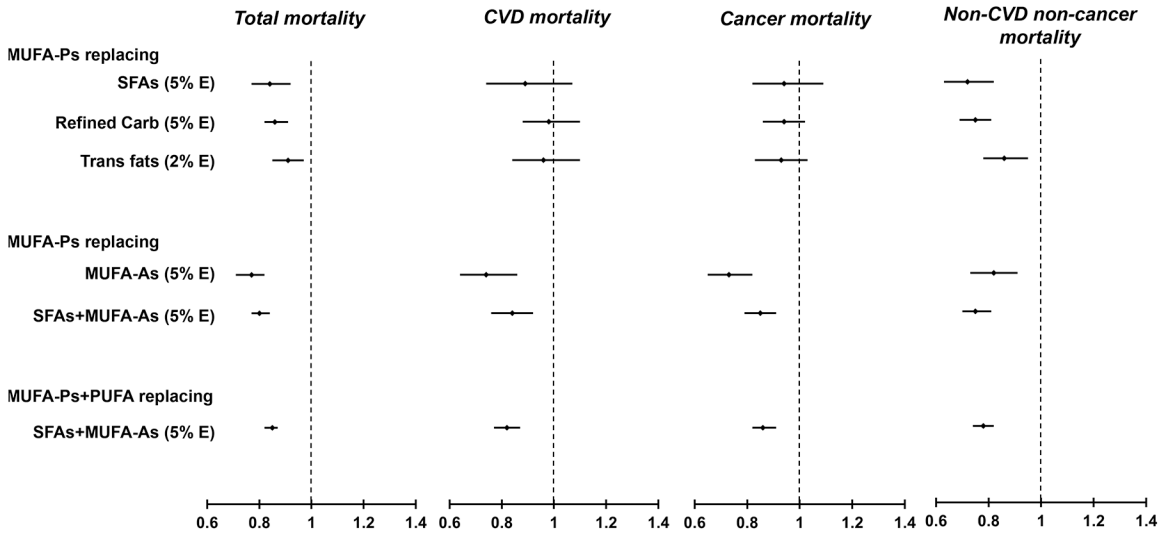

Figure 1. Risk of total and cause-specific mortality for substitution analysis replacing other nutrients with MUFAs

Abbreviations: MUFA, monounsaturated fatty acids; MUFA-P, MUFA from plant sources; MUFA-A, MUFA from animal sources; NHS, Nurses' Health Study; HPFS, Health Professional's Follow-up Study; SFA, saturated fatty acids.

Hazard ratios were adjusted for age, ethnicity (Caucasian, and other ethnicity), smoking status (never, former, current (1–14, 15–24, or ≥25 cigarettes/day, alcohol intake (grams/day: 0, 0.1–4.9, 5.0–14.9, and >15.0 in women, 0, 0.1–4.9, 5.0–29.9, and >30.0 in men), family history of myocardial infarction (yes/no), family history of diabetes (yes/no), family history of cancer (yes/no), menopausal status and post-menopausal hormone use (pre-menopause, post-menopause (never, former, or current hormone use), for women), physical activity (<3, 3.0–8.9, 9.0–17.9, 18.0–26.9, ≥27.0 METs/week), current aspirin use (yes/no), multivitamin use (yes/no), baseline hypertension, baseline hypercholesterolemia, BMI (<23, 23–24.9, 25–29.9, 30–34.9, >35kg/m^2), intakes of total energy, fruits and vegetables and coffee intake (in quintiles); For refined carbohydrate substitution, models were further adjusted for energy from protein, whole grain carbohydrates, *trans* fats, PUFAs, and SFAs; For *trans* fats substitution, models were further adjusted for total fats, PUFAs, and SFAs; For SFA substitution, models were further adjusted for total fats, *trans* fats, and PUFAs; All MUFA-Ps models were further adjusted for MUFA-As, and vice versa.

† Study estimates from two cohorts were pooled using a fixed effects model.

Table 1.

Age-standardized characteristics according to MUFA intake at the mid-point of follow-up (2002)

	NHS			HPFS		
Variable *	MUFA-P					
	Q1	Q3	Q5	Q1	Q3	Q5
	12007	12008	12007	5497	5497	5497
Total MUFAs,% energy	9.4±2.0	11.6±1.6	14.4±2.1	9.8±2.3	12.0±1.8	14.4±2.1
MUFA-Ps,% energy	3.7±0.6	5.9±0.3	9.2±1.7	4.0±0.7	6.2±0.3	9.2±1.5
MUFA-As,% energy	5.4±1.8	5.5±1.5	4.9±1.5	5.6±2.1	5.6±1.8	5.0±1.7
Age, years	68.9±7.1	67.4±7.1	67.0±6.9	68.4±9.0	66.9±8.9	67.7±8.7
Caucasian, %	97	98	98	94	96	97
Alcohol intake, g/day	5.7±11.5	5.6±10.1	7.2±11.2	13.3±17.5	12.5±15.6	12.4±16.0
Current smoking, %	8	8	8	4	4	4
Physical activity, METs/week	18.4±24.4	16.7±20.9	18.1±21.4	35.7±40.9	34.9±41.7	35.5±40.1
BMI, kg/m^2	26.7±5.4	26.6±5.3	26.1±5.1	23.4±8.8	24.2±7.9	23.9±7.9
Hypertension at midpoint (2002)	55	53	49	48	45	42
Hypercholesterolemia at midpoint (2002)	63	63	63	53	55	53
Family history of myocardial infarction, %	38	38	37	33	31	32
Family history of diabetes, %	25	25	24	21	21	20
Family history of cancer, %	44	46	45	27	27	28
Multivitamin use,%	60	62	62	55	58	57
Current use of Aspirin, %	32	34	34	45	48	47
Any use of postmenopausal hormone, %	67	71	72			
Total energy, kcal	1614±423	1757±441	1811±470	1843±506	2010±534	2095±572
Total fats,% energy	24.3±4.9	28.9±4.2	32.9±4.8	24.8±5.6	29.5±4.6	33.3±4.9
PUFAs,% energy	4.6±0.8	5.7±0.9	6.6±1.4	4.7±0.9	5.8±0.9	6.9±1.4
n-3 PUFAs,% energy	0.6±0.2	0.6±0.1	0.7±0.2	0.6±0.2	0.7±0.2	0.7±0.3
n-6 PUFAs,% energy	3.9±0.7	5.0±0.8	5.8±1.3	4.1±1.0	5.2±1.0	6.2±1.6
SFAs,% energy	9.1±2.5	10.1±2.1	10.3±2.3	9.0±2.7	10.0±2.3	10.3±2.3

	NHS			HPFS		
Trans fats,% energy	1.2±0.3	1.6±0.4	1.7±0.6	1.2±0.4	1.6±0.5	1.8±0.7
Proteins,% energy	19.4±3.0	17.9±2.4	16.8±2.4	19.1±3.1	17.7±2.4	16.5±2.4
Fruit and vegetables, serving/day	5.9±2.4	5.5±2.2	5.6±2.3	6.3±2.9	5.9±2.5	5.8±2.6
Coffee intake, servings/day	2.0±1.4	2.2±1.4	2.2±1.5	1.8±1.6	1.9±1.5	1.9±1.6
Modified AHEI [†]	31.6±7.1	31.3±7.0	34.6±7.5	31.6±8.3	30.9±7.7	34.0±8.2
	MUFA-A					
	Q1	**Q3**	**Q5**	**Q1**	**Q3**	**Q5**
N	12007	12007	12007	5497	5497	5497
Total MUFAs,% energy	9.9±2.5	11.6±1.9	13.7±1.9	9.8±2.5	12.0±1.8	14.3±1.8
MUFA-Ps,% energy	6.5±2.5	6.2±1.9	5.8±1.8	6.7±2.4	6.5±1.8	6.0±1.6
MUFA-As,% energy	3.2±0.7	5.3±0.2	7.6±1.0	3.0±0.8	5.4±0.3	8.2±1.1
Age, years	69.4±7.1	67.5±7.1	66.4±6.9	68.1±9.0	67.4±9.0	67.3±8.8
Caucasian, %	97	98	98	95	96	96
Alcohol intake, g/day	6.2±10.8	6.3±10.8	5.4±10.2	12.2±16.2	13.4±16.8	11.2±14.7
Current smoking, %	4	7	13	1	4	6
Physical activity, METs/week	23.3±26.0	17.1±22.2	13.3±18.4	42.7±45.4	33.9±38.7	30.7±41.5
BMI, kg/m^2	25.0±4.5	26.6±5.0	27.8±5.9	22.9±7.2	24.4±7.6	24.2±9.3
Hypertension at midpoint (2002)	48	53	56	41	44	47
Hypercholesterolemia at midpoint (2002)	67	64	58	57	54	48
Family history of myocardial infarction, %	38	38	36	35	31	28
Family history of diabetes, %	24	24	26	20	21	21
Family history of cancer, %	45	46	45	27	28	28
Multivitamin use,%	68	63	53	63	58	49
Current use of Aspirin, %	35	35	31	51	48	43
Any use of postmenopausal hormone, %	72	71	65			
Total energy, kcal	1714±444	1754±445	1729±476	1923±526	1997±540	2057±590
Total fats,% energy	23.7±4.6	28.7±3.8	33.9±4.2	23.6±5.0	29.3±3.8	35.0±4.1
PUFAs,% energy	5.4±1.3	5.7±1.2	5.8±1.2	5.6±1.4	5.8±1.1	6.0±1.2
n-3 PUFAs,% energy	0.6±0.2	0.6±0.2	0.6±0.2	0.7±0.2	0.7±0.2	0.6±0.2

	NHS			HPFS		
n-6 PUFAs,% energy	4.7±1.2	5.0±1.1	5.1±1.1	5.0±1.5	5.2±1.3	5.2±1.3
SFAs,% energy	7.3±1.4	9.8±1.2	12.6±1.8	7.0±1.5	9.9±1.3	12.8±1.8
Trans fats,% energy	1.2±0.4	1.5±0.4	1.8±0.5	1.2±0.5	1.6±0.5	1.9±0.5
Proteins,% energy	17.2±2.7	18.0±2.6	18.9±2.7	16.9±2.7	17.6±2.6	18.8±2.7
Fruit and vegetables, serving/day	6.7±2.6	5.6±2.1	4.7±2.0	7.3±3.0	5.8±2.4	4.9±2.1
Coffee intake, serving/day	1.9±1.4	2.2±1.4	2.3±1.5	1.6±1.4	1.9±1.5	2.2±1.7
Modified AHEI[†]	36.7±7.0	31.9±6.5	28.7±6.7	38.3±7.4	31.0±7.0	26.8±6.7

Abbreviations: NHS, Nurses' Health Study; HPFS, Health Professional's Follow-up Study; MUFA, monounsaturated fat; MUFA-P, MUFAs from plant sources; MUFA-A, MUFAs from animal sources; MET, metabolic equivalent task; BMI, body mass index; AHEI, alternative health eating index; SFA, saturated fatty acids; PUFA, polyunsaturated fatty acids.

[*] Values are means (SD) or percentages and are standardized to the age distribution of the study population.

[†] Modified by excluding fat components.

Table 2.

Hazard Ratios (95% CIs) of total and cause-specific mortality according to MUFA intake in NHS and HPFS pooled

		Quintiles of MUFA intake (% energy)					
		Q1	**Q2**	**Q3**	**Q4**	**Q5**	***P* for trend**
Total mortality							
	Cases/person-years	4574/379071	4037/379760	3939/379654	4030/379389	4092/378630	
Total MUFAs	Model 1	1	0.99 (0.95, 1.03)	1.06 (1.01, 1.10)	1.13 (1.08, 1.18)	1.21 (1.16, 1.27)	<0.001
	Model 2	1	0.99 (0.95, 1.04)	1.01 (0.97, 1.06)	1.04 (0.99, 1.09)	1.00 (0.95, 1.06)	0.50
	Model 3	1	0.93 (0.89, 0.98)	0.92 (0.88, 0.97)	0.91 (0.87, 0.96)	0.84 (0.79, 0.89)	<0.001
	Cases/person-years	5327/377503	4334/379286	3808/379871	3752/379897	3451/380306	
MUFA-Ps	Model 1	1	0.89 (0.85, 0.92)	0.83 (0.79, 0.86)	0.83 (0.79, 0.86)	0.77 (0.73, 0.80)	<0.001
	Model 2	1	0.94 (0.90, 0.98)	0.88 (0.84, 0.92)	0.86 (0.82, 0.90)	0.79 (0.76, 0.83)	<0.001
	Model 3	1	0.95 (0.91, 1.00)	0.90 (0.86, 0.95)	0.90 (0.86, 0.94)	0.84 (0.80, 0.89)	<0.001
	Cases/person-years	3873/379974	3812/379939	3940/379823	4139/379262	4908/377885	
MUFA-As	Model 1	1	1.10 (1.05, 1.15)	1.20 (1.15, 1.26)	1.35 (1.29, 1.41)	1.67 (1.60, 1.75)	<0.001
	Model 2	1	1.10 (1.05, 1.15)	1.15 (1.10, 1.21)	1.21 (1.16, 1.27)	1.32 (1.26, 1.39)	<0.001
	Model 3	1	1.05 (1.00, 1.11)	1.08 (1.03, 1.14)	1.11 (1.05, 1.18)	1.16 (1.08, 1.24)	<0.001
Cardiovascular mortality							
	Cases/person-years	1033/379071	885/379760	887/379654	889/379389	894/378630	
Total MUFAs	Model 1	1	0.97 (0.88, 1.06)	1.09 (0.99, 1.19)	1.10 (1.01, 1.21)	1.22 (1.12, 1.34)	<0.001
	Model 2	1	1.01 (0.92, 1.11)	1.12 (1.01, 1.24)	1.15 (1.04, 1.28)	1.16 (1.04, 1.30)	<0.01
	Model 3	1	0.94 (0.85, 1.04)	1.01 (0.91, 1.12)	1.00 (0.89, 1.13)	0.96 (0.84, 1.09)	0.79
	Cases/person-years	1129/377503	955/379286	831/379823	780/379897	793/380306	
MUFA-Ps	Model 1	1	0.87 (0.79, 0.94)	0.82 (0.75, 0.90)	0.77 (0.70, 0.84)	0.79 (0.72, 0.87)	<0.001
	Model 2	1	0.94 (0.86, 1.02)	0.91 (0.83, 1.00)	0.85 (0.77, 0.94)	0.89 (0.80, 0.99)	<0.01
	Model 3	1	0.96 (0.88, 1.05)	0.94 (0.85, 1.04)	0.89 (0.81, 0.99)	0.96 (0.86, 1.07)	0.31
	Cases/person-years	886/379974	831/379286	877/379823	930/379262	1064/377885	
MUFA-As	Model 1	1	1.07 (0.97, 1.18)	1.19 (1.08, 1.31)	1.37 (1.24, 1.50)	1.62 (1.48, 1.78)	<0.001

			Quintiles of MUFA intake (% energy)					
			Q1	Q2	Q3	Q4	Q5	*P* for trend
	Model 2		1	1.04 (0.94, 1.16)	1.11 (0.99, 1.24)	1.18 (1.05, 1.33)	1.20 (1.04, 1.38)	<0.01
	Model 3		1	1.03 (0.93, 1.14)	1.09 (0.97, 1.22)	1.15 (1.01, 1.30)	1.16 (1.00, 1.35)	0.03
Cancer mortality								
		Cases/person-years	1471/380877	1410/381180	1376/381046	1499/380710	1547/380248	
Total MUFAs	Model 1		1	1.04 (0.96, 1.12)	1.08 (1.00, 1.16)	1.21 (1.13, 1.31)	1.29 (1.20, 1.39)	<0.001
	Model 2		1	1.06 (0.98, 1.14)	1.06 (0.98, 1.15)	1.16 (1.07, 1.26)	1.13 (1.04, 1.23)	<0.01
	Model 3		1	1.01 (0.94, 1.10)	0.99 (0.91, 1.08)	1.05 (0.96, 1.15)	0.99 (0.90, 1.10)	0.91
		Cases/person-years	1735/3379452	1465/380886	1392/381219	1370/381159	1370/381342	
MUFA-Ps	Model 1		1	0.90 (0.84, 0.97)	0.89 (0.83, 0.95)	0.89 (0.82, 0.95)	0.86 (0.80, 0.92)	<0.001
	Model 2		1	0.95 (0.88, 1.02)	0.94 (0.87, 1.02)	0.93 (0.86, 1.00)	0.89 (0.82, 0.96)	<0.01
	Model 3		1	0.97 (0.90, 1.04)	0.98 (0.91, 1.06)	0.98 (0.90, 1.06)	0.96 (0.88, 1.05)	0.43
		Cases/person-years	1326/381444	1340/381296	1358/381176	1490/380643	1784/379500	
MUFA-As	Model 1		1	1.09 (1.01, 1.17)	1.15 (1.07, 1.24)	1.32 (1.23, 1.43)	1.63 (1.51, 1.75)	<0.001
	Model 2		1	1.09 (1.00, 1.18)	1.11 (1.02, 1.21)	1.21 (1.10, 1.33)	1.32 (1.18, 1.47)	<0.001
	Model 3		1	1.08 (0.99, 1.17)	1.10 (1.00, 1.20)	1.20 (1.09, 1.32)	1.29 (1.15, 1.45)	<0.001
Non-cardiovascular and non-cancer mortality								
		Cases/person-years	2073/381379	1741/381855	1673/381802	1640/381578	1647/381297	
Total MUFAs	Model 1		1	0.97 (0.91, 1.03)	1.03 (0.96, 1.10)	1.06 (0.99, 1.13)	1.14 (1.07, 1.22)	<0.001
	Model 2		1	0.95 (0.89, 1.02)	0.94 (0.88, 1.01)	0.91 (0.85, 0.98)	0.86 (0.79, 0.93)	<0.001
	Model 3		1	0.88 (0.83, 0.95)	0.84 (0.78, 0.90)	0.78 (0.72, 0.85)	0.70 (0.63, 0.77)	<0.001
		Case/person-years	2360/380294	1913/381513	1583/381840	1599/381930	1319/382254	
MUFA-Ps	Model 1		1	0.89 (0.84, 0.95)	0.80 (0.75, 0.85)	0.82 (0.77, 0.88)	0.69 (0.65, 0.74)	<0.001
	Model 2		1	0.95 (0.89, 1.01)	0.84 (0.79, 0.90)	0.84 (0.79, 0.91)	0.71 (0.66, 0.76)	<0.001
	Model 3		1	0.95 (0.89, 1.01)	0.84 (0.78, 0.90)	0.84 (0.78, 0.91)	0.71 (0.65, 0.77)	<0.001
		Case/person-years	1660/381966	1640/381940	1404/381887	1713/381561	2057/380556	
MUFA-As	Model 1		1	1.12 (1.04, 1.20)	1.25 (1.16, 1.33)	1.34 (1.25, 1.43)	1.70 (1.59, 1.81)	<0.001

		Quintiles of MUFA intake (% energy)					
		Q1	**Q2**	**Q3**	**Q4**	**Q5**	***P* for trend**
	Model 2	1	1.09 (1.01, 1.17)	1.14 (1.06, 1.24)	1.13 (1.04, 1.23)	1.24 (1.12, 1.37)	<0.001
	Model 3	1	1.05 (1.02, 1.07)	1.03 (0.96, 1.11)	1.05 (0.97, 1.14)	1.01 (0.92, 1.10)	0.05

Hazard ratios and 95% confidence intervals were calculated in Cox proportional hazards models; NHS, Nurses' Health Study; HPFS, Health Professional's Follow-up Study; MUFA, monounsaturated fat; MUFA-P, MUFAs from plant sources; MUFA-A, MUFAs from animal sources.

Model 1, adjusted for age; Model 2, further adjusted for ethnicity (Caucasian, and other ethnicity), smoking status (never, former, current (1–14, 15–24, or ≥25 cigarettes/day), alcohol intake (gram/day: 0, 0.1–4.9, 5.0–14.9, and >15.0 in women, 0, 0.1–4.9, 5.0–29.9, and >30.0 in men), family history of myocardial infarction (yes/no), family history of diabetes (yes/no), family history of cancer (yes/no), menopausal status and post-menopausal hormone use (pre-menopause, post-menopause (never, former, or current hormone use), for women), physical activity (<3, 3.0–8.9, 9.0–17.9, 18.0–26.9, ≥27.0 METs/week), current aspirin use (yes/no), multivitamin use (yes/no), baseline hypertension, baseline hypercholesterolemia, BMI (<23, 23–24.9, 25–29.9, 30–34.9, >35kg/m^2), intakes of total energy, energy from *trans* fats, fruits and vegetables, and coffee intake (in quintiles). Model 3, further adjusted for percentage of energy from SFAs. MUFA-P models were further adjusted for MUFA-A, and vice versa. Study estimates from two cohorts were pooled using a fixed effects model.