ALINEA

NUTRITION

JULY 2020

www.alineanutrition.com

TABLE OF

CONTENTS

Guasch-Ferré M, Zong G, Willett WC, et al. Associations of Monounsaturated Fatty Acids From Plant and Animal Sources With Total and Cause-Specific Mortality in Two US Prospective Cohort Studies. Circ Res. 2019;124(8):1266-1275.

What We Know, Think We Know, or Are Starting to Know

Despite the now ubiquitous popularity of the Mediterranean diet in both the lay and research communities, the role of the primary source of fats in that dietary pattern - monounsaturated fats - has been more unclear than one would be forgiven for thinking.

In the early metabolic ward studies by Ancel Keys and colleagues, which carefully examined the effects of different sources of fats on blood cholesterol levels, indicated that monounsaturated fats had a neutral effect [(1)]. What we know now, which wasn't differentiated then as the delineation between LDL-C and HDL-C had yet to fully be recognised, was that MUFA may only slightly lower LDL-C and increase HDL-C, i.e., this may reflect a 'neutral' effect on total blood cholesterol levels [(2)].

What we have also come to know is that not any one food can be described as fully either a saturated or unsaturated fat. Lard, for example, contains ~43% saturated fatty acids and ~62% unsaturated fatty acids, of which ~47% is oleic acid. Yes, the same oleic acid found in olive oil, illustrating the importance of the overall food matrix for biological activity, and the full nutritional composition of the food matrix.

This is a crucial point: when it comes to monounsaturated fats, significant proportions are derived from animal-source foods that we may often associate with saturated fats - red meats, cooking fats. This has led to the important research question: could some confusing findings in epidemiological research on the relationship between monounsaturated fats and health outcomes be mediated by the source of these fats?

The Study

The Nurses' Health Study [NHS] and Health Professional's Follow-Up Study [HPFS] are two long-term prospective cohort studies in the United States. The NHS began in 1976 recruiting female nurses aged 30-55 at baseline, while the HPFS began in 1986 in male healthcare professionals aged 40-75 at baseline.

The validation process for the dietary assessment has been ongoing*. Food-frequency questionnaires [FFQ] were administered every 4-yrs, and food intake was calculated as a cumulative average for all available FFQs completed by participants, to represent long-term diet and minimise within-person variability.

Monounsaturated fats [MUFA] were calculated as total MUFA and source of MUFA, which were distinguished: animal-sourced MUFA [MUFA-A] included cooking fats, dairy products, eggs, poultry, processed and unprocessed red meats, and fish; plant-sourced MUFA [MUFA-P] included plant-based cooking oils, salad dressing, margarines, bread and cereals, fruits, vegetables, legumes, nuts, and seeds. The correlation coefficient for for total MUFA was 0.58, and 0.65 for oleic acid.

*Geek Box: Dietary Assessment Validation in the Nurses Health Study

When it comes to dietary assessment in nutritional epidemiology, we know that validation process is integral to the generation of reliable data. The validation process in the Nurses Health Study [NHS] is an example of particular rigour in this regard. Starting in 1980, an initial food-frequency questionnaire was administered, and over the course of the following year a total of four separate 1-week diet records, with foods and drinks measured, were completed by a representative subgroup in the cohort. Doing 4, spread across seasons, allowed for any potential seasonal variations in dietary intake to be captured. The FFQ was administered then for a second time in 1981, providing the investigators with a second measure to compare the performance of the FFQ in measure diet against the data from the 4-weeks of dietary records. In 1984, the FFQ was revised, and in 1986-1987, a further two 1-week dietary records were completed to compare the reproducibility, i.e., the consistency of the FFQ across repeated measures in the same person. The FFQ was further revised based on this updated data. This process resulted in strengthened correlation coefficients for major nutrients of interest, highlighting that rigorous validation processes improve the reliability of dietary data in epidemiology. The NHS validation process, due to its rigour, has been repeated in other cohorts, notably the EPIC-Oxford cohort in the UK.

Results: Over 22yrs of follow-up, there were 20,672 documented deaths in both cohorts. Participants with higher MUFA-P had more health-promoting characteristics and higher Health Eating Index Score; participants with higher MUFA-A had less health-promoting characteristics and lower Health Eating Index Score. Total MUFA quintiles were the same in both groups: the highest [Quintile 5] 14.4% vs. the lowest [Quintile 1, the reference group] 9.4%. In participants with higher MUFA-P, the highest MUFA-P was 9.2% vs. 3.7%, and MUFA-A was 5.0% vs. 5.4%. In participants with higher MUFA-A intake, the the highest MUFA-A was 8.2% vs. 3.2%, and MUFA-P was 6.0% vs. 6.5%.

In relation to the primary outcomes, the results from the fully adjusted analysis, which included adjustment for saturated fat [SFA], comparing the highest quintile to lowest, are set out below. Percentage increases or decreases in risk are written only for findings that are statistically significant:

- ***Flavonoid polymers***
    - Total MUFA: 16% reduction in risk [HR 0.84, 95% CI 0.79–0.89]
    - MUFA-P: 16% reduction in risk [HR 0.84, 95% CI 0.80–0.89]
    - MUFA-A: 16% increase in risk [HR 1.16, 95% CI 1.08–1.24]
- ***Cardiovascular Mortality***
    - Total MUFA: HR 0.96, 95% CI 0.84–1.09
    - MUFA-P: HR 0.96, 95% CI0.86–1.07
    - MUFA-A: HR 1.16, 95% CI 1.00–1.35

- ***Cancer Mortality***
    * Total MUFA: HR 0.99, 95% CI 0.90–1.10
    * MUFA-P: HR 0.96, 95% CI 0.88–1.05
    * MUFA-A: 29% increase in risk [HR 1.29, 95% CI 1.15–1.45]

- ***Non-CVD/Cancer Mortality***
    * Total MUFA: 30% reduction in risk [HR 0.70, 95% CI 0.63–0.77]
    * MUFA-P: 29% reduction in risk [HR 0.71, 95% CI 0.65–0.77]
    * MUFA-A: HR 1.01, 95% CI 0.92–1.10

Substitution analysis* was also conducted modelling the effects of isocaloric replacement of other nutrients my either MUFA-P, MUFA-A, or a combination of MUFA-P+PUFA. The results for significant findings only are presented as follows:

- ***MUFA-Ps replacing:***
    * SFAs [5%E]:
        · Total Mortality - 16% reduction in risk [HR 0.84, 95% CI 0.77—0.92]
        · Non-CVD/Cancer Mortality - 28% reduction in risk [HR 0.72, 95% CI 0.63—0.82]
    * Refined carbohydrates [5%E]:
        · Total Mortality - 14% reduction in risk [HR 0.86, 95% CI 0.82—0.91]
        · Non-CVD/Cancer Mortality - 25% reduction in risk [HR 0.75, 95% CI 0.69—0.81]
    * Trans fats [2%E]:
        · Total Mortality - 14% reduction in risk [HR 0.86, 95% CI 0.82—0.91]
        · Non-CVD/Cancer Mortality - 25% reduction in risk [HR 0.75, 95% CI 0.69—0.81]

- ***MUFA-Ps replacing:***
    * MUFA-As [5%E]:
        · Total Mortality - 23% reduction in risk [HR 0.77, 95% CI 0.71—0.82]
        · CVD Mortality - 26% reduction in risk [HR 0.74, 95% CI 0.64—0.86]
        · Cancer Mortality - 27% reduction in risk [HR 0.73, 95% CI 0.65—0.82]
        · Non-CVD/Cancer Mortality - 18% reduction in risk [HR 0.82, 95% CI 0.73—0.91]
    * SFAs+MUFA-As [5%E]:
        · Total Mortality - 20% reduction in risk [HR 0.80, 95% CI 0.77—0.84]
        · CVD Mortality - 16% reduction in risk [HR 0.84, 95% CI 0.76—0.92)
        · Cancer Mortality - 15% reduction in risk [HR 0.85, 95% CI 0.79—0.91)
        · Non-CVD/Cancer Mortality - 25% reduction in risk [HR 0.75, 95% CI 0.70—0.81]
        ·

- ***PUFA+MUFA-Ps replacing:***
  - SFAs+MUFA-As [5%E]:
    - Total Mortality - 15% reduction in risk [HR 0.85, 95% CI 0.82—0.87]
    - CVD Mortality - 18% reduction in risk [HR 0.82, 95% CI 0.77—0.87]
    - Cancer Mortality - 14% reduction in risk [HR 0.86, 95% CI 0.82—0.91]
    - Non-CVD/Cancer Mortality - 22% reduction in risk [HR 0.78, 95% CI 0.74—0.82]

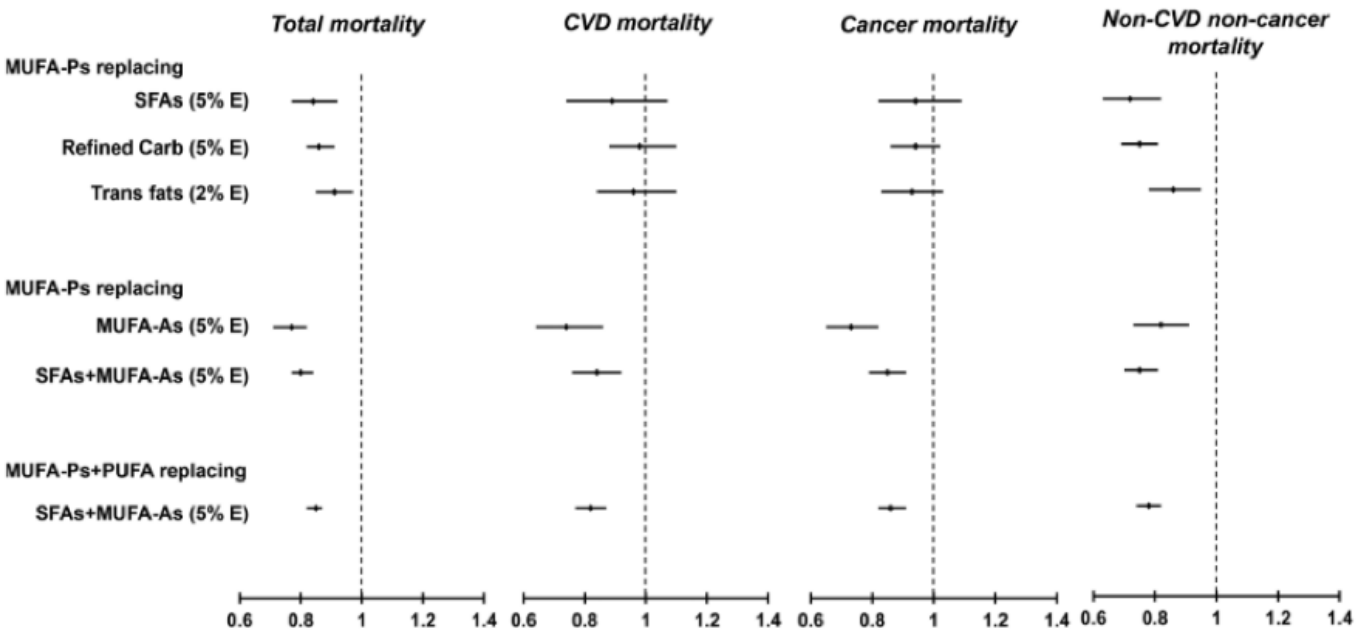

Figure *from study illustrating the hazard ratios for the mortality outcomes from the substitution analysis, i.e., the effects of 5% of energy from MUFA-P replacing 5% of energy from SFA, refined carbs, or trans-fats. The substitution analysis also modelled the effects of 5% energy from MUFA-P replacing 5% energy from MUFA-A, and from a combination of MUFA-A+SFA. Finally, the effects of a combination of MUFA-P+PUFA replacing SFA+MUFA-A was analysed.*

*Geek Box: Substitution Models

There are two ways to think about potential confounders in nutritional epidemiology: confounding from other non-dietary lifestyle factors, like smoking, and confounding from other nutrients which may be correlated with the nutrient exposure of interest. The former can be accounted for in an adjustment model; the latter can be addressed through careful substitution modelling. So what is substitution modelling, and how does it work? In nutritional epidemiology, it is standard practice to adjust for total energy: this is because all nutrients positively correlate with total energy intake, and adjusting for energy provides a means to assess the effects of the nutrient, independent of total energy. From that, researchers may want to investigate the effects of replacing one nutrient with another. Because total energy is adjusted for, this can be done assuming isocaloric substitution, for example, what is the effect of replacing 5% of dietary energy from sugar with 5% of energy from wholegrain carbohydrates. Let's take an example of the effects of isocaloric replacement of saturated fats with unsaturated fats [without distinguishing between MUFA and PUFA, for simplicities sake]. In this model, you would have total energy + total fat, adjusted for total energy + saturated fat, adjusted for total fat. Because all fat subtypes are under the umbrella of total fat, this means all that is excluded is unsaturated fats. So by energy-adjusting total fat and saturated fat, the effect of unsaturated fats on the outcome of interest is the effect of these fats replacing saturated fat. So when you read about substitution analysis, this is [albeit in a very simplified explanation!] what is going on - examining the effects of isocalorically substituting one nutrient with another while holding other nutrients and total energy constant.

The Critical Breakdown

Pros: The dietary assessment and validation process is one of the most robust in nutritional epidemiology. The fatty acid content of foods were analysed in laboratory conditions periodically during the follow-up period, to account for changes in the food supply. Using substitution models with inter-correlated nutrients could account for potential nutrient confounding. The 22yr follow-up is longer than many other cohorts, and large number of deaths provides more statistical power.

Cons: Both cohorts are 95% White health professionals, and not representative of the wider general US population. The intakes of MUFA-A and MUFA-P changed over the course of the follow, and the 2002 follow-up was used for MUFA quintile, which may yield effects not representative of current intakes [see ***Relevance***, below]. While this 'Con' is unavoidable as nutrients were the primary exposure of interest, the complex relationship between these various nutrients in foods suggests a food-based analysis would be interesting in the future.

Key Characteristic

The distinct analysis of MUFA source, including distinguishing MUFA from trans fats, provides a more refined analysis that goes some way to clear some of the confusing findings in relation to MUFA from prospective cohort studies. Due the exact chemical configuration of trans fats, which may have one [mono] double-bond, trans-fats have often historically been analysed within the sum of MUFA [(3)]. However, the MUFA we generally associate with health benefits are cis-MUFA, in particular oleic acid, which accounts for 92% of all MUFA consumed: in countries like Greece, cis-MUFA may contribute up to 22% of total daily energy intake [(4)]. However, cis-MUFA are also the predominant MUFA in animal fats, and in the American diet animal fats are one of the primary sources of cis-MUFA [(4)]. Thus, even within the categorisation of cis-MUFA, it is important to distinguish between the source of these fats in the diet, and the respective contributions of plant-derived vs. animal derived cis-MUFA on related health outcomes. The present study separate single-bond trans-fats from cis-MUFA, to avoid this inter-nutrient confounding. Further, by calculating the sum of MUFA-A and MUFA-P from their respective sources, the substitution analysis provided greater insight into the health effects potentially mediated by food source.

Interesting Finding

While there was no effect observed on CVD risk comparing high vs. low quintiles of total MUFA, MUFA-A, or MUFA-P, the substitution analysis revealed a different picture. Perhaps most interesting was the effect of MUFA-P replacing MUFA-A, a 26% reduction in CVD risk, - was greater than the effect of MUFA-P replacing a combination of SFA+MUFA-A, in which CVD risk decreased by 16%. Swapping MUFA-P for SFA directly was associated with an 11% reduction in risk, but this finding did not reach statistical significance. And, the combination of PUFA+MUFA-P replacing 5% of energy from SFA+MUFA-A was associated with an 18% reduction in CVD risk.

So what could be going on? It can be challenging to investigate dietary factors that are subcomponents of another, i.e., polyunsaturated, monounsaturated, and saturated fats, are all subcomponents of total dietary fat. Often they may be tightly correlated: MUFA-A and SFA, and PUFA and MUFA-P, respectively correlated together. As stated in the Geek Box, above, the substitution models allow for testing the independent effects of MUFA-P. Thus, these findings may reflect the independent effects of consuming MUFA from plant sources, which is independent from the fatty acid matrix of animal fats.

Relevance

This is an important study insofar as the effects of MUFA have remained unclear, to such an extent that no specific recommendations are made for MUFA intake in the population, and question marks remain over whether MUFA are associated with reduced risk of chronic disease [5]. As we have seen, however, merely classifying 'MUFA' alone may reflect a proxy for animal fat consumption, and also may not consider the potential for trans-fats to be considered as MUFA. In a meta-analysis of 11 cohort studies by Jakobsen et al. [3], the substitution of 5% energy from SFA with MUFA appeared to show a significant and pronounced increase in risk for myocardial infarction. However, in the included studies the primary source of MUFA was animal fat, and trans-fats were included within the calculation of MUFA.

Given the presence of MUFA in animal fat, a higher intake of SFA in the diet will often correspond to a concomitant higher energy derived from MUFA. The source of MUFA is thus important, and if we look to the Mediterranean diet as an example, in which between 16-29% energy is derived from MUFA alone with the primary source being plant-derived olive oil, this MUFA intake occurs in the context of a diet with only 6-8% SFA. An analysis of the NHS and HPFS cohorts in 2018 that distinguished between MUFA-A and MUFA-P in relation specifically to coronary heart disease found a 17% reduction in risk for CHD when MUFA-P were substituted for SFA, and 24% reduction in risk for CHD when MUFA-P were substituted for MUFA-A [6]. The effects of enriching diets with MUFA from plant sources - extra virgin olive oil and nuts in particular - has been confirmed in dietary interventions, including the OmniHeart and PREDIMED trials [7,8]. Thus, this distinction between the source of MUFA is not academic.

In both the NHS and HPFS cohorts, the mean percentage of energy from MUFA-Ps increased from 5.8% to 6.3% to 7.9% during the follow-up period, whereas MUFA-As decreased from 5.4% to 5.5% to 4.2%–4.4%. This may reflect a growing consuming awareness of the health effects of these fats, and/or changes in the composition of foods in the food supply. Either way, it will be interesting to see further analyses making this distinction from other populations, particularly among European cohorts.

Application to Practice

70yrs of research has indicated that unsaturated fats are preferable to saturated fats for cardiometabolic health, but questions have remained over the effects of MUFA per se. More recent analyses, including the present study, indicate that the source of MUFA is an important mediator of the health effects associated with cis-MUFA and oleic acid, with a preference for plant-derived sources.

References

1. Keys A, Anderson J, Grande F. Prediction of Serum-Cholesterol Responses of Man to Changes in Fats in the Diet. The Lancet. 1957;270(7003):959-966.
2. Mensink R, Zock P, Kester A, Katan M. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. The American Journal of Clinical Nutrition. 2003;77(5):1146-1155.
3. Jakobsen M, O' Reilly E, Heitmann B, Pereira M, Bälter K, Fraser G et al. Major types of dietary fat and risk of coronary heart disease: a pooled analysis of 11 cohort studies. The American Journal of Clinical Nutrition. 2009;89(5):1425-1432.
4. Joris P, Mensink R. Role of cis-Monounsaturated Fatty Acids in the Prevention of Coronary Heart Disease. Current Atherosclerosis Reports. 2016;18(7).
5. Schwingshackl L, Hoffmann G. Monounsaturated Fatty Acids and Risk of Cardiovascular Disease: Synopsis of the Evidence Available from Systematic Reviews and Meta-Analyses. Nutrients. 2012;4(12):1989-2007.
6. Zong G, Li Y, Sampson L, Dougherty L, Willett W, Wanders A et al. Monounsaturated fats from plant and animal sources in relation to risk of coronary heart disease among US men and women. The American Journal of Clinical Nutrition. 2018;107(3):445-453.
7. Estruch R, Ros E, Salas-Salvadó J, Covas M. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. N Engl J Med. 2018;378(e34).
8. Appel L, Sacks F, Carey V, Obarzanek E, Swain J, Miller E et al. Effects of Protein, Monounsaturated Fat, and Carbohydrate Intake on Blood Pressure and Serum Lipids. JAMA. 2005;294(19):2455.