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## Association of Dietary, Circulating, and Supplement Fatty Acids With Coronary Risk: A Systematic Review and Meta-analysis

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**Background:** Guidelines advocate changes in fatty acid consumption to promote cardiovascular health.

**Purpose:** To summarize evidence about associations between fatty acids and coronary disease.

**Data Sources:** MEDLINE, Science Citation Index, and Cochrane Central Register of Controlled Trials through July 2013.

**Study Selection:** Prospective, observational studies and randomized, controlled trials.

**Data Extraction:** Investigators extracted data about study characteristics and assessed study biases.

**Data Synthesis:** There were 32 observational studies (512 420 participants) of fatty acids from dietary intake; 17 observational studies (25 721 participants) of fatty acid biomarkers; and 27 randomized, controlled trials (105 085 participants) of fatty acid supplementation. In observational studies, relative risks for coronary disease were 1.03 (95% CI, 0.98 to 1.07) for saturated, 1.00 (CI, 0.91 to 1.10) for monounsaturated, 0.87 (CI, 0.78 to 0.97) for long-chain  $\omega$ -3 polyunsaturated, 0.98 (CI, 0.90 to 1.06) for  $\omega$ -6 polyunsaturated, and 1.16 (CI, 1.06 to 1.27) for trans fatty acids when the top and bottom thirds of baseline dietary fatty acid intake were compared. Corresponding

estimates for circulating fatty acids were 1.06 (CI, 0.86 to 1.30), 1.06 (CI, 0.97 to 1.17), 0.84 (CI, 0.63 to 1.11), 0.94 (CI, 0.84 to 1.06), and 1.05 (CI, 0.76 to 1.44), respectively. There was heterogeneity of the associations among individual circulating fatty acids and coronary disease. In randomized, controlled trials, relative risks for coronary disease were 0.97 (CI, 0.69 to 1.36) for  $\alpha$ -linolenic, 0.94 (CI, 0.86 to 1.03) for long-chain  $\omega$ -3 polyunsaturated, and 0.86 (CI, 0.69 to 1.07) for  $\omega$ -6 polyunsaturated fatty acid supplementations.

**Limitation:** Potential biases from preferential publication and selective reporting.

**Conclusion:** Current evidence does not clearly support cardiovascular guidelines that encourage high consumption of polyunsaturated fatty acids and low consumption of total saturated fats.

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## Comments

Posted on March 19, 2014

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**Conflict of Interest:** None Declared

The meta-analysis of dietary fatty acids and risk of coronary heart disease by Chowdhury et al. (1) contains multiple errors and omissions, and the conclusions are seriously misleading, particularly the lack of association with N-6 polyunsaturated fat. For example, two of the six studies included in the analysis of N-6 polyunsaturated fat were wrong. The relative risks for Nurses' Health Study (NHS) (2) and Kuopio Ischemic Heart Disease Study (KIHD) (3) were retrieved incorrectly and said to be above 1.0. However, in the 20-year follow-up of the NHS the relative risk for highest vs lowest quintile was 0.77 (95 percent CI: 0.62, 0.95);  $p$ -trend = 0.01 (the authors seem to have used the RR for N-3 alpha-linolenic acid from a paper on sudden cardiac death), and in the KIHD the relative risk was 0.39; 95% confidence interval [CI], 0.21-0.71) (the origin of the number used in the meta-analysis is unclear). Also, relevant data from other studies were not included (4 and 5).

Further, the authors did not mention a pooled analysis (6) of the primary data from prospective studies, in which a significant inverse association between intake of polyunsaturated fat (the large majority being the N-6 linoleic acid) and risk of CHD was found. Also, in this analysis, substitution of polyunsaturated fat for saturated fat was associated with lower risk of CHD. Chowdhury et al. also failed to point out that most of the monounsaturated fat consumed in their studies was from red meat and dairy sources, and the findings do not necessarily apply to consumption in the form of nuts, olive oil, and other plant sources. Thus, the conclusions of Chowdhury et al. regarding the type of fat being unimportant are seriously misleading and should be disregarded.

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Posted on March 19, 2014

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With great interest we read the meta-analysis of Chowdhury and co-workers titled "Association of Dietary, Circulating, and Supplement Fatty Acids with Coronary Risk" published in volume 160 of the *Annals of Internal Medicine* (1). In their manuscript, the authors systematically reviewed prospective and observational studies as well as randomized controlled trials investigating the associations between fatty acid consumption and coronary disease using both dietary intake and circulating fatty acids as measures. One of the findings was a null association of total and individual monounsaturated fatty acids (MUFA) with coronary risk (CHD). There has been a lot of debate regarding the potential role of MUFA in the pathogenesis of atherosclerosis. In a recently published review article on MUFA and cardiovascular disease (CVD) summarizing the results of sixteen systematic reviews and meta-analyses of controlled trials and cohort studies, MUFA turned out to have a favorable influence on several cardiovascular risk factors and CVD endpoints (2). Some of the controversial findings might be explained by the origin of MUFA in the respective studies resulting in a confounder that should be taken into account when comparing different dietary fats. Adopting a western diet means that MUFA is predominantly supplied by foods of animal origin, while in south European countries, extra virgin olive oil is the most dominant source of fat. Results of the recently published PREDIMED trial demonstrated major cardiovascular benefits of olive oil and nuts when compared to a low-fat diet (3). As a major outcome parameter, the risk of stroke was reduced, an event which has not been included in the meta-analysis by Chowdhury and co-workers. A recent cohort study observed a significant association between dietary olive oil, higher plasma oleic acid and reduced risk of stroke (4). Extra virgin olive oil is regarded to be the genuine driver of the Mediterranean diet and was found to be associated with a 26% reduced risk of all-cause mortality in the Spanish branch of the EPIC study (5). Furthermore, adherence to Mediterranean diet was associated with a reduced risk of all-cause mortality, CVD, cancer, and neurodegenerative disease (6). Thus, the results of the present meta-analysis, warrants further investigations with respect to the correlations between MUFA and cardiovascular risks. Future meta-analyses should focus on MUFA and CVD (combining CHD and stroke), and should differentiate between the different dietary sources of the fatty acids (e.g. oleic acid, olive oil).

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## **Correction**

Posted on March 20, 2014  
Rajiv Chowdhury, MD, PhD

University of Cambridge

Our recent meta-analysis contained the following numerical errors. First the summary estimate for total saturated fatty acids in prospective cohort studies of dietary fatty acid intake should be 1.03 (95% CI, 0.98 to 1.07) based on 20 studies, 276,763 participants and 10155 events. Second the summary estimate for total monounsaturated fatty acids in prospective cohort studies of dietary fatty acid intake should be 1.00 (95% CI, 0.91 to 1.10) based on 9 studies, 144,219 participants and 6031 events. Third the number of participant included in the analysis of alpha-linoleic in prospective cohort studies of dietary fatty acid intake should be 157,258 participants and 7431 events. Fourth the summary estimate for total long-chain omega-3 fatty acids in prospective cohort studies of dietary fatty acid intake should be 0.87 (95% CI, 0.78 to 0.97) based on 16 studies, 422,786 participants and 9089 events. Fifth the summary estimate for total omega-6 fatty acids in prospective cohort studies of dietary fatty acid intake should be 0.98 (95% CI, 0.90 to 1.06) based on 8 studies, 206,376 participants and 8155 events. Sixth the summary estimate for the effect of omega-6 fatty acids in randomized controlled trials should be 0.86 (95% CI, 0.69 to 1.07) based on 8 studies, 459 events/7245 participants in the intervention group and 515 events/7231 participants in the control group. These corrections, however, do not affect the main conclusions reported in the original article. The article has been corrected online.

## **Correction**

Posted on March 20, 2014  
Emanuel Di Angelantonio, MD, PhD

University of Cambridge

Numbers in the paper and supplementary material have been corrected and updated. The relative risks for dietary N-6 polyunsaturated fat for Nurses' Health Study (NHS) is based on the most relevant and updated publication. The relative risk for dietary N-6 polyunsaturated for the Kuopio Ischemic Heart Disease Study (KIHD) is correct and has been provided by the study investigators through correspondence (as noted in the supplementary material). The 2 additional studies mentioned in the Willett et. al. comment are included in the corrected analysis. These alterations have not changed the conclusions (including the lack of association with N-6 polyunsaturated fat).

Posted on March 24, 2014

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Chowdhury et al. conclude that their findings do not “yield clearly supportive evidence for current cardiovascular guidelines that encourage high consumption of polyunsaturated fatty acids and low consumption of saturated fats.” Current guidelines recommend intakes of polyunsaturated fatty acids (typically 5 to 11% total energy) that are modestly higher than those currently consumed in most western countries, and saturated fatty acid intakes below 10% total energy. They are based on the totality of relevant evidence linking fatty acids and cardiovascular risk.

In this regard, there is an important body of epidemiological evidence that Chowdhury et al. did not consider, presumably, because their meta-analysis was based on aggregate data. A pooled analysis of participant data from 11 cohort studies, including 2155 coronary deaths among 344,696 persons by Jakobsen et al. found a 26% reduction in coronary deaths when a 5% lower energy intake from saturated fatty acids was combined with a higher intake of polyunsaturated fatty acids(1). This important evidence extends knowledge about dietary fatty acids showing the effects of saturated fat on coronary disease, not in isolation from other macronutrients, but when replaced by other fatty acids or carbohydrate – as would occur in those following dietary guidelines.

Serum total cholesterol, a powerful causal risk factor for cardiovascular disease, is lowered to a predictable extent when n-6 polyunsaturated (or monounsaturated) fatty acids replace saturated fatty acids (2). The randomised controlled trials reporting clinical outcomes are more difficult to interpret; most were initiated many decades ago, involved a variety of intervention diets, and have sparse information about participant compliance. Nevertheless a meta-analysis of such trials by Mozaffarian et al. showed increasing intake of polyunsaturated in place of saturated fat resulted in a 19% reduction in risk of coronary events which closely matched predictions based on the effects of dietary fats on the total:HDL cholesterol ratio (3). The corresponding summary estimate reported by Chowdhury et al. includes one additional study, the re-analysis of the Sydney Diet and Heart Study (4). The inclusion of this study, which involved the recommendation of a diet very high in polyunsaturated fatty acids and reported relatively discrepant findings to the other studies, contributed to the slightly wider confidence interval.

We submit that the results by Chowdhury et al. do not contradict previous meta-analyses of aggregate data. While nutritional guidelines should be regularly reviewed we find no evidence here to suggest that current recommendations are inappropriate.

Lisa Te Morenga; Phd

Jim Mann; PhD, DM

Murray Skeaff, Phd

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3. Mozaffarian D, Micha R, Wallace S. Effects on coronary heart disease of increasing polyunsaturated fat in place of saturated fat: a systematic review and meta-analysis of randomized controlled trials. *PLoS Med.* 2010;7(3):e1000252.
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Posted on March 27, 2014

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**Conflict of Interest:** None Declared

Chowdhury et al in their recent meta-analysis in the *Annals of Internal Medicine* (1) reported no association of saturated fat (SAFA) with coronary risk, thereby casting doubt on cardiovascular guidelines that advocate increased intake of polyunsaturated fat (PUFA) at the expense of SAFA. Chowdhury et al examined SAFA, monounsaturated fat (MUFA) and polyunsaturated fat (PUFA) as separate entities. This method, however, is flawed because the health effect of a macronutrient that delivers a substantial amount of daily calories, such as SAFA, cannot be studied in isolation but depends on which other macronutrient(s) are replaced.

SAFA are beneficial when they replace trans fatty acids (2). We also know that replacing SAFA with carbohydrates (i.e. low-fat diet instead of high SAFA diet) does not confer heart health benefit because both LDL and HDL cholesterol will be reduced, with no change in the LDL/HDL ratio. When MUFA are consumed instead of SAFA, there is a probable benefit. For PUFA, the case is convincing based on prospective epidemiological studies and randomized controlled trials (2). Replacing 5% of daily energy as SAFA with PUFA would lower CHD risk by 13% on basis of cohort studies and will reduce the risk by 10% on basis of randomized controlled trials (3). Furthermore, it is a misconception that a substantial replacement of SAFA (e.g. 5 en%) could be achieved with omega-3 PUFA. In western diets, alpha-linolenic acid combined with fish fatty acids can provide at most 2-3 en%. In these diets, most sources of omega-3 are also high in omega-6. The authors refer to the meta-analysis of Ramsden et al (4), which showed a significantly reduced CHD risk when replacing SAFA with PUFA based on 'mixed omega-3 plus omega-6 trials'. It should be emphasized, however, that in these trials the level of omega-6 was much higher than that of omega-3 PUFA.

The estimates of the associations and effects sizes that Chowdhury et al. report for PUFA are fully compatible with earlier analyses of the same data that did take macronutrient replacement into account (2,5,6). The authors' conclusion that "Current evidence does not clearly support cardiovascular guidelines that encourage high consumption of PUFA and low consumption of total SAFA" is therefore misleading. Dietary guidelines should always be based on the totality of available evidence.

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## **Taking a broader approach to the role of dietary fats in cardiovascular disease**

Posted on March 30, 2014

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We read with interest Chowdhury's(1) paper: "Association of Dietary, Circulating, and Supplement Fatty Acids with Coronary Risk" concluding that the current evidence: "does not clearly support cardiovascular guidelines that encourage high consumption of polyunsaturated fatty acids and low consumption of total saturated fats"(1). This paper is timely given conjecture around the association between dietary fats and cardiovascular disease (CVD) and the implications for clinical practice. From a physiological, nutrition and clinical/public health perspective, we would argue that CVD prevention/management guidelines should diverge from a narrow reductionist approach focusing on individual nutrients towards a whole-of-diet approach that considers the potential of diet to influence underlying pathophysiological mechanisms that are salient to CVD, particularly vascular inflammation.

From a physiological perspective, current CVD guidelines are based on the putative etiology of CVD as a condition of lipid accumulation, to which dietary intake is a significant contributor. However, powerful evidence identifies (auto)immune-inflammatory and oxidative stress as key initiators of atherosclerosis. While blood lipids are still considered to be important in CVD progression, their position in the causal chain may be as key mediators of the relationship between inflammation and CVD, rather than having a primary causal influence on the atherosclerotic process(2). Despite this framework being the "burgeoning area of cardiovascular medicine"(3), the focus of diet-related research in CVD prevention remains predominantly on cholesterol reduction (and by association, saturated fat consumption). As the modern, Western diet is increasingly characterized by pro-inflammatory properties, including insufficient consumption of nutrient and fiber-dense foods and overconsumption of ultra-processed food products that contain energy dense sugars and hydrogenated plant-based oils, it is more pertinent to consider whole-of-diet as a key driver of this inflammatory process.

From a nutrition perspective, the single nutrient approach that underpins current CVD guidelines around saturated fats is problematic. Stanton argues that while a reductionist approach is useful for scientific purposes, it neglects context(4); the importance of sources of fatty acids and its effects when consumed with other foods. For example, fatty acids may be beneficial when consumed with vegetables, rich in anti-inflammatory phytochemicals(5).

Finally, from a clinical/public health perspective, the focus on single nutrients results in a chasm between research and real-world pragmatism, where no nutrient is consumed in isolation and excess is as important as deficiency. CVD clinical guidelines and public health strategies thus need to move beyond reductionism to a more practicable approach where whole-of-diet has the potential to ameliorate vascular inflammation.

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## **Effect of trans-palmitoleic acid**

Posted on March 29, 2014  
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It is with great interest I read the meta-analysis and review by Chowdhury et al. regarding the association of various fatty acids with coronary risk. Although the authors did report data regarding palmitoleic acid on coronary risk, not mentioned in this meta-analysis and review is the potential impact of trans-palmitoleic acid on coronary risk. In the 2010 Prospective cohort study by Mozaffarian et al., the effect of trans-palmitoleic acid on vascular risk factors and especially diabetes risk was assessed. (1)

Trans-palmitoleic acid is generally acquired from exogenous sources, until recently not being thought to be endogenously synthesizable. It is created by fermentation in the rumen of dairy cattle. Trans-palmitoleic acid levels constitute a marker for consumption of dairy fat although a recent publication does suggest a pathway used for endogenous synthesis. (2) In the Mozaffarian study, increasing levels of plasma trans-palmitoleic acid were associated with lower levels of insulin resistance, decreased c-reactive protein levels, higher high density lipoprotein levels, and a substantially reduced incidence of diabetes (multivariate hazard ratios of 0.41). No data was reported on coronary risk. Given the salutary effect, in the Mozaffarian study, of trans-palmitoleic acid on multiple cardiovascular risk factors, and the considerable contribution of dairy fat in the over-all saturated fat intake of most populations, perhaps dairy fat consumption could account for much of the mitigation of the heretofore expected worsened cardiovascular risk with increased levels of saturated fat intake.

I look forward to the inclusion of data on trans-palmitoleic acid levels and their impact on coronary risk in future nutrition-cardiovascular risk association studies. I'd like butter on that slice of bread, please!

Mark McCaulley, MD, FACP

1. Dariush Mozaffarian, MD, DrPH; Haiming Cao, PhD; Irena B. King, PhD; Rozenn N. Lemaitre, PhD, MPH; Xiaoling Song, PhD; David S. Siscovick, MD, MPH; and Gökhan S. Hotamisligil, MD, PhD Trans-Palmitoleic Acid, Metabolic Risk Factors, and New-Onset Diabetes in U.S. Adults: A Cohort Study *Ann Intern Med.* 2010;153(12):790-799.

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## **Public health implications of an uncritical fanfare of a single publication**

Posted on April 7, 2014

The authors form the steering committee of the IEM, the International Expert Movement on the Health significance of fat quality in the diet

International Expert Movement Steering Committee

**Conflict of Interest:** International activities of the IEM are held under the auspices of the International Union of Nutritional Sciences (IUNS) and funded by an unrestricted educational grant from Unilever.

A recent analysis of different types of studies on dietary fat and the risk of heart disease questions current dietary guidelines on fat quality in the diet. A close look at the authors' report reveals serious flaws in their data collection and analysis.

Guidelines for healthier fat intakes must account for what replaces the items that are restricted. We now know that replacing saturated fat with sugar and refined carbohydrates does not reduce the risk of heart disease, but replacement with polyunsaturated fats does. This is the current scientific consensus and is the basis of current recommendations to replace saturated fat in the diet with unsaturated fats.

Our primary concern is the public health implications of an uncritical fanfare of a single publication. Data show that mixed messages such as this report offers increase the public's confusion and skepticism about effective dietary guidance. Ongoing scientific discussions about dietary factors, including saturated fat, and health are the foundation of scientific and public health progress. However, debunking the evidence about dietary fat and the risk of heart disease without constructive, science-based recommendations the public can actually use is at the very least unhelpful and contributes negatively to public health.

The new analysis published last week does not bring new scientific data or insights. The practical dietary recommendations on fat in the diet therefore remain the same: reduce the intake of saturated fat ('hard' fat as found in fatty meat, whole milk dairy products, butter, pies) and eat products low in saturated fat and high in unsaturated fats such as lean meats, reduced fat dairy foods, liquid vegetable oils and products made with these oils.

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### **The serious consequences of ignoring the ecological fallacy**

Posted on April 7, 2014  
Frank Davidoff, Irwin H. Rosenberg

Editor Emeritus, Annals of Internal Medicine; University Professor of Medicine and Nutrition, Tufts University

The recent review by Chowdhury et al (1) provides a sobering reappraisal of the widely presumed association between dietary fat and coronary disease. Unfortunately, their otherwise careful study accepts uncritically the assumption that size of an intervention's effect in individual members (or subgroups) of a study population is the same as it is in the entire study population; that is, the review fails to avoid the ecological fallacy.

Kent et al (2) identify two potentially serious clinical consequences of ignoring the ecological fallacy; both are due to the inherent risk-based heterogeneity of absolute treatment effects (3), which has been shown to vary as much as 20-fold between study population subgroups with the

highest vs. lowest baseline risk for adverse outcomes (2). The first problem is failure to recognize that some interventions whose efficacy is statistically confirmed in an entire study population provide no meaningful benefit to sizeable subgroups of that population. For example, warfarin prevents stroke more effectively than aspirin in the overall population of patients with non-valvular atrial fibrillation, but the subgroup of patients without additional risk factors for stroke does not benefit incrementally from warfarin therapy (2). The second, and opposite, problem is failure to recognize that some interventions provide true benefit in subgroups of a study population even though the intervention is not shown statistically to “work” in the population as a whole. The inclusion of study populations at widely varying baseline risk for adverse coronary events in the review by Chowdhury et al (1) greatly increases the likelihood that its broadly negative conclusion is, at least in part, falsely negative.

Interestingly, although risk-based targeting of clinical interventions is a neglected (and perhaps resisted) approach in many areas of clinical practice, including drug therapy (4), it is rapidly gaining acceptance as an appropriate, effective, and efficient clinical strategy in cancer screening (5). Kent et al propose a multivariable technique for measuring the impact of clinical interventions in subgroups at different levels of baseline risk; the technique is relatively straightforward, has substantial statistical power, and avoids most of the usual methodological pitfalls of “one-variable-at-a-time” subgroup analyses (2).

In our view, truly evidence-based dietary recommendations on dietary fat will be possible only when we have answered the crucial questions of what changes in dietary fat (if any) lower the rate of coronary events, in whom, and under what conditions, by careful risk-stratified examination of these causal relationships.

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## **No Vindication for Saturated Fatty Acids.**

Posted on April 15, 2014

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Chowdhury and colleagues analysed eight studies, namely ARIC, EPIC-NORFOLK, KIID, LURIC, NSHDS, ULSAM, VIP and Whitehall, for the association of circulating blood SFA levels and relative risk (RR) for coronary outcomes [1]. From our point of view, the results of NSHDS and VIP have been misinterpreted, and the studies should be excluded for the following reasons.

First, data from VIP [2,3] have been included in the evaluation of NSHDS, as stated in [4]. Second, VIP and NSHDS assessed the association between high intakes of SFA from dairy products (indicated by pentadecanoic acid (C15:0) and heptadecanoic acid (C17:0) or their sum in serum lipid esters) with cardiovascular disease [3,4]. In both studies, negative associations between milk-fat intake and first-ever myocardial infarction were found. Neither of the two studies described the association of circulating blood total SFA on coronary outcomes. Importantly, C15:0 and C17:0 contribute only 0.5-1.0% of the fatty acids in total phospholipids [4]. In contrast, the total SFA amount in plasma phospholipids ranges between 40-45%, which is mainly composed of palmitic acid (C16:0) with approx. 50-60% and stearic acid (C18:0) with approx. 30-40% of the total SFA amount [5]. Thus, C15:0 and C17:0 are markers for milk or ruminant fat intake [3,4], but not for total SFA intake, and there are several SFA sources, such as baking margarines, coconut oil and palm oil, which do not contain C15:0 and C17:0. In agreement with this, we also found that proportions of C15:0 and C17:0 in human erythrocyte membranes are between 1.0-2.9% of total SFA and show no correlation with the concentration of total SFA (unpublished data). When we repeated the meta-analysis after excluding VIP and NSHDS we found a positive association of total SFA blood levels and coronary outcomes (RR 1.21, CI 1.04-1.40). This finding contradicts the overall conclusion drawn by Chowdhury and colleagues [1].

Proper communication of health risks of dietary habits is essential to achieve appropriate changes in lifestyle habits and to improve cardiovascular health. The results of the meta-analysis gave rise to misleading headlines like 'Animal fat is not bad for the heart' in the national lay press. Consumers may continue their unhealthy dietary habits in response to such simplified messages. Due to the impact of meta-analyses on the general public, thoroughly and reasonable selection of studies and careful evaluation of data are vital for the accuracy of results and for protecting people from harm.

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Chowdhury et al. concluded that “current evidence does not clearly support guidelines that encourage high consumption of polyunsaturated fatty acids and low consumption of total saturated fats” by misrepresenting the strongest evidence for those guidelines.

An earlier meta-analysis found a 19% reduction in CHD risk in randomized clinical trials that replaced saturated fat with omega-6 polyunsaturated fats. In Supplement Figure 14, Chowdhury et al. found no significant reduction in risk because they included one additional trial, the Sydney Diet Heart Study, which (according to a footnote) provided subjects with a margarine high in trans fatty acids. Without the SDHS, Chowdhury found the same 19% reduction in risk. Was that critical finding omitted from the printed study because it contradicted the authors’ main conclusion?

Furthermore, Chowdhury et al. incorrectly referred to the eight trials examined as “supplementation” trials. In fact, those trials reduced saturated fats and replaced them with polyunsaturated fats, precisely what most guidelines recommend. The evidence from these trials trumps observational studies—plagued by imprecise dietary intake data and possible residual confounding—that have failed to find an association between fatty acids and heart disease risk.

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1 Chowdhury R, Warnakula S, Kunutsor S, et al. Association of dietary, circulating, and supplement fatty acids with coronary risk. *Ann Intern Med* 2014; 160(6):398-406.

2 Mozaffarian D, Micha R, Wallace S. Effects on coronary heart disease of increasing polyunsaturated fat in place of saturated fat: a systematic review and meta-analysis of randomized controlled trials. *PLoS Med.* 2010 doi: 10.1371/journal.pmed.1000252.

## Four types of evidence are reviewed and meta-analysed

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### PROSPECTIVE STUDIES

On omega-6 fatty acids Chowdhury et al have 8 studies. In Fig 3. KIHD is incorrect: omega-6 and Linoleic Acid (LA) were protective. And in HPFS, LA was inversely related to fatal heart disease.

There are at least seven OTHER prospective studies not in Chowdhury et al. In 5 of these, including large ones (1) (2) omega-6 or LA were negatively related to coronary heart disease (CHD). Hence omega 6 should be to the left in the forest plot in 11/15 studies.

### BLOOD LIPID FATTY ACID'S

On LA, Chowdhury et al have 10 studies in their forest plot (Fig 10). One of these is incorrect: in ARIC, LA and omega-6 were lower in CHD cases (not higher), and the references for LURIC report free fatty acids (FFAs) not type of fatty acid.

There are at least seven OTHER reports on blood omega-6 and CHD, two with large numbers (3) (4). In all of them LA (or in one study P/S) tended to be protective. Hence, in the forest plot omega-6 should be to the left in 13/16 studies.

### ADIPOSE TISSUE FATTY ACIDS

Only one study in Chowdhury et al includes LA. There are also eight OTHER reports of adipose tissue FAs and CHD. Six of them found LA lower in cases. A very useful review by W.S. Harris et al (2007) has 7 articles on adipose tissue FAs and CHD, none included in Chowdhury et al.

### DIET TRIALS AND SUPPLEMENATION

Chowdhury et al don't distinguish between these two very different types of trials. Most of the papers reviewed by Chowdhury et al report simple supplementation with fish oil on EPA+DHA.

But it seems incorrect to combine supplement trials with diet trials for meta-analysis. In Diet trials the experimental group were asked to eat both less saturated fats and more PUFAs. These diet trials were very hard work. We can't in 2014 expect any new ones, so we have to make the most of those we have.

In the forest plot for omega-6 in Fig 14, SDHS is the obvious outlier. The SDHS authors originally wrote: "...comparison of the mean diets of those who died with those who survived revealed only trivial differences."(5)

The numbers for a protective effect of LA/omega-6 FAs on coronary risk would be stronger if Chowdhury et al had reviewed the whole literature and avoided occasional errors.

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- (2) Goldbourt U, Yaari S & Medalie JH. Factors predictive of long-term heart disease mortality among 10,059 Israeli civil servants and municipal employees. *Cardiology* 1993; 82:100-121
- (3) Miettinen TA, Naukkarinen V, Huttunen JK, Mattila S & Kumlin T Fatty acid composition of serum lipids predicts myocardial infarction. *Brit Med J* 1982; 285:993-996
- (4) Block RC, Harris WS, Reid KJ & Spertus JA. Omega-6 and trans fatty acids in blood cell membranes: a risk factor for acute coronary syndromes? *Am Heart J* 2008; 156:1117-1123
- (5) Woodhill JM, Palmer J, Leelarthaeapin B, McGilchrist C & Blacket RB. Low fat, low cholesterol diet in secondary prevention of coronary heart disease. *Adv Exp Med Biol* 1978; 109:317-330

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We appreciate that Chowdhury et al. have corrected some of the gross errors in their original paper (1); we note that the inverse association of intake of long chain N-3 polyunsaturated fatty acids (PUFA's) with CVD risk is now significant. We also appreciate the sensitivity analysis showing that with exclusion of the outlying Sydney Diet Heart Study, the randomized trials show benefit of replacing saturated fat with PUFA's. The extreme diet used in that study was never recommended or consumed in the US and included a trans-fat based margarine and probably very little N-3 PUFA's because sunflower oil was used to replace other fats as much as possible. However, other serious problems with Chowdhury et al. remain, including:

1. In the abstract and discussion, the nonsignificant findings for biomarkers of long chain N-3 fatty acid intake are based on total long chain N-3 PUFA's in only four studies. However, in the supplementary tables, long chain N-3 PUFA's were actually examined in 13 studies, and findings for the specific long chain PUFA's (EPA and DHA) were robustly and significantly inverse. Thus, both the result for both intake and biomarkers for long chain N-3 fatty acids support benefit. While the findings for RCT's are variable, this would be expected because many of the populations studied had relatively high intakes of N-3 fatty acids, and most individuals would likely experience little benefit.

2. The analysis for N-6 PUFA's still includes only 8 studies, and omits other studies included in the Jakobsen pooled analysis of original data (2) as well as other published papers.

3. The data on N-6 PUFA intake from the Kuopio Heart Study, the study with the most positive association, are erroneous because the denominator is almost double the number of healthy subjects (3). Contrary to what Chowdhury et al. state in their methods, they apparently included individuals with prevalent CVD at baseline instead of limiting the analysis those to healthy persons. The original study reported an RR of 0.38 (95% CI, 0.20-0.70) for fatal CVD among those with higher intake of polyunsaturated fats.

4. The discussion still does not acknowledge the earlier pooled analysis of primary data based on a larger number of studies, which allowed direct comparisons among different types of fats, and in that analysis substitution of saturated fats with PUFA's was associated with lower risks of CHD (2).

5. The large body of data showing that replacing saturated fats with monounsaturated fatty acids or PUFA's reduces LDL cholesterol is still not recognized.

Although Chowdhury et al. say in their revision that their conclusions did not change, a more inclusive and correct review of available evidence would support the replacement of saturated fat with polyunsaturated fatty acids.

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1. Chowdhury R, Warnakula S, Kunutsor S, Crowe F, Ward HA, Johnson L, et al. Association of dietary, circulating, and supplement fatty acids with coronary risk. *Ann Intern Med.* 2014; 160:398-406.
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## Author's Response

Posted on July 1, 2014

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Our systematic review and meta-analysis of the published literature aimed a priori to quantify three aspects of the evidence on fatty acids and coronary heart disease (CHD).

First, we considered results on self-reported dietary fatty acid intake from 32 prospective studies (512,420 participants, 15,945 CHD cases), constituting >90% of the relevant data published before July 2013. We found essentially null associations of saturated, monounsaturated and omega-6 polyunsaturated fatty acids with CHD, whereas intake of long-chain omega-3 polyunsaturated fatty acids was associated with lower CHD risk and intake of trans fatty acids was associated with higher CHD risk. In contrast with the claim by Willett et al, our paper stated that prospective studies were eligible for inclusion in this review if they involved either participants from general populations or patients with stable cardiovascular disease at study entry, which explains the inclusion of both types of participants from the Kuopio Heart Study (the investigators of which provided us with updated data following correspondence). However, as alluded to by Willett et al, we could not include 5 studies known to have information on dietary intake of omega-6 polyunsaturated fatty acids and CHD because they had published insufficient numerical information and did not respond to our requests for further details.<sup>1</sup> Nevertheless, as these studies comprised only about 15% of the relevant available data on omega-6 polyunsaturated fatty acids, it is unlikely their inclusion would have materially altered the relative risk we observed for CHD of 0.98 (95% CI 0.90-1.06).

Second, we considered results on the relative concentrations of individual circulating fatty acids from 17 prospective studies (25,721 participants, 5519 CHD cases). We found a possible inverse association between margaric acid and CHD, and possible positive associations between palmitic and stearic acids and CHD. We found some evidence that circulating levels of eicosapentaenoic and docosahexaenoic acid (the 2 main types of long-chain omega-3) and arachidonic acid were each associated with lower CHD risk. In contrast with the suggestion by Willett et al, the aforementioned results featured prominently in the review, such as in Figure 2 and in the results and discussion sections. As suggested by Dawczynski et al, our review emphasized results based on individual fatty acids (rather than on the total composition in each class of fatty acid) because the studies included typically measured different sets of individual fatty acids, thereby making it difficult to interpret results based on total compositions. However, as powerful prospective studies are now measuring large and uniform panels of individual fatty acids,<sup>2</sup> they should enable reliable evaluation of hypotheses pertaining both to total and individual fatty acid compositions.

Third, we considered 27 randomized controlled trials of fatty acid supplementation or replacement (105,085 participants, 6229 CHD cases). In aggregate, these trials have not

suggested clear benefits after supplementation with alpha-linolenic acid (relative risk: 0.97, 0.69-1.36) or with long-chain omega-3 fatty acid (0.94, 0.86-1.03), or replacement of saturated fat with omega-6 polyunsaturated fatty acid (0.86, 0.69-1.07). Although our finding for long-chain omega-3 fatty acid supplementation has been reinforced by a further null trial published since our meta-analysis,<sup>3</sup> Willett et al and Davidoff et al correctly point out that future trials (and/or individual participant meta-analyses of these trials) could identify subgroups that benefit from such supplementation. In contrast with the claim by Liebman et al, our results section described a subsidiary analysis that omitted the Sydney Diet Heart Study (a trial which had used a margarine-based supplementation high in trans fat),<sup>4</sup> yielding a relative risk of 0.81 (0.68-0.98) for the remaining 7 trials of omega-6 polyunsaturated fatty acid interventions. However, as appreciated by Te Morenga et al, this sub-analysis is difficult to interpret because it is of borderline statistical significance and because it is not clearly supported by other analyses, such as the relative risk of 0.92 (0.76-1.12) observed in the 3 available trials reporting at least 100 CHD events (which should be less prone to selective publication than are the smaller trials).

We agree that nutritional guidelines should be based on the totality of evidence, including routes of evidence that were outside the scope of our meta-analysis of CHD studies. Schwingshackl et al allude to evidence on stroke and additional cardiovascular outcomes. McCaulley alludes to a single prospective study that has reported inverse associations between circulating trans-palmitoleic acid and cardiovascular risk factors. Willett et al and others allude to evidence from metabolic ward studies reporting that replacement of dietary calories from saturated fat with polyunsaturated fat leads to small, but potentially important, reductions in low-density lipoprotein cholesterol concentration.<sup>5</sup> Lartey et al, Geleijnse et al, and other correspondents allude to previous statistical modelling of individual participant data from prospective studies, which has yielded a hazard ratio for CHD of 0.87 (0.77-0.97) per 5% lower energy intake from saturated fatty acids and a concomitant higher energy intake from polyunsaturated fatty acids<sup>1</sup>.

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## **Bias in selection of trials in meta-analysis**

Posted on July 9, 2014

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On July 1, Di Angelantonio, Chowdhury et al. posted a rebuttal to the many criticisms of their paper (1). The rebuttal included the statement: “In contrast with the claim by Liebman et al, our results section described a subsidiary analysis that omitted the Sydney Diet Heart Study (a trial which had used a margarine-based supplementation high in trans fat)”. (2)

But the results section of the original paper never contained that subsidiary analysis. The authors inserted it later, possibly after they had seen our criticism (3). A comparison of the original version (<http://annals.org/article.aspx?articleid=1846638> , Supplements tab) with the current version shows where the paper was edited (page 403, above ‘Assessment of Publication Bias’).

The authors now appear to agree that in randomized clinical trials, replacing saturated by polyunsaturated fat reduces CHD risk by 19% ( $P < 0.05$ ). However, they continue to ignore this finding “because it is not clearly supported by other analyses, such as the relative risk of 0.92 (0.76-1.12) observed in the 3 available trials reporting at least 100 CHD events (which should be less prone to selective publication than are the smaller trials).” (2) This selection of 3 trials reporting at least 100 CHD events is new; the original paper reported additional analyses “excluding trials that had recorded fewer than 50 coronary disease outcomes” (but not excluding the Sydney trial in which subjects consumed margarines high in trans fat).

This emphasis on selective publication diverts attention from the real issue. As the authors stated themselves, “There was generally no evidence of publication bias”. (1) The real issue in this meta-analysis is the way in which the authors included or excluded published trials. An objective analysis of trials that replace saturated fat with omega-6 polyunsaturated fats would not have included a trial that used a high-trans-fat margarine in the first place. Subsidiary analyses of arbitrary subgroups of trials were also unwarranted, and the corrections to the original version do not repair the damage caused by the paper's misleading conclusions.

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