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Trans Fatty Acid Isomers in Mortality and Incident Coronary Heart Disease Risk

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While nutrition remains a cornerstone to prevent adverse health outcomes, including chronic noncommunicable conditions such as cardiovascular disease (CVD)[1] and cancer,[2] the quantity and quality of various whole foods and nutrients to promote optimal health are still being debated. This is of particular relevance to the effects of dietary fatty acids on CVD-related outcomes, where, for instance, a supposed unfavorable role of total dietary saturated fatty acids[3,4] and a beneficial role of marine omega-3 fatty acids[5] have been questioned. Furthermore, recent epidemiological evidence[6] suggests that when individual fatty acids are examined, associations between specific fatty acid subtypes and coronary risk may vary importantly within each family of fatty acid group considered, indicating that individual fatty acid subtypes (and their food sources) might be more relevant in determining the subsequent disease risk than any composite fatty acid group in isolation.

Amidst the uncertainty regarding the optimal intake of fatty acids for cardiovascular and overall health, the evidence regarding *trans* fatty acids (ie, unsaturated fats with at least 1 double bond in the *trans* configuration) seems generally consistent. Concordant evidence from controlled trials and observational studies demonstrates that consumption of *trans* fatty acids adversely affects vascular risk factors, and is strongly and independently associated with a positive risk of coronary outcomes.[4,7] Various landmark prospective cohort studies have reported strong increased relative risks of CVD outcomes for higher consumption of *trans* fat, including the Nurses' Health Study,[8] the Zutphen study,[9] the Health Professionals Follow-up Study,[10] and the Alpha-Tocopherol, Beta-Carotene trial,[11] with a 23% overall increased risk of coronary heart disease (CHD) for each additional 2% energy intake from total *trans* fat when all available epidemiological evidence was combined.[10] Additionally, similar positive associations for *trans* fat intake with breast cancer,[12] ovarian cancer,[13] and colorectal cancer[14] have been reported. More recently, the Reasons for Geographical and Racial Differences in Stroke cohort[15] showed that detrimental associations of total *trans* fat consumption on health translated to a 24% higher risk of total mortality among participants in the highest compared to the lowest quintiles of consumption at baseline.

The proposed pathways through which increased levels of *trans* fatty acid consumption may affect health outcomes include adverse effects on intermediate risk factors such as circulating lipids, endothelial function, and inflammation.[7] These, coupled with evidence from the epidemiologic and intervention studies, have prompted current public health guidelines in the United States (US) and many other nations to recommend restriction of *trans* fatty acid consumption.[1,16] The US Food and Drug Administration has recently issued a preliminary statement that partially hydrogenated vegetable oil (PHVO), the major source of *trans* fat in processed foods, will no longer be "generally recognized as safe"[17]—a measure that should considerably reduce the amounts of *trans* fat found in processed foods in the United States.

Nevertheless, self-reported dietary intake assessment may be limited in the ability to accurately reflect an individual's consumption of nutrients, due to measurement error, recall bias, selective reporting, and incompleteness of food composition databases.[18,19] More importantly, dietary assessment tools are most efficient to capture total *trans* fatty acid consumption, leaving possible differential effects of individual *trans* fatty acid subtypes and specific isomers generally unaddressed, which is also reflected in the guidelines and policies that are currently targeting reduction of total *trans* fats (produced principally through the process of partial hydrogenation). Objective biomarkers of fatty acids, such as circulating or adipose tissue concentrations, in this regard, may provide a more accurate and comprehensive measure of dietary exposure[20] and offer an intriguing prospect to

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investigate the effects of *trans* fatty acid subtypes and their specific isomers, including *trans* palmitoleic (t-16:1), *trans* oleic (t-18:1), and *trans* linoleic (t-18:2) isomers.

In this issue of *Journal of the American Heart Association*, Wang et al[21] attempt to address this key gap in the existing literature by assessing whether plasma phospholipid compositions of *trans* fatty acid subtypes and their isomers are associated with total, cardiovascular and nonvascular mortality, and incident CHD outcomes in the Cardiovascular Health Study (CHS). During 31 494 person-years of follow-up, this study ascertained >1700 deaths and >600 incident CHD events, considerably more than many previous studies of individual *trans* fatty acid biomarkers and CVD-related outcomes.[7] CHS found that the t/t-18:2 isomer was associated significantly with increased risk of total mortality, owing principally to a strong positive association with CVD-related deaths. Participants in the top quintile of circulating plasma t/t-18:2 composition had a 23% higher risk of total mortality compared to those in the lowest quintile, and had a 40% higher risk of CVD mortality. Additionally, in the multivariate model, mutually adjusted for other *trans* fatty acids, t/c-18:2 was also associated with an increased risk of overall mortality and incident CHD. There were indications of generally greater within-person variability over time for these *trans*-isomers of omega-6 linoleic acid. When the authors applied regression dilution correction, the risk associations became further pronounced. Interestingly, there was an inverse association of circulating plasma c/t-18:2 composition with total and nonfatal CHD, which was, however, abolished following subsidiary analyses to exclude events that occurred in the first 2 years of follow-up. Finally, as initially hypothesized by the authors, there was no important association for either t-16:1 or t-18:1 isomers with study outcomes.

These findings appear to be broadly consistent with the prior observational studies that report similar potentially diverse associations across *trans* palmitoleic (t-16:1), *trans* oleic (t-18:1), and *trans* linoleic (t-18:2) fatty acids in relation to CVD risk. As in the CHS, the majority of studies investigating biomarkers of *trans* fatty acids have reported particularly strong increased risks of CHD and sudden cardiac death with increasing levels of total t-18:2.[7] By contrast, the evidence regarding an association of t-16:1 and t-18:1 biomarkers with CVD outcomes is somewhat mixed,[7] with the Nurses' Health Study,[22] an Australian case–control study,[23] and the EURAMIC Study[24] reporting increased risks, whereas a large case–control study in Costa Rica[25] and the Cardiac Arrest Blood Study[26] reporting a lack of significant association with vascular outcomes. The current study, therefore, reinforces earlier suggestions that t-18:2 may be detrimental for optimal health and that the differential effects of these *trans* fatty acids compared with t-16:1 and t-18:1 should be further evaluated in future studies. Perhaps more importantly, this is the first study to date to investigate specific t-18:2 isomers, including c/t-, t/c-, and t/t-18:2 fatty acids, and to report that t/t-18:2 isomers may be particularly more potent in increasing CVD risk compared to other *trans* fat isomers including c/t- and t/c-18:2.

A few limitations of this study (albeit generally addressed by the authors) should be highlighted to put the results into context. First, plasma phospholipids measurements were done in 2 separate time points—increasing a possibility of laboratory drift for t/t-18:2 levels. Following exclusion of the earlier population subset (enriched with early CHD cases), significance of the observed associations disappeared in the models that adjusted for other *trans* fatty acid subtypes. A positive direction of the associations, however, was sustained, suggesting that the lack of significance might be due to limited power available in these supplementary analyses. Nevertheless, the possibility of bias in the original risk estimate due to differential measurement error cannot be completely ruled out. It was also noteworthy that the laboratory coefficient of variations for t-18:2 was 8%.

Second, the isomers c/t- and t/c-18:2 occur in similar food sources[27] and were unsurprisingly highly correlated (Spearman's r=0.78), although were not as extreme as the intercorrelation of specific t-18:1 isomers (for which the authors decided [appropriately] not to investigate individual associations). Nevertheless, one should consider the possibility that the potential detrimental association of t/c-18:2 with total mortality and CHD, and the inverse association of c/t-18:2 with total and nonfatal CHD were to some extent a result of collinearity. The uncertainty regarding these specific associations is further underlined by the findings that t/c-18:2 was only associated after mutual adjustment for other fatty acid subtypes, whereas the association of c/t-18:2 attenuated after excluding cases in the first 2 years of follow-up. Therefore, these results, while importantly advance the literature, also highlight the need for further scientific work. Similarly, while no important association was observed for total t-18:1 fatty acids, a potential causal role (or a lack of it) for specific t-16:1 and t-18:1 subtypes is difficult to appreciate from observational findings. Finally, as the authors pointed out, this study was conducted in an elderly population, and the results may, therefore, be affected by a survivor bias.[21] Studies in populations including younger participants and from different regions across the United States and worldwide—potentially exposed to different sources and amounts of *trans* fat[28]—should be conducted to inform whether these associations are similar in such populations.

If further characterized and established in future studies, the implications of these findings for public health policies are considerable. Food sources substantially contributing to total *trans* fat consumption include fried foods, margarine,

processed meats, bakery products, and biscuits.[27] Current policies generally focus on limiting total *trans* fat in the diet, by targeting industrial use of PHVO containing *trans* fatty acids.[16,29] However, the major dietary and biomarker component of total *trans* fat, including that derived from PHVO, is comprised of t-18:1 isomers, which, however, was unrelated to total or CVD mortality in the CHS.[21] Among a range of foods containing PHVO, bakery foods were the only dietary source significantly associated with levels of t-18:2 plasma biomarkers in the CHS, and diet explains a small proportion (2%) of the total variation in t-18:2 biomarker levels in this population.[27] This observation, further supported by the lack of correlation of t/t-18:2 with other plasma phospholipid *trans* fatty acid isomers, suggests that biomarker levels of t-18:2 isomers, which were associated with CVD in the CHS, may be related to other specific food sources and/or other metabolic processes. Indeed, previous studies have shown that *trans* fatty acid isomers, including t/t-18:2, can also be derived from sources other than PHVO, such as vegetable oil deodorization and high-temperature frying.[30,31] Additionally, some studies have reported that genetic variants, such as in the SCD1 gene,[32,33] as well as personal circumstances including gender[34] and use of hormonal contraception,[32] and interplay of other individual plasma fatty acids such as omega-3 eicosapentaenoic acid,[35] may importantly influence the circulating levels of *trans* fatty acid isomers.

In summary, based on this important CHS report, if the detrimental effects of *trans* fat on health are indeed due specifically to the t/t-18:2 isomer (and possibly also to the t/c-18:2 isomer), this may have strong implications for future guidelines and policies on reducing dietary *trans* fat. Such implications could include measures to reduce *trans* fat in foods that contain these specific isomers and targeting of other industrial processes (additional to targeting PHVO) from which they are derived. However, prior to such translation at the policy level, it is crucial to reliably investigate (1) the association of specific *trans* fatty acid isomers in other populations, including younger participants and across different regions; (2) specific food sources of t/t-18:2 isomers in such populations and explore other, nondietary, determinants on biomarker levels of specific *trans* fatty acid isomers; (3) potential differential incorporation of specific *trans* fatty acid isomers into different biomarker lipid fractions and tissues—potentially explaining heterogeneity in findings regarding the association of t-16:1 and t-18:1 isomers with CVD across studies; and (4) biological mechanisms underlying differential effects of specific *trans* fatty acid isomers with disease risk. Therefore, the current study while reinforces existing recommendations to reduce *trans* fat consumption in the population, it stimulates future scientific work to further contextualize these important findings.

Disclosures

None.

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