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TABLE OF

CONTENTS

Dehghan M, Mente A, Zhang X, Swaminathan S, Li W. Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study. Lancet. 2017;390:2050–62.

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

Cardiovascular disease remains the leading cause of mortality globally [1]. Over the past 50-years there have been shifting global trends in risk. In developing countries like the UK and US, while cardiovascular disease remains the leading cause of mortality, the absolute level of annual mortality has been reduced by more than half [2,3]. In the UK, for example, coronary heart disease accounted for 166,000 deaths 1961; by 2009 that figure had been reduced by 52% to 80,000 [3]. In the US between 1980 and 2008 heart disease deaths decreased by 64%: from 345 deaths per 100,000 to 123/100,000 [4]. These declining trends in developed countries are attributable to a combination of primary prevention and treatment (statins), and secondary prevention factors including declining rates in smoking, population-wide blood cholesterol and blood pressure, and dietary changes [3,4].

However, over 75% of cardiovascular disease deaths now occur in low or middle-income countries [1]. In high-income countries the increasing trends in population increasing adiposity has added to the traditional risk factors of smoking, inactivity, alcohol, and high-animal fat diets [3,4]. With a recent scrutiny on refined carbohydrates and added sugars in the typical Western diet pattern and the contentions that these dietary constituents are primarily responsible for increasing population trends in adiposity, this has generated a narrative of, “we were wrong about fat, sugar is to blame”.

A central tenet of this narrative is that there is no association between saturated fat and heart disease risk [5,6]. In support of this position it is argued that where saturated fats are replaced with carbohydrates, there is no reduction in risk of heart disease. This is then framed against national dietary guidelines that were introduced in the late 1970’ s and early 1980’ s, which are accused of having caused a shift in population diet patterns to a “low-fat” diet high in carbohydrate [5,6]. This is at the core of suggesting that as heart disease remains the leading cause of mortality, carbohydrates are more implicated as a dietary risk factor than saturated

The Study

The Prospective Urban Rural Epidemiology [PURE] study was a large-scale prospective cohort study* including three high-income countries [the UAE, Canada, and Sweden]. 11 middle-income countries [Brazil, China, Chile, Argentina, Colombia, Iran, Malaysia, occupied Palestinian territory, Poland, South Africa, and Turkey], and 4 low-income countries [India, Pakistan, Bangladesh, Zimbabwe]. Subjects were followed up over an average of 7.4-years, with primary outcomes being total mortality and major cardiovascular events [including fatal cardiovascular disease, non-fatal myocardial infarction, stroke, and heart failure].

*Geek Box: Prospective Cohort Studies

In the biomedical model, a randomised controlled trial is considered the 'gold standard' of scientific evidence, particularly where an RCT tests an effect of an intervention on hard endpoints. However, in nutrition, doing long-term RCTs on hard endpoints is a practical and ethical impossibility; trying to maintain behaviours over the long-term is a practical issue, while it would be unethical to place subjects on a diet deficient in a given nutrient, or excessively high in a potentially harmful dietary constituent, over the long-term. Nutritional epidemiology is therefore where the effects of diet on long-term health outcomes is primarily examined. Amongst the different observational designs available, prospective cohort studies provide the best option for assessing the impact of a long-term exposure (diet) on diseases with long latency periods (cardiovascular disease, cancer, etc.). The prospective nature of cohort studies makes them more robust as they are able to mitigate a number of biases, for example recall bias, reverse causation, and selection bias, that often arise in other observational designs [16]. A prospective design allows researchers to update potential confounders to be adjusted for, as additional or new information on potential confounders may be included prior to analysis [16]. If all relevant confounders are accounted for, a well-conducted prospective cohort study can mimic an RCT; and ultimately any truly long-term RCT in nutrition becomes about as 'controlled' as a prospective cohort study over time. In this respect, prospective cohort studies are the best observational design to examine the relationship between diet and health outcomes over the true long-term. They are not perfect, no design is: when coming to conclusions, we consider the totality of evidence.

Having included countries from different income strata, the authors then categorised countries as 'Asian' or 'non-Asian' regions, nominally to reflect the typically higher proportion of carbohydrates in the diet in Asian countries. The countries included in the Asian region were Bangladesh, India, China, Malaysia, and Pakistan. Every other country was designated under one broad non-Asian region.

Dietary intake was then categorised by quintiles [meaning the data was divided into 5 groups] of intake based on percentages of total energy intake, and the lowest quintile category was used as the reference group for both regions. The authors modelled the effects of replacing 5% energy from carbohydrate with 5% energy from either saturated and unsaturated fats, and adjusted for education, smoking, physical activity, waist:hip ratio, diabetes history, urban or rural location, and total energy intake. Hazard ratios* were calculated and presented with 95% confidence intervals for percentages of energy from carbohydrate, protein, fat, and types of fat.

*Geek Box: Hazard Ratios

Hazard ratios, or 'HRs', are used to express the chance of an event occurring in a reference or treatment group compared to the control group, over a period of time. They are calculated by looking at the rate at which events occur, for example, how many deaths occur per 1000 person-years ('person-years' being a calculation based on the number of years a participant spent in a study). They are used commonly in prospective cohort studies because they reflect the time survived during the period of observation until an event (for example, a heart attack – if that is an outcome of interest) occurred. Because the risk associated with diet-disease interactions isn't constant - someone doesn't have a heart attack after eating one cheeseburger, but may have one over 10-years of poor diet - HR's are used because they reflect risk over time. HR's are useful because they provide a quantitative summary of the results that is more easily communicated. It is important to note that expressing a HR as a percentage, for example, "a 30% increase in risk for heart disease" is always the risk <u>relative to the reference or control group</u>. So it is always a comparison, and this is important for interpreting nutrition research, because no nutrient exists in a vacuum: if one nutrient is high, often another has been replaced by it. So 'high' or 'low' can be relative to whatever has been replaced in the diet. Lesson: always look a little closer at the data to see what the actual levels of a nutrient were, the type of nutrient looked at, and how that might relate to the differences in risk observed between two groups.

Results: Comparing the highest quintile of carbohydrate intake [77.2% energy] to the lowest [46.4% energy], there was a statistically significant 28% increase [in risk associated with total mortality, and 36% increase in risk for non-cardiovascular mortality. No significant associations were found for carbohydrate intake and cardiovascular mortality, major cardiovascular disease, myocardial infarction, or stroke.

In comparing the highest quintile of total fat [35.3% energy] to the lowest [10.8% energy], there were significant 23% and 30% reductions in risk associated with total and non-cardiovascular mortality, respectively. No significant associations were observed between total fat and the other endpoints. For saturated fats, compared to the lowest quintile of intake [2.8% energy], the highest quintile [13.2% energy] had a significant reduction in risk associated with total mortality, stroke, and non-cardiovascular mortality [no significant associations with other endpoints]. Further, the replacement of 5% energy from carbohydrate with 5% energy from saturated fat was associated with a 20% reduction in risk for stroke.

The Critical Breakdown

Pros: A large number of individuals - 133,335 - were available for analysis. For countries without a validated food frequency questionnaire [FFQ] the researchers validated FFQ's against multiple 24-hour recalls. This is a 'Pro' because within-person variance [that is, the difference in an individual's day-to-day diet] may be large in low-middle income countries (7). For example, let's say that white rice is the daily staple, but once a week pork is consumed. If a single 24-hour recall was taken on the day pork was eaten, this would misrepresent the diet as a whole. Conversely, if a 24-hour recall was taken on the day without the pork, it could look like the diet is deficient in protein. Taking several 24-hour recalls may have allowed the researchers to capture this potential variation. The authors do not, however, give the exact number in the supplementary data. This is unlikely to be an issue given the use of FFQ [which assesses frequency of intake] as the dietary collection method, as FFQ are oriented toward capturing average intake over time, which is the exposure of interest (7). In addition, because the sample size [i.e., the numbers in the study] was so large, this would also provide a better overall average and minimise the chance of within-person variance.

While it is standard practice in epidemiology, total energy intake was adjusted for. Why is this important? Because it is the equivalent of, for example, matching calories between diets in a controlled intervention; it allows the researchers to determine whether the observed effect of a nutrient is due to the nutrient itself, rather than an influence of total energy intake (7).

Cons: Despite the perception of thoroughness in doing a large study across 18 countries in 5 continents, this has the potential to be a major limitation. From a design perspective, it is arguably inappropriate to do a correlation study across such divergent populations; not even comparing 'apples with oranges', but more a comparison of 'apples and salmon'. Pooling data from subjects with diverse baseline diets, food sources, socio-economic status, country or region-specific risk factors, could make any true associations difficult to detect. In the baseline characteristics, for example, the African cohort had a 30% smoking prevalence compared to 15% in Europe and North America. While smoking was adjusted for in the analysis, we know that smoking is more prevalent in low socioeconomic status areas and in the developing world; thus, it may be low SES associated with poor nutritional status, and health outcomes, in this study.

This could tie to a second issue, which is the manner in which the authors attempted to adjust for socioeconomic status: by adjusting for education and study centre, which nominally tracks with country income. However, education is a poor proxy for income, and ultimately income is what dictates access to resources, including nutrition (8). The authors do acknowledge the potential for this to have been an issue, given the potential for high-carbohydrate, low-fat diets to be a proxy for poverty.

Including populations from a mix of developed and developing countries may also be problematic in relation to another limitation of the study, which is that dietary intake was only measured at baseline. Only doing a baseline dietary assessment in epidemiology is acceptable if there is relative stability in the population diets being studied [7]. However, we know from studies in different population cohorts that stability in diet over time differs, and that it is difficult to generalise reproducibility in one population to another [7]. In this case, those generalisations have been made for 18 countries. For example, for certain countries the authors related the country-specific FFQ to national nutrient databases. This is questionable given the rapidly changing characteristics of diet in the low-middle income countries. For example, the authors reported average total fat intake in the Chinese population as 17%, however, data from the Chinese National Nutrition and Health Monitoring Survey indicates current population average fat intake at 30-33% at the time of the study, consistent with a recent trend toward a more 'Western' diet pattern [9,10].

Key Characteristic

1. The first is the average saturated fat intake in the entire cohort: 8% total energy. The European and North American, and Middle Eastern, countries averaged 10.9% and 10.2%, respectively. All of these ranges are congruent with recommendations from the World Health Organisation to national bodies, and more particularly with a comprehensive analysis of thresholds intake wherein the 10% mark is associated with the greatest reduction in total cardiovascular events [11]. Given the association between saturated fat and CVD occur at higher thresholds of intake, the lack of a comparative group with intakes >18% means that the relationship between saturated fat and CVD was not testable as a hypothesis in this study.

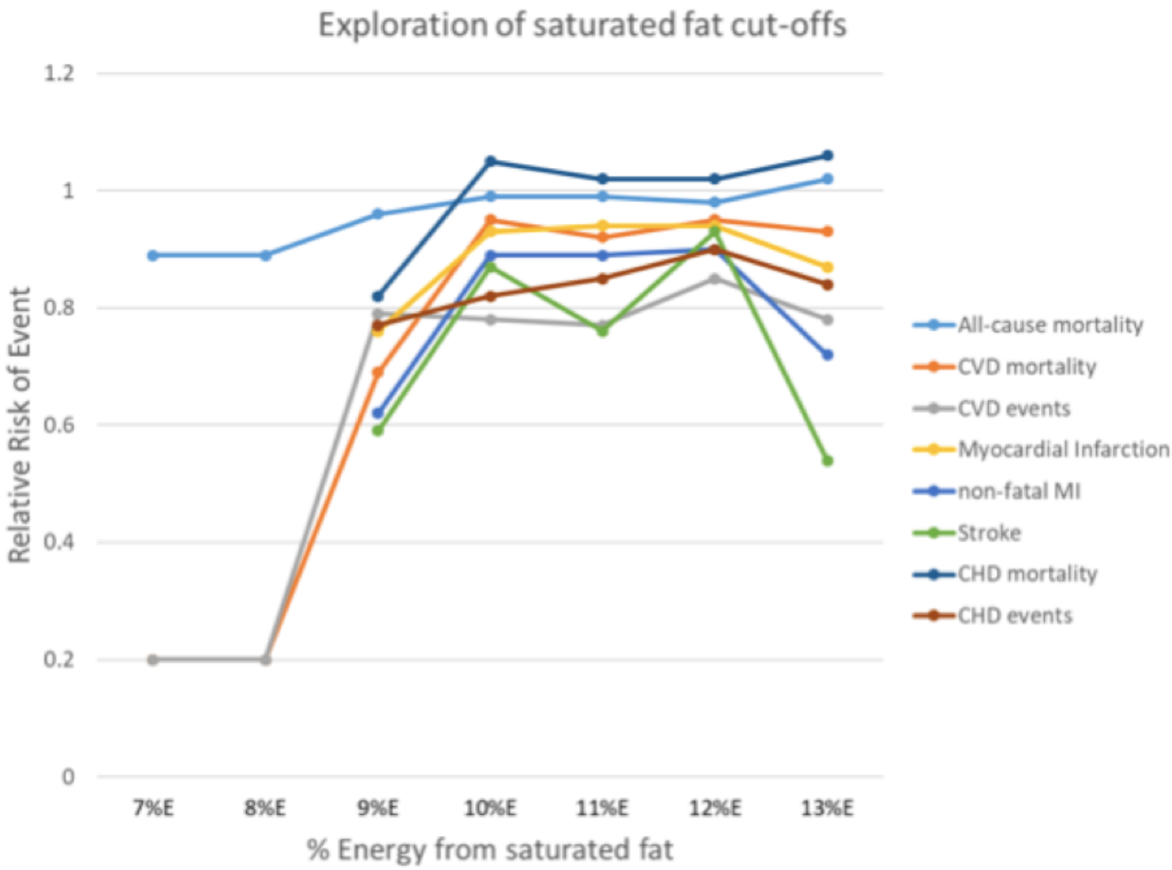

***Figure** taken from [11] illustrating cut off points for percentage energy from saturated fats on different outcomes, with the most significant effect evident for total CVD events (grey line) dropping off below 10% energy.*

2. The second can be summed up in a quote from the paper itself: "*We were __unable to quantify separately the types of carbohydrates__ (refined vs whole grains) consumed. However, carbohydrate consumption in low-income and middle-income countries is mainly from refined sources."* [Emphasis added]. In a cohort where over half of the subjects consumed at least 60% of energy from carbohydrates, and given the importance of carbohydrate quality to health outcomes, this failure to quantify sources of carbohydrate separately is unjustifiable. It means the effect of replacement cannot be clear, as we know from prospective cohort studies that do quantify carbohydrate type that there are divergent effects: wholegrain carbohydrates reduce risk for CVD, while when SFA are replaced with refined carbohydrate risk remains similar. This again confirms that any study purporting to examine relationships between carbohydrate and saturated fat that fails to quantify carbohydrate type will generate 'null' associations [12].

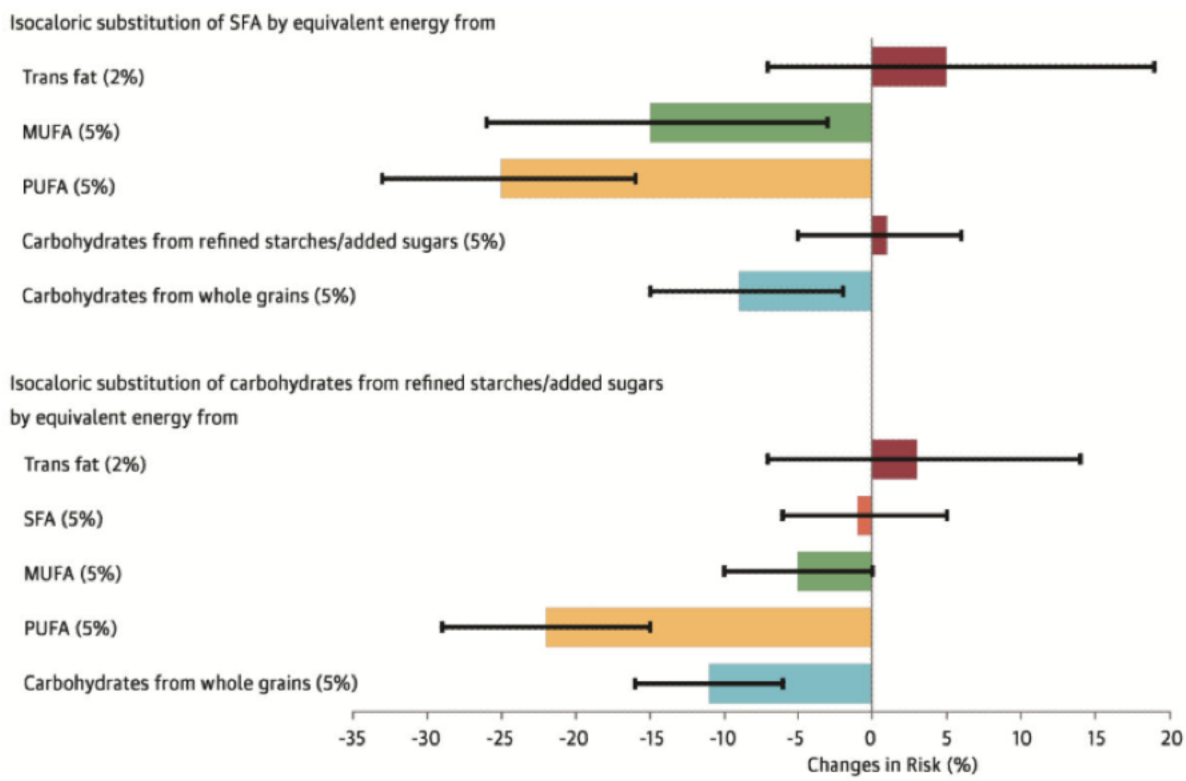

***Figure** taken from [12] illustrating the substitution effects of replacing 5% of energy from saturated fat (**top graph**) and refined carbohydrate/added sugars (**bottom graph**) with trans fats (**red bar**), monounsaturated fat (green bar), polyunsaturated fat (**yellow bar**), and wholegrain carbohydrates (**blue bar**). The graph demonstrates a 'null' effect of substituting saturated fat for carbohydrates from refined carbohydrate sources/added sugars, or substituting carbohydrate from refined sources with saturated fat.*

Interesting Finding

The preponderance of data from low-middle income Asian countries yields some interesting data, and potential explanations for the results. Quintile 1, i.e., the lowest intake of saturated fats was very low: 2.9% in Asian countries and 5.1% in non-Asian. This reflects a nutritionally inadequate diet, one with limited overall food choice and with reliance on one dietary staple, which in this cohort was white rice. By analysing risk comparing the highest vs. the lowest quintile, where the highest quintiles were 12-13.9% saturated fat, it is inevitable that a favourable effect of the higher quintile would be observed, given it likely represents a more nutritionally complete diet and diversity in food availability.

This is particularly true where the effect of increasing saturated fat was modelled against replacing 5% energy from carbohydrate, and where we know from the paper a majority of the Asian populations consumed >60% energy from carbohydrate, and that the source was largely refined carbohydrate. If the diet is so inadequate that it contains 2.9% saturated fats, increasing that to 8% is likely to represent improved nutritional status, and health outcomes [13]. The authors acknowledge that a very high carbohydrate, low fat diet might be a proxy for poverty and access to healthcare, but stated that they adjusted for factors that would account for socio-economic status.

However, knowing the composition of the diet was largely refined carbohydrate, and with the lowest quintile of saturated fat indicating dietary inadequacy, what this study really showed was that a precarious level of intake is associated with dying early [13].

Interestingly, the lowest risk for saturated fat intake and both total mortality and major CVD and was observed in Quintile 4, or between 8.9-10.2% energy. If anything, a closer scrutiny reveals this paper likely supports the 10% threshold for SFA intake. So when you hear this study cited for support that “higher saturated fat intake is necessary for health”, keep in mind that “higher” is relative: increasing from 3% to 10% might be positive in populations facing nutritional inadequacy; increasing from 10% to 18% would likely increase cardiovascular mortality risk. Consider this in light of the recent Hooper et al. review which found the greatest benefit to reducing CVD risk was found where saturated fats averaged 18% in the diet, and the average reduction was 8% [11].

Relevance

The authors state: "*Our findings do not support the current recommendation to limit total fat intake to less than 30% of energy and saturated fat intake to less than 10% of energy.*" Let's be clear about a few aspects of this interpretation:

It is impossible to support the conclusions arrived at by the authors in relation to saturated fat, when the average saturated fat intake of the entire study was 8% - consistent with a threshold of intake we associate with reduced risk of cardiovascular events.

This is really important: the majority of deaths in the study were from non-cardiovascular causes. There were no significant associations with cardiovascular disease and mortality, and the public health recommendations for saturated fat are made specifically on the basis of cardiovascular health. 75% of the study population consumed <10% energy from saturated fat. Contrary to the authors conclusions, their findings in fact are congruent with recommendations for population saturated fat intake.

The predominance of refined carbohydrate as a dietary staple in the majority of the PURE cohort also precludes the authors' conclusion that 'limiting' carbohydrate might improve health, having regard to the influence of carbohydrate type and quality on risk. Their conclusion is a misleading generalisation, as low-middle income countries with high reliance on refined carbohydrate would improve health by increasing dietary adequacy (and security), not simply lowering intake, while developed countries would benefit from altering carbohydrate source from refined to wholegrain, which could in turn reduce total levels of intake [15]. In addition, there are other benefits from the micronutrient and bioactive food component levels in wholegrain and unrefined carbohydrate sources that contribute to health [15].

Application to Practice

This study has taken a root within certain circles as support for the 'eating more saturated fat is good for you, cut the carbs' narrative. Having regard to this, for the application let's be clear: the citing of this study as evidence of a lack of association between saturated fat and cardiovascular disease is a misrepresentation of the findings.

The current recommendations remain valid. The emphasis should remain on unsaturated fats (extra virgin olive oil, rapeseed oil, other vegetable oils, different nuts, seeds, oily fish, etc.) and wholegrain versions of carbohydrates (wholegrain versions of rice or pastas, grains, other grains like oats, barley, and in addition legumes and pulses).

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