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Low Vitamin D Levels in Painful Diabetic Peripheral Neuropathy

Becky McCall

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Lower vitamin D (25-hydroxyvitamin D) levels are found in patients with painful diabetic peripheral neuropathy (DPN) compared to those with painless DPN, patients with diabetes without any neuropathy, and healthy people, shows a study unique for its rigorous control for seasonal sunlight and physical activity.

"This is the first time a study has corrected for these confounders [sunlight and physical activity]. The findings have major clinical significance because painful DPN is distressing and disabling," said lead author Solomon Tesfaye, MD, consultant endocrinologist at the Royal Hallamshire Hospital, Sheffield, UK, who discussed the findings with *Medscape Medical News* in an interview.

Not only have previous studies failed to robustly control for seasonal sunlight exposure and physical activity, which have a significant impact on vitamin D levels, most have not differentiated between people with painful and painless DPN. In addition, these prior studies have lacked detailed assessment of peripheral neuropathy including measurement of skin intra-epidermal nerve density.

"The finding is a big deal because it opens up a whole new area of research," asserted Tesfaye. "It's a very common disorder with 25% of patients with diabetes having neuropathic pain, many of whom are undiagnosed and suffering in silence because they believe it is just part of the aging process," he explained.

He added that the small proof-of-principle study was a borne out of anecdotal findings that vitamin D supplements or injections given to patients with painful DPN improved their pain.

The article was published online August 13 in *Diabetic Medicine*.

Differentiating Between Painful and Painless DPN

In total, 45 white Europeans with type 2 diabetes and 14 healthy volunteers participated in the study. Those with type 2 diabetes were then divided into three further groups (17 with painful DPN, 14 with painless DPN, and 14 with no DPN).

Seasonal sunlight exposure and daily activity were measured, a lower limb skin biopsy was performed, and 25-hydroxyvitamin D was measured from July to September (summer season) in all patients. The relationship of vitamin D with measures of small and large nerve fiber function was also assessed using quantitative sensory testing, skin biopsy, and nerve conduction studies.

Essentially, after adjusting for age, body mass index, activity score, and sunlight exposure, vitamin D levels were significantly lower in those with painful DPN (34.9 nmol/L) than healthy volunteers (62.1 nmol/L), those with no DPN (49.6 nmol/L), and those with painless DPN (53.1 nmol/L). Vitamin D was the only independent variable found to be significant with an inverted odds ratio of 1.11, write the researchers.

Explaining the results with regard to the measurement of peripheral neuropathy, Tesfaye said they found that lower vitamin D levels correlated with a lower (more abnormal) cold detection threshold ($r = 0.39$, $P = .02$) using quantitative sensory testing (QST). On skin biopsy, considered the gold standard for diagnosing and assessing small fiber neuropathy, lower subepidermal nerve fiber densities also correlated with lower levels of vitamin D ($r = 0.42$, $P = .01$).

"Patients with painful DPN were found to have less sensitivy, i.e., only detected cold at 11°C and had low numbers of small nerve fibers," reported the endocrinologist, who is an expert in the field of DPN.

The findings suggest that vitamin D deficiency may contribute to the development of painful DPN by playing a role in the pathogenesis of small-fiber neuropathy particularly affecting nociceptors, he and his coauthors explain.

He highlighted that not only is painful DPN underdiagnosed, but even when it is identified there is a paucity of effective medication available.

Current therapies, typically amitriptyline or gabapentin among others, work in just one third of patients and only improve pain by approximately 50%.

Side effects can be considerable and common. "These drugs kill the pain but 'kill' the patient too. If we have something that is physiologically active and improves pain without the side effects then the finding here is a major triumph."

However, he cautions that this is a small, early study and much more research is needed to prove causality between low vitamin D levels and painful DPN. "A randomized, double-blind, prospective clinical trial is needed, and I'm going to apply to do it."

"If causality is confirmed, this will have a significant impact on clinical practice as there would be a clear rationale for early screening and treatment for low vitamin D in people with painful DPN."

Diabet Med. Published online August 13, 2018. Abstract

Tesfaye has reported no relevant financial relationships.

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Common drug for diabetic foot pain isn't effective, B.C. researchers say

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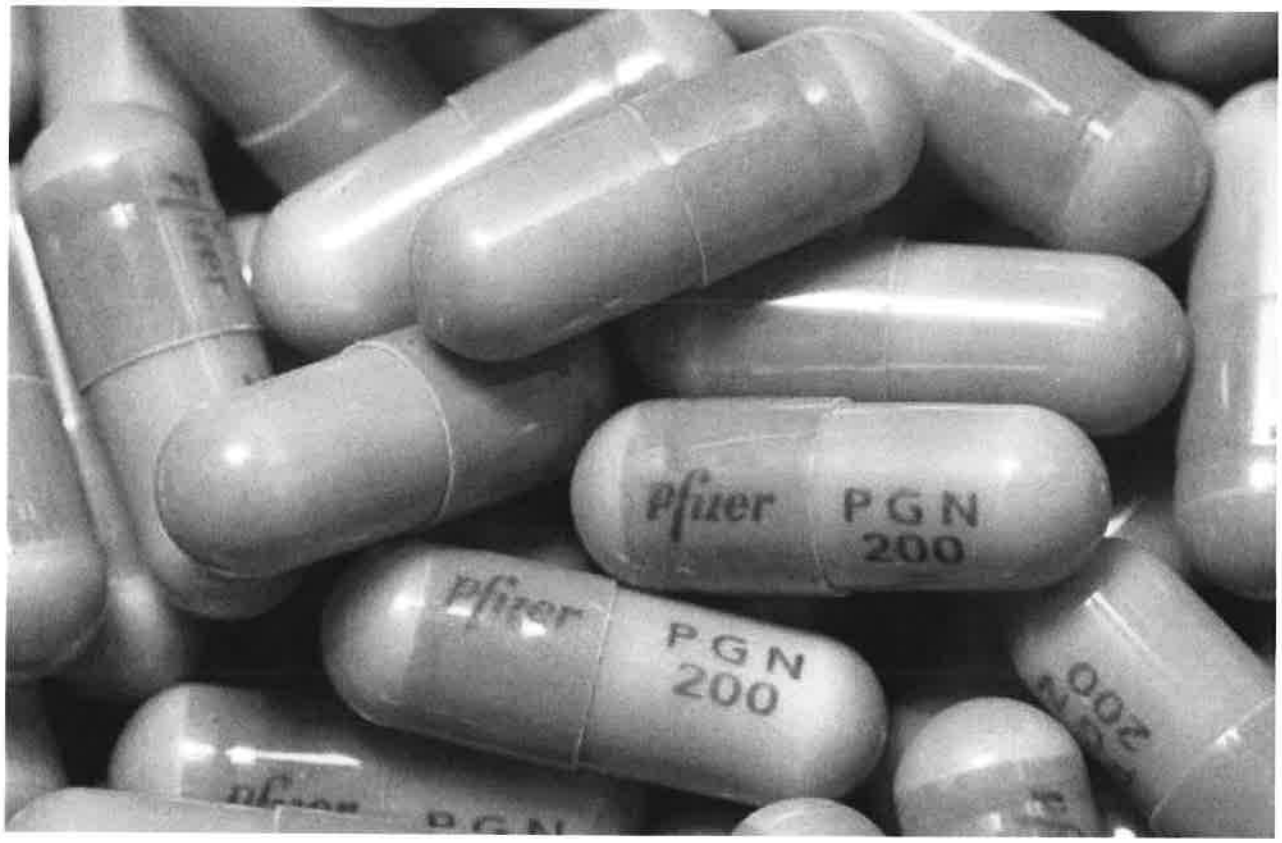

A report by the Therapeutics Initiative at UBC suggests Lyrica only helps about one in 10 of the people to whom it is prescribed. *JB REED / BLOOMBERG NEWS*

A pain medication that rarely works as promised had a 17-fold increase in prescriptions over a decade, says the latest research (http://www.ti.ubc.ca/2016/01/19/96-benefits-and-harms-of-drugs-for-neuropathic-pain/) from the Therapeutics Initiative at the University of B.C.

Its report says only about one in 10 patients will gain relief from pregabalin (trade name Lyrica), which is used to treat peripheral neuropathy — usually foot pain caused by diabetes — and other discomfort. Therapeutics Initiative is think-tank that reviews the usefulness of prescribed drugs and offers advice to B.C.'s doctors and pharmacists.

The latest work released Tuesday concludes that pregabalin, and two other painkillers studied, gabapentin and duloxetine (Cymbalta), all have little effect on pain despite extensive marketing campaigns promoting them.

Co-author Dr. Tom Perry, a clinical assistant professor in the department of anesthesiology, pharmacology and therapeutics at UBC, says doctors often tell patients to take these medications in higher doses and for a longer time than the evidence supports. Patients should know within days whether the medications are working for them, he says.

"These drugs are intended to make someone feel better; if you're not feeling better, why take it?"

Perry and co-author Aaron Tejani, a clinical assistant professor in Pharmaceutical Sciences, looked information on gabapentin, pregabalin and a number of other medications gathered by Cochrane Reviews which evaluate scientific research from around the world. They found expectations of the drugs' effectiveness far outstripped the evidence and likely drives an increasing number of prescriptions.

In B.C., pregabalin prescriptions rose 17 fold from 2005 through 2014, compared with a 1.8-fold increase in people receiving gabapentin.

Gabapentin is now available as a generic drug, but was formerly trademarked medication called Neurontin manufactured by Pfizer. The pharmaceutical giant agreed to pay $430 million in U.S. fines (http://www.reuters.com/article/us-pfizer-neurontin-settlement-idUSKBN0ED1IS20140602) in 2004 after marketing it for unapproved uses such as migraine headaches and pain.

Combined costs of gabapentin, pregabalin, and duloxetine were over $52 million in British Columbia during 2014, says the Therapeutics Initiative report, of which Pharmacare paid over $13 million, mostly for gabapentin.

Pregabalin, also manufactured by Pfizer for neuropathic pain, is not covered under B.C.'s publicly funded Pharmacare following a recommendation by a national drug advisory committee in 2005 (https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_Lyrica_Jan26-06.pdf) . As a result, patients either pay for it out-of-pocket or through private health insurance,

Worse than simply buying a medication that's not working, Perry says pregabalin is often prescribed to older adults who may become drowsy or lose their balance because of it.

Therapeutics Initiative is funded by the B.C. Ministry of Health through a grant to UBC.

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Comments

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Metformin Link to Vitamin B_{12} Deficiency, Neuropathy in Diabetes

Miriam E Tucker

September 25, 2015

STOCKHOLM — Metformin-related vitamin B_{12} deficiency might contribute to clinically significant peripheral neuropathy in diabetes patients, new research suggests.

Guidelines from European Association for the Study of Diabetes (EASD) and the American Diabetes Association do mention vitamin B_{12} deficiency as a risk of metformin treatment for type 2 diabetes, but they don't make recommendations for screening or supplementation, said Mattijs Out, MD, an internist of vascular medicine at Bethesda Diabetes Research Center, Hoogeveen, the Netherlands, who presented the findings last week at the European Association for the Study of Diabetes 2015 Meeting.

"This is important. The consequences of vitamin B_{12} deficiency, like neuropathy or mental changes, may be profound. Even more, they may be difficult to diagnose, because they may be ascribed to old age or diabetes itself and may be or become irreversible. On the other hand, vitamin B_{12} deficiency is relatively easy to diagnose, and treatment is easy, cheap, and effective," Dr Out commented.

Previous research from Dr Out's group and others has linked metformin use to vitamin B_{12} deficiency (<150 pmol/L), raising concern that the drug may be contributing to peripheral neuropathy separate from the effect of the diabetes itself.

In the current study, Dr Out and colleagues examined, for the first time, a very specific biomarker for tissue B_{12} deficiency, methylmalonic acid (MMA), and examinedthe impact of that on a validated neuropathy score; they found that the overall increase in MMA outweighed the benefit derived from metformin's glucose-lowering effect.

But during the question-and-answer period, some doctors expressed skepticism, stating that they hadn't seen very high rates of vitamin B_{12} deficiency in decades of metformin use.

Session moderator Guntram Schernthaner, MD, professor of medicine at the Medical University of Vienna, Austria, told *Medscape Medical News*, "I measure only in suspected cases and have almost never found a relationship.... The data aren't strong enough in my opinion. I recommend a large database study to investigate how often it's occurring."

Dr Schernthaner added, "You can measure [vitamin B_{12}] if you suspect [deficiency], but the key question is whether you should have routine screening. But before you recommend this, you have to prove it's a true effect."

Measuring Metformin's Opposing Effects: HbA_{1c} vs MMA

Dr Out and colleagues aimed to dissect the two opposite effects of metformin: a reduction in HbA_{1c}, which would be expected to improve neuropathy scores, and an increase in MMA, a marker of B_{12} depletion leading to worsening of peripheral neuropathy.

Data were from the Hyperinsulinemia: the Outcomes of its Metabolic Effects (HOME) study of 390 insulin-treated patients with type 2 diabetes from three outpatient clinics in the Netherlands, who were randomized to 850-mg metformin or placebo three times daily for a mean of 4.3 years.

The original study, published in 2010, found that long-term treatment with metformin increased the risk of vitamin B_{12} deficiency by 19% ($P < .001$), which resulted in 5% greater homocysteine concentrations ($P = .09$).

The current analysis includes data collected over those 4.3 years from 17 visits in which measurements of HbA_{1c} and of the clinically validated Valk Neuropathy Score (*Diabet Med.* 1992;9:716-721) were collected and six visits in which MMA was measured.

Using structural equation modeling with adjustment for age and cardiovascular risk factors and accounting for renal clearance of MMA, Dr Out and colleagues determined that after 4.3 years, metformin treatment was associated with a mean increase in MMA of 0.039 µmol/L (P = .001).

Per "gram-year" of metformin (similar to "pack-years" of cigarettes), there was an overall nonsignificant increase in neuropathy score of 0.032 (P = .34).

This reflects metformin's competing protective effect, Dr Out noted.

However, with the 0.039-µmol/L increase in MMA factored in, the net effect came to a 0.25-point increase in the Valk neuropathy score, he pointed out.

Clinical Implications As of Now?

Dr Out commented, "With over 100 million prescriptions of metformin per year, many patients may be at risk," adding that clinical options include screening for vitamin B_{12} deficiency after 4 years of metformin use or simply supplementing all patients, possibly with a combination metformin-vitamin B_{12} pill.

To *Medscape Medical News*, he commented, "I think it's always a problem when a side effect is doctor-induced. I think there are enough data to suggest supplementation."

But Dr Schernthaner disagrees. "I would say this isn't good enough....You need first a large analysis of vitamin B_{12} to determine the real level [of deficiency]."

The study was sponsored by Altana, Lifescan, Merck-Lipha, Merck Sharpe & Dohme, and Novo Nordisk. Dr Out and Dr Schernthaner have no relevant financial relationships.

European Association for the Study of Diabetes 2015 Meeting; Stockholm, Sweden. Abstract 220, presented September 18, 2015.

Send comments and news tips to news@medscape.net.

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PURE Shakes Up Nutritional Field: Finds High Fat Intake Beneficial

Sue Hughes

August 29, 2017

BARCELONA, SPAIN — A new study of dietary habits in 135,000 people around the world is set to shake up the nutrition field, with results showing high fat intake—including saturated fat—was associated with a reduced risk of mortality.

The PURE study, which followed participants from 18 countries for 7 years, also found that high carbohydrate intake was associated with an increased risk of mortality, although the data do not discriminate between processed and unprocessed carbohydrates.

While the study found a beneficial effect of increasing consumption of fruit, vegetables, and legumes on mortality, the maximum benefit was seen at three to four servings a day (equivalent to 375–500 g/day), with no additional benefit with higher intakes. The benefit from fruit, vegetables, and legumes was greater if they were eaten raw rather than cooked.

There was no association of either fat (total or saturated) or carbohydrate intake or fruit/vegetable/legume intake with major cardiovascular-disease events.

Dr Salim Yusuf

Senior author of the PURE study, Dr Salim Yusuf (McMaster University, Hamilton, ON), commented to *theheart.org / Medscape Cardiology*: "My hope is that our results will stop the whole population from feeling guilty if they eat fat in moderation. While very high fat intake—when it accounts for 40% or more of your dietary intake—may be bad, the average fat intake is about 30% and that's okay. We're all afraid of saturated fat, but actually we shouldn't be. Saturated fat in moderation actually appears good for you.

"Also, you don't need to stress out trying to eat five or more portions of fruit and vegetables, when three or four will probably have the same benefits. We've had enough evangelism in dietary guidelines. We need more moderation."

He added: "My advice to the general population to lead a healthy lifestyle is don't smoke and take exercise—those two things are very clearly beneficial. And then I would say maintain a reasonable weight. You don't want to be too overweight but you also don't want to be too skinny. Eat a balanced diet—a bit of meat, fish, several portions of fruit and vegetables, but you don't have to be vegan or eat an excessive amount of plants to be healthy.

"This is good old-fashioned advice. When I showed these results to my mother, she said, 'Why did you bother doing this study? This is what our grandmothers and their grandmothers have been advocating for centuries.' And actually she is right."

The study was presented today at the European Society of Cardiology 2017 Congress. It was also published as two separate papers in the *Lancet*—one on the fat and carbohydrate outcome data[1] and one on fruit/vegetables/legumes outcome data[2]. A third paper in *Lancet Diabetes and Endocrinology* focuses on effects of the different dietary patterns on lipid levels and blood pressure[3].

The PURE trial documented 5796 deaths and 4784 major cardiovascular-disease events.

Hazard Ratio for Total Mortality (Highest Quintile vs Lowest Quintile)

Group	HR (95% CI)	*P* for trend
Carbohydrate	1.28 (1.12–1.46)	0.0001

Total fat	0.77 (0.67–0.87)	<0.0001
Saturated fat	0.86 (0.76–0.99)	0.0088
Monounsaturated fat	0.81 (0.71–0.92)	<0.0001
Polyunsaturated fat	0.80 (0.71–0.89)	<0.0001

Directly Contradictory to Recent AHA Advisory

The saturated-fat findings will be particularly controversial, especially in the cardiology community, which has traditionally held the mantra that saturated fat is the number-one dietary enemy.

Indeed, just a few weeks ago, the American Heart Association issued a new "advisory" recommending minimizing intake of saturated fat and replacing it with polyunsaturated fat or carbohydrate. The PURE findings appear to be in direct contradiction to this advice.

Commenting on this at her hotline presentation, PURE co–lead author Dr Mahshid Dehghan (McMaster University) said: "The upper levels of saturated fat intake in our study (mean 10%–13% of dietary energy) was associated with a significantly reduced mortality compared with low levels of saturated fat, and very low saturated-fat intake appears harmful. Current guidelines that recommend total fat below 30% and saturated fat below 10% of energy intake are not supported by our data."

Yusuf commented further: "The AHA guidelines are not based on the best evidence—saturated fat was labeled as a villain years ago, and the traditional church has kept on preaching that message. They have been resistant to change."

The AHA issued a statement in response to the PURE data stating "a nutrition study of PURE's scale and scope is extremely challenging" and suggesting the PURE results "be interpreted with significant caution."

The AHA says the self-reported food frequency questionnaire used as the study tool "poses some limitations." Specifically, "Individuals tend to over- or underrecall food intake, in general. In addition, the tool may not fully account for cultural differences in food patterns and may underrepresent locally relevant foods."

But the AHA added: "While we feel it's important to pay attention to saturated fats and refined carbohydrates, they are just part of the puzzle. Consumers should focus on an overall balanced diet."

Co–chair of ESC hotline session, Dr Laura Mauri (Brigham and Women's Hospital, Boston, MA), congratulated the PURE investigators for "this incredible source of information" but asked how the data can be compared with the randomized trials such as PREDIMED with the Mediterranean diet.

Dehghan replied: "Randomized trials of nutrition are difficult to conduct, as people need to be followed for many years, which is not really feasible. Observational studies with biomarker data probably give better information as long as there is extensive adjustment for confounding."

Others questioned whether the PURE data were applicable to a US population, as the study included only three Western countries (Canada, Sweden, and Poland), which contributed just 12% of the study participants.

Dehghan responded on this to *theheart.org / Medscape Cardiol*ogy "We believe our message is relevant to the US population. Our data included saturated-fat levels up to about 18% of dietary intake, and the average saturated-fat intake in the US is 14%. But more important, we found that low levels of saturated fat are harmful. The AHA is recommending saturated fat should be less than 6% of energy intake. Our study suggests that this is linked to higher mortality levels."

She added that an analysis of Asian vs non-Asian countries, which have very different dietary patterns, showed the same results, with higher mortality linked to lower fat and higher carbohydrate intake.

While she acknowledged that a low-fat/high-carbohydrate profile may be a proxy for poverty, she pointed out that the PURE results had been "extensively adjusted for many confounders, including household income—more so than in any previous study."

She reported a model in which which replacing 5% of energy from carbohydrate with polyunsaturated fat was associated with a statistically significant 11% reduction in mortality. Replacing 5% of carbohydrate with saturated fat, monounsaturated fat, or protein was associated with smaller nonsignificant reductions in mortality. All these substitutions had no effect on cardiovascular disease in the model.

Asked what the mechanism could be behind the mortality effects if it wasn't cardiovascular, Dehghan said: "We think it is a noncardiovascular mechanism—maybe cancer, infectious disease, or respiratory disease—but we don't have enough events as

yet to make any statements on this. We hope to find more data on cause of deaths as we keep following the population in the future."

In a comment accompanying the PURE publication in the Lancet[4], Drs Christopher E Ramsden and Anthony F Domenichiello (National Institutes of Health, Bethesda, MD), suggest that one potential explanation for the better mortality with higher fat levels in PURE could be that nutrient-dense meats corrected one or more nutrient deficiencies that are common in many of the countries included in the study.

They also suggest that the processed foods, including added sugars and refined grains, are likely driving the adverse mortality effects with carbohydrates.

They conclude: "The PURE study is an impressive undertaking that will contribute to public health for years to come. Initial PURE findings challenge conventional diet–disease tenets that are largely based on observational associations in European and North American populations, adding to the uncertainty about what constitutes a healthy diet. This uncertainty is likely to prevail until well-designed randomized controlled trials are done. Until then, the best medicine for the nutrition field is a healthy dose of humility."

Biomarker Data

In the biomarker paper, the PURE investigators report that intake of total fat and each type of fat was associated with higher concentrations of total cholesterol and LDL cholesterol but also with higher HDL cholesterol and apolipoprotein A1 (apoA1), and lower triglycerides, ratio of total cholesterol to HDL cholesterol, ratio of triglycerides to HDL cholesterol, and ratio of apolipoprotein B (apoB) to apoA1.

Higher carbohydrate intake was associated with lower total cholesterol, LDL cholesterol, and apoB, but also with lower HDL cholesterol and apoA1 and higher triglycerides, ratio of total cholesterol to HDL cholesterol, ratio of triglycerides to HDL cholesterol, and apoB-to-apoA1 ratio.

Higher intakes of total fat, saturated fatty acids, and carbohydrates were associated with higher blood pressure, whereas higher protein intake was associated with lower blood pressure.

Replacement of saturated fatty acids with carbohydrates was associated with the most adverse effects on lipids, whereas replacement of saturated fatty acids with unsaturated fats improved some risk markers (LDL cholesterol and blood pressure), but seemed to worsen others (HDL cholesterol and triglycerides).

The authors conclude: "Our data are at odds with current recommendations to reduce total fat and saturated fats. Reducing saturated-fatty-acid intake and replacing it with carbohydrate has an adverse effect on blood lipids. Substituting saturated fatty acids with unsaturated fats might improve some risk markers, but might worsen others. Simulations suggest that the apoB-to-apoA1 ratio probably provides the best overall indication of the effect of saturated fatty acids on cardiovascular disease risk among the markers tested. Focusing on a single lipid marker such as LDL cholesterol alone does not capture the net clinical effects of nutrients on cardiovascular risk."

In a comment accompanying the biomarker paper[5], Drs Nita G Forouhi and Fumiaki Imamura (University of Cambridge School of Clinical Medicine, UK) and Dr Naveed Sattar (Oxford Centre for Diabetes, Endocrinology and Metabolism, UK) point out that because diet varied substantially between world regions (eg, the estimated mean saturated fat intake in China is 5.6% of total energy vs about 11% in North America and Europe), pooling data across regions might be problematic. They also recommend that the cross-sectional evidence should be considered hypothesis generating and that the prospective findings need to be replicated.

But they conclude: "For now, despite some caveats, the PURE study's findings broadly support the notion that reducing total fat intake may be unwarranted and that replacing saturated fat intake with (refined) carbohydrates is not a good recipe for cardiovascular health."

The PURE study was funded from more than 50 sources including the Population Health Research Institute at McMaster University, the Heart and Stroke Foundation of Ontario and Canada, and the Canadian Institutes of Health Research. The researchers report no relevant financial relationships.

For more from theheart.org | Medscape Cardiology, follow us on Twitter and Facebook.

References

1. Dehghan M, Mente A, Zhang X, et al. Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): A prospective cohort study Lancet 2017: DOI:10.1016/ S0140-6736(17)32252-3. Abstract