

TOPIC COLLECTION: ASSOCIATION BETWEEN DIET QUALITY, CARDIOVASCULAR RISK, AND MORTALITY WORLDWIDE

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Letter from the NEJM Group Guest Editor

Carbohydrate-containing foods and beverages have variable effects on health. So-called “poor-carbohydrate foods” have low amounts of fiber, more refined grains than whole grains, and a high glycemic index (a measure of how much 50 gm of carbohydrate raises the blood glucose level). It is broadly agreed that whole-grain and high-fiber foods help prevent chronic disease and that a diet with a low glycemic index helps with prevention and treatment of diabetes. But it remains unclear whether a diet with a low glycemic index also helps reduce cardiovascular risk; most data on this question come from high-income countries.

In the PURE study, published in the *New England Journal of Medicine*, Jenkins and colleagues followed over 130,000 adults on five continents for a median of 9.5 years, using food frequency questionnaires to assess the content and glycemic index of each subject’s diet. The primary outcome was a major cardiovascular event (cardiovascular death, nonfatal myocardial infarction, stroke, or heart failure) or death from any cause. After adjustments for potential confounders, patients whose diets were in the highest quintile for glycemic index were more likely to have a major cardiovascular event or to die than those with diets in the lowest quintile (hazard ratio 1.51 for those with preexisting cardiovascular disease and 1.21 for those without). The association between glycemic index and risk for cardiovascular disease or death was greater in those with body-mass index ≥ 25 .

This study establishes the association of high-glycemic-index diets with increased risk for cardiovascular disease and death across multiple countries and geographic and economic regions. While we may counsel our patients to increase fiber and whole grains in their diets, patients in many parts of the U.S. face geographic and economic barriers to obtaining food with high-quality carbohydrates. Support for our patients can go beyond individual counseling to include advocacy for improved distribution of affordable healthy foods to communities that may currently lack such access.

In related research recently summarized in NEJM Journal Watch, Swaminathan et al. used the data from the PURE study to establish an association between higher intake of refined grains and increased cardiovascular risk; Al-Shaar et al. found that higher intake of red meat was associated with increased cardiovascular risk among U.S. male health professionals; Huang et al. demonstrated that higher intake of plant proteins was associated with a lower overall mortality rate; and Li et al. found that people who met five criteria for a healthy lifestyle — including a high-quality diet — could expect an additional 7 to 10 years of disease-free survival compared with those who met none of the five criteria.

Bruce Soloway, MD

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ORIGINAL ARTICLE

Glycemic Index, Glycemic Load, and Cardiovascular Disease and Mortality

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ABSTRACT

BACKGROUND

Most data regarding the association between the glycemic index and cardiovascular disease come from high-income Western populations, with little information from non-Western countries with low or middle incomes. To fill this gap, data are needed from a large, geographically diverse population.

METHODS

This analysis includes 137,851 participants between the ages of 35 and 70 years living on five continents, with a median follow-up of 9.5 years. We used country-specific food-frequency questionnaires to determine dietary intake and estimated the glycemic index and glycemic load on the basis of the consumption of seven categories of carbohydrate foods. We calculated hazard ratios using multivariable Cox frailty models. The primary outcome was a composite of a major cardiovascular event (cardiovascular death, nonfatal myocardial infarction, stroke, and heart failure) or death from any cause.

RESULTS

In the study population, 8780 deaths and 8252 major cardiovascular events occurred during the follow-up period. After performing extensive adjustments comparing the lowest and highest glycemic-index quintiles, we found that a diet with a high glycemic index was associated with an increased risk of a major cardiovascular event or death, both among participants with preexisting cardiovascular disease (hazard ratio, 1.51; 95% confidence interval [CI], 1.25 to 1.82) and among those without such disease (hazard ratio, 1.21; 95% CI, 1.11 to 1.34). Among the components of the primary outcome, a high glycemic index was also associated with an increased risk of death from cardiovascular causes. The results with respect to glycemic load were similar to the findings regarding the glycemic index among the participants with cardiovascular disease at baseline, but the association was not significant among those without preexisting cardiovascular disease.

CONCLUSIONS

In this study, a diet with a high glycemic index was associated with an increased risk of cardiovascular disease and death. (Funded by the Population Health Research Institute and others.)

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*A complete list of investigators in the PURE study is provided in the Supplementary Appendix, available at NEJM.org.

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Refined Grains Associated with Risks for Cardiovascular Disease

Not all carbohydrates are equal.

Higher intake of carbohydrates has been associated with higher risks for cardiovascular disease and death in various studies, but most did not differentiate between refined and unrefined grains. To understand associations by carbohydrate type, investigators used data from the Prospective Urban and Rural Epidemiology (PURE) study, an epidemiological study conducted across five continents.

At baseline, the 137,130 participants were free of cardiovascular disease and had completed validated culture-specific food-frequency questionnaires, which were used to assess intakes of refined grains, whole grains, and white rice. At a median follow-up of 9.5 years, 9.2% experienced a primary outcome, which was a composite of death and major cardiovascular events (cardiovascular death, nonfatal myocardial infarction, heart failure, or stroke). Higher intake of refined grains was associated with higher risk. In a multivariable analysis, the hazard ratio for the highest category of intake of refined grains (about 7 servings/day or ≥ 350 g/day), compared with the lowest category (< 50 g/day), was 1.28 for the composite outcome, 1.33 for major cardiovascular events, and 1.27 for mortality. No significant associations were found between intake of whole grains or white rice and risks.

COMMENT

The associations in this study between carbohydrates and adverse outcomes were restricted to refined grains. Because PURE incorporates data (and eating patterns) from 21 countries, some rural and some urban, it is unclear how generalizable the data are to any particular country. Other study limitations are inherent to any epidemiological analysis, but these data provide support for current dietary guidelines that recommend limiting intake of refined grains. — **Karol E. Watson, MD, PhD, FACC**

Dr. Watson is Director of the UCLA Barbra Streisand Women's Heart Health Program, Codirector of the UCLA Program in Preventive Cardiology, and Director of the UCLA Cardiology Fellowship.

Swaminathan S et al. Associations of cereal grains intake with cardiovascular disease and mortality across 21 countries in Prospective Urban and Rural Epidemiology study: Prospective cohort study. **BMJ** 2021 Feb 3; 372:m4948. (<https://doi.org/10.1136/bmj.m4948>)

Red Meat and Cardiovascular Risk, Revisited

In men, consuming sources of protein other than red meat was associated with lower CV risk.

High consumption of red meat might be associated with excess risk for coronary heart disease (CHD) and cardiac-related mortality, but the evidence has been equivocal (e.g., *NEJM JW Gen Med* Nov 15 2019 and *Ann Intern Med* 2019; 171:756; *NEJM JW Gen Med* Jun 27 2019; [e-pub] and *BMJ* 2019; 365:2110). Many previous studies failed to specify sources of energy in comparator diets, which also might have been atherogenic (i.e., high in other sources of saturated fats).

Researchers followed more than 40,000 U.S. male health professionals (average age at baseline, 53) for 30 years, starting in 1986; they collected detailed food frequency data every 4 years and data on cardiovascular risk factors, lifestyle, and medical events biennially. Higher total intake of red meat was associated significantly with higher risk for CHD. Similarly, significant associations were seen for processed and unprocessed red meat intake and CHD. Compared with intake of red meat, equivalent intake of plant proteins (from legumes, nuts, and soy), high and low-fat dairy products, whole grains, and eggs all were associated significantly with lower CHD risk (e.g., hazard ratio, 0.86 for plant protein vs. red meat).

COMMENT

A number of potential mechanisms might contribute to these findings, including effects of saturated fat, cholesterol, and iron found in red meat, and unsaturated fat, fiber, and antioxidant content of plant-based protein sources. The extent to which these results generalize to women is unclear, and the findings might not apply to countries or ethnic groups whose dietary constituents differ substantially from high-income Western diets.

— **Bruce Soloway, MD**

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Al-Shaar L et al. Red meat intake and risk of coronary heart disease among US men: Prospective cohort study. **BMJ** 2020 Dec 2; 371:m4141. (<https://doi.org/10.1136/bmj.m4141>)

Plant-Protein Intake Is Associated with Lower Mortality at 16 Years

Replacing egg and red meat protein with plant protein might promote health and longevity.

High-protein diets, especially those in which proteins are substituted for carbohydrates, have health benefits (e.g., lower blood pressure, improved lipids, weight loss). However, little is known about the health effects of various dietary proteins: plant or animal. In this prospective study, researchers determined associations between plant-protein intake and overall or cause-specific mortality.

Study participants (416,000; age range, 50–71) completed baseline demographic, lifestyle, and dietary questionnaires in 1995 or 1996. The median daily energy intake from protein was 15% (40% from plant and 60% from animal sources). During 16 years of follow-up, 78,000 deaths occurred. After adjustment for multiple variables, plant-protein intake was significantly inversely associated with all-cause death ($\approx 13\%$ lower per 10 g/1000 kilocalorie intake increment). Similar results were obtained for cardiovascular-related death and across subgroups. Replacing 3% of energy from animal-protein sources with plant sources was associated with 10% lower mortality risk in both sexes.

COMMENT

In this study, which was subject to residual confounding, higher plant-protein intake and replacing animal with plant protein were associated with lower overall and cardiovascular-related mortality. The authors speculate that the benefits of consuming plant-based proteins are related to plant-protein components (e.g., amino acids) and metabolites. These results suggest dietary protein choice — plant versus animal — affects health.

— **Paul S. Mueller, MD, MPH, FACP**

Dr. Mueller is Regional Vice President — Southwest Wisconsin, Mayo Clinic Health System, and Professor of Medicine and Biomedical Ethics, Mayo Clinic College of Medicine and Science in La Crosse, WI.

Huang J et al. Association between plant and animal protein intake and overall and cause-specific mortality. *JAMA Intern Med* 2020 Jul 13; [e-pub]. (<https://doi.org/10.1001/jamainternmed.2020.2790>)

Just How Much of a Benefit Do We Get from a Healthful Lifestyle?

A long-term analysis suggests that adopting such a lifestyle at midlife might add as long as 10 years of disease-free life.

Virtually everyone knows that a healthful lifestyle — never smoking, normal body-mass index (BMI), moderate-to-vigorous physical activity, moderate alcohol intake, and a higher-quality diet — is good for their health. What very few people know is *just how much* benefit they get from achieving *all* these lifestyle goals.

A Harvard team examined data from about 111,000 people at age 50 and followed them prospectively for as long as 34 years. Healthful lifestyle factors were measured repeatedly and systematically, and development of various diseases and death were recorded. The primary endpoint was life expectancy free from diabetes, cardiovascular diseases, and cancer. Women who met all the healthful lifestyle measures had an additional 10.7 years of disease-free life compared with women who met no healthful lifestyle measures. For men, the number was 7.6 additional disease-free years.

COMMENT

Most of my patients know that a healthful lifestyle is good for them, but very few appreciate just how good — which negatively affects their desire to adopt one. This report might be helpful in that regard. You can say to your 50-year-old patient: “Adopting a healthful lifestyle (compared with not doing so) might allow you to live an additional 7 to 10 *disease-free* years.” For many, that would be an attractive and meaningful goal.

— **Anthony L. Komaroff, MD**

Dr. Komaroff is Professor of Medicine at Harvard Medical School.

Li Y et al. Healthy lifestyle and life expectancy free of cancer, cardiovascular disease, and type 2 diabetes: Prospective cohort study. *BMJ* 2020 Jan 8; 368:l6669. (<https://doi.org/10.1136/bmj.l6669>)