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EDITORIAL COMMENT

Is it as Simple as Adding a Bowl of Muesli?*

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Coronary artery disease (CAD) and cardiovascular disease (CVD) are largely preventable through improving risk factors such as diet.[1] Plant-based dietary patterns rich in vegetables, fruits, and whole grains and that limit intake of red meat, eggs, ultraprocessed foods, refined grains, and sugar sweetened beverages are associated with a decreased risk of CVD and are part of most guideline recommendations.[2,3] Specific dietary components also significantly impact cardiometabolic risk, with HRs for coronary heart disease for whole grains 0.78 (95% CI: 0.71-0.86), whole fruits of 0.94 (95% CI: 0.91-0.98), legumes 0.86 (95% CI: 0.78-0.94), marine fish 0.79 (95% CI: 0.67-0.92), green leafy vegetables 0.76 (95% CI: 0.62-0.94), and nuts and seeds 0.76 (95% CI: 0.69-0.84), compared to extremes.[4] What remains unclear is whether specific foods have a direct impact on CVD risk.[5] *Can we eat one food every day and decrease our risk of CAD?* In this study in this issue of *JACC: Advances*, Park et al[6] used genome wide association study (GWAS) analyses of individual dietary traits and plasma metabolites to explore associations of specific foods and contributing pathways to CVD risk.

A 2-sample Mendelian randomization (MR) study was performed to estimate the effect of 13 dietary traits on CAD risk. Dietary traits with enough genetic variants (single-nucleotide polymorphisms [SNPs]) to use as variables for analysis were included. Genetic variants related to dietary traits were taken from GWAS analyses of the United Kingdom Biobank (UKB). UKB is a longitudinal, population-based cohort of 500,000 adults aged 40 to 69, primarily of European descent. Nominal dietary information on consumption by common food groups over the last year was collected at the time of recruitment. A 24-hour recall questionnaire of the participant's reported food intake was also performed. Summary GWAS statistics on CAD risk were taken from the Coronary Artery Disease Genome-Wide Replication and Metanalysis and the Coronary Artery Disease Genetics 9 (CARDIoGRAMplusC4D) consortium.

In the primary analysis, the authors showed that nominal consumption of muesli, as the cereal participants mainly ate over the last 1 year was statistically negatively associated with CAD (OR: 0.74, 95% CI: 0.65-0.84, $P = 5.385 \times 10\text{-}4$). Muesli is a classically European breakfast that involves oats, grains, nuts, seeds, dried or fresh fruit, milk, and honey. Components of muesli have been associated with decreased CVD risk, and the relationship between muesli and reduced CVD risk has been observed in population-based cohort studies.[7] In this analysis, no other dietary traits were associated with either an increase or decrease in CAD risk.

The authors then performed a secondary GWAS analysis on 171 plasma metabolites available to participants from the UKB. Acetate, a short-chain fatty acid (SCFA) produced by the microbiota, was found to be associated with the genetic variants related to muesli intake. This is the first study to look for intestinal metabolite mediators of decreased CVD related to genetic variants in dietary intake, specifically acetate. Acetate, propionate, and butyrate are 3 of the main SCFAs produced by the gut in response to fiber intake and are felt to be immune-regulatory,

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anti-inflammatory, and potentially beneficial in CVD. In animal models, acetate has been shown to decrease blood pressure and cardiac hypertrophy.[8] This study adds evidence correlating increased SCFAs with reduced CVD.

The use of GWAS to study dietary traits and how they relate to chronic diseases is in its infancy,[5,9,10] and only 1 previous study has used GWAS to investigate dietary traits and CAD risk.[5] Park et al[6] evaluated distinctly different dietary traits than the previous study, though both used the UKB to identify genetic variants related to dietary traits and CAD risk.[5] The use of genetic variants for muesli intake enhances prior observations and provides additional mechanisms for further study.[7]

We commend the authors for continuing to shed light on the impact of individual food items on CVD. Studying data from a biobank, however, can have many limitations. For instance, the authors state that they "estimate the causal effects of 13 dietary traits on CAD risk" but unfortunately, they excluded the 3 largest dietary correlates with CAD and cardiovascular mortality due to the absence of data in the dietary history: unprocessed red meat, eggs, and processed red meat.[11-13] Additionally, it would have been useful to understand how CAD risk was defined by the CARDIoGRAMplusC4D biobank, whether based on a risk calculator or evidence of an angiographic disease or event.

Park et al identify that their study is limited by the assumptions of any MR study. It is assumed that the genetic variants (SNPs) are strongly associated with muesli intake and that they are not associated with CVD risk by any other pathway other than muesli. The components of muesli such as whole grain oats and fruits have been shown individually to have an impact on CVD; however, that may not be true for all components of muesli. Clinicians should become familiar with the limitations of MR studies, as they will be increasingly used with the availability of GWAS data.

According to the authors' note, food intake is made within the complex context of an individual's food environment. Socioeconomic status, structural racism, and food insecurity impact food choices as well as CVD risk.[3] The epigenetics and default food environment impacted by social determinants of health are likely common confounders between muesli intake and CVD intake.[3,14] The presence of common confounders between the genetic variants, exposure, and outcome violates the assumption of MR studies.

Nominal consumption of muesli, as the cereal participants mainly ate over the last year, was the only dietary trait that was associated with a decrease in CAD risk. Ordinal consumption of muesli over the last 24 hours estimated a nonstatistically significant association with CVD risk. The authors did not find any association between milk type (full cream or skimmed) and CVD risk. This is discordant with the Zhou et al[15] retrospective analysis estimating a decrease in CVD risk associated with skimmed or semiskimmed milk in UKB participants.[15]

The GWAS study by Yang et al[5] on the UKB found a decreased CVD risk with cheese intake and a protective effect of dried fruit on blood pressure. From the methods of the current study, cheese intake did not have enough genetic variants to be included. Given that these MR studies were on the same biobank participants, additional studies are needed to confirm these genetic variants and associations with CVD. Methodological information on which dietary traits and SNPs are included and excluded is needed, as clinicians seek to interpret MR studies going forward.

This study generates interesting hypotheses. Further studies are needed to address the limitations and challenges presented by this initial foray into the use of MR techniques to connect nutrition habits and CVD with genetic proclivities and susceptibilities. While it is too early to recommend adding muesli to a diet specifically for reduction in heart disease risk, a wealth of evidence indicates that eating a more plant-forward, high-fiber diet will be beneficial.

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REFERENCES

1. WHO. Cardiovascular diseases (CVDs). World health organization. 2021. Accessed January 25, 2024. https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)

2. 2020 Dietary Guidelines Advisory Committee, Dietary Patterns Subcommittee. *Dietary Patterns and Risk of Cardiovascular Disease: A Systematic Review*. USDA Nutrition Evidence Systematic Review; 2020.

3. Lichtenstein AH, Appel LJ, Vadiveloo M, et al. 2021 American Heart Association Council on Lifestyle and Cardiometabolic Health; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on cardiovascular Radiology and Intervention; Council on Clinical Cardiology; and Stroke Council. 2021 Dietary Guidance to improve cardiovascular health: a scientific statement from the American Heart Association. *Circulation*. 2021;144(23):e472-e487. https://doi.org/10.1161/cir.0000000000001031

4. Aggarwal M, Ornish D, Josephson R, et al. Closing gaps in lifestyle adherence for secondary prevention of coronary heart disease. *Am J Cardiol*. 2021;145:1-11. https://doi.org/10.1016/j.amjcard.2021.01.005

5. Yang M, Gao X, Xie L, et al. Causal associations between dietary habits and CVD: a Mendelian randomisation study. *Br J Nutr*. 2023;130(12):2104-2113. https://doi.org/10.1017/s000711452300140x

6. Park JK, Petrazzini BO, Bafna S, et al. Muesli intake may protect against coronary artery disease: Mendelian randomization on 13 dietary traits. *JACC: Adv*. 2024;3:100888.

7. Xu X, Parker D, Inglis SC, Byles J. Can regular long-term breakfast cereals consumption benefits lower cardiovascular diseases and diabetes risk? a longitudinal population-based study. *Ann Epidemiol*. 2019;37:43-50. https://doi.org/10.1016/j.annepidem.2019.07.004

8. Marques FZ, Nelson E, Chu PY, et al. High-fiber diet and acetate supplementation change the gut microbiota and prevent the development of hypertension and heart failure in hypertensive mice. *Circulation*. 2017;135(10):964-977. https://doi.org/10.1161/circulationaha.116.024545

9. Cole JB, Florez JC, Hirschhorn JN. Comprehensive genomic analysis of dietary habits in UK Biobank identifies hundreds of genetic associations. *Nat Commun*. 2020;11(1):1467. https://doi.org/10.1038/s41467-020-15193-0

10. Mullins VA, Bresette W, Johnstone L, Hallmark B, Chilton FH. Genomics in personalized nutrition: can you "eat for your genes". *Nutrients*. 2020;12(10):3118. https://doi.org/10.3390/nu12103118

11. Pan A, Sun Q, Bernstein A, Schulze M, Manson J. Red meat consumption and mortality. *Arch Intern Med*. 2012;172(7):555. https://doi.org/10.1001/archinternmed.2011.2287

12. Zhong VW, Van Horn L, Cornelis MC, et al. Associations of dietary cholesterol or egg consumption with incident cardiovascular disease and mortality. *JAMA*. 2019;321(11):1081-1095. https://doi.org/10.1001/jama.2019.1572

13. Spence JD, Srichaikul K, Jenkins DJA. Cardiovascular harm from egg yolk and meat: more than just cholesterol and saturated fat. *J Am Heart Assoc*. 2021;10(7):e017066. https://doi.org/10.1161/jaha.120.017066

14. Powell-Wiley TM, Baumer Y, Baah FO, et al. Social determinants of cardiovascular disease. *Circ Res*. 2022;130(5):782-799. https://doi.org/10.1161/circresaha.121.319811

15. Zhou J, Wu Z, Lin Z, Wang W, Wan R, Liu T. Association of milk consumption with all-cause mortality and cardiovascular outcomes: a UK Biobank based large population cohort study. *J Transl Med*. 2023;21(1):130. https://doi.org/10.1186/s12967-023-03980-4

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