



COMMENT ON LEE ET AL.

Relation of Change or Substitution of Low- and No-Calorie Sweetened Beverages With Cardiometabolic Outcomes: A Systematic Review and Meta-analysis of Prospective Cohort Studies. *Diabetes Care* 2022;45:1917–1930

Diabetes Care 2023;46:e97–e98 | <https://doi.org/10.2337/dc22-1930>

Amée M. Buziau,^{1,2,3}
 Gabriëlla A.M. Blokland,⁴
 Casper G. Schalkwijk,^{2,3}
 Jean L.J.M. Scheijen,^{2,3}
 Pomme I.H.G. Simons,^{1,2,3}
 Simone J.P.M. Eussen,^{2,5,6}
 Pieter C. Dagnelie,^{1,2}
 Marleen M.J. van Greevenbroek,^{2,3}
 Anke Wesselius,^{7,8}
 Coen D.A. Stehouwer,^{1,2} and
 Martijn C.G.J. Brouwers^{1,2}

With interest we read the article in *Diabetes Care* from Lee et al. (1), who performed a systematic review and meta-analysis of prospective cohort studies and showed that substitution of low- and no-calorie sweetened beverages for sugar-sweetened beverages was associated with a lower cardiometabolic risk. Although the authors carefully attempted to mitigate the influence of residual confounding, they deservedly conclude that they were most likely unable to exclude both unmeasured and measured residual confounding (1).

Mendelian randomization (MR) is a powerful approach to study the lifelong effects of an exposure of interest on outcomes, independent of the disruptive effects of confounders. We recently studied a common variant in the gene encoding ketohexokinase (*KHK*) (2). *KHK* catalyzes the phosphorylation of fructose, the main caloric constituent of sugar-sweetened beverages. Impaired *KHK* function results in reduced fructose metabolism and, eventually, urinary fructose excretion (2). We showed that the

rs2304681 minor A allele, a common missense variant in *KHK*, was associated with greater urinary fructose excretion and protection from colorectal cancer (2).

To gain more insight into the causal association between dietary fructose and cardiometabolic outcomes, we studied the association between the rs2304681 minor A allele and cardiometabolic disease by using publicly available databases.

We found that the rs2304681 minor A allele was associated with lower intrahepatic lipid content, assessed by magnetic resonance imaging in the UK Biobank cohort ($\beta -0.028 \pm 0.008$, $n = 36,703$) (3). Protective effects were also observed for the risk of type 2 diabetes in the combined Asian Genetic Epidemiology Network (AGEN) and European Diabetes and Mental Health Adaptive Notification Tracking and Evaluation (DIAMANTE) trial cohorts (fixed-effects meta-analysis odds ratio [OR] 0.985, 95% CI 0.975, 0.994, $n = 1,331,670$) (4), the risk of hypertension in the UK Biobank cohort (OR 0.988, 95% CI 0.976,

0.999, $n = 440,285$) (3), and the risk of myocardial infarction for the combined Coronary Artery Disease Genome-wide Replication and Meta-analysis plus the Coronary Artery Disease Genetics (CARDIoGRAMplusC4D) and UK Biobank cohorts (fixed-effects meta-analysis OR 0.976, 95% CI 0.961, 0.992, $n = 583,191$) (3,5).

We subsequently conducted two-sample MR analyses (TwoSampleMR package in R). The previously reported association between the rs2304681 minor A allele and (\log_{10} -transformed) urinary fructose (2) was used as exposure and the hitherto-reported associations between the rs2304681 minor A allele and cardiometabolic disease were used as outcomes. We found that genetically proxied impaired fructose metabolism protects from intrahepatic lipid accumulation (Wald ratio -0.63 , 95% CI -0.98 , -0.28 , $P < 0.001$), type 2 diabetes (Wald ratio -0.35 , 95% CI -0.57 , -0.13 , $P = 0.002$), hypertension (Wald ratio -0.28 , 95% CI -0.55 , -0.01 , $P = 0.040$), and myocardial infarction (Wald ratio -0.54 , 95% CI -0.90 , -0.19 , $P = 0.003$).

¹Department of Internal Medicine, Maastricht University Medical Center+, Maastricht, the Netherlands

²CARIM School for Cardiovascular Disease, Maastricht University, Maastricht, the Netherlands

³Laboratory for Metabolism and Vascular Medicine, Division of General Internal Medicine, Department of Internal Medicine, Maastricht University Medical Center+, Maastricht, the Netherlands

⁴Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, Netherlands

⁵Department of Epidemiology, Maastricht University, Maastricht, the Netherlands

⁶CAPHRI Care and Public Health Research Institute, Maastricht University, Maastricht, the Netherlands

⁷NUTRIM School for Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, the Netherlands

⁸Department of Complex Genetics and Epidemiology Maastricht University, Maastricht, the Netherlands

Corresponding author: Martijn C.G.J. Brouwers, mcgj.brouwers@mumc.nl

© 2023 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. More information is available at <https://www.diabetesjournals.org/journals/pages/license>.

Our findings suggest that fructose per se has harmful cardiometabolic effects and, therefore, support and substantiate the conclusions of Lee et al. (1) on the use of water or low- and no-calorie sweetened beverages as a health strategy to reduce the intake of sugar-sweetened beverages.

Funding and Duality of Interest. This study was supported by the Dutch Diabetes Research Foundation (personal grant 2017.82.004 to M.C.G.J.B.). The Maastricht Study was supported by the European Regional Development Fund via OP-Zuid, the Province of Limburg, the Dutch Ministry of Economic Affairs (grant 31O.041), Stichting De Weijerhorst (Maastricht, the Netherlands), the Pearl String Initiative Diabetes (Amsterdam, the Netherlands), School

for Cardiovascular Diseases (CARIM, Maastricht University, Maastricht, the Netherlands), School for Public Health and Primary Care (CAPHRI, Maastricht University, Maastricht, the Netherlands), School for Nutrition and Translational Research in Metabolism (NUTRIM, Maastricht University, Maastricht, the Netherlands), Stichting Annadal (Maastricht, the Netherlands), and Health Foundation Limburg (Maastricht, the Netherlands) and by unrestricted grants from Janssen-Cilag B.V. (Tilburg, the Netherlands), Novo Nordisk Farma B.V. (Alphen aan den Rijn, the Netherlands), Sanofi Netherlands B.V. (Gouda, the Netherlands), and Medtronic (Tolochenaz, Switzerland). No other potential conflicts of interest relevant to this article were reported.

References

1. Lee JJ, Khan TA, McGlynn N, et al. Relation of change or substitution of low- and no-calorie sweetened beverages with cardiometabolic out-

comes: a systematic review and meta-analysis of prospective cohort studies. *Diabetes Care* 2022;45:1917–1930

2. Buziau AM, Law PJ, Blokland G, et al. Genetically proxied ketohexokinase function and risk of colorectal cancer: a Mendelian randomisation study. *Gut*. 10 May 2022 [Epub ahead of print]. DOI: 10.1136/gutjnl-2021-326299

3. Sudlow C, Gallacher J, Allen N, et al. UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med* 2015;12:e1001779

4. Shah PD, Schooling CM, Borrell LN. Impact of liability to periodontitis on glycemic control and type II diabetes risk: a Mendelian randomization study. *Front Genet* 2021;12:767577

5. Nikpay M, Goel A, Won HH, et al. A comprehensive 1,000 Genomes-based genome-wide association meta-analysis of coronary artery disease. *Nat Genet* 2015;47:1121–1130