Circulation: Heart Failure

EDITORIAL

Can Two Coffees a Day Keep the Heart Doctor Away?

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Almost 15 years after I transitioned to the United States, my native British accent remains relatively unscathed, and my understanding of cricket still far exceeds that of baseball. However, I have certainly adopted a new coffee habit and cannot recall the last time I brewed a pot of tea. My choice of beverage is a popular one: 400 million cups of coffee are consumed daily in the United States, and more than half of Americans are daily coffee drinkers. Given this enthusiasm for coffee, any health consequences are of clear public health importance. Historically, there were cancer concerns, with the World Health Organization classifying coffee as a potential carcinogen from 1991 to 2016. The original epidemiological associations between coffee consumption and lung cancer became a textbook example of confounding in biomedical research: individuals with high coffee consumption were more likely to also smoke, and the apparent association between coffee and lung cancer disappeared once adjusted for the smoking covariate.[1] Furthermore, a potentially favorable relationship emerged between moderate coffee consumption and cardiometabolic conditions, including lower rates of type 2 diabetes, stroke, coronary heart disease, and heart failure (HF), gradually exonerating the beverage choice.[2–5] Given the estimated 960 000 new HF diagnoses annually in the United States and a lifetime HF risk beyond age 45 years of at least 20%,[6,7] should habitual coffee consumption now be promoted as a healthy lifestyle choice to decrease HF development?

See Article by Stevens et al

In this issue of *Circulation: Heart Failure*, Stevens et al[8] report that 2 or ≥3 cups per day of caffeinated coffee consumption is associated with lower long-term incident HF among 21 361 participants in 3 longitudinal cardiovascular health cohort studies (FHS [Framingham Heart Study], ARIC [Atherosclerosis Risk in Communities], and CHS [Cardiovascular Health Study]) using machine learning models.[8] There was no relationship observed between caffeinated coffee and the risk of subsequent coronary heart disease or cardiovascular disease overall. Conversely, decaffeinated coffee was associated with an increased risk of incident HF, although this was only detected within the FHS cohort.

This reported association between moderate coffee consumption and lower HF risk is in line with prior observational cohort analyses using traditional multivariable modeling. A meta-analysis of 5 prospective cohorts from Sweden and Finland combining 140 220 participants described a J-shaped relationship between coffee consumption and incident HF. A cup was defined as 150 or 100 mL within the Swedish and Finnish studies, respectively. The nadir of HF risk coincided with 4 cups of coffee per day.[2] However, among 20 433 men in the Physicians' Health Study, there was no detectable relationship between either coffee or caffeine intake and subsequent HF, although the risk of atrial fibrillation was lower for those drinking 1 to 3 cups per day.[9,10] Consumption of 1 to 5 cups of caffeinated or decaffeinated coffee was associated with lower cardiovascular and all-cause mortality across 3 cohorts of health professionals in the United States.[11] A further nuance was recently proposed from a large Norwegian cohort: 1 to 4 cups per day of filtered coffee was associated

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For Disclosures, see page 191.

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with the lowest mortality, whereas drinking ≥9 cups per day of unfiltered coffee was associated with the highest mortality.[12] Thus, it has been proposed specifically that filtered coffee, without sugar or other additives, may be analogous to whole grains and vegetables as a dietary source of phenolic phytochemicals that could offer antioxidant protection from HF.[13]

The principal gap that must be addressed is causal inference. The work of Stevens et al[8] and the prior publications about coffee consumption and HF risk are all based upon observational cohorts with multivariable analyses. Despite appropriate adjustment for the key confounder of smoking, multiple potential sources of bias of sources remain in these analyses that may obscure the true nature of whatever biological relationship exists between coffee or caffeine and HF development. These threats to validity can be grouped into information biases, selection biases, and residual confounding. The potential for information bias is significant: serving sizes, caffeine content, methods of roasting and grinding, timing of consumption, and the presence of additives such as sugar and dairy products could all influence the effect of coffee on the cardiovascular system. These details are not likely to be accurately captured by closed-ended methods such as food frequency questionnaires nor by open-ended methods such as dietary recalls. Selection bias can be introduced by differential follow-up periods given the long latency anticipated between dietary exposures and HF development, and it is entirely plausible that a healthy-user bias exists, whereby individuals without baseline cardiovascular concerns consume more coffee than those already experiencing precursors of heart disease. There is evidence suggesting a healthy-user bias, or even reverse causation, in the current study because the 2 and ≥3 cup/day groups have less baseline hypertension and diabetes than the 0 and 1 cup/day groups. Unmeasured environmental, nutritional, or lifestyle confounders that relate both to the coffee exposure and HF outcome remain a strong possibility and could create an apparent relationship when none is truly present or overestimate a marginal effect. The current cohort study adjusts only for the FHS cardiovascular disease risk score, whereas further stratification by socioeconomic status and workplace environments would be particularly germane for examination of this coffee-HF relationship. The divergent association of incident HF for caffeinated versus decaffeinated coffee prompts concern that one or more of these biases could be in play.

In contrast to prior observational cohort analyses, Stevens et al[8] moved beyond traditional statistical modeling to draw on machine learning techniques that elevate the importance of the coffee findings. Their broad hypothesis-free approach to the examination of candidate dietary and lifestyle factors with potential cardiovascular effects incorporated 204 potential measures using supervised machine learning to construct random forest models. The benefit of this approach is that relationships within the data drive feature selection, allowing the strongest risk factors to rise to prominence even in the setting of colinearity. In that regard, it is intriguing that coffee ranked in importance alongside age, blood pressure, heart rate, and weight for their associations with HF and thus became the focus of the project. Validation through traditional survival modeling corroborated the importance of coffee as an HF risk factor in this dataset, although the potential for false discovery remains. Artificial intelligence techniques, including machine learning, are becoming an integral component of our research infrastructure and hold particular promise in synthesizing the complex, multidimensional, heterogenous relationships believed to explain the biological and sociological pathways connecting dietary choices to subsequent HF.[14] Novel features such as geolocation information, participant-driven food and beverage photographs, physical activity sensors and social network analyses offer a future state where creative approaches to cardiovascular nutrition will allow us to ask more ambitious research questions than appeared possible with traditional unidimensional statistics. Data fidelity and high-quality model validation will remain essential components to build confidence in these approaches, but the potential benefits of moving from participant-reported dietary recalls towards real-time monitoring of complex dietary patterns could be transformative. Artificial intelligence techniques are anticipated to accelerate the precision nutrition agenda introduced by the ambitious 2020 to 2030 Strategic Plan for the National Institutes of Health Nutrition Research.[15]

Regardless of the analytic methods used, it will be crucial to progress beyond observational data into clinical trials and mechanistic studies that fulfill the objectives of precision nutrition and improve population health. The randomized clinical trial remains the gold standard for assignment of causality and has been successfully deployed for short-term coffee interventions documenting the impact on blood pressure, lipids, and glucose hemostasis.[1] High-yield hypotheses for small clinical trials include whether caffeine-induced diuresis or improved insulin sensitivity might lie on a mechanistic pathway towards HF prevention. Short-term coffee interventions could also rapidly define the serum metabolomic dose-response. Full resolution of molecular mechanisms would not be essential before advocating for coffee consumption but establishing biological plausibility for a role in HF prevention is necessary. The existing observational studies have not refined the HF end point between preserved versus reduced ejection fraction phenotypes, and although prevention of coronary disease did not seem responsible per the current study, some appreciation of the vascular, myocardial, or systemic metabolic targets would be helpful. Coffee is entirely plant-based and can be a major dietary source of polyphenols and phenolic acids. Future mechanistic investigations of the proposed

coffee-induced cardiovascular protection mediated by phytochemical antioxidant, detoxification, and cellular repair effects, for example, via the Nrf2 (nuclear factor erythroid 2-related factor-2) pathway in particular,[13] may deepen our overall understanding of HF pathogenesis.

Given the relative global acceptability, tolerability, accessibility, and affordability of coffee, the proposition that moderate habitual coffee intake could be a dietary choice that meaningfully prevents subsequent HF warrants further exploration within clinical trials. A single-component nutritional intervention trial with coffee would be far easier to design and successfully implement than a complete dietary pattern approach for HF prevention, such as the Mediterranean diet. At a minimum, the current study appears to offer additional reassurance for those of us partial to a caffeinated cup of coffee that this beverage choice is unlikely to result in long-term cardiovascular harm.

ARTICLE INFORMATION

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Disclosures

None.

REFERENCES

1. Poole R, Kennedy OJ, Roderick P, Fallowfield JA, Hayes PC, Parkes J. Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes. *BMJ*. 2017;359:j5024. doi: 10.1136/bmj.j5024
2. Mostofsky E, Rice MS, Levitan EB, Mittleman MA. Habitual coffee consumption and risk of heart failure: a dose-response meta-analysis. *Circ Heart Fail*. 2012;5:401–405. doi: 10.1161/CIRCHEARTFAILURE.112.967299
3. Shao C, Tang H, Wang X, He J. Coffee consumption and stroke risk: evidence from a systematic review and meta-analysis of more than 2.4 million men and women. *J Stroke Cerebrovasc Dis*. 2021;30:105452. doi: 10.1016/j.jstrokecerebrovasdis.2020.105452
4. O'Keefe JH, Bhatti SK, Patil HR, DiNicolantonio JJ, Lucan SC, Lavie CJ. Effects of habitual coffee consumption on cardiometabolic disease, cardiovascular health, and all-cause mortality. *J Am Coll Cardiol*. 2013;62:1043–1051. doi: 10.1016/j.jacc.2013.06.035
5. Carlström M, Larsson SC. Coffee consumption and reduced risk of developing type 2 diabetes: a systematic review with meta-analysis. *Nutr Rev*. 2018;76:395–417. doi: 10.1093/nutrit/nuy014
6. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, de Ferranti SD, Floyd J, Fornage M, Gillespie C, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. *Circulation*. 2017;135:e146–e603. doi: 10.1161/CIR.0000000000000485
7. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Delling FN, et al; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2020 update: a report from the American Heart Association. *Circulation*. 2020;141:e139–e596. doi: 10.1161/CIR.0000000000000757
8. Stevens LM, Linstead E, Hall JL, Kao DP. Association between coffee intake and incident and heart failure risk - a machine learning analysis of the FHS, ARIC, and CHS. *Circ Heart Fail*. 2021;14:181–188. doi: 10.1161/CIRCHEARTFAILURE.119.006799
9. Bodar V, Chen J, Sesso HD, Gaziano JM, Djoussé L. Coffee consumption and risk of heart failure in the Physicians' Health Study. *Clin Nutr ESPEN*. 2020;40:133–137. doi: 10.1016/j.clnesp.2020.09.216
10. Bodar V, Chen J, Gaziano JM, Albert C, Djoussé L. Coffee consumption and risk of atrial fibrillation in the Physicians' Health Study. *J Am Heart Assoc*. 2019;8:e011346. doi: 10.1161/JAHA.118.011346
11. Ding M, Satija A, Bhupathiraju SN, Hu Y, Sun Q, Han J, Lopez-Garcia E, Willett W, van Dam RM, Hu FB. Association of coffee consumption with total and cause-specific mortality in 3 large prospective cohorts. *Circulation*. 2015;132:2305–2315. doi: 10.1161/CIRCULATIONAHA.115.017341
12. Tverdal A, Selmer R, Cohen JM, Thelle DS. Coffee consumption and mortality from cardiovascular diseases and total mortality: does the brewing method matter? *Eur J Prev Cardiol*. 2020;27:1986–1993. doi: 10.1177/2047487320914443
13. Kolb H, Kempf K, Martin S. Health effects of coffee: mechanism unraveled? *Nutrients*. 2020;12:1842–1856.
14. Wiemken TL, Kelley RR. Machine learning in epidemiology and health outcomes research. *Annu Rev Public Health*. 2020;41:21–36. doi: 10.1146/annurev-publhealth-040119-094437
15. NIH Nutrition Research Task Force 2020-2030 Strategic Plan for the National Institutes of Health Nutrition Research. 2020. https://dpcpsi.nih.gov/sites/default/files/2020NutritionStrategicPlan_508.pdf. Accessed January 13, 2021.