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Is it caffeine? Coffee consumption and future risk of type 2 diabetes among women with a history of gestational diabetes

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Caffeine is the most commonly used psychoactive substance in the world and has been associated with a range of health outcomes, including lower risks of Parkinson's disease and type 2 diabetes (T2D) (1). Common food sources of caffeine include coffee, tea, caffeine-containing sodas, energy drinks, and chocolate. In most regions of the world, coffee is the predominant caffeine source, but some exceptions have been noted in countries with a strong tea culture, such as the United Kingdom, Ireland, China, and Japan (2, 3). In recent years, both higher caffeine and coffee intakes have been associated with more favorable health outcomes in the general population (1, 4). Nonetheless, caution is advised for specific populations, such as pregnant women, due to its possible adverse influences on pregnancy and offspring outcomes (5). For instance, the American College of Obstetricians and Gynecologists recommends that women limit caffeine intake to <200 mg/d (approximately two 6-oz cups of coffee per day) during pregnancy, since intake at such levels has not been associated with miscarriage or preterm birth (6).

Gestational diabetes (GDM) is a form of diabetes diagnosed in pregnant women who did not previously have the condition. The global prevalence of GDM is estimated to be 14%, but with substantial regional variation (7). Not only is GDM associated with adverse pregnancy and birth outcomes, but women with a history of GDM are also at a substantially higher risk of developing full-fledged T2D later in life (8, 9). Thus, the identification of modifiable risk factors that can lessen the postdelivery adverse impact of GDM is a pressing research need.

In this issue of the *American Journal of Clinical Nutrition*, Yang et al. (10) elegantly demonstrated that after a median follow-up of 24 years, habitual caffeinated coffee consumption was inversely associated with the risk of developing T2D among 4522 predominantly Caucasian women with a history of GDM from the Nurse's Health Study II. In weight-stable populations, increased intakes of certain food items will be followed by decreased intakes of other foods or beverages. To this end, the substitution analysis in this study provided complementary evidence that replacement of less healthy beverages (sugar- and artificially sweetened beverages) with total or caffeinated coffee was associated with a lower risk of T2D after GDM. Moreover, in a subset of the population ($n = 512$), caffeine and caffeinated coffee consumption were associated with improved glucose metabolism parameters (lower C-peptide concentrations), albeit with more consistent trends observed for caffeinated coffee consumption, as it was also associated with a lower insulin concentration. The study was strengthened by its long follow-up within a large cohort of participants with a history of GDM and rich dietary data.

Although the study shed light on the possibility of lowering the future T2D risk with coffee consumption among a high-risk population with previous GDM, some unanswered questions and limitations are worth noting. Firstly, coffee contains a complex mixture of biologically active chemicals other than caffeine, including polyphenols (e.g., chlorogenic acid), alkaloids (e.g., trigonelin), and diterpenes (e.g., cafestol) (11). Levels of these chemicals in coffee are dependent on brewing methods. For instance, concentrations of diterpenes, a family of compounds known for their cholesterol-raising properties, are highest in boiled coffee, followed by espresso, and finally filtered coffee (12). Although decaffeinated coffee was similarly associated with improved glucose metabolic profiles in a subset of participants in this study, it was not associated with a decreased risk of T2D. Therefore, it is unclear whether caffeine is the compound responsible for the lower risk of T2D. The study investigators did not examine caffeinated tea consumption, which could have provided further insights on the potential involvement of caffeine in reducing T2D risks, especially in countries where tea is the predominant caffeine source. Secondly, the severity of GDM was not considered, which could have introduced bias if severity is related to both postdelivery coffee consumption and T2D. Thirdly, the study population involved predominantly white, highly educated, and health-conscious nurses, which limits the generalizability of the study results.

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In conclusion, the study provided initial evidence that higher caffeinated coffee intake can be promoted in place of other, less healthy beverages to improve metabolic profiles of women with a history of GDM. As the authors themselves acknowledged, the findings should be replicated in other populations with different confounding structures to generate corroborating evidence. In addition, the exact mechanism of this association remains unclear. Although epidemiologic evidence often precedes biological evidence, an understanding of the exact mechanism by which caffeine or other compounds in caffeine-containing beverages affects glycemic parameters will help us decide whether and how best to incorporate coffee or caffeine-containing beverages as part of a healthy diet for tertiary prevention of worse health outcomes due to GDM. To this end, perhaps multiple dimensions of -omics data (e.g., genomics and metabolomics) can help untangle the mechanism. However, it should be kept in mind that most limitations of traditional biomarkers, although generally regarded to be more objective than self-reports of diet, likely also apply to markers or fingerprints based on metabolomics. For example, commonly used biomarkers for caffeine intake, such as serum or plasma caffeine and paraxanthine, both have a short half-life (<8 h), thus casting doubt on their suitability to reflect habitual caffeine intake. Disentangling the potential causal pathway of coffee and caffeine-containing beverages and glucose metabolism will likely require an integrative approach combining various data sources, including reliable habitual beverage intakes (with information on brewing methods), genetic polymorphism data of the caffeine metabolism or preference (for Mendelian randomization), and serial metabolomics data. Although randomized controlled trials are desired to establish causality, long-term compliance with dietary interventions is challenging. An alternative is to replicate the results in well-designed cohort studies that have collected or are going to collect longitudinal data on postpartum diet, metabolites, genetic polymorphism and other -omics data, the T2D diagnosis, and other glycemic parameters. Mechanistic studies using animal models may also lend support to our quest to understand this association, although the usual caution regarding the transferability of results from animal models to human models should be exercised.

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