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EDITORIAL

Moderate Coffee Intake Can Be Part of a Healthy Diet

Coffee is one of the most frequently consumed beverages worldwide. In the United States, about 75% of adults drink coffee, and 50% drink it daily (1). Coffee is a major source of caffeine, with wide variation in the amount among different types of coffee (8 mg of caffeine per fluid ounce of instant coffee, 12 mg per fluid ounce of brewed or drip coffee, and 64 mg per fluid ounce of espresso). In addition, coffee contains several bioactive substances, including polyphenols, diterpenes, and melanoidins, also with wide variability depending on the blend and the roasting and brewing methods. Adding sugar, cream, or cream substitutes adds calories. Because of the widespread consumption of coffee, understanding its health effects is important.

A recent systematic review concluded that consumption of up to 400 mg of caffeine per day in healthy adults (300 mg/d in pregnant women) was not associated with acute toxicity or adverse cardiovascular, behavioral, bone and calcium, or developmental and reproductive effects (2). Other studies and systematic reviews have suggested that coffee intake may be associated with lower risk for metabolic syndrome, diabetes, cardiovascular disease, and death (3). In this issue, 2 large studies provide new evidence on the association of coffee intake with mortality.

EPIC (European Prospective Investigation into Cancer and Nutrition), a large cohort of more than 520 000 men and women from 10 European countries with an average follow-up of 16 years, found an inverse relationship between coffee intake and all-cause mortality in men and women (4). The findings were consistent across countries, which adds to their generalizability given that populations in different countries used different coffee preparation methods and had different drinking patterns.

The MEC (Multiethnic Cohort) study followed more than 185 000 African Americans, Native Hawaiians, Japanese Americans, Latinos, and whites for an average of 16 years and also found inverse associations between coffee intake and all-cause mortality in all racial/ethnic groups examined, although the association was not statistically significant in Native Hawaiians (5). This study substantially increases the generalizability of previous findings across the racial/ethnic spectrum.

Does coffee intake reduce all-cause mortality, or is the inverse association just a reflection of uncontrolled confounding? A protective effect of coffee is biologically plausible. Polyphenols and other bioactive compounds in coffee have antioxidant properties, and coffee intake is associated with reduced insulin resistance, inflammation, and biomarkers of liver function (4). The findings in EPIC (4) and the MEC study (5) were also consistent across racial/ethnic groups, countries, and multiple subgroups that were examined.

The association of coffee intake with mortality, however, was modest and sensitive to confounding. In both studies (4, 5), the adjusted reductions in the hazard ratio for all-cause mortality associated with coffee intake were less than 20% across doses, and the inverse association with all-cause mortality was evident only after adjustment for smoking. Smoking is associated with coffee intake and is a cause of increased mortality, and population studies need to adjust for it to obtain measures of association that better reflect the potential causal effect of coffee consumption.

In addition to smoking, however, coffee consumption is associated with other behavioral, dietary, socioeconomic, and health-related factors that may be difficult to measure and model in epidemiologic studies, opening the possibility of uncontrolled confounding. In an accompanying editorial (6), Localio and colleagues estimate that the inverse hazard ratio of 0.82 for all-cause mortality associated with intake of 4 or more cups of coffee per day in the MEC study could be explained by an unmeasured confounder (or combination of confounders) associated with a risk ratio of 1.56 or higher with both the exposure and the outcome. This analysis was consistent with sensitivity analyses conducted in EPIC (4) and the MEC study (5) showing that the associations of coffee intake with mortality had only limited robustness to weak or moderate uncontrolled confounding. Of course, these analyses do not imply that uncontrolled confounding accounts for the observed findings, and both studies adjusted for various potential confounders in addition to smoking. However, the determinants of coffee intake are complex, and a better understanding of coffee-drinking behavior is needed to confidently exclude uncontrolled confounding.

Mendelian randomization analyses have also tried to elucidate the causal effect of coffee on health outcomes (7–9). A genetic score associated with coffee intake was not associated with increased or decreased risk for all-cause death, cardiovascular disease, or diabetes. Although these findings do not support a causal effect of coffee consumption, they should also be interpreted carefully. Because the analyses considered a limited number of genetic variants that explained only a small fraction of the variability of coffee consumption, they had limited power (9). Although the genetic score is not subject to traditional confounding, the genes associated with coffee intake are involved in caffeine metabolism and have pleiotropic effects on the metabolism and regulation of other compounds and on other traits and behaviors, such as smoking, body mass index, lipid levels, and blood pressure. Furthermore, coffee intake is a complex behavior, coffee itself is a heterogeneous exposure, and the putative benefits may depend on components other than caffeine.

Recommending coffee intake to reduce mortality or prevent chronic disease would be premature. However, it is increasingly evident that moderate coffee in-

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take up to 3 to 5 cups per day or caffeine intake up to 400 mg/d is not associated with adverse health effects in adults and can be incorporated into a healthy diet (10).

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