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Letter: Comments

### **Effects of Coffee Consumption on Mortality Are Uncertain**

Gunter and colleagues report that people in the highest quartile of coffee consumption have a 7%-10% higher risk of death compared to non-drinkers in a study of over 450,000 adults from 10 European countries.<sup>1</sup> However, this association was reversed after adjustment for covariates. In the multivariable adjusted model, high coffee consumption is related to a 12% lower mortality risk in men and a 7% lower risk in women. The authors suggest that coffee may confer health benefits.

The instability of the results in relation to covariate adjustments raised our concern about the validity of this conclusion. Here we elaborate on the possibility that the findings may be attributable to bias and confounding by unmeasured or imprecisely measured risk factors. For example, some diseases and symptoms related to hypersensitivity or intolerance to coffee consumption might also be linked to shorter life expectancy contributing to a spurious association between coffee consumption and mortality (NICE Evidence Search Caffeine. <https://www.evidence.nhs.uk>). Socioeconomic health determinants, such as income, occupational position and neighbourhood characteristics, are related to coffee consumption<sup>2</sup> and mortality.<sup>2-4</sup> Such factors may have affected the results but were not controlled for in the analyses. This interpretation is consistent with the result that the coffee consumption-mortality relation was more marked in men than women, as

was the association between coffee consumption and education, another socioeconomic health resource.<sup>1</sup>

According to calculations of the e-value,<sup>5</sup> a single confounder, related to coffee consumption and mortality risk, and with a hazard ratio of 1.5 could entirely explain the 12% lower mortality in men with high coffee consumption. In women, the corresponding hazard ratio would be 1.4. Thus, even minor uncontrolled risk and protective factors, including those listed above, have, in combination, the potential to bias the findings by Gunter and colleagues.<sup>1</sup> Indeed, Mendelian randomisation analyses, which are more protected from bias and confounding than the observational findings of Gunter and others, do not support protective effects for high coffee consumption in relation to cardiovascular disease or all-cause mortality.<sup>3</sup>

The US NIH, with support from the alcohol industry, is starting a \$100 million clinical trial to obtain a definitive answer to the question of whether moderate alcohol consumption prevents heart attacks. As coffee consumption is more widespread and possibly more amenable to change than alcohol consumption, a large-scale trial of coffee consumption is equally justified to obtain definite conclusions about its health effects.

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