Coffee Consumption and All-Cause Mortality: It May Be Premature to Advise Limiting Coffee Consumption in Younger Nonsmokers

To the Editor: I read with great interest the recent article by Liu et al[1] on the health consequences of coffee consumption. Their methodological approach was strong, and their findings were reported clearly. However, I disagree with their conclusion that on the basis of the study's findings, "it seems appropriate to suggest that younger people avoid heavy coffee consumption (ie, averaging >4 cups per day)."

Liu et al reported that at baseline, the coffee drinkers in the Aerobics Center Longitudinal Study cohort, like many other populations, were more likely to smoke cigarettes. The authors did an excellent job in handling this well-recognized association. Their multivariate models (2 and 3) were adjusted for smoking. The authors recognized that residual confounding from smoking could still exist and that this could lead to the appearance of a mortality risk from coffee. Indeed, this was mentioned in their "Limitations" section. To eliminate possible residual confounding, the authors stratified their analysis by smoking status and presented their findings separate from the article as supplemental online material. The authors reported that "we did not observe the significant association between coffee consumption and all-cause mortality both in current smokers and non-current smokers."

The supplemental figures actually show what appears to be an inverse relationship for male nonsmokers between coffee consumption and all-cause mortality for consumption of 8 to 14 through 22 to 28 cups per week, with a hazard ratio below 1 for the latter category. Female nonsmokers in all coffee consumption categories appear to have hazard ratios that approximate the null value without the appearance of increased risk with increased coffee consumption even in the highest consumption category (>28 cups per week).

Although moderation in all things has historically been good advice, the recommendation for younger people to cut back on their coffee consumption does not appear to be well supported by the data presented.

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1. Liu J, Sui X, Lavie CJ, et al. Association of coffee consumption with all-cause and cardiovascular disease mortality. *Mayo Clin Proc.* 2013;88(10):1066-1074.

http://dx.doi.org/10.1016/j.mayocp.2013.10.002

Factors Affecting the Association of Coffee Consumption With All-Cause and Cardiovascular Disease Mortality

To the Editor: We read with great interest the recent article by Liu et al[1] concerning the association of coffee consumption with all-cause and cardiovascular disease mortality. We particularly applaud the thoroughness of their data collection, including 43,727 participants over a median follow-up of 17 years. Considering the pervasive nature of global coffee consumption, studies of this scale are both valuable and ubiquitously relevant. However, we have some concerns regarding the conclusions drawn from the data and would be interested if the authors could clarify some of these points.

One apparent trend was that participants with the highest coffee consumption were less healthy than participants with lower coffee consumption. The authors confirm this by reporting, "Men and women who consumed higher amounts of coffee were more likely to smoke and had lower levels of [cardiorespiratory fitness]."[1] These participants managed the least time on a treadmill and had the highest level of inactivity, and the men in this category had the highest rate of parental cardiovascular disease. Although it appears that any individual confounding effect from cardiorespiratory fitness was statistically addressed, it is not clear that the cumulative effects of multiple risk factors were accounted for in the statistical analysis.

Most concerning was that the confounding effect from smoking was not adequately addressed. The authors concede this point in their discussion, stating that "smoking is likely to be one of the most important factors to cause residual confounding in this investigation."[1] It is well known that smoking can induce changes in hepatic enzymes and increase the clearance of caffeine, in turn leading to a higher rate of coffee consumption in smokers.[2,3] It is also widely established that smoking is a strong independent predictor of mortality.[4] Further, a recent study that evaluated the association of coffee drinking with all-cause mortality confirmed that coffee drinkers were more likely to smoke, and after adjusting for the confounding variable of smoking, coffee consumption was actually associated with decreased mortality.[5] We question whether the conclusions of the study by Liu et al can be supported without accounting for this "residual confounding" of smoking.

The authors also comment on the homogeneity of the cohort, stating that the uniformity of the participants increases the internal validity of the study.[1] Although this may lend credence to the data, we suggest that external validity may be more critical, because the widespread use of coffee begs the immediate question of how applicable these results are beyond the confines of this study.

The pervasive use of coffee worldwide behooves us as research scientists

to report conclusions about its use with utmost accuracy. This is particularly important in light of the multiple studies that have touted the health benefits of coffee consumption. Although we applaud Liu et al for their important study, we are cautious about a potential disconnect between the data and their conclusions. Ultimately, it is evident that future investigations are merited to elucidate the relationship between coffee consumption and mortality.

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http://dx.doi.org/10.1016/j.mayocp.2013.10.010

Importance of Sleep Disorders in Assessing the Association Between Coffee Consumption and All-Cause Mortality

To the Editor: Liu et al[1] have reported an interesting observational study in which they found a positive relationship between very high coffee consumption and all-cause mortality among men and among both men and women aged less than 55 years.[1] Because the general finding for men appears to be attributable to the increased risk among those younger than 55 years, the authors concluded that "on the basis of these findings, it seems appropriate to suggest that younger people avoid heavy coffee consumption (ie, averaging >4 cups per day)." However, while this study's findings are suggestive, it may be premature to make any clinical recommendations based on these results.

This study has a number of strengths, including both a relatively large number of participants and adjustment for a broad array of potential confounders, but one key variable that was not included in the study was sleep disorders. Because one of the traditional uses of coffee is to compensate for feelings of sleepiness, it is reasonable to suppose that this may prove an important confounder, with higher consumption positively related to sleep disorders and the presence of sleep disorders positively related to all-cause mortality.

Daytime sleepiness has been documented to be an independent risk factor for stroke and other vascular disease,[2] and both insufficient and excessive sleep have been associated with an increased risk of all-cause mortality.[3,4] Even more striking, the relationship between sleep disorders and all-cause mortality exhibits an age dependency similar to that reported by Liu et al. Lavie et al[5] found that the excess mortality attributable to sleep apnea among men was limited to those younger than 50 years, and similar trends are also found in the relationship between long or short sleep and all-cause mortality.[3]

Of course, it is also possible that the causal pathway flows instead from excessive coffee consumption to insomnia and thence to an increased risk of mortality. Determining whether one or both of these scenarios explains the increased risk of mortality will require further research that takes sleep into account. It will also be important to measure sleep, coffee intake, and mortality at multiple time points throughout the study in order to establish the temporal sequence between sleep and coffee consumption and to account for changes in these variables over time.

The study by Liu et al[1] is an important contribution toward a better understanding of the relationship between coffee intake and all-cause mortality, but the state of the science may be too young at this time to enable clinicians or public health authorities to provide specific advice to patients.

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http://dx.doi.org/10.1016/j.mayocp.2013.10.005

Heavy Coffee Drinking and Age-Dependent All-Cause Mortality

To the Editor: The study by Liu et al[1] reported in the October 2013 issue of *Mayo Clinic Proceedings* associated heavy coffee drinking with increased all-cause mortality in people younger than 55 years. A previous study,[2] however, associated heavy coffee drinking with a *decrease* in all-cause mortality. Both studies included large populations with long follow-up and made adjustments for smoking, alcohol consumption, and other potential health effectors. In both studies, a similar effect was attributed to either caffeine or caffeine-free drinks.[1,2] Thus, the agent searched for was not the caffeine.

Coffee, especially when brewed, contains many antioxidants such as