

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.

Michael G. Wagner
Kapil G. Kapoor, MD
Alan L. Wagner, MD
 Wagner Macula & Retina Center
 Virginia Beach, VA

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.
2. Plowchalk DR, Rowland Yeo K. Prediction of drug clearance in a smoking population: modeling the impact of variable cigarette consumption on the induction of CYP1A2. *Eur J Clin Pharmacol.* 2012;68(6):951-960.
3. Parsons WD, Neims AH. Effect of smoking on caffeine clearance. *Clin Pharmacol Ther.* 1978;24(1):40-45.
4. Kenfield SA, Wei EK, Rosner BA, Glynn RJ, Stampfer MJ, Colditz GA. Burden of smoking on cause-specific mortality: application to the Nurses' Health Study. *Tob Control.* 2010;19(3):248-254.
5. Freedman ND, Park Y, Abnet CC, Hollenbeck AR, Sinha R. Association of coffee drinking with total and cause-specific mortality [published correction appears in *N Engl J Med.* 2012;367(3):285]. *N Engl J Med.* 2012;366(20):1891-1904.

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

To the Editor: Liu et al¹ 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 al⁵ 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 al¹ 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.

Alan J. Card, PhD, MPH, CPH, CPHQ
 Evidence-Based Health Solutions, LLC
 Notre Dame, IN

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.
2. Boden-Albala B, Roberts ET, Bazil C, et al. Daytime sleepiness and risk of stroke and vascular disease: findings from the Northern Manhattan Study (NOMAS). *Circ Cardiovasc Qual Outcomes.* 2012; 5(4):500-507.
3. Hublin C, Partinen M, Koskenvuo M, Kaprio J. Sleep and mortality: a population-based 22-year follow-up study. *Sleep.* 2007;30(10):1245-1253.
4. Gallicchio L, Kalesan B. Sleep duration and mortality: a systematic review and meta-analysis. *J Sleep Res.* 2009;18(2):148-158.
5. Lavie P, Lavie L, Herer P. All-cause mortality in males with sleep apnoea syndrome: declining mortality rates with age. *Eur Respir J.* 2005;25(3):514-520.

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Heavy Coffee Drinking and Age-Dependent All-Cause Mortality

To the Editor: The study by Liu et al¹ 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

chlorogenic acid, ferulic acid, and various flavonoids. It has been suggested that in a regular American diet, coffee is the main source of antioxidants.³ Antioxidants neutralize free radicals in the body and curb their potential damage to body cells. However, free radicals also play central active roles in cross-body protection and tissue regeneration.

Reactive oxygen species (ROS) such as hydrogen peroxide and superoxide are used by the immune system (neutrophils) to attack invading bacteria. Reactive oxygen species also induce apoptosis in cancer cells. At least in part of the cases, cancer cells wield antioxidants to thwart these attacks.⁴ Watson⁴ suggested that the ROS produced in anticancer therapies, either ionizing or chemical, are the main effective agents. This potentially explains why resistance to both therapies often occurs simultaneously. Reactive oxygen species also activate after-stress adaptations of skeletal muscles, including their remodeling. They are regularly produced in the muscles to scavenge dead muscle fibers and other tissue debris. This may explain why consumption of powerful antioxidants, such as resveratrol, blocks cardiovascular benefits of physical exercise.⁵ Finally, overconsumption of antioxidants (such as vitamin E) could be related to all-cause mortality.⁶

The two faces of ROS suggest that the body, as part of its homeostasis, should maintain an oxidative balance between ROS and antioxidants. The optimal balance may vary from one person to another, depend on an individual's health condition, or vary among distinct tissues. It is common knowledge that ROS levels in the body are elevated with age. Therefore, coffee, a major source of antioxidants, may push the oxidation balance toward ROS deficiency. In such a situation, crucial defense and regenerative processes of the body might become suppressed. Because young people's levels of ROS are already relatively low, they are likely to be more vulnerable to

this effect. This explanation could account for the age-dependent effect of coffee consumption in the study by Liu et al.¹ At old age, however, the extra amounts of ROS should be able to deal with more ingested antioxidants without dropping too low. In the study by Freedman et al,² only the good aspects of heavy coffee drinking were observed. This is most likely because more than 75% of the participants in that study were older than 55 years.

A comparison between ROS levels before and after periods of heavy coffee drinking in people of different ages is required to further support the ROS hypothesis. This research may also help in identifying types of ROS whose levels associate with all-cause mortality, especially in young people.

Eliyahu Greitzer, MSc

Herzliya, Israel

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.
2. Freedman ND, Park Y, Abnet CC, Hollenbeck AR, Sinha R. Association of coffee drinking with total and cause-specific mortality [published correction appears in *N Engl J Med.* 2012;367(3):285]. *N Engl J Med.* 2012;366(20):1891-1904.
3. Eastman P. Research into antioxidants brings good news for coffee and mushrooms. *Oncology Times UK.* 2005;2(11):18-19.
4. Watson J. Oxidants, antioxidants and the current incurability of metastatic cancers. *Open Biol.* 2013; 3(1):120144.
5. Gliemann L, Schmidt JF, Olesen J, et al. Resveratrol blunts the positive effects of exercise training on cardiovascular health in aged men. *J Physiol.* 2013; 591(pt 20):5047-5059.
6. Miller ER III, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med.* 2005; 142(1):37-46.

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In Reply—Association of Coffee Consumption With All-Cause and Cardiovascular Disease Mortality

We thank Drs Katz, Wagner, Card, and Greitzer et al for their interest in our

article on coffee consumption and mortality.¹ Due to the observational nature of our study design, the association of coffee consumption with all-cause mortality or disease-specific mortality could not be verified as representing causality because of unmeasured or unknown potential confounding factors or alternative explanations. We agree with Wagner et al that the confounding effect from smoking could potentially play an important role in this association. Hence, we controlled for smoking status in the multivariate modeling. However, simply controlling for smoking status as a dichotomous variable does not eliminate the possibility of residual confounding from smoking because simplified binary smoking status could not provide the precise information to reflect the true influence of smoking. Therefore, we further stratified the analysis by smoking status, and the results were shown in supplemental online material. We did not observe any significant association between coffee consumption and all-cause mortality either in current smokers or in non-current smokers. In males, the magnitude and pattern of the association between coffee consumption and all-cause mortality were similar across smoking status. In females, however, the point estimate among nonsmokers tended to be lower than among smokers; nevertheless, no statistical significance was observed. Regarding the cumulative effects of multiple risk factors such as parental history of cardiovascular disease and other cardiovascular disease risk factors, they were accounted for in the multivariate statistical analyses, which were presented in Table 3.

Another important point from Wagner et al concerns internal and external validity. The homogeneity of our cohort highly enhanced the internal validity of our findings because of the minimized likelihood of confounding by ethnicity, education, and socioeconomic status. Regarding external validity, previous studies also documented that our study participants