

chlorogenic acid, ferulic acid, and various flavonoids. It has been suggested that in a regular American diet, coffee is the main source of antioxidants.<sup>3</sup> 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.<sup>4</sup> Watson<sup>4</sup> 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.<sup>5</sup> Finally, overconsumption of antioxidants (such as vitamin E) could be related to all-cause mortality.<sup>6</sup>

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.<sup>1</sup> 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,<sup>2</sup> 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.

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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.<sup>1</sup> 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

were similar on key clinical variables such as lipids, glucose, and blood pressure to participants in other large epidemiological studies in the United States.<sup>2,3</sup> However, our study patients may have differed from the general population in other important ways. Although we urge caution against overgeneralizing the results we reported, it is unlikely that the observed association between coffee consumption and mortality would be any less important among other populations. Unlike other studies in the literature, we also accounted for the important variable of cardiorespiratory fitness, which was precisely measured by exercise treadmill testing. We do believe that more research is needed in other diverse populations to elucidate not only the relationship between coffee consumption and mortality but also the mechanism behind any observed relationships.

In addition to chance and confounding, we agree with Card that sleep disorders might act as an important mediator or an effect modifier on the causal pathway between coffee consumption and mortality. As he suggested, future research with multiple time measures of coffee consumption and sleep status data is warranted to clarify the temporal sequence and determine how changes in these variables over time affect the association between coffee consumption and mortality.

Finally, in comparison with previous studies, one of our important findings was the positive association of heavy coffee consumption with all-cause mortality among both men and women who were younger than 55 years. The underlying potential mechanism could be the hypothesis proposed by Greitzer that the levels of reactive oxygen species are modified by heavy coffee consumption and that this modification varies by age. Further research is also needed to test this hypothesis.

Regarding the comments by Katz, we agree that our data are not strong enough to be used to “scare” young people from drinking 4 or more cups of coffee per day. However, our data suggest that the association between high coffee consumption and higher mortality in younger people seems to be mostly independent of smoking. Nevertheless, we cannot say that the coffee per se caused the higher mortality because other factors involved in this association, including sleep disorders as discussed by Card, or other confounders, such as a stress-prone personality or high-stress lifestyle, as well as other factors may also be involved. As Katz suggested, there is some sense in moderation, and as we stated in the video that accompanied the online publication of our article (<http://youtu.be/Y0wwDSBwVqU>), we agree with Mark Twain’s comments, “All things in moderation, including moderation.” And as Hippocrates said centuries ago, “If we could give every

individual the right amount of nourishment and exercise, not too little and not too much, we would have found the safest way to health.” Considering this, we believe that it is quite reasonable for most young individuals to consider keeping their coffee intake at less than 4 cups per day (eg, 2-3 cups), at least on most days, which is keeping with the theme of moderation and has been suggested elsewhere.<sup>4</sup>

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