excreted in urine. However, the concentration of these metabolites in urine is subjected to many confounding factors. For example, it is reported that the rate of caffeine metabolism is variable, with caffeine consumers being slow, intermediate, or fast metabolizers. This is highly attributable to genetic factors related to the CYP1A2 phenotype and liver function in general, and it is important to be taken into account when assessing caffeine health effects using urinary caffeine metabolites. Also, variability in excretion highly depends on the timing of the last intake of caffeine and previous habitual consumption. Ponte et al assessed the timing of the last intake of a caffeinated beverage, but it was not very clear whether this parameter was used as a confounding factor in the analysis. Also, habitual caffeine consumption should be taken into account. Previous studies have shown that people are more sensitive to the diuretic effect of caffeine after a short period of abstinence from caffeinated beverages compared with regular consumers; this results in an increased caffeine clearance. Use of high regular consumers in the same analysis with high nonregular consumers may have confounded the results. It is likely that stratification for habitual vs nonhabitual caffeine consumers might provide a clearer outcome. Finally, specific types of coffee, beyond caffeine per se (ie, Greek coffee), may exert more favorable effects on vascular properties (ie, endothelial function), which is another interesting field for further investigation.

In addition, data regarding caffeine consumption are lacking although the authors make conclusions regarding caffeine intake. The authors have previously published in the same population study that caffeine consumption, assessed using food frequency questionnaires, is associated with caffeine urinary metabolites. These questionnaires offer valuable information in epidemiological studies, but are subject to recall bias. Also, they give a sense of the frequency of consumption of specific amounts of caffeinated beverages, in a short period of time rather than the specific amount consumed the day of the 24-hour urine collection. Perhaps using 24-hour dietary recalls or even food diaries would offer better information regarding actual caffeine intake during the day of the urine collection and the previous day; this is to match intake with caffeine intake and metabolites and consequently to more accurately assess their association with PP and PWV. In our view and on the basis of available data, we have a lot more to learn concerning the effects of caffeine intake on arterial wall properties and blood pressure.

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Potential Competing Interests: The authors report no competing interests.


https://doi.org/10.1016/j.mayocp.2018.06.008

In Reply—Caffeine Effects on Arterial Stiffness: To Drink or Not to Drink

To the Editor: We thank Karatzi et al for their letter and the issues they raised. The authors stressed the fact that the rate of caffeine metabolism is variable and that it is highly attributable to genetic factors related to the CYP1A2 phenotype and liver function in general. We cannot agree more and have actually acknowledged this in the Limitation section of our article as follows: “although we considered major factors, the biological half-life of caffeine is highly variable among individuals (2-10 hours) and is influenced by several genetic and nongenetic determinants (eg, liver function) that we could not account for.” It is true that information on habitual caffeine consumption, period of abstinence, and types of coffee could have been useful to further control for potential confounding.

We fully agree with Karatzi et al who underscore that questionnaires on caffeine intake are subject to recall bias. This is the reason why we have collected in our study objective information using caffeine urinary excretion instead of self-reported intake. Although Karatzi et al suggested that 24-hour dietary recall or even food diaries would offer better information regarding caffeine intake, we believe that these questionnaires are not...
much more immune to bias as compared with other questionnaires. In addition, the use of these questionnaires would not help us in deciphering the role of caffeine metabolites, namely, paraxanthine, theobromine, and theophylline, in cardiovascular health. Using data from urinary excretion instead of questionnaires, we found strong positive associations of paraxanthine and theophylline with arterial stiffness. This finding is in line with the fact that paraxanthine is a very potent methylxanthine, and even slightly more potent than caffeine.

Regarding the timing of the last caffeinated beverage, it was standardized, but indeed we have not adjusted the analyses for that parameter. We also have not systematically collected information on the different types of coffee. Finally, we fully agree with the authors that we all have a lot more to learn concerning the effects of caffeine intake on arterial wall properties and blood pressure. We hope that our study will encourage further research to increase knowledge in this field.

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Potential Competing Interests: The authors report no competing interests.


https://doi.org/10.1016/j.mayocp.2018.06.007