

Coffee and homocysteine^{1,2}

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The early history of coffee includes an account of an Abyssinian goat herder in ≈850 AD who observed his goats dancing around what later became known as the coffee bush. He tasted the berries himself and, according to the legend, joined in the dance (1). This psychoactive effect, mediated by caffeine, probably contributed to the world-wide popularity of coffee as a beverage.

Although a recent overview concluded that coffee consumption may protect against colorectal adenomas and cancer (2), the medical focus on coffee has generally been related to its potential adverse health effects. Reports have linked coffee consumption with increased risk of cardiovascular disease, several cancers, and pregnancy complications (1). Today, the combined evidence of ill effects is rather weak, but public awareness of this debate has probably contributed to the decline in coffee consumption, at least in the United States (1).

Total homocysteine (tHcy) is the sum of several circulating homocysteine (Hcy) species that can be measured in plasma or serum. There is convincing evidence that high concentrations of this sulfur amino acid is an indicator of increased risk of cardiovascular morbidity and mortality (3). Furthermore, elevated tHcy concentrations have frequently been reported in women experiencing pregnancy complications or adverse pregnancy outcomes (4).

Folate and cobalamin deficiencies are among the most prevalent causes of elevated tHcy (5). A common 677C→T substitution in the gene coding for methylenetetrahydrofolate reductase (MTHFR), a key enzyme in folate and Hcy metabolism, is associated with an elevated tHcy concentration under conditions of impaired folate status (6). Recently, several observational studies have suggested that lifestyle factors other than dietary intake of B vitamins may influence tHcy concentrations. In the Hordaland Homocysteine Study, smoking and heavy coffee drinking were associated with elevated tHcy concentrations, even after adjustment for other factors that influence tHcy (7). Three additional observational studies addressed the issue of coffee drinking and tHcy. No significant difference in tHcy concentrations on the basis of coffee consumption was observed in the first of these studies (8). The investigators of the second study noted a statistically nonsignificant relation (9), whereas a significant association was shown in the third study (10).

Until now, no intervention studies have addressed the issue of smoking or coffee drinking as causes of elevated plasma tHcy. The study by Grubben et al (11) in this issue of the Journal is therefore most welcome. Their results stem from a randomized crossover trial carried out in 64 Dutch men and women. Half of the participants were assigned to a 2-wk regimen of 1 L unfiltered coffee/d and the rest to 2 wk of water, milk, chocolate

drink, tea, or broth. After an 8-wk washout period, the experiment was repeated with the treatments switched. Blood samples were drawn at the end of each treatment period.

Grubben et al observed a difference of 1.2 μmol/L (≈10%) in mean plasma tHcy concentrations between the coffee and no-coffee periods. In the Vitamin, Teachers and Longevity observational study, the adjusted difference was 1.3 μmol/L (10) when the tHcy concentrations of drinkers of 3–9 cups coffee/d were compared with those of nondrinkers of coffee. In the Hordaland Homocysteine Study (7), in which the tHcy concentrations of consumers of 5–8 cups coffee/d were compared with those of nondrinkers of coffee, the difference was 1.1 μmol/L. Thus, the magnitude of the effect in this study showed good overall agreement with the observational studies. The short intervention period of only 2 wk suggests that coffee may exert an acute effect on homocysteine homeostasis.


The randomized design of this study eliminated many sources of bias that may have been present in previous observational studies. However, consumption of 1 L strong coffee/d may affect diet composition and other lifestyle factors influencing tHcy. Of such factors, tobacco use probably did not change much during the trial; therefore, it is unlikely that it confounded the results. Protein intake, on the other hand, was actually slightly higher during the coffee intervention. However, protein intake and plasma tHcy were shown recently to be inversely related (10).

Unfiltered coffee was used in this intervention study, and the factor responsible for the tHcy elevation was not identified. Notably, caffeine is a methyl xanthine. Some methyl xanthines are known to act as vitamin B-6 antagonists. Interestingly, the vitamin B-6 concentration was markedly lower during coffee administration than during the no-coffee period. Because vitamin B-6 usually does not influence fasting tHcy concentrations, the significance of this finding is uncertain. Folate concentrations did not change significantly between the coffee- and no-coffee periods. Thus, interference with folate function was probably not responsible for the effect of coffee on tHcy. Because users of vitamin supplements were not eligible for the study, the question of whether administration of vitamin B weakens or prevents the effect of coffee could not be addressed. This question deserves attention in future studies.

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A second issue, which only can be addressed in larger trials, is the possibility of a selective effect of coffee on the lower tail and middle ranges of the tHcy distribution. In the Hordaland Homocysteine Study, coffee drinking was associated with a decreased likelihood of having a very low tHcy concentration but was not related to very high tHcy concentrations. A different pattern of association was observed for smoking and low folate intake. Both of these factors increased the risk of hyperhomocysteinemia and decreased the probability of having a low tHcy concentration (7). If confirmed, this observation may be relevant when the clinical implications of the effects of coffee drinking on tHcy concentrations are judged. Finally, it has been shown that the response of tHcy to folate and some drugs is related to the 677C→T MTHFR genotype (12, 13). Conceivably, the tHcy response to coffee may also be modulated by genetic factors.

Grubben et al elegantly showed that a high consumption of unfiltered coffee caused an elevation in tHcy concentrations of 1 $\mu\text{mol/L}$. Because the habit of coffee drinking is widespread, the consequences at the population level may not be negligible. However, the effect of coffee is modest and much less than the changes associated with variation in B-vitamin status. On the basis of current knowledge about the relation between Hcy concentrations and disease, these results should not cause additional concern for the general public, who still may enjoy drinking coffee. 

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