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# Letter to the Editor

## RESPONSE TO BAGGOTT AND TAMURA: "SERUM IRON PARAMETERS AND PLASMA TOTAL HOMOCYSTEINE CONCENTRATIONS"

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In their comment on our article, Baggott and Tamura suggest that plasma total homocysteine concentrations may serve as a marker for excess body iron stores. They refer to a study conducted in five healthy volunteers in which non–protein-bound iron was found to catalyze the conversion of thioethers, such as methionine and S-adenosylmethionine, into homocysteine (1). The authors hypothesize that the association between iron stores and homocysteine concentrations may underlie the apparent lack of any significant effects of B-vitamin supplementation on occlusive vascular disease.

In our recently published article, we reported that increased concentrations of serum iron and ferritin were associated, cross-sectionally, with decreased cognitive performance in the folic acid and carotid intima-media thickness (FACIT) population (2). Plasma total homocysteine did not confound the observed associations as results were similar regardless if homocysteine concentrations were included in the analyses.

We evaluated the relationship between serum iron parameters, *HFE* C282Y genotype, and plasma total homocysteine in our study sample. We found that carriers of the *HFE* C282Y mutation did not differ significantly from noncarriers in terms of homocysteine concentrations ($t = -.677$, $p = .499$). In addition, the concentrations of serum iron, total iron-binding capacity, transferrin saturation, and non–transferrin-bound iron were not significantly correlated with homocysteine concentrations at baseline ($r = -.064$, $p = .068$; $r = .005$, $p = .885$; $r = -.066$, $p = .060$; and $r = -.042$, $p = .236$, respectively). However, serum ferritin, which is an indicator of body iron stores, showed a significant positive correlation with plasma total homocysteine at baseline (Spearman's rank correlation coefficient = .125, $p < .001$).

At first glance, our data on serum ferritin seem to support the hypothesis that plasma total homocysteine concentrations may serve as a marker for body iron stores as put forward by Baggott and Tamura. Also, in line with the authors' hypothesis, we did not observe any effect of 3-year folic acid supplementation on the risk of cardiovascular disease, as measured by carotid intima–media thickness, in the FACIT study, despite a significant reduction in plasma total homocysteine (3).

However, in a previous study performed in the FACIT population, we showed that serum iron parameters, including ferritin and non–transferrin-bound iron, were not related to carotid intima–media thickness (4). These findings do not offer support for the authors' hypothesis that excess free iron or iron stores might increase the risk of cardiovascular disease.

Furthermore, although we did not demonstrate any effect of 3-year supplementation with folic acid on cardiovascular disease risk, we did find a significant improvement in cognitive performance concomitant with the observed decrease in homocysteine concentrations (3). In contrast, serum ferritin, which showed a negative relationship with cognition, significantly increased over 3 years of follow-up (mean change [95% confidence interval] = 16.6 μg/L [6.7–26.4], $p = .001$) (2). These divergent findings suggest that the relationship between iron parameters and cognitive performance on the one hand and the relationship between folate–homocysteine metabolism and cognition on the other may be mediated by different mechanisms. In addition, our findings contradict the notion that excess iron stores may catalyze or promote the formation of homocysteine in vivo. If plasma total homocysteine was to represent the amount of body iron stores, changes in homocysteine concentrations over time would be expected to parallel, at least in part, the changes in serum ferritin.

A final remark should be made with regard to the range of plasma total homocysteine concentrations in the FACIT trial. As participants with plasma total homocysteine concentrations <13 μmol/L or >26 μmol/L were excluded from the study, it cannot be ruled out that the correlations between serum iron parameters and homocysteine observed in this study may differ to a certain extent from those obtained in other populations.

In conclusion, our findings regarding the associations between serum iron parameters, plasma total homocysteine, and risk of cardiovascular disease in a large population of older adults do not appear to support the notion that excess iron stores may, at least partly, be responsible for the increased risk of cardiovascular disease often attributed to homocysteine.

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