Editorial

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Population determinants of homocysteine[1–3]

Stein Emil Vollset, Helga Refsum, and Per Magne Ueland

Total serum or plasma homocysteine (tHcy) is a risk factor for a series of pathologic conditions, including cardiovascular disease (1), adverse outcomes and complications of pregnancy (2), Alzheimer disease, and cognitive dysfunction (3). Factors associated with tHcy concentrations are therefore important both for understanding the possible pathogenic role of homocysteine in these conditions and for assessing confounding of the observed disease-tHcy relations. In the past few years, several large studies identified factors that are associated with tHcy concentrations in the general population (4–7). These studies resolved many of the controversies inherited from the earlier years of homocysteine research, which were dominated by smaller studies that yielded conflicting results on tHcy determinants. For example, a series of studies showed that smoking is associated with elevated tHcy concentrations (8), and randomized trials have confirmed that heavy coffee drinking increases tHcy (9, 10). In this issue of the Journal, the article by Jacques et al (11) confirms the association between smoking and tHcy. It also extends our understanding of the relation between coffee intake and homocysteine concentrations by showing that consumption of caffeine-containing soft drinks is associated with moderate increases in tHcy concentrations.

The study was based on a sample of 1960 men and women, aged 28–82 y, from the Framingham Offspring cohort. The subjects had blood samples drawn and completed a food-frequency questionnaire between 1991 and 1994. Relations were investigated between tHcy and its possible dietary determinants (estimated intake of B vitamins, protein, and methionine), some lifestyle factors (smoking status, alcohol use, and caffeine use), biochemical determinants (serum creatinine, plasma vitamin B-6, vitamin B-12, and folate), and other factors (body mass index, blood pressure, and antihypertensive medication). Except for blood pressure, all the above-mentioned factors showed significant associations with tHcy. For example, the investigators found that tHcy was ≈1.5 μmol/L higher in heavy smokers than in nonsmokers. Although most of these associations were reported in earlier studies, this report on population determinants of tHcy from the Framingham Offspring cohort is the most comprehensive to date. Strengths of the current report include methodologic rigor, the use of fasting blood samples, and assessment of nutrient intake on the basis of a validated food-frequency questionnaire. The large sample size allowed precise estimation of both the absolute and the relative strengths of the various determinants of tHcy.

With adjustment for age and sex, the largest differences in tHcy concentrations were found between groups with contrasting plasma folate, plasma vitamin B-6, plasma vitamin B-12, folate and riboflavin intakes, use of vitamin B supplements, serum creatinine, smoking status, age, and sex. To identify a set of best predictors, a backward selection algorithm was used. This approach further included alcohol use, caffeine intake, use of antihypertensive medication, and body mass index as important predictors of tHcy.

The article suggests a role of riboflavin, which is not surprising in view of riboflavin's role as a cofactor for methylenetetrahydrofolate reductase. The strength of the association is of a magnitude similar to the recently reported difference in plasma tHcy between upper and lower quartiles of plasma riboflavin (12).

The published data on the relation between alcohol and tHcy do not show a consistent pattern (8). Chronic alcohol abuse is associated with markedly elevated tHcy. Moderate alcohol consumption was investigated in several population-based studies with conflicting results. The positive relation between alcohol use and tHcy in the present study contrasts with the strong negative relation reported in the Welsh Caerphilly cohort. In that cohort, the inverse relation was attributed to the folate content of beer consumed in Wales (5).

An important determinant of tHcy concentrations that was not included in the current study is the common 677C→T polymorphism of the methylenetetrahydrofolate reductase gene. Persons with the TT variant of this polymorphism, which occurs in ≈10% of white populations, have tHcy concentrations that are 2–4 μmol/L higher than those in CC individuals. Data from the Hordaland Homocysteine Study suggested that TT individuals who also smoked and were heavy coffee drinkers were particularly susceptible to severely elevated tHcy concentrations (13).

We know from intervention studies that manipulation of intakes of folate, vitamin B-12, and coffee cause changes in tHcy concentrations. For other tHcy determinants, intervention studies are not possible or have not been carried out. Adjustment for potential confounding factors is an attempt to address causality issues in observational studies, but the strategy has limitations, and adjusted estimates of effect should be interpreted cautiously. In nutritional epidemiology both measurement errors and strong associations between dietary factors, vitamin status, and lifestyle

[1] From the LOCUS for Homocysteine and Related Vitamins, University of Bergen, Bergen, Norway.

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[3] Address correspondence to SE Vollset, Section for Medical Statistics, University of Bergen, Armauer Hansens hus, N-5021 Bergen, Norway. E-mail: stein.vollset@uib.no.

make data analysis especially challenging and standard statistical methods may not fully capture the complexities of the data (14, 15). For example, in the present data set, intakes of riboflavin and vitamin B-6 were strongly correlated ($r = 0.81$). Because of this colinearity, the interpretation of the model containing both vitamins is not clearcut. In particular, the P values associated with the 2 correlated factors are likely to deceive readers who use this information to decide which factor has a more important causal role. The complexity in analysis and interpretation is further illustrated by the observation of an inverse relation between protein or methionine intake and tHcy concentrations. This association disappeared after adjustment for dietary folate and vitamin B-6 intake, suggesting that vitamins that accompany a protein-rich diet mediate the homocysteine-lowering effect more than does the protein load itself. However, in another study (16), which showed high correlations among dietary energy, protein, folate, riboflavin, and vitamin B-6 intakes, an inverse association between protein intake and tHcy concentrations was maintained after adjustment for vitamin intake and total energy intake.

In this study of the Framingham Offspring cohort, which used blood samples collected before the folate fortification era, the plasma concentration of folate was by far the strongest determinant of tHcy. The difference in tHcy between upper and lower plasma folate quintiles was ≈4 μmol/L. The other factors studied accounted for differences of 0.5–2.0 μmol/L. The determinants of tHcy are likely to vary by age and sex and among countries, depending on the B-vitamin content of the national diet. Future research priorities include studying determinants of tHcy in relevant population subgroups and in the now folate-fortified US population. Finally, assessment of the combined effect of several tHcy determinants may be needed to identify effects of potential clinical relevance.

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