AMI risk unless they influence the AMI risk themselves. If previous evidence is considered, only calcium and fiber intakes could have produced a spurious association like the one observed. This was not the case in our data set, within the limits of the measurement precision of the dietary variables. Confounding by coffee intake and plasma ascorbate would be expected to attenuate rather than enhance the observed association between serum ferritin and AMI risk. An adjustment for coffee intake strengthened the observed association between serum ferritin and AMI risk, whereas allowing for plasma ascorbate did not have much effect. Serum selenium had no association with serum ferritin; consequently, an additional adjustment for serum selenium did not affect the relation of ferritin with AMI risk. We assessed only dietary carotene intake in the Kuopio Ischaemic Heart Disease Risk Factor Study baseline. An adjustment for carotene intake did not attenuate the impact of ferritin on AMI risk either.

In Cox proportional hazards models that include serum ferritin as a binary variable, all the same covariates as in our original analysis (listed, e.g., in the abstract) and in separate models either jointly or one at a time—plasma ascorbate, serum selenium, body mass index, weekly alcohol intake, and the mean daily intakes of saturated fats, cholesterol, carotenes, calcium, fiber, and coffee—the relative hazard for serum ferritin of at least 200 μg/L was 2.12 (p<0.01) or higher. In the model with all 26 covariates simultaneously (including five dummy variables indicating examination years), the adjusted relative hazard was 2.90 (95% confidence interval, 1.55–5.41; p<0.001).

MacDonald raises the issue of cross-population comparisons. In our view, comparisons between populations do not provide useful evidence for causal inferences, because they are susceptible to ecological fallacy—confounding of between-population associations by other within-population characteristics. For instance, the finding that coronary heart disease is rare in Japan does not provide any evidence against the relation between hypertension and coronary heart disease (CHD). In the case of China, there is a specific reason for not generalizing Chinese findings: the mean serum cholesterol level in China is very low. On the basis of our study, serum ferritin would have no impact on CHD at very low serum cholesterol levels. Similarly, in France and Scotland, there are other dietary and other environmental and genetic factors behind the low and high occurrences, respectively, of CHD, such as serum lipids and antioxidants. In our view, parallel trends in a risk factor and disease incidence over age groups does not provide strong evidence either in favor of or against a causal hypothesis.

As we stated in the discussion of our article, there is a possibility that the hemochromatosis gene covaries with another gene, which would be the true causal factor instead of high stored iron. However, the eastern Finnish male population does not differ substantially with regard to mean or median serum ferritin from other western male populations. The median serum ferritin in our study population was 127 μg/L (compared with, e.g., 94 μg/L in Washington state). However, the intake of antioxidants was relatively low,1–3 and the mean serum low density lipoprotein (LDL) cholesterol was relatively high. Because of the observed synergism between serum ferritin and serum LDL cholesterol, it is possible that the impact of elevated serum ferritin levels is greater in eastern Finnish men than in populations with lower LDL cholesterol levels.

References

High Stored Iron Levels
We have read the article “High Stored Iron Levels Are Associated With Excess Risk of Myocardial Infarction in Eastern Finnish Men” (Salonen et al, Circulation 1992;86:803–811) with great interest.

We certainly agree that it is important to ascertain the various risk factors for coronary heart disease (CHD) and that the possibility that high iron stores are among the risk factors must be further investigated. However, we have some comments regarding serum ferritin and hemoglobin values.

The range of serum ferritin values in the subjects studied were 10–227 μL. The values in each end of the range indicate pathology in the subjects, which in itself might influence the susceptibility to CHD or acute myocardial infarction (AMI). Serum ferritin values <25 μL in adult men indicate occult bleeding, in most cases from the gastrointestinal tract caused by tumors, gastric ulcer, or other pathological processes. Hemoglobin values down to 105 g/L also suggest that some of the subjects do have occult bleeding, the cutoff value for male subjects being 130 g/L. It would be of interest in order to evaluate the results to know how many of the subjects had such abnormal values for serum ferritin and hemoglobin.

On the other hand, in male subjects, serum ferritin values >200–300 μL also indicate pathological processes such as chronic infectious and inflammatory diseases, alcohol abuse with liver involvement, or primary or secondary hemochromatosis. The fact that 25% of the participants had serum ferritin values >200 μL/L and 6% had values >400 μL/L (certainly pathologically high values) indicate that a considerable number of the subjects cannot be considered normal. It is not possible to state that the high iron stores per se are a risk factor for CHD when it is equally likely that the underlying disease causing high iron stores constitutes the risk factor.

Furthermore, the authors state that in their study, the serum ferritin levels decreased with age. This is in contrast to all known studies among normal individuals where the serum ferritin levels are shown to increase with increasing age both for men and for menopausal women. The fact that in this population serum ferritin values decrease might indicates that the subjects were not characteristic of a normal population. We therefore suggest that the relation between AMI and serum ferritin values >200 μL only reflects the relation between AMI and other pathological conditions such as alcohol abuse or chronic infections and not a relation between AMI and light iron overload. It is also known that a
relation exists between AMI and hemochromatosis, which is a pathological iron overload. However, hemochromatosis patients cannot be considered as normal male subjects.

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Reply

Borch-Johnsen and Halvorsen emphasize in their letter that both very high and very low values of serum ferritin reflect pathological disease conditions. This is true. The same phenomenon also concerns all previously established risk factors for coronary disease such as serum low density lipoprotein cholesterol concentration and blood pressure. In epidemiological studies concerning disease etiologies it is, however, customary not to exclude persons with other diseases out of the study sample. If persons with various conditions were excluded, the results would not be representative of the general population. Instead, coexisting diseases are considered in the statistical analysis as potential confounding factors. To confound the association between a risk factor and disease risk, a factor has to have a relation with the risk of disease. In our data, intestinal bleeding–inducing diseases such as peptic ulcer or gastritis or colon diseases had no association with the risk of acute myocardial infarction (AMI). For this reason, the inclusion of these conditions in multivariate Cox models predicting AMI risk did not affect the impact of serum ferritin concentration even though both gastric (mean±SD, 135±129 μg/L versus 171±151 μg/L; p<0.001 for difference) and colonic (139±116 μg/L versus 169±151 μg/L; p=0.007) conditions were associated with reduced serum ferritin levels.

Borch-Johnsen and Halvorsen also bring up inflammatory diseases, alcohol abuse with liver involvement, and hemochromatosis as other possible confounding conditions. We have dealt in detail with the issue of inflammatory diseases in our reply to Weiss and coworkers, showing that in our data set, serum ferritin levels were not affected either by inflammatory processes or by macrophage activation. Alcohol abuse, as measured by frequency of drunkenness (r=0.196, p<0.001) and hangover (r=0.162, p<0.001), was positively associated with serum ferritin concentration. Also, serum gammaglutamyltransaminase concentration (r=0.270, p<0.001) and the weekly consumption of alcohol (r=0.224, p<0.001) were associated with serum ferritin. These associations could be due to the iron absorption–enhancing effect of alcohol. However, none of these variables describing alcohol intake had any association with the risk of AMI in our data, as mentioned in our article (Reference 2, page 806). We agree with Borch-Johnsen and Halvorsen in that hemochromatosis or its gene could be associated with AMI risk directly or could covary with other phenotypes or genes that could be the real etiologic factors, as we discussed in our article (Reference 2, pages 809–810). This remains to be elaborated on further studies. On the basis of our findings, we would extrapolate that the excess risk of AMI in hemochromatosis patients particularly is due to their increased body iron stores and chronic exposure of arteries and myocardium to elevated redox-active iron.

Like Weiss and coworkers, Borch-Johnsen and Halvorsen also dismiss the observed association between the estimated dietary intake of iron and AMI risk, which could not possibly have been caused by covariation with any disease states unless iron intake is affected by diseases. There was no evidence of that in our data.

Our finding that serum ferritin concentration started to decrease from approximately the age of 50–54 years on could be caused by either a reduction in the absorption of dietary iron from middle age on or by a selective mortality, assuming that men with higher serum ferritin had higher mortality. We will be able to address this question after a longer follow-up period.

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References

Iron and Ischemic Heart Disease

Salonen et al1 reported an association between increasing iron stores and risk for myocardial infarction among Finnish men followed in the Kuopio Ischemic Heart Disease Risk Factor Study (KIHD). To determine whether the same association was present among US adults, we used data from the NHANES I Epidemiologic Follow-up Study (NHEFS) to examine the association between increasing iron stores and risk for fatal and nonfatal ischemic heart disease (IHD) events.

Ferritin level, the measure of iron stores used by Salonen et al, is not available in the NHEFS; however, transferrin saturation is. Transferrin saturation is a valid indicator of iron stores2 when very low or very high: saturations <15% are likely to be related to low iron stores, whereas those with saturations >60% are likely to be related to high iron stores.2

Since a number of chronic conditions affect transferrin saturation and these same conditions may be associated with IHD, persons with the following chronic conditions were excluded from the analysis: myocardial infarction, angina, cerebrovascular disease, congestive heart failure, diabetes, cancer, chronic bronchitis, and Crohn’s disease/enteritis. In addition, our analysis was limited to persons between 45 and 74 years of age (n=1,450).

There was no difference in mean transferrin saturation between persons who developed IHD (mean, 29.14%) and those who did not (mean, 29.64%). When persons with a transferrin saturation <15% were used as the referent, the relative risk for IHD after adjusting for age, race, sex, education, marital status, cigarette smoking, systolic blood pressure, serum cholesterol level, body mass index, alcohol intake, physical activity, and erythrocyte sedimentation rate was 1.0 (95% CI, 0.6–1.9) for saturations between 15% and 30%; 1.1 (95% CI, 0.6–2.1) for saturations between 30% and 45%; 0.7 (95% CI, 0.3–1.7) for saturations between 45% and 60%; and 1.6 (95% CI, 0.6–3.9) for saturations >60%. Persons with saturations >60% accounted for 2% of the cohort. When the groups were stratified by sex, men with saturations >60% had a relative risk of 0.8 (95% CI, 0.2–3.4) and women had a relative risk of 2.6 (95% CI, 0.7–9.2).

The only evidence of a substantial association between increasing iron stores and risk for IHD occurred at very high saturations, whereas Salonen et al1 reported that men with ferritin levels >200
High stored iron levels.
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