Coronary Heart Disease and Iron Status
Meta-Analyses of Prospective Studies

John Danesh, MBChB, MSc; Paul Appleby, MSc

Background—Studies of iron status and coronary heart disease (CHD) have yielded conflicting results. In a systematic review ("meta-analysis"), we quantitatively assessed epidemiological associations reported in prospective studies.

Methods and Results—Studies were identified by computer-assisted searches of the published literature, scanning of relevant reference lists, hand searching of relevant journals, and discussions with relevant authors. The following was abstracted: size and type of cohort, mean age, mean duration of follow-up, assay methods, degree of adjustment for confounders, and relationship of CHD risk to the baseline assay results. Twelve studies were identified, involving a total of 7800 CHD cases, with several reporting on >1 marker of iron status. For serum ferritin, with 570 CHD cases in 5 studies, comparison of individuals with baseline values ≥200 versus <200 µg/L yielded a combined risk ratio of 1.0 (95% CI, 0.8 to 1.3). For transferrin saturation, with 194 CHD cases in 5 studies, comparison of individuals in the top third with those in the bottom third of baseline measurements yielded a combined risk ratio of 0.9 (95% CI, 0.7 to 1.1). Comparisons of individuals in top and bottom thirds of baseline measurements also yielded nonsignificant risk ratios in combined analyses of studies involving total iron-binding capacity (combined risk ratio, 1.0; 95% CI, 0.7 to 1.5), serum iron (0.8; 95% CI, 0.7 to 1.0), and total dietary iron (0.8; 95% CI, 0.7 to 1.1).

Conclusions—Published prospective studies do not provide good evidence to support the existence of strong epidemiological associations between iron status and CHD. (Circulation. 1999;99:852-854.)

Key Words: epidemiology ■ coronary disease ■ iron ■ meta-analysis

Epidemiological studies of iron status and coronary heart disease (CHD) have yielded conflicting results, with claims ranging from strongly positive associations to strongly negative associations. To help clarify the actual evidence, we report a systematic review ("meta-analysis") of published prospective studies, in which CHD events were recorded for several years after baseline measurement of iron status. Such studies should be less prone to bias than retrospective studies, because they limit the influence of preexisting disease itself on iron levels.

Methods

Long-term prospective studies published before 1998 that reported on correlations between CHD and markers of iron status were sought by Medline searches; scanning of relevant reference lists; hand searching of cardiology, epidemiology, and other relevant journals; and discussion and/or correspondence with authors of relevant reports. Computer searches used combinations of key words relating to iron status (iron, ferritin, transferrin) and to disease (CHD, myocardial infarction, atherosclerosis, vascular disease). All relevant studies identified were included.²⁻¹⁴ Non–English-language articles were to be translated. The following were abstracted: size and type of cohort (ie, population-based or selected on the basis of previous vascular disease), mean age and follow-up duration, assay methods, and degree of adjustment for potential confounders (see Figure legend). Iron status has been measured by use of various different blood markers and dietary questionnaires (Table), with different studies reporting risk ratios on the basis of different cutoff levels, including comparisons of thirds, quarters, fifths, etc, or as increases in risk for a given increase in the relevant factor. The risk ratios derived from such publications for this review compare individuals in the top third versus those in the bottom third of baseline measurements, assuming a log-linear association with disease risk over the midrange of baseline values (of transferrin saturation, total iron-binding capacity, serum iron, or total dietary iron). For serum ferritin, however, comparisons involve levels of ≥200 versus <200 µg/L, in keeping with comparisons in published studies. Summary estimates of the risk ratios from all studies for each marker of iron status were obtained by combining the separate estimates of inverse-variance-weighted log risk ratios from each study. This was done even when different studies used different assay methods for the same marker, because cases were compared directly only with controls within the same studies. CIs were obtained by normal approximations, with 99% CIs used for the individual study results to take account of the increased scope for the play of chance in multiple comparisons, and 95% CIs used for overall results for each marker. Heterogeneity was assessed by standard χ² tests.
pressure), and several also adjusted for markers of social class and chronic disease at baseline (Figure).

**Serum Ferritin**

Five prospective studies of CHD and serum ferritin (all involving immunological assays) were identified,2–7 involving a total of 570 cases (weighted mean age at baseline, 55 years; weighted mean follow-up, 8 years). There was some evidence of heterogeneity among these 5 studies ($\chi^2 = 11.8; P = 0.02$). Overall, comparison of individuals with serum ferritin measurements $\geq 200$ versus those $<200$ mg/L at baseline yielded a combined risk ratio for CHD of 1.03 (95% CI, 0.83 to 1.29).

**Transferrin Saturation**

Five other prospective studies involved transferrin saturation and CHD,8–12 including a total of 6194 cases (weighted mean age at baseline, 56 years; weighted mean follow-up, 14 years). There was no heterogeneity among these 5 studies ($\chi^2 = 3.3; P > 0.1$). Overall, comparison of individuals with transferrin saturation values in the top third with those in the bottom third at baseline yielded a combined risk ratio for CHD of 0.92 (95% CI, 0.74 to 1.14).

**Total Iron-Binding Capacity**

Only 3 of the studies of transferrin saturation and CHD10–12 and 1 of the studies of serum ferritin and CHD6 reported on

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### Some Characteristics of Different Markers of Iron Status

<table>
<thead>
<tr>
<th>Marker</th>
<th>Serum Ferritin</th>
<th>Transferrin Saturation</th>
<th>TIBC</th>
<th>Serum Iron Concentration</th>
<th>Total Dietary Iron Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>Large protein</td>
<td>Ratio of serum iron to TIBC</td>
<td>Marker of serum transferrin levels</td>
<td>Unbound iron</td>
<td>Estimated from food diaries or food frequency questionnaires</td>
</tr>
<tr>
<td>Relevance</td>
<td>Marker of total body iron stores</td>
<td>Marker of circulating iron available to tissues</td>
<td>Transferrin transports ferric ions into cells</td>
<td>Marker of iron release into plasma</td>
<td>Weakly correlates with serum ferritin</td>
</tr>
<tr>
<td>Approximate baseline mean (SD)</td>
<td>160 (100) mg/L</td>
<td>30 (10)%</td>
<td>65 (10) mmol/L</td>
<td>18 (6) mmol/L</td>
<td>15 (5) mg/d</td>
</tr>
<tr>
<td>Approximate self correlation (r)*</td>
<td>$\approx 0.7$</td>
<td>$&lt; 0.5$</td>
<td>$&lt; 0.5$</td>
<td>$&lt; 0.5$</td>
<td>$&lt; 0.5$</td>
</tr>
</tbody>
</table>

TIBC indicates total iron-binding capacity.

*Correlation coefficient between 2 measurements of the same factor taken some years apart in the same individual.

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Prospective studies of coronary heart disease and markers of iron status. Solid squares are proportional to the number of cases, with horizontal lines representing CIs. Degree of adjustment for confounders: $+$, age and sex only; $++$, these plus smoking; $+++$, these plus standard vascular risk factors; $++++$, these plus markers of social class; $+++++$, these plus information on chronic disease at baseline.
total iron-binding capacity, involving a total of 2755 cases (weighted mean age at baseline, 58 years; weighted mean follow-up, 13 years). There was no heterogeneity among these 4 studies ($\chi^2=0.1; P>0.1$). Overall, comparison of individuals with levels of total iron-binding capacity in the top third versus those in the bottom third at baseline yielded a combined risk ratio for CHD of 0.98 (95% CI, 0.66 to 1.46).

**Serum Iron**
A separate prospective study,\(^{13}\) as well as 2 of the studies of transferrin saturation and CHD,\(^{10,11}\) reported on serum iron, involving a total of 2848 cases (weighted mean age at baseline, 58 years; weighted mean follow-up, 14 years). There was some evidence of heterogeneity among these 3 studies ($\chi^2=8.1; P=0.02$). Overall, comparison of individuals with serum iron values in the top third versus those in the bottom third at baseline yielded a combined risk ratio for CHD of 0.83 (95% CI, 0.67 to 1.03).

**Total Dietary Intake**
A separate questionnaire-based study,\(^{14}\) as well as 2 of the studies of blood markers of iron status and CHD,\(^{2,10}\) reported on total dietary iron intake according to food diaries, involving a total of 2535 cases (weighted mean age at baseline, 59 years; weighted mean follow-up, 10 years). There was no heterogeneity among these 3 studies ($\chi^2=4.6; P>0.1$). Overall, comparison of individuals with total daily iron intake in the top third versus those in the bottom third at baseline yielded a combined risk ratio for CHD of 0.84 (95% CI, 0.66 to 1.06).

**Discussion**
The present systematic review of prospective reports does not support the existence of strongly positive or strongly negative epidemiological associations between iron status and CHD. Because of potential limitations, however, it cannot rule out the possibility of any weak associations. First, assays for iron status are widely available, so other relevant studies of iron status and CHD may well exist that have not yet been reported. Indeed, separate results for CHD were not reported in a few long-term prospective studies of iron status and cancer mortality,\(^{16,17}\) but any bias owing to the absence of those studies is not likely to be substantial because they include <5% of the deaths in the available studies. Moreover, several studies in the present review did not provide separate results for each marker of iron status reported to have been measured, and such selective reporting could obscure or mimic any real association.\(^{18}\) Second, certain chronic conditions, such as liver disease and inflammatory diseases, might alter iron levels and therefore produce distorted associations with CHD. But attempts to control for the possible effects of preexisting disease on iron markers by statistical adjustment for disease or for various inflammatory markers at baseline, by the exclusion of those known to have preexisting diseases, or by omission of any CHD events during the first few years of follow-up did not substantially change the associations in the published studies. Furthermore, all identified studies involved population-based samples, which should be less prone to bias than cohorts defined on the basis of previous vascular disease. Finally, most of the published studies reviewed in this article related CHD risk only to measurements of iron status made at baseline. Yet, even levels of serum ferritin, which are regarded as the most reliable markers of iron status, can fluctuate markedly within individuals over time (Table). Failure to correct for this regression dilution\(^{19}\) can lead to associations of disease risk with baseline levels that are substantially weaker than the corresponding associations with usual levels might be. Therefore, further measurement of iron status, particularly serum ferritin, in some large studies with serial measurements might change the present overall results and their interpretation. Nevertheless, the overall findings in available prospective studies are fairly consistent among the different markers of iron status, and they provide no good evidence for the existence of strong epidemiological associations between iron status and CHD.

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**References**
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