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# Iron status and its association with coronary heart disease: Systematic review and meta-analysis of prospective studies

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ABSTRACT

**Background**: Observations in the past have hypothesized an association between body iron status and coronary heart disease (CHD). Epidemiological studies to date have however been inconclusive without the existence of strongly positive or strongly negative associations between iron status and coronary heart disease. **Objectives**: To investigate the association between iron status and coronary heart disease. **Data sources**: A systematic review was performed using the databases PubMed and Cochrane Library. Search terms included iron, ferritin, transferrin, total iron binding capacity, coronary heart disease and angina. **Study selection**: Only prospective studies investigating the association of body iron status and coronary heart disease were included. All participants were free from coronary heart disease at baseline. There were no language or geographic restrictions imposed on the search strategy. **Data extraction**: Independent extraction of articles by 2 authors using predefined data fields. **Data synthesis**: All pooled analyses were based on random-effects models. A total of 17 studies were identified for analysis, involving a total of 9236 cases of coronary heart disease and 156,427 participants. Several studies reported more than 1 marker of iron status. For serum ferritin, comparison of individuals in the top third versus the bottom third of baseline measurements yielded a combined risk ratio of 1.03 (95%CI, 0.87−1.23) for CHD/MI. For transferrin saturation, the combined risk ratio for CHD/MI was 0.82 (95% CI, 0.75−0.89) for individuals in the top third versus the bottom third of baseline measurements. Comparison of individuals in top and bottom thirds of baseline measurements yielded non-significant risk ratios of studies involving total iron-binding capacity (combined risk ratio, 0.99; 95% CI 0.86−1.13) and serum iron (combined risk ratio, 0.87; 95% CI 0.73−1.04). For serum iron, the combined risk ratio for CHD/MI after excluding the study by Morrisson et al. [1] was 0.80 (95% CI, 0.73−0.87). **Conclusions**: The results suggest that there is a negative association of transferrin levels and coronary heart disease with high transferrin saturations being associated with a lower risk of CHD/MI. There was also a negative association of serum iron and CHD/MI after one study [1] was excluded. There is no significant association between the other markers of iron status and CHD. It is however difficult to infer causality from these findings due to limitations in terms of reverse causality bias and residual confounding.

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## 1. Introduction

A wide variety of risk factors such as smoking, hyperlipidaemia, obesity, and diabetes have been established as useful predictors for atherosclerosis and CHD [2]. In addition to these classic risk factors, the possibility that a high body iron status has a role in atherosclerosis was first postulated by JL Sullivan [3].

Iron is an essential mineral needed for oxygen metabolism, with most of the iron in the body residing in circulating red blood cells. Under physiologic conditions, the body has a stable pool of iron [4].

*Abbreviations:* AMI, acute myocardial infarction; CHD, coronary heart disease; CI, confidence interval; CVA, cerebrovascular accident; ES, effect Size; ICD, international classification of diseases; IHD, ischaemic heart disease; MI, myocardial infarction; PVD, peripheral vascular disease; RR, risk ratio; SD, standard deviation; TIBC, total iron binding capacity.

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Sullivan's paper and other experimental studies [5] reported several observations which support the association of high body iron status and coronary heart disease. These include:

(1) HFE hereditary haemochromatosis, which involves a mutation in the HFE gene, results in increased iron uptake. Studies [6,7] have reported an increased incidence of CHD in individuals who carry this mutation.
(2) Clinical observations: The increase in serum ferritin levels (which is a marker of body iron stores) with age correlates with the increased CHD risk. The male: female ratio for median serum ferritin levels for ages 18–45 years in Sullivan's article [3] was 3.8, which was similar to the increased risk for heart disease in males in this age group. In contrast, the male: female ratio of serum ferritin in post-menopausal women is similar and the risk of CHD approaches that of males in this age group.
(3) Ecological data: There have also been studies [8,9] which report an association between reduction in stored iron levels through voluntary blood donation and a reduced risk of myocardial infarction.
(4) Laboratory experiments: It is well established that oxidative stress has an integral role in the pathogenesis of atherosclerosis. The ease with which iron is easily oxidised and reduced makes it able to generate oxidised low-density lipoproteins (LDL) and oxygen free radicals that can contribute to vessel wall damage and atherosclerosis. Collective data from experimental studies, including animal studies reveal that iron chelators (agents which remove iron) prevent the oxidation of LDL and vessel wall damage [3,4].

Epidemiological studies so far investigating the association of iron status and CHD have yielded conflicting results. The objective of this paper was to critically appraise all the epidemiological data available to date and perform a systematic review on the association between body iron status and coronary heart disease.

## 2. Methods

### 2.1. Data sources and searches

The electronic databases Pubmed (1960–September 2014) and the Cochrane Library (up to September 2014) were systematically searched for studies investigating the association of iron status and coronary heart disease.

The MESH terms used were words relating to iron status ("iron" OR "ferritin" OR "transferrin" OR "total iron binding capacity") and to disease ("Coronary Heart Disease" OR "myocardial infarction" OR "angina"). Two independent reviewers (SDD and SK) performed all aspects of the search strategy, examined the abstracts for relevance, and reviewed the full text articles in detail as indicated. There were no major discrepancies between reviewers with regard to study inclusion or data extraction. Minor discrepancies in extraction of clinical characteristics were resolved by consensus and arbitration by a third independent reviewer (AJ).

#### 2.1.1. Study selection and data extraction

For this systematic review, only prospective studies were included. In all the studies, participants were free from coronary heart disease at baseline. The exposure of interest was body iron status. The disease endpoint of interest was a binary outcome reported either as an event or mortality from coronary heart disease or myocardial infarction.

Definitions of coronary heart disease and myocardial infarction were based on the ICD codes.

There were no language or geographic restrictions imposed in the search strategy. Abstracts were excluded based on the relevancy of the topic, type of study (in vitro and animal studies were excluded), and publication type (reviews, letters and editorials were excluded). All retrospective studies and studies evaluating different end points compared to those specified above were excluded. Two authors (SDD and SK) independently extracted data. AJ reviewed and arbitrated any disagreements.

From each study the following were extracted: the measure of iron status and cardiac endpoint reported, the population studied, the number of cases reported and the potential confounders and the relevant effect measure of the exposure.

#### 2.1.2. Data synthesis and analysis

The studies we reviewed used different methods to present the effect of body iron status on the risk of CHD/MI. Different cutoff levels of body iron status, including comparisons of tertiles, quartiles, quintiles, or an increase of a standard deviation or a unit of an iron marker was used to report the risk ratios in different studies. It was necessary to transform the different methods of presentation to a uniform one to enable us to perform quantitative comparisons and perform a synthesis of the results from different papers. For this review, the risk ratios from these publications were converted to compare individuals in the top third and the bottom third of baseline measurements. This refers to the ratio of incident cases of CHD/MI in the top tertile versus the bottom tertile of any particular iron marker. The two assumptions necessary to make this conversion were 1) A log-linear association with disease risk over the midrange of baseline values (for ferritin, transferrin saturation, TIBC and serum iron) and 2) The quantitative variable i.e the various iron markers have a normal distribution [10].

There were studies, which reported a combined risk ratio for males and females, whereas others reported sex specific risk ratios. For the purpose of this paper a combined risk ratio was obtained for the latter studies by calculating a pooled effect of both sexes using a fixed effects model meta-analysis.

Summary estimates of the risk ratios from all studies for each marker of iron status were combined using the inverse variance method. A random effects meta-analysis model was used. All the risk ratios were presented with 95% confidence intervals and p values of less than 0.05 were considered as statistically significant in all analyses.

Heterogeneity between studies was assessed by examining clinical characteristics as well as by formal statistical testing using the $I^2$ statistic [11].

Small study bias was assessed by plotting the standard error of the logarithm of the effect estimate versus the logarithm of the effect estimate for each study. The symmetry of the funnel plots was assessed both visually, and quantitatively with Egger's test, to see if the effect decreased with increasing sample size.

We also carried out predefined subgroup analyses on study region, case definition used, degree of adjustment and gender (Fig. 4A–D). The quantitative influence on these study characteristics on the effect size was further investigated using meta-regression (Table 2).

Meta-analysis was performed using Stata 11 according to the PRISMA guidelines.

## 3. Results

### 3.1. Systematic review

The systematic literature search identified 654 relevant references (Fig. 1). After screening titles and abstracts, we excluded

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