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META-ANALYSIS

Dietary intake of heme iron and risk of cardiovascular disease: A dose–response meta-analysis of prospective cohort studies

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Abstract *Background and aims:* Iron is thought to play a fundamentally important role in the development of cardiovascular disease (CVD). This meta-analysis was performed to investigate the dose–response association between dietary intake of iron (including heme and non-heme iron) and the risk of CVD.
Methods and results: We performed a search of the PubMed and Embase databases for prospective cohort studies of the association between dietary iron intake and CVD risk. Thirteen articles comprising 252,164 participants and 15,040 CVD cases were eligible for inclusion. Heme iron intake was associated significantly with increased risk of cardiovascular disease, and the pooled relative risk (RR) for each 1 mg/day increment was 1.07 (95% confidence interval: 1.01 to 1.14, I^2 = 59.7%). We also found evidence of a curvilinear association ($P < 0.05$ for non-linearity). In contrast, we found no association between CVD risk and dietary non-heme (0.98, 0.96 to 1.01, I^2 = 15.8%) or total iron (1.00, 0.94 to 1.06, I^2 = 30.4%). Subgroup analyses revealed that the association between heme iron intake and CVD risk was stronger among non-fatal cases (1.19, 1.07–1.33) and American patients (1.31, 1.11–1.56).
Conclusions: Higher dietary intake of heme iron is associated with an increased risk of cardiovascular disease, whereas no association was found between CVD and non-heme iron intake or total iron intake. These findings may have important public health implications with respect to preventing cardiovascular disease.

Introduction

Cardiovascular disease (CVD) has long been a significant public health problem. It causes maximum disability-adjusted life-years (DALYs) as reported by the Global Burden of Disease Study [1]. Although the prevalence of CVD has declined in developed countries (e.g. the United Kingdom and the United States) [2,3], the prevalence has increased considerably in developing countries. Indeed, a

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recent study reported that in the coming ten years, CVD is projected to be a major cause of morbidity and mortality in many developing countries [4].

Dietary factors are thought to play a fundamentally important role in CVD development [5]. Recently, several successive meta-analyses suggested that the consumption of red meat might be associated with the risk of CVD [6–8]. This positive correlation has been attributed – at least partly – to heme iron, which is abundant in red meat. Generally speaking, iron is a "double-edged sword" for living systems. Iron is essential for a wide range of key biological functions, including oxygen transport and cellular respiration. On the other hand, excessive levels of iron – particularly heme iron – can increase oxidative stress, leading to enhanced lipid peroxidation [9,10], a typical protein modifications, and DNA damage [11]. Several meta-analyses of prospective cohort studies revealed a positive correlation between heme iron intake and the risk of type 2 diabetes mellitus and some types of cancer [12–14].

Several prospective cohort studies examined the association between heme iron intake and the risk of various forms of CVD or total CVD outcome. However, the overall conclusion remains controversial, as the results of these studies were not consistent. One recent meta-analysis by Hunnicutt et al. investigated the correlation between dietary iron intake and the risk of coronary heart disease (ICD-9 codes 410–414 and ICD-10 codes $I^2$0– $I^2$5); however, this study did not categorically cover all cardiovascular diseases (i.e. codes 390–459 and I01–I99)[15]. Thus, to the best of our knowledge, no meta-analysis has been performed to examine the specific association between dietary heme iron intake and CVD risk.

To investigate this association, we performed a systematic review and dose–response meta-analysis of all available prospective cohort studies in order to examine the dose–response association between long-term intake of iron and total CVD outcome.

Methods

The design, implementation, analysis, and reporting of our meta-analysis were performed in accordance with the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) protocol [16].

Search strategy

We performed a search of the PubMed and Embase databases for studies published through July, 2014. We searched for prospective cohort studies that examined the association between dietary intake of heme iron and the risk of CVD. The following terms were used for the PubMed search (similar terms were used to search Embase): ("dietary iron" OR "heme iron" OR "haem iron" OR "iron intake" OR "iron consumption") AND ("cardiovascular disease" OR "coronary heart disease" OR "myocardial infarction" OR "heart failure" OR "stroke" OR "cerebrovascular disease" OR "hypertension" OR "hypertensive disease" OR "ischemic heart disease" OR "ischaemic heart disease"). The references included in the relevant articles retrieved were also reviewed to identify additional potential publications. We restricted our search to human studies. Finally, we applied no language restriction to the search. Two authors (XF and PA) conducted the literature search independently.

Selection of articles

Studies that satisfied the following four criteria were included in our meta-analysis: 1) published prospective cohort studies; 2) the exposure of interest was dietary iron intake, including heme iron, non-heme iron, and total iron; 3) the outcome was risk of CVD, including morbidity of coronary heart disease (CHD), stroke, hypertensive disease, heart failure, and/or CVD-related mortality; 4) the authors reported the relative risk estimates, including 95% confidence intervals, for at least three quantitative categories of dietary iron intake. The study selection process is depicted diagrammatically in Fig. 1.

During screening, we excluded retrospective and/or cross-sectional studies, non-human studies, and non-original studies (e.g. reviews, editorials, and commentaries). Studies of other exposures and endpoints were also excluded.

Data extraction

Two authors (XF and PA) extracted detailed information from each included article independently. Disagreements were resolved through group discussion with the third author (FW). For each study that met the selection criteria, we extracted the following information: basic information (e.g. author, publication year, age and gender of the cohort, cohort size, and number of cases); study characteristics (e.g. the name and geographic location of the study, and

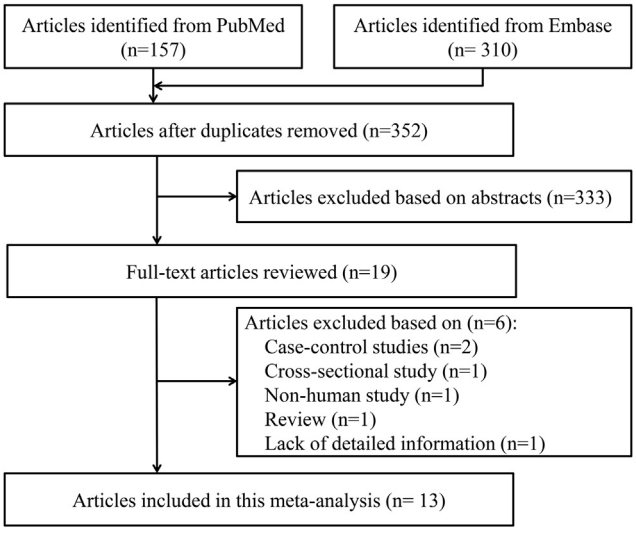

Figure 1 Flow diagram of literature search and study selection.