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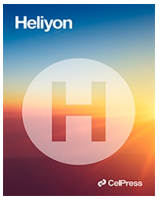

Research article

Effect of iron status on myocardial infarction: A two-sample Mendelian randomization study

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ABSTRACT

Background: In observational studies, connections have been identified between iron status and myocardial infarction (MI). The significance of changes in iron status as either a risk factor or a result of MI remains unclear.

Methods: We obtained our instrumental variables from a meta-analysis of three GWASs in Iceland, the UK, and Denmark, which discovered 62 independent sequence variants across 56 loci linked to blood iron levels, ferritin, total iron binding capacity (TIBC), transferrin saturation (TSAT), and the Genetics of Iron Status (GIS) database for transferrin. To evaluate the connection between iron status markers and myocardial infarction (MI), we used three GWAS datasets focused on MI outcomes. The chosen datasets included one representing the European population (ebi-a-GCST011364: n case = 14,825, n control = 380,970; finn-b-I9_MI: n case = 12,801, n control = 187,840) and another with a mixed population (ieu-a-798: n case = 43,676, n control = 128,199). The primary method used in our study was inverse variance-weighting, while we also assessed heterogeneity and horizontal pleiotropy to enhance the robustness of our findings.

Results: The main analysis with the inverse variance-weighted method showed no significant impact of iron marker levels on MI risk in the ebi-a-GCST011364 and finn-b-I9-MI cohorts. In contrast, the ieu-a-798 cohort indicated that higher ferritin levels had a protective effect against MI (OR = 0.87, 95 % CI 0.78–0.98, P = 0.03). Additionally, TSAT showed an association with decreased MI risk (OR = 0.91, 95 % CI 0.84–0.98, P = 0.01). No significant correlations were observed for other iron status traits examined in this study. Evaluations of horizontal pleiotropy and heterogeneity showed no abnormalities, further strengthening the reliability of our results.

Conclusions: Our multi-cohort MR analysis suggests a potential protective effect of higher ferritin levels and TSAT against MI risk. These findings contribute to our understanding of the relationship between iron status markers and cardiovascular health, offering insights for future research and potential therapeutic interventions.

1. Introduction

Myocardial infarction (MI) is a sudden decrease or cessation of blood flow brought on by coronary artery disease that results in immediate myocardial necrosis and severe chronic ischemia and hypoxia. With the age of onset getting younger and younger, MI as a devastating disease has a great threat to human health. A favorable prognosis and the prevention of MI depend on early diagnosis and

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prompt treatment [1]. Impaired iron metabolism may significantly contribute to myocardial infarction (MI). Iron metabolism was reflected by iron, ferritin, transferrin, and total iron binding capacity, and the results caused by iron metabolism may be bidirectional - an increase or decrease in iron levels [2]. Some studies indicated that iron is essential in many physiological processes of the heart, iron metabolism abnormalities may lead to many cardiovascular diseases [3]. Meanwhile, high heme iron intake was significantly associated with increased the risk of MI [4]. In a study involving an elderly Dutch population, elevated serum ferritin concentrations were linked to a higher risk of MI, indicating that ferritin may have a detrimental impact on the risk of ischemic heart disease [5]. Other studies indicate that ferroptosis is a key mechanism of cardiomyocyte death in the affected area, potentially playing a crucial role in the pathological processes of heart disease [6].

Iron is a crucial trace element required for oxygen delivery, consumption, and mitochondrial activity. The Cardiovascular disease related to iron metabolism are a key concern in cardiovascular medicine. Iron metabolism abnormalities can injure the heart and cause heart failure (HF). In patients with HF and iron deficiency (ID), this study demonstrated that intravenous iron reduces the risk of hospitalizations for heart failure, but whether this is associated with a reduction in cardiovascular or all-cause mortality remains uncertain [7]. One study found that severe iron excess may cause cardiac injury, whereas iron shortage is linked to poor prognosis in patients with HF [8]. In a nutshell, there is conflicting epidemiological evidence about the relationship between iron level and the risk of cardiovascular disease, and there is no long-term evidence supporting the idea that MI is influenced by iron status in the general population.

Mendelian randomization (MR) is an emerging epidemiological method used to assess causal relationships between modifiable exposures and disease risk by employing genetic variants as proxies or instruments [9]. When the premise of the necessary assumptions of the model is met, the genetic variants detecting exposure are associated with the disease if a causal relationship is found between exposure and the associated disease. Due to the random assignment of these variations at conception, their link with illness outcomes is largely unaffected by possible environmental confounding variables from observational studies and bias from reverse causation [10]. Therefore, MR can provide a more accurate estimate of causal linkages.

In conclusion, it remains unclear whether body iron or its indicators, such as serum ferritin levels, serve as independent risk factors for MI. We hypothesized that iron status plays a role in influencing MI risk. In this study, we employed a two-sample Mendelian randomization approach to explore the relationship between various iron status measures (including serum iron, ferritin, transferrin, TIBC, and TSAT) and MI risk.

2. Methods

Three key assumptions must be satisfied if the causal estimate of MR research is to be believed: 1) The chosen genetic instrumental variables (IVs) must be strongly linked to exposure [10]. 2) The selection of genetic instrumental variables does not influence the outcome, irrespective of the exposure, indicating the absence of horizontal pleiotropy [11]. 3) The selected genetic instrumental variables are not associated with potential confounders. Fig. 1 illustrates the design of the current study. Ethical approval or agreement from participants was not required because data were obtained from publicly available databases and previous studies.

2.1. Data sources

A genome-wide association study (GWAS) analysis involving participants of European ancestry was conducted to identify instrumental variables for iron status as the exposure. All analyses were performed using R software (4.0.5) with the two-sample MR (V 0.5.6) [12] and MR-pleiotropy residual sum and outlier (MR-PRESSO) (V 1.0) [13] packages.

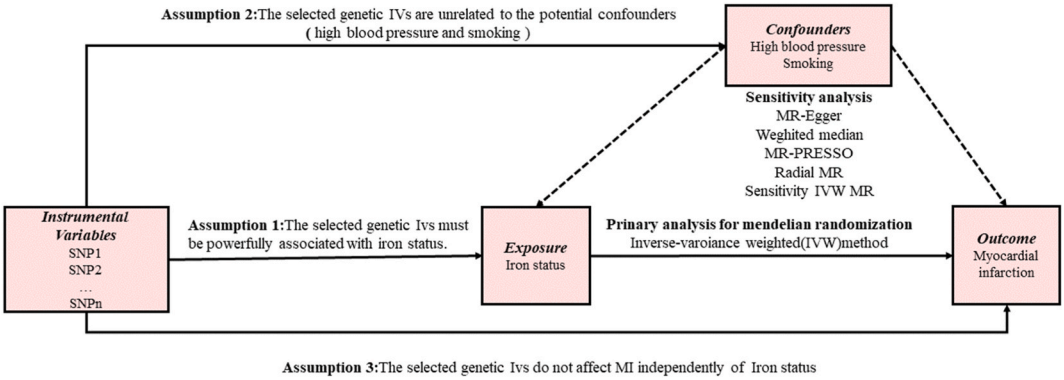

Fig. 1. An overview of this Mendelian randomization (MR) study design.
Abbreviations: SNP, single nucleotide polymorphism; MR-Egger, Mendelian randomization-Egger; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier test; Radial MR, Radial Mendelian randomization.

2.2. Selection of instrumental variables

The Genetics of Iron Status Consortium conducted a meta-analysis of genome-wide studies to estimate associations between iron status biomarkers and single nucleotide polymorphisms (SNPs) [14]. Our instrumental variables were derived from a meta-analysis of three GWAS conducted in Iceland, the UK, and Denmark, focusing on GIS blood levels of iron [N = 163,511 (Iceland, 123,314; UK, 40, 197)], ferritin [N = 246,139 (Iceland, 172,764; UK, 39,648; Denmark 33,727)], transferrin [N = 23,986 (GIS)], TIBC [N = 135,430 (Iceland, 95,314; UK, 40,116)], and TSAT [N = 131,471 (Iceland, 91,308; UK, 40,163)]. Age and major component scores were adjusted, and male and female estimates were analyzed individually before combining.

In this study, SNPs were classified as instrumental variables. All selected SNPs fulfilled these criteria: 1) No linkage disequilibrium was observed (pairwise $r^2 = 0.1$, window size = 5000 kb); 2) palindromic structures were absent. Based on the three criteria, 65 SNPs were emerged (iron, 12; ferritin, 25; transferrin, 15; TIBC, 12; TSAT, 8) (Supplementary Table S1). When the appropriate SNPs were unavailable in MI GWAS, proxy SNPs with substantial LD ($r^2 > 0.8$) were used to replace the chosen SNPs. The first-stage regression, represented by the F statistic, was utilized to evaluate the strength of the instruments, calculated using the formula: $F = (R^2/k)/([1-R^2]/[n-k-1])$, where R^2 indicates the proportion of variability in iron status attributable to the SNPs; k is the number of instruments; and n is the sample size [15]. To mitigate potential weak instrumental variable bias, an F value greater than 10 was deemed sufficient for the main study [16].

2.3. SNP-MI association estimates

In the pursuit of robust outcomes concerning the intricate relationship between iron status and myocardial infarction, the present investigation strategically embraces a composite approach. This study embarks upon the meticulous selection of three distinct genome-wide association studies (GWAS) datasets associated with myocardial infarction, sourced from the authoritative platform at https://gwas.mrcieu.ac.uk/. The selected datasets are characterized as follows: ebi-a-GCST011364 (comprising n case = 14,825 and n control = 380,970, representative of the European population) [17], finn-b-I9_MI (comprising n case = 12,801 and n control = 187,840, also from the European population), and ieu-a-798 (comprising n case = 43,676 and n control = 128,199, encompassing a mixed population). The utilization of these diverse GWAS datasets is driven by the intention to attain enhanced robustness in the analysis outcomes, while concurrently broadening the breadth and scope of data under examination.

2.4. Statistical analysis

The inverse-variance weighted (IVW) method served as the primary approach for evaluating the causal relationship between iron status and myocardial infarction (MI) [18]. A fixed-effects model was applied when the p-value from Cochran's Q test was greater than 0.05; otherwise, a random-effects model was employed.

MR-Egger approach was used to assess the potential pleiotropy impacts in sensitivity analyses. The causal influence was evaluated using MR-Egger regression, which calculated the slope from the weighted regression of the relationships between instrumental variables and outcomes against the associations with exposures, where the intercept term represented the average pleiotropic effect [12, 19]. Pleiotropy was evaluated using maximum likelihood, weighted median, penalized weighted median, radial MR, and MR-PRESSO testing methods. The weighted median will offer consistent estimates of causal influence if >50 % of SNPs are effective IVs [16]. MR-PRESSO can detect pleiotropy, eliminate outlying SNPs, and evaluate impact estimations [18]. Furthermore, a leave-one-out analysis was conducted to assess the impact of outlying values on the results. To account for potential confounding effects, the pleiotropy of each selected SNP was examined at the GWAS significance threshold ($p < 5 \times 10^{-8}$) using the PhenoScanner V2 database (http://www.phenoscanner.medschl.cam.ac.uk/) [13].

3. Results

Supplementary Table S9 contains comprehensive details regarding the selected SNPs.

3.1. MR estimates

A total of 65 independent genome-wide significant SNPs associated with iron status traits were selected to construct the instrumental variable: 12 linked to iron, 25 to ferritin, 15 to transferrin, 12 to total iron binding capacity (TIBC), and 8 to transferrin saturation (TSAT). The association between iron status traits and myocardial infarction risk was investigated using two cohorts, including ebi-a-GCST011364 and finn-b-I9-MI. MR Results did not reveal a significant effect of iron markers levels on the risks of MI. However, analysis of a third cohort, ieu-a-798, indicated a protective role of ferritin levels against MI (OR = 0.87(0.78–0.98), P = 0.03). TSAT was also found to be associated with decreased MI risk (OR = 0.91(0.84–0.98), P = 0.01). No such correlation was observed for the other iron status traits examined in this study. The assessment of both horizontal pleiotropy and heterogeneity failed to reveal any abnormalities in the obtained findings, thus further enhancing the reliability of the results.

3.2. Sensitivity analyses

The IVW MR, MR-Egger, and other estimates exhibited directionally consistent effects but with broader CIs than the IVW estimates

(see Table 1).

Given their lower statistical power compared to the main analysis, these methods were utilized solely to validate an effect estimate that aligned directionally with the main IVW MR findings, rather than to evaluate statistical significance based on specific p-value thresholds. Cochran Q statistics revealed modest heterogeneities for iron indicators **(see Supplementary material, Tables S10–12)**.

Sensitivity analyses employing the weighted median, penalized weighted median, and MR-PRESSO methods (see Table 2) demonstrated consistent directional effects **(see Supplementary Material, Tables S3–8)**. These analyses incorporated genetic instruments identified through the GWAS search, each linked to at least one biomarker of iron status.

When the p-value exceeds 0.05, horizontal pleiotropy is not detected, and the results are considered conclusive. For the five biomarkers, the MR-Egger intercepts were not significantly different from zero ($p = 0.525$, 0.573, 0.117, 0.582, and 0.114 for serum iron, ferritin, transferrin, TIBC, and TSAT, respectively), indicating no evidence of pleiotropy in relation to MI (see Table 1).

Supplementary Figs. S3–S14 display forest plots, scatter plots, funnel plots, and leave-one-out plots for iron status.

4. Discussion

4.1. Findings in context

In this study, a two-sample MRanalysis found no evidence of a causal relationship between genetically predicted iron status and the risk of MI in European populations. Sensitivity analyses further indicated that the results were generally robust.

Iron is a vital trace metal essential for various biological processes, including cellular immunity and oxidative metabolism, etc. [20]. Gene regulatory systems involving ferritin, transferrin, and transferrin receptors maintain strict iron homeostasis within cells. Iron absorption, transport, and utilization are mediated through both transferrin receptor-dependent and non-transferrin receptor--dependent mechanisms. Any disruption in these pathways or their connections can result in disease [2]. The effects of fluctuating iron status in coronary blood vessels can be manifested as ferroptosis of endothelial cells, vascular smooth muscle cells, and macrophages in atherosclerotic plaques. This effect can aggravate endothelial dysfunction and macrophage activation, allowing the inflammatory state to persist, promoting the formation of plaque necrotic cores and the occurrence of plaque bleeding, thereby further accelerating the development of atherosclerosis, and leading to serious cardiovascular events [21,22].

Nevertheless, this hypothesis remains a subject of debate, as inconsistencies in findings across clinical studies with differing experimental designs continue to raise questions. One side agreed with this assumption. Based on a large body of preclinical and clinical evidence, iron-related oxidative stress is speculated to have a role in the etiology of atherosclerotic cardiovascular disease [21–25]. Patients with iron deficiency had a 73 % increased risk of cardiovascular mortality and non-fatal MI in multivariate Cox regression analysis [9]. Previous studies have shown that hepcidin expression, both at the messenger RNA and protein levels, was significantly increased in rat models of hypoxia and MI [26]. A recent randomized controlled trial (RCT) observed an association between iron status and MI [27].

Table 1
MR statistical sensitivity analyses.

Outcome	Exposure	Method	OR	95 % CI	*P* Value
Myocardial infarction (ieu-a-798)	Iron	MR Egger	0.927	0.741–1.160	0.525
		Weighted median	0.933	0.835–1.042	0.220
		Inverse variance weighted	0.913	0.790–1.055	0.219
		Simple mode	0.900	0.725–1.117	0.361
		Weighted mode	0.906	0.812–1.011	0.107
	Ferritin(log_{10})	MR Egger	0.934	0.738–1.181	0.573
		Weighted median	0.815	0.685–0.969	0.021
		Inverse variance weighted	0.874	0.775–0.985	0.027
		Simple mode	0.795	0.589–1.072	0.145
		Weighted mode	0.791	0.597–1.050	0.118
	Transferrin	MR Egger	1.064	0.991–1.142	0.117
		Weighted median	1.027	0.984–1.071	0.223
		Inverse variance weighted	1.016	0.968–1.067	0.515
		Simple mode	1.059	0.984–1.140	0.150
		Weighted mode	1.028	0.990–1.067	0.178
	TIBC	MR Egger	1.033	0.924–1.155	0.582
		Weighted median	1.062	1.003–1.124	0.038
		Inverse variance weighted	1.069	0.977–1.170	0.144
		Simple mode	1.455	1.100–1.925	0.024
		Weighted mode	1.064	1.007–1.125	0.049
	TSAT	MR Egger	0.901	0.807–1.006	0.114
		Weighted median	0.911	0.836–0.993	0.034
		Inverse variance weighted	0.908	0.843–0.977	0.010
		Simple mode	0.870	0.769–0.985	0.063
		Weighted mode	0.909	0.839–0.986	0.0546

IVW indicates inverse variance weighted; MR, Mendelian randomization; OR, odds ratio; TIBC, total iron binding capacity; TSAT, Transferrin saturation.

Table 2
MR-PRESSO estimates between iron status and myocardial infarction (ieu-a-798).

Iron status trait	Raw estimate				Outlier corrected estimate			
	N	OR	95%CI	P-value	N	OR	95%CI	P-value
Iron	12	0.913	0.790–1.055	0.219	11	0.917	0.832–1.010	0.120
Ferritin	25	0.874	0.775–0.984	0.027	25	0.874	0.775–0.984	0.027
Transferrin	15	1.016	0.911–1.050	0.515	13	0.988	0.939–1.039	0.649
TIBC	12	1.069	0.977–1.170	0.144	12	1.069	0.977–1.170	0.144
TSAT	8	0.908	0.843–0.977	0.010	8	0.908	0.843–0.977	0.010

SNP, single-nucleotide polymorphism; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier test; CI, confidence interval; OR, odds ratio; TIBC, total iron binding capacity; TSAT, Transferrin saturation.

Whereas the other holds the opposite attitude. For instance, other rigorous researchers found no link between high ferritin levels and acute MI [28,29]. The idea that elevated serum ferritin levels are linked to MI was refuted in another investigation [30]. Kiechl discovered two unique risk profiles associated with age [31,32]. The lowering of body iron storage in individuals with peripheral vascular disease had no impact on all-cause mortality, cardiovascular death, non-fatal myocardial infarction, or stroke, according to research by Zacharski et al. in a randomised controlled study [33]. One study did not demonstrate any association between a composite endpoint of CHD and serum ferritin levels [34–36]. Additionally, another study suggested that lower serum iron levels did not provide protection against coronary artery disease (CAD) but instead increased the risk of CAD in older females [37].

Moreover, contrary to the iron-heart theory, key indicators of iron status, such as serum iron and TSAT, reveal a significant inverse correlation between iron levels and cardiovascular risk [33]. Serum iron, ferritin, transferrin, TIBC, and TSAT are quantifiable iron status indicators that can be used as phenotypic indicators of total iron status [14,38,39]. For instance, in a randomized clinical trial, Zacharski et al. demonstrated that iron status had minimal influence on cardiovascular mortality, non-fatal MI, and other outcomes in patients with peripheral vascular disease, even when iron levels were reduced. Additionally, data showed no association between iron stores and atherosclerosis [33,40]. Patients with iron deficiency do not show significant increases in cardiac iron levels, which may make them more susceptible to severe atrophy and cardiac apoptosis during acute MI. Furthermore, the chemical mechanisms that cause iron deficiency's harmful effects have not been fully understood. Studies examining the effects of iron chelation treatment on the physiological environment in acute MI have produced conflicting findings. Improvements in heart function were shown in certain trials, however infarct size was not reduced [1].

Ferritin, the primary intracellular cytosolic storage protein for iron, releases iron during shortages and stores excess iron when available [41,42]. Transferrin can carry iron in circulation and relieve intracellular iron deposition; thus, it has anti-atherosclerosis, anti-inflammatory, anti-oxidative, and anti-vascular damage effects. Total iron binding capacity (TIBC) reflects serum transferrin levels. As a proxy for transferrin, TIBC is less susceptible to rapid fluctuations in concentration compared to plasma iron levels, which can vary significantly throughout the day and are affected by food intake. Therefore, TIBC serves as a more stable indicator of iron status [43,44]. Beerenhout et al. believe that patients established on haemodialysis with low levels of transferrin have poor nutritional status and are therefore more susceptible to infection, further causing the occurrence and development of diseases such as MI [43,44]. The clinical physiology of transferrin saturation (TSAT) widely fluctuates. Clinical studies have shown that many chronic diseases also have reduced TSAT. However, other researchers take a different view. A meta-analysis of 47 studies found no significant association among iron, TIBC, transferrin, and acute MI, but TSAT was significantly negatively associated with acute MI [45]. Indeed, indicators of iron status have been linked to inflammation, liver illness, renal failure, and cancer, which might impact observational relationships with cardiovascular disease [37].

It is important to note that most studies investigating the relationship between body iron stores and coronary heart disease (CHD) risk have used serum ferritin as the clinical marker of iron status [3,46]. However, in inflammatory conditions such as acute myocardial infarction (MI), serum ferritin levels can be elevated while serum iron decreases [22]. Therefore, ferritin alone may not accurately reflect iron status in the context of acute MI. The mechanisms by which elevated body iron levels might contribute to increased risk of acute MI warrant discussion. These may include enhanced oxidation of LDL cholesterol, increased oxidative damage, promotion of lipid peroxidation, worsened reperfusion injury, and atherogenic properties [47], as well as increased proliferation of vascular smooth muscle cells [48]. A combination of these factors, alongside other CHD risk factors such as hypertension and inflammation, could be implicated. For instance, inflammation significantly impacts ferritin levels, contributing positively to the progression of endothelial dysfunction, plaque formation, and the pathogenesis of myocardial infarction (MI) [49]. Elevated iron storage, reflected by higher ferritin concentrations, can produce reactive nitrogen species and harmful oxygen free radicals, which act as catabolic factors in the metabolic processes associated with myocardial infarction (MI) [50]. Furthermore, elevated ferritin concentrations promote inflammation and tissue damage, leading to endothelial injury in patients with myocardial infarction (MI) [22]. When transferrin levels decrease or transferrin binding capacity is surpassed, excess free iron generates hydroxyl radicals through the Fenton reaction. This process damages mitochondria and produces reactive oxygen species (ROS), ultimately leading to cell damage and death [51,52]. Additionally, ROS may interact with mitochondria, resulting in oxidative stress and mitochondrial malfunction [52]. Notably, oxidative stress and mitochondrial dysfunction influence the onset of MI [53,54].

4.2. Strengths and limitations

This study has several strengths. To begin with, we selected single nucleotide polymorphisms (SNPs) identified in genome-wide association studies as instrumental variables. These SNPs are associated with blood levels of ferritin (N = 246,139), total iron binding capacity (N = 135,430), iron (N = 163,511), and transferrin saturation (N = 131,471). This approach ensures that the selected SNPs possess sufficient strength to function as instrumental variables for the Mendelian randomization analysis. Additionally, in selecting outcome datasets, we aimed to include multiple cohorts to make our results more accurate and generalizable while minimizing potential confounding and heterogeneity from various sources.

However, we observed some heterogeneity in Mendelian randomization results across different cohorts. This could be attributed to differences in population backgrounds and preferred cohort collection periods - the ieu-a-798 dataset is older relative to the other two cohorts, possibly introducing confounding. Furthermore, the ieu-a-798 population was more genetically diverse as a mixed population, while another cohort comprised entirely of European ancestry individuals from a genome-wide association study, implying genetic backgrounds may have introduced additional confounding to our analyses. Overall, heterogeneous effects across population subgroups highlights the need for large, diverse and well-phenotyped cohorts to validate causal inferences from Mendelian randomization and ensure generalizability.

5. Conclusions

The MR study showed that iron status was not causally linked with MI. The GWAS data highlighted opportunities for further research. The combined detection of iron status has many advantages in preventing, diagnosing, and treating cardiovascular disease. Future research should analyze the causative association in other populations with varied ethnic origins using individual-level data and the likely underlying mechanism to gain insights into prospective MI prevention techniques.

CRediT authorship contribution statement

Xiaozhuo Xu: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Data curation. **Jing Liu:** Validation, Funding acquisition, Data curation. **Yilin Huang:** Resources. **Xu Han:** Writing – review & editing, Validation, Supervision, Funding acquisition.

Data availability statement

The article/Supplementary Material contains the original contributions given in the study; further questions should be referred to the respective authors.

The datasets for this study can be found in the [GWAS] [IEU OpenGWAS project (mrcieu.ac.uk)] and [Bell, S., Rigas, A.S., Magnusson, M.K. et al. A genome-wide meta-analysis yields 46 new loci associating with biomarkers of iron homeostasis. Commun Biol 4, 156 (2021). https://doi.org/10.1038/s42003-020-01575-z)].

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Xu Han reports financial support was provided by Natural Science Foundation of Jiangsu Province. Xu Han reports financial support was provided by The Third Phase Scientific Research Project for the Construction of Superior Disciplines in Traditional Chinese Medicine at Nanjing University of Chinese Medicine. Xu Han reports financial support was provided by Special Plan for the Science and Technology Development of Traditional Chinese Medicine of Jiangsu Province. Xiaozhuo Xu reports financial support was provided by Jiangsu Province Postgraduate Practice Innovation Program. Jing Liu reports financial support was provided by Jiangsu Province Graduate Research and Innovation Program. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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