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Narrative Review

# The complementary roles of iron and estrogen in menopausal differences in cardiometabolic outcomes

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SUMMARY

Biological hormonal changes are frequently cited as an explanatory factor of sex and menopause differences in cardiometabolic diseases (CMD) and its associated risk factors. However, iron metabolism which varies between sexes and among women of different reproductive stages could also play a role. Recent evidence suggest that iron may contribute to CMD risk by modulating oxidative stress pathways and inflammatory responses, offering insights into the mechanistic interplay between iron and CMD development. In the current review, we provide a critical appraisal of the existing evidence on sex and menopausal differences in CMD, discuss the pitfall of current estrogen hypothesis as sole explanation, and the emerging role of iron in CMD as complementary pathway. Prior to menopause, body iron stores are lower in females as compared to males, but the increase during and after menopause, is tandem with an increased CMD risk. Importantly, basic science experiments show that an increased iron status is related to the development of type 2 diabetes (T2D), and different cardiovascular diseases (CVD). While epidemiological studies have consistently reported associations between heme iron intake and some iron biomarkers such as ferritin and transferrin saturation with the risk of T2D, the evidence regarding their connection to CVD remains controversial. We delve into the factors contributing to this inconsistency, and the limitation of relying on observational evidence, as it does not necessarily imply causation. In conclusion, we provide recommendations for future studies on evaluating the potential role of iron in elucidating the sex and menopausal differences observed in CMD.


## 1. Introduction

The investigation and acknowledgment of biological sex differences have risen as a crucial subject in various medical disciplines, prominently in the realm of cardiometabolic diseases (CMD) [1]. Consistent evidence indicates that CMD, notably cardiovascular diseases (CVD) and type 2 diabetes mellitus (T2D), together with accompanying risk factors including obesity, dyslipidemia,

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inflammation, and modifiable lifestyle risk factors exhibit distinct sex-specific patterns. Furthermore, reproductive stages, such as menopause, may also play a role in CMD development and trajectory in females [2]. Changes of risk of CMD during menopausal transition are shown in Fig. 1. The underlying mechanisms of these sex and life stages differences in CMD remain unclear. Estrogen deficiency has been traditionally considered as the main cause for increasing risk of CMD during menopause. Still, recent evidence does not fully support this hypothesis [3,4] and changes in iron status have been suggested as a complementary explanation [5,6]. A deeper understanding of how levels of iron biomarkers differ with sex and menopause status could provide novel insights into sex and menopausal disparities in CMD. Thus, we aimed to provide an overview and a comprehensive summary of sex differences and contribution of menopause in the development of CMD outcomes in the light of the emerging role of iron as a complementary pathway. In this review, we highlight the advancement in the field, the pitfalls, and gaps, and provide recommendations for future research.

## 2. Method

We searched Medline, Embase, Cochrane, PubMed, Web of Science and Google Scholar to identify relevant articles. Studies were included if they.

(i) reported on the association of menopause status (e.g., postmenopausal vs. premenopausal women) with cardiometabolic outcomes and iron biomarkers/iron body status; or reported the association of iron biomarkers and supplements with risk of cardiometabolic outcomes; or reported the mediating role of iron biomarkers on the association between menopause and cardiometabolic risk.
(ii) were conducted in females (human), or, in studies including both sexes, provided results differentiated by sex.
(iii) were cross-sectional, prospective, clinical trials, systematic reviews, or meta-analysis. The search strategy combined terms related to menopause, menopause transition, female aging, hormone therapy, iron biomarkers/status, iron

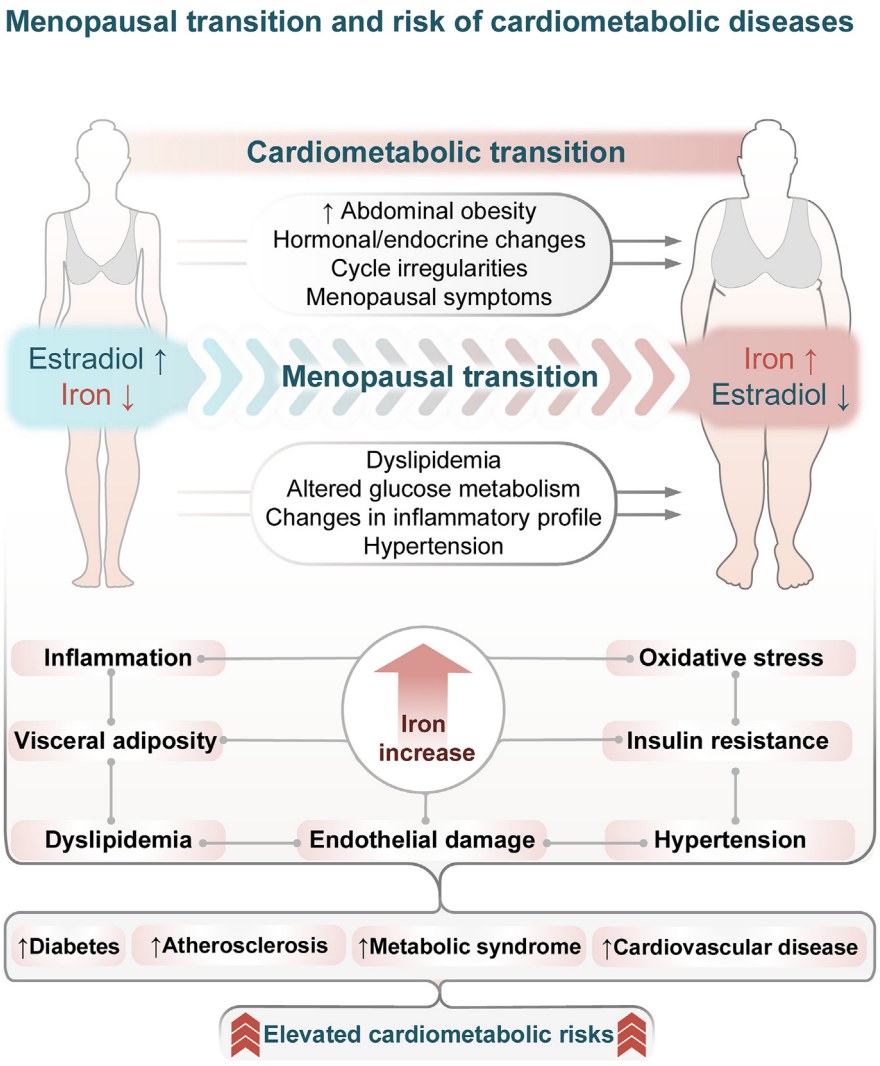


**Fig. 1.** Menopausal transition and risk of cardiometabolic diseases.

supplements, cardiovascular risk, type 2 diabetes, cardiovascular disease, blood lipids, glucose metabolism markers such as blood glucose, insulin and HbA1c and obesity. We also expanded our search to include articles from reference lists of the initially identified papers and relevant review articles. This snowballing method allowed us to capture additional articles that might have been missed through our initial search strategy. No language or date restrictions were applied. For the associations between iron and cardiometabolic diseases, 48 papers were selected, of which 11 were reviews or systematic reviews, 6 were meta-analyses (including systematic reviews) and 31 were individual studies.

## 3. Epidemiology of cardiometabolic diseases: how sex and menopause differentiate risk profiles?

### 3.1. Impact of sex and menopause on cardiovascular disease and heart failure risk

Substantial efforts have been made to characterize CVD risk profiles for both sexes, namely regarding the presentation, diagnosis, and treatment [7]. CVD are the main cause of death in both sexes [7]. At 50–55 years (around the age of menopause), and despite similar lifetime risks for CVD, males are more likely to develop coronary heart disease (CHD) as a first event, while females are more likely to have cerebrovascular disease or heart failure (HF) as their first event [8]. Multiple epidemiological studies have identified male sex as an independent risk factor for higher CHD morbidity and CHD-related death [9–11]. In the ONTARGET and TRANSCEND studies, a combined population of, 9378 female and 22,168 male participants were followed for more than 4.5 years. Females had almost 20 percent lower risk than males for all major CVD outcomes, including CVD-specific mortality (adjusted RR = 0.83, 95% CI: 0.75–0.92), MI (adjusted RR = 0.78, 95% CI: 0.68–0.89), and a lower combined endpoint for mortality and CVD outcomes (adjusted RR = 0.81, 95% CI: 0.76–0.87) [11]. In premenopausal females, serious manifestations of CHD, including myocardial infarction (MI) and sudden death, were relatively rare. However, the occurrence and severity of CHD significantly rise after menopause. In fact, the rates are three times higher compared to females of the same age who are still in their premenopausal stage [12]. One consideration to keep in mind when interpreting sex differences is that primary care providers tend to prescribe different CVD medications to male and female patients who are at high risk of or have established CVD [13]. Furthermore, females with CVDs, in particular CHD, are generally about 10 years older than males at the time of presentation and may have a greater burden of risk factors [14,15]. This increased CVD risk might be partially attributed to the acquisition of an atherogenic profile during and after the menopausal transition [16]. Namely, after menopause, development of dyslipidemia, insulin resistance, high blood pressure, and fat redistribution contribute to the accelerated risk for CVD and as a result CMD (Fig. 1) [17].

HF is a heterogenous and life-threatening syndrome affecting over 60 million individuals globally. It is characterized by severe morbidity and mortality, poor quality of life, and an overwhelming burden on the healthcare systems [18]. Although HF appears to affect both sexes equally, females at an older age are at greater risk than males [19]. Indeed, after the age of 65, the incidence rate of HF triples for females, whereas it only doubles for males [20]. Recently, menopause has emerged as a female-specific risk factor for some forms of HF [21]. For instance, males are predisposed to HF with reduced ejection fraction (HFrEF), whereas females are more susceptible to HF with preserved ejection fraction (HFpEF). Compared with males of similar age, the incidence of HFpEF in postmenopausal females increases sharply, suggesting a close relationship between left ventricular diastolic dysfunction and estrogen deficiency [22]. Why this might occur is not completely known, but it has been suggested to be related to a greater prevalence of hypertensive CVD and hypertrophy in females. Risk factors for HF in females with CHD were examined in the HERS trial among 2391 females with established CHD devoid of HF at baseline [23]. After a mean follow-up of 6 years, 10% (237) developed HF and the T2D was the variable associated with the greatest increase in HF risk (adjusted HR = 3.1). Females with T2D and at least three other risk factors had an annual HF incidence of 8.2%. Emerging epidemiological evidence suggests that early menopause is positively associated with incident HF [24–26]. Results from the ARIC study, a large prospective observational cohort of white and black females with a median follow-up of 21 years showed a generally inverse association between age at menopause and incident HF [27].

### 3.2. Impact of sex and menopause on type 2 diabetes

Research findings consistently demonstrate sex differences in the etiology, epidemiology, prevention, management, and prognosis of type 2 diabetes. In most parts of the world, diabetes is more prevalent in men than in women, especially in middle-aged populations [28,29]. The pathophysiology and prognosis of T2D also differs between males and females; impaired fasting glucose is more common among males, while impaired glucose tolerance is more common among females [30]. Recently, novel connections between iron metabolism and the pathogenesis of T2D have been revealed. These relationships are bidirectional, with iron influencing glucose metabolism and glucose metabolism impacting various iron metabolic pathways in return [31,32].

A meta-analysis of six clinical trials reported that females have a higher tendency to experience hypoglycemia during insulin treatment, while the effect of insulin on $HbA_1C$ levels was more pronounced in males [33]. In individuals diagnosed with T2D at the age of 40, males are estimated to lose 11.6 life-years, while females are estimated to lose 14.3 life-years. This suggests a gender-based difference in life expectancy reduction, with females experiencing a greater impact [34]. The effect of T2D on CVD severity also differs between sexes. A meta-analysis of 64 prospective studies including 775,385 individuals (12,539 stroke cases) showed that the excess risk of stroke associated with T2D was 27% greater in females than in males, independently of other risk factors for stroke [35]. T2D frequently coincides with the timing of the menopausal transition. Potential mechanisms linking menopause and T2D include changes in body composition and in sex steroids [36]. This change in body composition results in increased cytokine production, leading to a pro-inflammatory state. This pro-inflammatory state is associated with increased peripheral insulin resistance and a predisposition to T2D [37], while the changes in sex hormones are accompanied by an adverse cardiometabolic profile that might predispose to T2D [38,39].

### 3.3. Impact of sex and menopause on hypertension and dyslipidemia

Hypertension (HTN) affects around 1.13 billion people worldwide, and is considered a “silent killer”, contributing to the development of coronary artery disease, stroke and renal morbidity and mortality [40]. The development of HTN and HTN-related complications differs considerably by sex [41]. Compared to females, males aged 18–39 and 40–59 years show a higher prevalence of HTN (9.2% and 37.2% vs. 5.6% and 29.4%, respectively), but after 60

years, this ratio is reversed (58.5% males vs. 66.8% females) [42]. Females tend to be protected from HTN until midlife and menopause [43]. Most observational data show that menopause is associated with a 2-fold increase in risk of HTN after adjusting for major confounders [44–46]. Compared to age-matched males, premenopausal females have lower (blood pressure) BP levels, while menopaused females have higher BP levels; those findings suggest that sex and/or sex hormones have a prominent role in HTN [47]. A prospective study compared the baseline and 5-year change in (systolic blood pressure) SBP levels between perimenopausal and post-menopausal females and age- and (body mass index) BMI-matched pre-menopausal females and males. The post-menopausal females had higher SBP at baseline, and SBP levels increased by ~5 mm Hg in perimenopausal and post-menopausal females, but not in age- and BMI-matched pre-menopausal females and males [48].

Dyslipidemia (i.e., elevated levels of total cholesterol, LDL cholesterol, or triglycerides, or low levels of HDL cholesterol), plays a substantial role in approximately one-third of ischemic heart diseases and about 2.6 million deaths and 29.7 million disability-adjusted life-years (DALYs) globally [49]. After age 50 years, TC and LDL-cholesterol levels tend to stabilize in males, while they increase in females [50]. At least part of this increase results from declining levels of estrogen, which result in down-regulation of the LDL receptor on the liver [51,52]. The decline in HDL-C is of concern in menopause [53]. The importance of some metabolic, behavioral, and psychosocial risk factors may differ by sex. Data from the Prospective Urban Rural Epidemiological (PURE) study, which followed adults from 21 countries for a decade, showed that LDL cholesterol and non-HDL cholesterol levels increased with age in females (after 55 years) and these levels were typically higher in females than in males. These differences have been attributable to menopause. Among post-menopaused females, TC, low-density lipoprotein cholesterol (LDL-C), and TG levels increase while HDL-C levels tend to decrease [54].

### 3.4. Impact of sex and menopause on obesity

Obesity is another major risk factor for the development of CMD [55]. A study conducted in adults aged 35 to 80 from 20 European countries showed that young to middle-aged males have a higher prevalence of overweight than females [56]. However, this trend reverses after the 45 years old, females become more likely to be overweight or obese than males [30]. Males and females show also anatomical differences in adipose tissue distribution, males accumulating body fat in the abdominal region, while females accumulate body fat in the lower part of the body. The menopausal transition is associated with weight gain in many females [70,71]. As females go through menopause, there is a shift in body fat accumulation, more fat being accumulated in the abdominal region [57]. As abdominal fat poses a higher risk of T2D, this shift in body fat and the increase in the prevalence of overweight and obesity in ageing females may also partially explain why females have a higher lifetime risk of developing T2D than males, especially after menopause [34]. In females, weight gain and increased abdominal obesity often occur in early postmenopausal stage [53].

## 4. Estrogen hypothesis and the pitfalls related to this hypothesis

The hypothesis most frequently put forward to explain sex differences in CMD is the estrogen hypothesis, which considers estradiol as cardioprotective in females. The age-related decline in estrogen levels, particularly during and after menopause, has been proposed as an explanation for the dramatic rise in T2D and CVD risk associated with menopause. This hypothesis has been supported by results from observational studies that demonstrate associations between higher androgen and lower estrogen levels with higher CVD risk factors in postmenopausal females, including elevated blood pressure, elevated levels of C-reactive protein (CRP) and increased insulin resistance [58,59].

### 4.1. Controversial role of estrogen in cardiometabolic diseases risk

Estrogen has been proposed as a key contributing factor to the observed sex differences in CMDs [60]. Early mechanistic models suggested that high estrogen levels could improve cardiometabolic health through a lipid-lowering effect and improvements in glucose metabolism and blood pressure levels [61,62]. However, recent data suggest that high estrogen levels, as observed during pregnancy, can lead to insulin resistance and adverse cardiometabolic effects [63,64]. The beneficial associations between endogenous estradiol and body fat distribution, glucose-insulin homeostasis, vasodilation and plasma lipoprotein levels observed in observational studies [39], have not been confirmed by randomized clinical trials [40].

Further recent observational studies reported potential undesirable health effects of endogenous estradiol as well, further challenging the traditional understanding of cardioprotective effects of estradiol. For instance, a large population-based study showed that endogenous estradiol favored the development of vulnerable carotid plaque composition and increased the risk of stroke in females with carotid atherosclerosis [65]. Similarly, endogenous estradiol was associated with increased risk of developing T2D in postmenopausal females [66,67].

## 5. Iron as a complementary hypothesis to estrogen

Compared to premenopausal females in reproductive age, iron stores are higher among males and postmenopausal females. In females, serum ferritin levels, which are indicative of body iron stores, exhibit significant variations across different life stages. During early life and after menopause, these levels are typically higher. However, in the pre-menopausal phase, due to the loss of blood from menstruation, iron levels are generally lower in females [68,69]. This difference in iron levels mirrors the differences in estrogen levels and makes iron a complementary hypothesis to estrogen regarding the greater incidence of CMD in males and postmenopausal females. The proposed mechanism is similar to the myocardial failure of iron storage diseases [70]. Changes in endocrine and physiological factors during and following menopause are shown in Fig. 2.

### 5.1. Iron metabolism

Iron is a micronutrient essential for cellular development and survival. Iron represents an important part of various enzymes involved in many important biological processes such as oxygen transport, cellular energy generation and DNA synthesis and repair [71,72]. A 20–25 mg/day is necessary to meet the iron requirements for erythropoiesis and cellular metabolism [73]. The majority (21–27 mg) of this iron is derived from recycling senescent erythrocytes by macrophages in the reticuloendothelial system, and only 1–2 mg per day is derived from intestinal absorption [73,74]. Daily iron loss is about 1–2 mg, predominantly through desquamation of epithelial cells of skin and intestines, and also minor blood losses which could be balanced by dietary sources and intestinal absorption [75]. Figure 3 shows the normal iron hemostasis and metabolism.

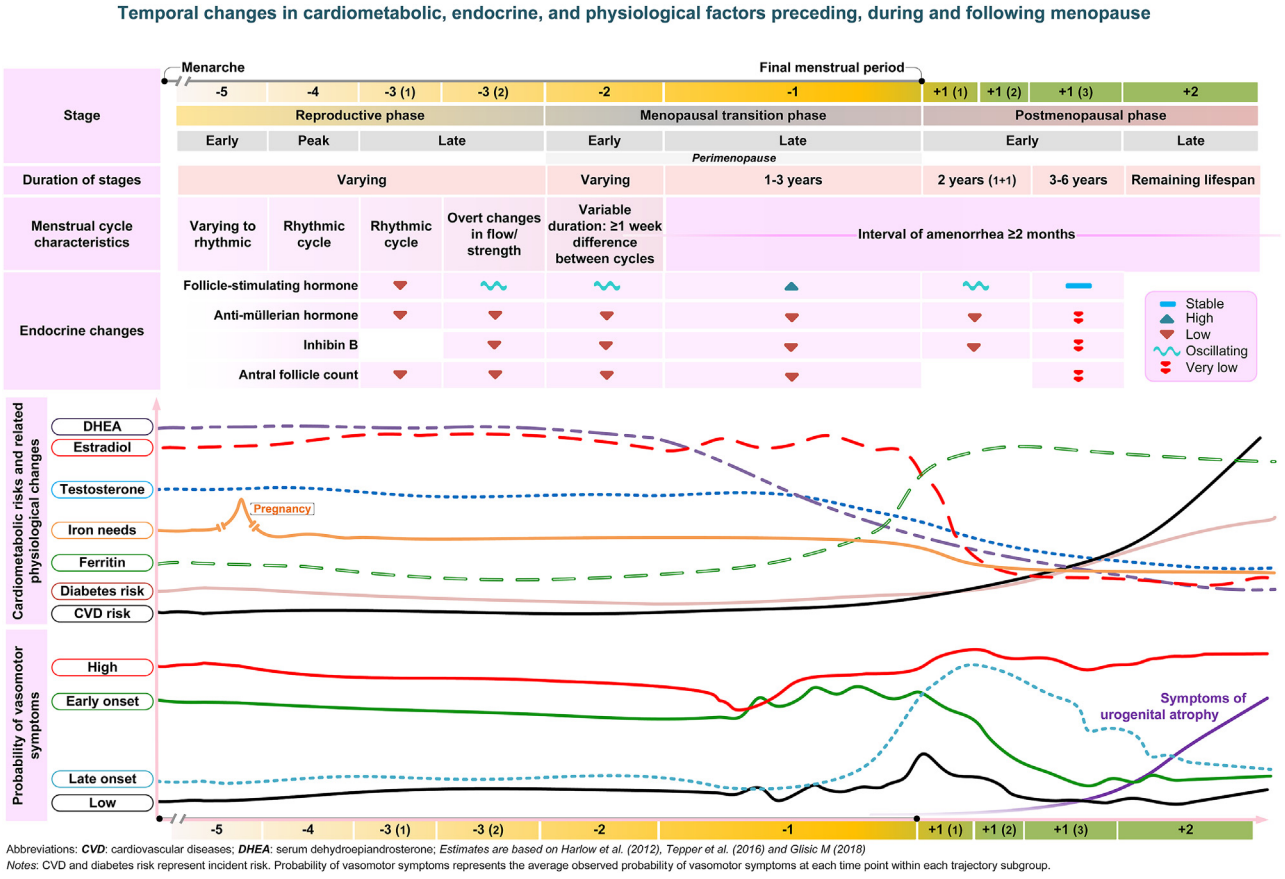


**Fig. 2.** Temporal changes in cardiometabolic, endocrine, and physiological factors preceding, during and following menopause.

### 5.1.1. Absorption

As iron is not synthesized in the body, it must be absorbed from dietary sources [76]. Common sources of heme iron are eggs, liver, read meat, and for non-heme iron spinach and other plant sources [76]. Dietary sources of heme iron (animal foods) have a higher bioavailability than do non-heme (plant foods) sources (30% vs. less than 10%). This is the reason why iron contained in fruits, grains and vegetables are difficult to absorb [76,77]. Physiological conditions that increase iron loss such as menstruation and lactation, are compensated with an increased absorption up to 3 mg per day [76,77]. Heme iron, found primarily in animal-based foods, is absorbed more efficiently than non-heme iron, found primarily in plant-based foods. In the small intestine, the intact heme molecule (with iron) is absorbed by the enterocytes (intestinal cells) primarily through a heme transporter. This transporter is thought to be the heme carrier protein (HCP1) in the luminal brush border membrane of duodenal enterocyte, although there may be other pathways as well [77,78]. Elemental iron exists in two forms; the reduced ferrous state ($Fe^{2+}$) and the oxidized ferric state ($Fe^{3+}$) [71,77]. Elemental iron can only be absorbed by enterocytes in its ferrous state ($Fe^{2+}$) [77]. Ferric iron ($Fe^{3+}$) is reduced by cytochrome B on the apical membrane of enterocytes [77]. Ferrous iron ($Fe^{2+}$) can then be absorbed by divalent metal ion transporter-1 (DMT-1) [71,76,77]. The uptake of ferrous iron ($Fe^{2+}$) needs acidic conditions which increase the solubility of ferrous iron ($Fe^{2+}$). Once in the enterocyte, iron could follow three ways: (1) it may be mobilized to the mitochondria in the synthesis of heme molecules, (2) it may be mobilized to ferritin and stored or (3) it may be exported from the enterocyte to other body sites. Ferrous iron ($Fe^{2+}$) is exported from the enterocyte by ferroportin on the basolateral membrane [76,77].

### 5.1.2. Ferritin

Ferritin is the primary cellular storage protein for iron. Within the ferritin molecule, iron is stored in the ferric form. On the other hand, small quantities of ferritin are present in human serum and are elevated in conditions of iron overload (see Fig. 4). Ferritin, functioning as an acute-phase reactant, may overestimate iron stores not only in inflammatory conditions but also specifically in infectious conditions [79,80]. Ferritin levels below approximately 60 μg/L stimulate dietary iron absorption from the upper small intestine. Low plasma iron concentrations limit iron uptake by erythrocytes, restrict hemoglobin synthesis and lead to anemia [81].

### 5.1.3. Soluble transferrin receptor

Soluble transferrin receptor (sTfR) is a general marker of erythropoiesis and, unlike ferritin, is considered not to be affected by the acute-phase response [82]. The transferrin receptor is cleaved and shed as a soluble form (sTfr) into the extracellular and intravascular space. Serum levels of sTfR hint at the presence of transferrin receptor that is not bound to transferrin. Consequently, lower levels of sTfR can be seen in conditions where the receptor is highly saturated with iron [79].

### 5.1.4. Hepcidin

Hepcidin (also called liver-expressed antimicrobial peptide or hepcidin antimicrobial peptide) is a peptide hormone produced in many tissues, but the primary site of synthesis is in the liver. Other tissues that produce hepcidin include macrophages in inflammation, adipocytes, and retinal cells. Hepcidin negatively regulates the absorption of dietary iron in the duodenum, the release of recycled iron from macrophages, and stored iron from hepatocytes.

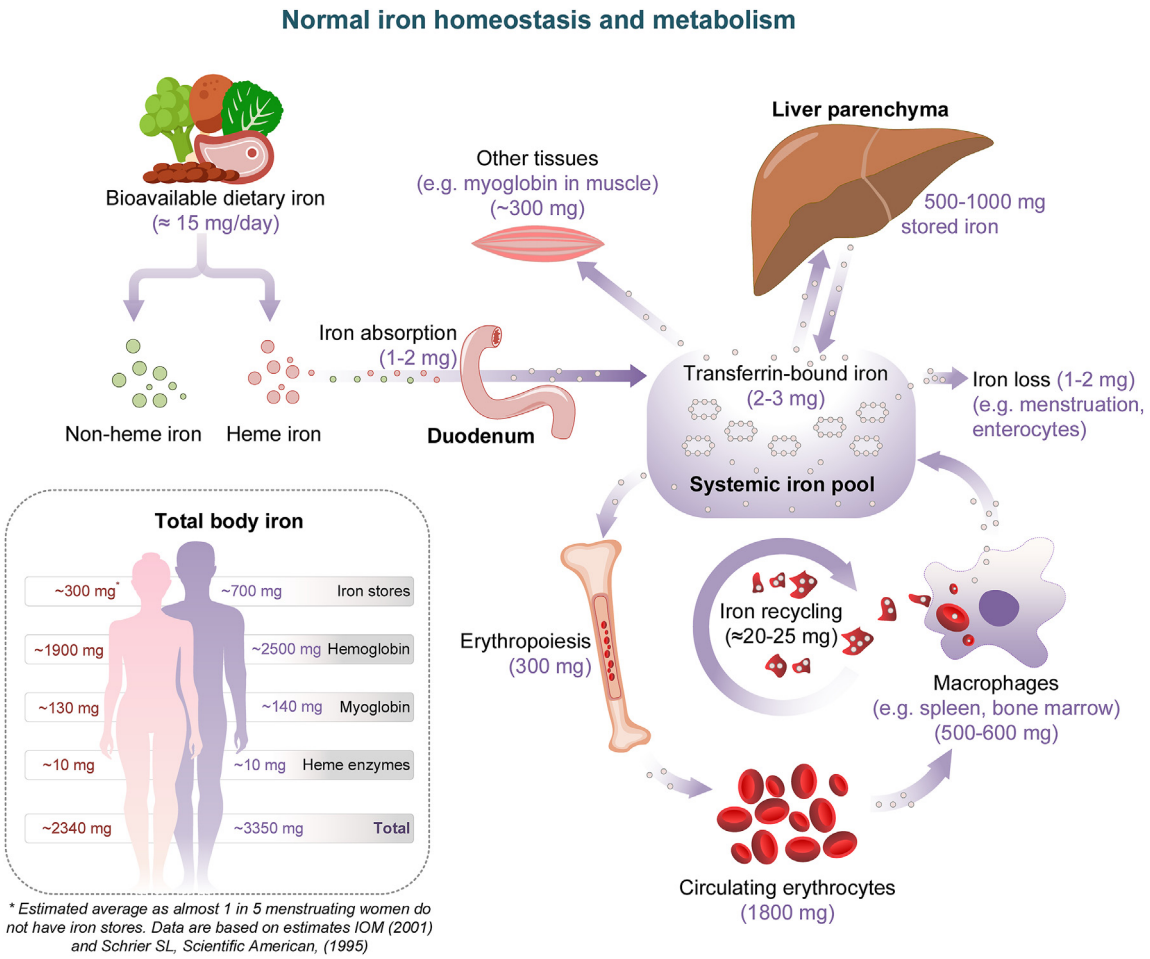


**Fig. 3.** Normal iron homeostasis and metabolism.

Hepcidin inhibits intestinal iron uptake through binding to ferroportin [83,84]. Hepcidin levels are higher during iron loading and inflammation, and lower during iron deficiency and increased erythropoietic activity [75].

### 5.2. Sex and menopause-related changes of iron homeostasis

There are important differences in iron levels between sexes during lifetime. Serum ferritin levels are relatively constant and similar between sexes from 3 years of age until adolescence [85]. In males, iron stores increased during adolescence and remain constant until age 70 years, after which they decline. In females, iron levels are lower than in males from adolescence until menopause, after which they increase due to the disappearance of the menstrual periods [72,73].

Although the increase in iron levels in menopause is considered within normal physiologic range, potential health problems in females (and in middle aged males) could be linked to this increase, which in turn can cause organ damage [74,75]. For instance, iron intervenes in the pathogenesis of many diseases such as ischemic heart disease, cancer, diabetes, infections, and neurodegenerative disorders [71,76]. Although iron overload is a frequent derangement of iron status reported in relation to the risk of T2D and metabolic syndrome (MetS), a systematic review of iron status and CVD showed that associations might exist with both iron overload and iron deficiency [77]. Figure 4 shows the underlying pathophysiology of iron deficiency and iron overload states.

### 5.3. Iron and cardiometabolic diseases: biological mechanisms

There are several pathophysiological mechanisms by which iron metabolism can induce heart disease. Iron has a fundamental role in mitochondrial function and various enzyme functions, and iron deficiency has a particular negative impact on cardiomyocyte mitochondrial function [86], causing cardiac dysfunction and failure [87].

An excess amount of iron can also be toxic by producing hydroxyl radicals, leading to oxidative damage to lipids, proteins, and DNA [88]. Iron-induced oxidative stress can trigger inflammatory pathways linked to the progression of CVD [89,90].

Iron has been shown to influence glucose homeostasis in pancreas β cells, hepatocytes, and adipose tissue [5]. Iron overload such as in hereditary hemochromatosis or numerous blood transfusions increases the risk of diabetes [91,92]. Conversely, anemia caused by iron deficiency leads to tissue hypoxia, triggering the release of erythropoietin and potentially impacting glucose metabolism [93]. Iron deficiency also affects pancreatic β cells, impairing insulin secretion [94]. Finally, iron-mediated cell death, namely, ferroptosis, has recently been reported to induce cardiomyocyte damage [95].

### 5.4. Dark side of iron: the role of iron in cardiometabolic diseases

Despite the huge number of studies on the pathophysiological mechanisms linking iron status with CMD risk, epidemiological

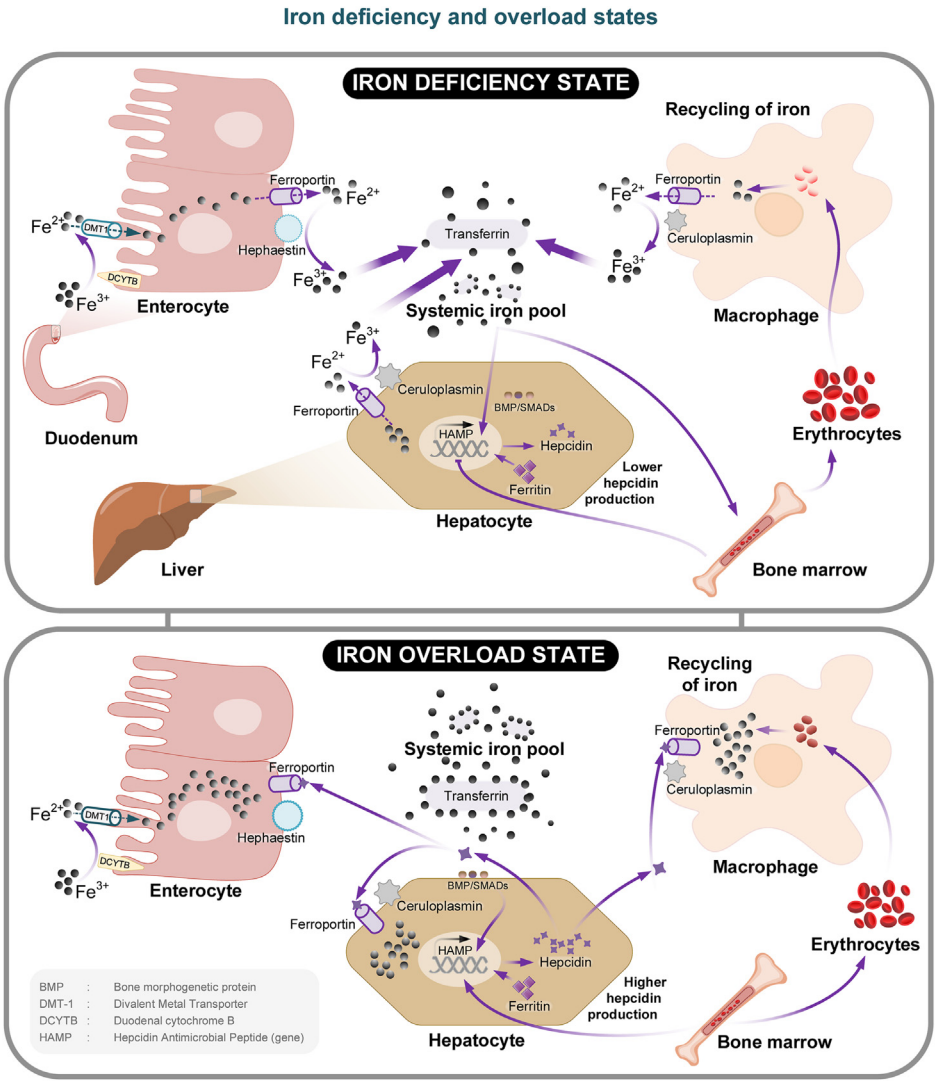


**Fig. 4.** Iron deficiency and overload states.

studies have yielded inconsistent results. Among the reasons for the conflicting results of epidemiological studies are the differences in the selection of the study sample, the methods used to evaluate iron biomarkers (i.e., serum iron, serum ferritin, transferrin saturation, transferrin to ferritin ratio, dietary iron intake), and the cutoff(s) used to define iron deficiency or iron overload. Also, different outcomes used in different studies (i.e., all-cause mortality, CVD-specific mortality, acute MI, stroke, CHD, coronary revascularization or intermediate end points) and different confounders [96]. In the following sections, we provide an overview of the evidence on the role of iron in CMD.

### *5.4.1. Iron and ischemic cardiovascular diseases*

The role of iron in the pathogenesis of CVD has increasingly been of interest in the field of public health. In 1981, Sullivan et al. proposed that the greater risk of CVDs in men and postmenopausal female, compared with premenopausal female, could be in part explained by the differences in body iron stores [70]. Since then, numerous epidemiological studies have shown that body iron status is associated with CVD risk [96–101]. A systematic review and meta-analysis of 17 prospective studies indicated a negative association between transferrin saturation and CVD, but no significant association between serum ferritin, total iron binding capacity (TIBC), serum iron and CVD [102]. This systematic review and meta-analysis found that the risk ratio of CHD for individuals in the top third compared with individuals in the bottom third of iron biomarkers were 0.80 (95% CI, 0.73–0.87) for iron, 0.82 (95% CI, 0.75–0.89) for transferrin saturation, 1.03 (95% CI, 0.87–1.23) for ferritin, and 0.99 (95% CI, 0.86–1.13) for transferrin. The nonsignificant results for ferritin and transferrin might be attributable to confounding caused by inflammation: inflammation could elevate serum levels of ferritin and lower those of transferrin, thereby potentially influencing the associations with an increased risk of CHD. The authors concluded that whereas their overall results may suggest a protective effect of higher body iron stores on risk of CHD, it is difficult to infer causality because of possible residual confounding and reverse causality bias. Similar findings were obtained in a two-sample Mendelian randomization study (MR) using genetic variants as instrumental variables for iron that are less prone to confounding by socioeconomic and lifestyle factors [103]. In this MR study, the authors found evidence of a protective effect of higher iron status on CAD risk. For one SD unit increase in genetically predicted iron biomarkers, the authors found odds ratio (95% confidence interval) 0.94 (0.88–1.00) for iron; 0.95 (0.91–0.99) for transferrin saturation, 0.85 (0.73–0.98) for log-transformed ferritin, and 1.08 (1.01–1.16) for transferrin. In summary, current

findings suggest that both iron deficiency and iron overload are associated with CHD or CAD risk (Table 1).

#### 5.4.2. Iron and heart failure

Heart failure represents a rapidly growing public health concern with a prevalence of 1–2% in the global population and ≥10% in those age ≥65 years [104,105]. Iron deficiency is highly prevalent in patients with HF, occurring in 37–50% of patients [106–112]. Results have shown that the etiology of iron deficiency in worsening HF is complex, multifactorial and seems to consist of a combination of reduced iron uptake (malnutrition, fluid overload), impaired iron storage (inflammation, chronic kidney disease), and iron loss (antiplatelets) [113–115]. To date, causal relationships remain largely unproven. However, in a prospective observational study included 546 patients with chronic HF, iron deficiency was present in 37% of patients and was related to an increased risk of death or need for heart transplantation [112]. The authors suggested that iron supplementation could be considered as a therapy to improve prognosis in patients with HF and iron deficiency. Indeed, a recent meta-analysis of large randomized controlled trials in over 3000 patients with HF and iron deficiency showed that intravenous iron, compared to standard care/placebo, reduced the primary outcome of hospitalization for heart failure and cardiovascular mortality by 25%. However, the effect was mainly driven by hospitalization for heart failure, while the evidence for cardiovascular and all-cause death was inconclusive [116]. On the opposite, iron overload such in haemochromatosis can lead to heart failure via the development of cardiomyopathy [117]. In summary, both iron deficiency and overload are associated with HF, albeit via different pathophysiological pathways (Table 2).

#### 5.4.3. Iron and type 2 diabetes

Iron and its markers have been closely related to glucose metabolism and T2D [118–122], Increased serum ferritin, reflecting body iron storage, is often associated with elevated blood glucose and insulin levels, as well as with increased risk of insulin resistance [123]. However, the results from large studies on iron and T2D incidence are inconsistent, some studies showing a positive association between iron levels and T2D [124–126], others failing to confirm this association [127–129]. The explanations for these contrasting findings might correspond to differences in recruitment, methods and iron measurements, the short follow-up and criteria for the diagnosis of T2D [130]. Also, iron metabolism should to be looked as a whole, including iron, transferrin and ferritin, rather than a as single marker, due to intra-individual variations in sideremia and changes over time depending on age, sex and menopause [131]. Results from meta-analyses suggest that several iron indices—including ferritin, transferrin saturation, and heme iron intake are associated with the risk of T2D development [132–135]. Using a Mendelian randomization approach, Wang and et al. examined the putative hypothesis that systemic iron status has a causal effect on risk of T2D [136]. The authors used genetic

**Table 1**
Summary table of studies assessing the association between iron and ischemic cardiovascular disease.

| First author, year of publication, reference | Study design | Study sample | Iron biomarkers | Outcome | Main results |
|---|---|---|---|---|---|
| Sudeep Das De, 2015 [102] | Systematic review and meta-analysis | 17 prospective studies | Serum iron, serum ferritin, transferrin, TSAT, TIBC | CAD | Transferrin levels were negatively associated with CAD risk. |
| Emanuela Lapice, 2013 [96] | Review | Cross sectional, longitudinal, and intervention studies | Iron intake, serum iron, serum ferritin, TSAT | CVD § | Iron deficiency and iron overload were modestly associated with increased CVD risk. |
| Carlos Muñoz-Bravo, 2013 [100] | Review | 55 studies: cross-sectional, longitudinal, intervention and meta-analyses | Iron intake, serum iron, serum ferritin, TSAT | CVD § | 27 studies supported the iron hypothesis, 20 found no evidence, and eight were contrary to the iron hypothesis. |
| JeromeL Sullivan, 1981 [70] | Review | Cross sectional, longitudinal and review studies | Serum iron, serum ferritin | CVD § | levels of stored iron contribute to the greater incidence of heart disease in men and postmenopausal women compared to premenopausal women. |
| Dipender Gill, 2017 [103] | Mendelian randomization | 48,972 participants | Serum iron, serum ferritin, transferrin, TSAT | CAD | Higher iron status was negatively associated with coronary artery disease risk. |
| Leo R. Zacharski, 2011 [101] | RCT | 636 participants with phlebotomy vs. 641 controls | Serum iron, serum ferritin | Death, nonfatal myocardial infarction, stroke | Lower ferritin predicted better outcomes. Phlebotomy reduced iron and prevented non-fatal heart attacks and strokes. |
| Derstine, 2003 [98] | Intervention study | 77 healthy men and women | Serum iron, serum ferritin, non-transferrin-bound iron | CVD risk factors | No association was found between LDL oxidative susceptibility and subtle dietary-associated variation in iron status |
| Usha Ramakrishnan, 2002 [99] | Prospective study | 4579 nonpregnant women | Serum ferritin | CVD risk factors | Higher ferritin levels were associated with higher triglyceride, total cholesterol, glucose, and diastolic blood pressure levels. |
| Mohammad Hassan Eftekhari, 2013 [97] | Case–control study | 100 cases with newly diagnosed CVD and 100 controls | Serum iron, serum ferritin, TIBC | CVD risk factors | Serum iron and ferritin were positively correlated with C-reactive protein levels. |

CAD, coronary artery disease; CVD, cardiovascular disease; RCT, randomized controlled trial; TIBC, total iron binding capacity; TSAT, transferrin saturation. § also includes heart failure.

**Table 2**
Summary table of studies assessing the association between iron and heart failure.

| First author, year of publication, reference | Study design | Study sample | Iron biomarkers | Outcome | Main results |
|---|---|---|---|---|---|
| Fraser J. Graham, 2023 [116] | Meta-analysis | 10 RCT | Intravenous iron | Composite of cardiovascular mortality and recurrent hospitalizations for HF | In patients with HF and ID, intravenous iron reduces the risk of hospitalization for HF but whether this is associated with a reduction in cardiovascular or all-cause mortality remains inconclusive |
| Goran Loncar,2021 [110] | Review | Cross sectional, longitudinal, systematic review and intervention studies | serum iron, serum ferritin, transferrin, intravenous iron, TSAT | morbidity and mortality in patients with HF | Emerging clinical trials emphasize the importance of iron supplementation in heart failure due to improved quality of life. Further large-scale studies are needed to confirm its impact on mortality and morbidity. |
| Hao Zhang, 2018 [117] | Review | Cross sectional, longitudinal, systematic review, and intervention studies | serum iron, serum ferritin, transferrin, intravenous iron, TSAT | Iron's role in HF | Iron overload such in haemochromatosis can lead to heart failure via the development of cardiomyopathy. |
| Inder S. Anand, 2018 [106] | Review | Cross sectional, longitudinal, and intervention studies | Serum iron, serum ferritin, transferrin, intravenous iron, TSAT | Prevalence of ID and anemia in patients with HF | Anemia and iron deficiency in heart failure patients present therapeutic challenges. While ESAs lack efficacy, intravenous iron therapy shows promise pending larger trials for long-term outcomes confirmation. |
| Darlington O Okonko, 2004 [113] | Review | Cross sectional, longitudinal, and intervention studies | serum iron, serum ferritin, transferrin | CHF | Anemia in chronic HF diminishes exercise capacity and survival, with causes often unknown, requiring treatment for better outcomes and understanding of pathogenesis. |
| Dirk H. van Dalen, 2022 [111] | Multicenter cohort study | 742 patients with acute HF | Serum iron, serum ferritin, TSAT | Prevalence of ID and anemia | High prevalence of ID in patients with acute HF |
| Haye H van der Wal, 2019 [114] | Cohort study | 2357 patients with HF | Serum ferritin, transferrin, TSAT | Composite of all-cause mortality and first HF rehospitalization | ID was an independent predictor of unfavorable outcome. |
| Ewa A. Jankowska, 2010 [112] | Cohort study | 546 patients with stable systolic CHF | Serum ferritin, TSAT | Mortality in patients with chronic HF | High prevalence of ID in patients with chronic HF. ID was an independent predictor of unfavorable outcome. |
| Christian Jacob, 2019 [108] | Retrospective claims database | 3,799,392 patients with any type of HF | Serum ferritin, TSAT | Mortality in patients with HF | HF patients with untreated incident ID had a significantly higher all-cause mortality than HF patients without iron deficiency. |
| Vojtech Melenovsky, 2016 [115] | Case-control study | 91 patients with HF, aged 37–57 and 38 HF-free controls | Myocardial iron | Mitochondrial function | Myocardial iron content was decreased, and mitochondrial function was impaired in HF |
| Tee Joo Yeo, 2014 [109] | Case-control study | 751 patients with HF, aged 50–75 and 601 controls | Serum iron, serum ferritin, transferrin, TSAT | HF readmissions and deaths | ID was an independent predictor of unfavorable outcome. Patients with HF and ID had higher all-cause mortality and higher health care costs. |
| Stephan von Haehling, 2017 [107] | Cross-sectional study | 1198 patients with chronic symptomatic HF | Serum ferritin, transferrin, TSAT | Prevalence of ID and anemia | High prevalence of anemia and ID in patients with chronic symptomatic HF. |

CHF, chronic heart failure; HF, heart failure; ID, iron deficiency; TSA, transferrin saturation; RCT, randomized controlled trial; ESAs, Erythropoiesis-stimulating agents.

variants associated with iron markers and assessed whether those variants were also associated with incident T2D. They found a positive association between the genetic variants for iron, ferritin, and transferrin saturation and incidence of T2D. However, it is important to acknowledge the complexity surrounding the establishment of causality. As acknowledged by the authors, potential pleiotropic bias, where a genetic variant can influence various traits, cannot be excluded (Table 3).

#### 5.4.4. Iron, hypertension and dyslipidemia

Increasing evidence suggests that iron metabolism plays an important role in the development of HTN [137–140]. A recent study, involving patients with essential hypertension with documented iron overload showed an activation of the sympathetic cardiovascular influences that occur in hypertension that was complicated by iron alterations [141]. This may represent one of the pathophysiological mechanisms responsible for the increased CVD

**Table 3**
Summary table of studies assessing the association between iron and diabetes.

| First author, year of publication, reference | Study design | Study sample | Iron biomarkers | Outcome | Main results |
|---|---|---|---|---|---|
| Setor K Kunutsor, 2013 [134] | Systematic review and meta-analysis | 12 studies with 185,462 participants | Serum ferritin, dietary heme iron intake | Incident T2D | Ferritin was positively associated with risk of T2D. |
| Zhuoxian Zhao, 2012 [132] | Systematic review and meta-analysis | 12 studies with ferritin levels (4366 T2D cases and 41,091 controls) and 4 heme-iron intake (9246 T2D cases and 179,689 controls) | Serum ferritin levels or dietary heme iron intake | Incident T2D | Ferritin and heme iron intake were positively associated with risk of T2D. |
| Wei Bao, 2012 [133] | Systematic review and meta-analysis | 11 prospective studies and meta-analysis of five studies | Serum ferritin, sTfR, sTfR to ferritin ratio, dietary (non)heme iron intake, supplemental iron intake | Incident T2D | Serum ferritin, sTfR and the sTfR to ferritin ratio and higher heme iron intake were positively associated with risk of T2D. No association of dietary intakes of total iron, non-heme iron, or supplemental iron intake with risk of T2D. |
| Ester Orban, 2014 [135] | Meta-analysis of observational studies | 46 studies | Serum ferritin, serum transferrin, TSAT, sTfR | Incident T2D | Ferritin and TSAT were positively associated with risk of T2D. |
| José Manuel Fernández-Real, 2015 [123] | Review | Cross sectional, longitudinal, review and intervention studies | Serum ferritin, serum transferrin, TSAT | Insulin action and T2D | Body iron stores should be considered as a potential therapeutic target in T2D management due to its significant influence on glucose metabolism. |
| José Manuel Fernández-Real, 2014 [122] | Review | Cross sectional, longitudinal, review and intervention studies | Serum ferritin, serum transferrin, TSAT | Glucose metabolism and T2D | Iron interacts with several pathways and mechanisms linked to Glucose metabolism and T2D. |
| Judith A. Simcox, 2013 [121] | Review | Cross sectional, longitudinal, review and intervention studies | Serum ferritin, serum transferrin, TSAT | incident T2D | Association between tissue iron stores and diabetes risk established; excess iron may induce diabetes, while deficiency linked to obesity-related risk. |
| Sundararaman Swaminathan, 2007 [120] | Review | Cross sectional, longitudinal, review and intervention studies | Serum ferritin, serum transferrin, TSAT | Incident T2D | Iron plays a pathogenic role in diabetes and its complications such as microangiopathy and atherosclerosis. |
| Xinhui Wang, 2021 [136] | Mendelian randomization | 48,972 individuals with genetic variants and case–control study (74,124 T2D cases and 82, 006 controls) | Serum iron, serum transferrin, TSAT | Incident T2D | Genetically instrumented serum iron, ferritin, and TSAT were positively associated with risk of T2D. Transferrin was inversely associated with risk of T2D. |
| Andrés Díaz-López, 2020 [130] | Cohort study | 206,115 participants | Serum ferritin | Incident T2D | Serum ferritin was higher in participants who developed T2D |
| Anitha Pitchika, 2020 [129] | Cohort study | 3232 participants | Serum ferritin, serum transferrin | Incident T2D | Ferritin was positively associated with risk of T2D in women but not in men or in the total population. No association was observed for transferrin. |
| Alex Aregbesola, 2018 [128] | Cohort study | 516 participants with impaired glucose tolerance | Serum adiponectin to ferritin ratio | Incident T2D | Changes of serum adiponectin to ferritin ratio were positively associated with risk of T2D and insulin sensitivity. |
| Clara Podmore, 2016 [124] | Cohort study | 11,052 patients with T2D and a random subcohort of 15,182 individuals | Serum iron, serum ferritin, transferrin, TSAT | Incident T2D | Serum ferritin and transferrin were positively associated with risk of T2D in both sexes. TSAT was negatively associated with risk of T2D only in women. Serum iron was not associated with risk of T2D. |
| Rui Jiang, 2004 [125] | Prospective nested case–control | 698 T2D cases and 716 controls | Serum ferritin, ratio of transferrin receptors to ferritin | Incident T2D | Higher ferritin and lower ratio of transferrin receptors to ferritin were positively associated with risk of T2D. |
| J Montonen, 2012 [126] | Case-cohort study | 607 incident T2D cases and 1969 controls | Serum ferritin, sTfR, and sTfR to ferritin ratio | Incident T2D | Ferritin was positively associated with risk of T2D. The sTfR to ferritin ratio was inversely associated with risk of |

(*continued on next page*)

**Table 3** (*continued*)

| First author, year of publication, reference | Study design | Study sample | Iron biomarkers | Outcome | Main results |
|---|---|---|---|---|---|
| | | | | | T2D. No significant association was observed for sTfR. |
| Megan L Jehn, 2007 [127] | Case-cohort study | 599 cases and 690 controls | Serum ferritin | Incident T2D | Ferritin may be only one of several metabolic abnormalities that eventually lead to diabetes, not a causative factor. |
| Alioune Badara Senghor, 2012 [118] | Case-control | 60 patients with T2D and 60 with pre-diabetes | Serum iron, serum ferritin, TIBC | Comparison of two groups | Serum ferritin levels were significantly higher in T2D compared with pre-diabetes. Iron and TIBC did not differ between groups. |
| M C Thomas, 2004 [119] | Cross-sectional survey | 820 patients with T2D | TSAT | Elevated TSAT | TSAT levels were higher in T2D compared to the general population. |

sTfR, soluble transferrin receptor; TIBC, total iron-binding capacity; TSAT: transferrin saturation; T2D, type 2 diabetes.

**Table 4**
Summary table of studies assessing the association between iron and hypertension or dyslipidemia.

| First author, year of publication, reference | Study design | Study sample | Iron biomarkers | Outcome | Main results |
|---|---|---|---|---|---|
| Yongjian Zhu, 2020 [142] | Cohort study | 8337 participants | Serum ferritin, serum transferrin and hemoglobin | Blood pressure | Transferrin and hemoglobin levels were positively associated with blood pressure and incident hypertension. |
| N. Kilani, 2015 [137] | Cohort study | 3271 participants | Serum iron, serum ferritin, serum transferrin | Incidence of MetS | Increased transferrin levels were positively associated with risk of MetS |
| Istvan S Vari, 2007 [139] | Cohort study | 469 men, 278 pre- and 197 post-menopausal women | Serum ferritin, serum transferrin, TSAT | Incidence of MetS | Ferritin and transferrin were positively associated with risk of MetS |
| Gino Seravalle, 2020 [141] | Case–control study | 17 healthy controls, 21 age-matched patients with hypertension and iron overload, 28 patients with hyper-tension and no iron overload | Serum iron, serum ferritin, serum transferrin, TSAT | Blood pressure variability and heart rate | Serum ferritin and TSAT were positively associated with hyperadrenergic state and altered blood pressure variability only in patients with hypertension and iron overload. |
| Piperno, Alberto, 2002 [138] | Case–control study | 88 patients with hypertension, 62 patients with hepatic iron overload syndrome and 102 healthy controls. | Serum iron, serum ferritin | Hypertension | Ferritin levels were higher in men with hypertension, but not in women. No association between transferrin and hypertension in both genders. |
| Jiang Li, 2017 [145] | Cross-sectional study | 7109 participants | Serum ferritin | Dyslipidemia | As serum ferritin quartiles increased, the odds ratios for high triglyceride, total cholesterol, and low-density lipoprotein cholesterol levels increased. |
| Cho, Geum Joon, 2011 [140] | Cross-sectional study | 1691 premenopausal women and 1391 postmenopausal women | Serum iron, serum ferritin, dietary iron intake | MetS | Ferritin levels were higher in MetS in postmeno-pausal women but not in premenopausal women |
| Michael J.A. Williams, 2002 [144] | Cross-sectional study | 815 participants | Serum ferritin | Triglycerides, total and HDL cholesterol, apolipoprotein B, Lp(a), CRP. | Ferritin was positively associated with triglyceride levels in both genders and with CRP in women. Ferritin was negatively associated with HDL cholesterol in men. |
| Martin Halle, 1997 [143] | Cross-sectional study | 93 participants | Serum ferritin | Triglycerides, VLDL, IDL and HDL cholesterol, VLDL apolipoprotein B, fasting plasma glucose. | Ferritin levels were not associated with blood pressure levels. High ferritin levels were associated with high triglyceride, VLDL cholesterol, VLDL apolipoprotein B, and with lower levels of Lp(a) and HDL cholesterol. |

CRP, c-reactive protein; CVD, cardiovascular disease; HDL, high density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein (a); MetS, metabolic syndrome; TSAT, transferrin saturation; VLDL, very-low density lipoprotein.

risk reported in the iron overload states. A Chinese study including 8337 adults aged ≥18 years reported that transferrin levels were positively associated with blood pressure and incident hypertension [142]. Other studies, including the previous one, reported that ferritin levels were associated with dyslipidemia [143–145]. Another study performed multivariable logistic regression analyses to estimate the odds ratios (ORs) for dyslipidemia, lipid parameters, the homeostasis model assessment of insulin resistance (HOMA-IR) and the risk of diabetes, according to sex-specific quartiles of serum ferritin by using the data of China Health and Nutrition Survey (2009 CHNS) indicated that serum ferritin levels are significantly associated with lipid parameters, independent of glucose metabolism disorders and components of metabolic syndrome [145] (Table 4).

## 6. Further studies and considerations on the current evidence

While existing studies have shed light on several aspects of the relationship between iron metabolism and estrogen influence on cardiometabolic outcomes, there remain areas warranting further investigation. Given the variability of iron markers, studies using repeated measures of iron biomarkers should be conducted to elucidate the iron hypothesis in sex differences in CMD. Sex-specific analyses and mechanistic investigations are essential, as are genetic studies to identify high-risk individuals. Mendelian randomization studies could also be applied to assess causal relationships between iron metabolism and CMD. In addition, well-designed clinical trials are imperative for evaluating the efficacy of interventions aimed at modifying iron status on CMD. In the critical evaluation of the findings of this review, it is important to recognize limitations such as the potential conflation of correlation with causation, where an observed association (e.g., between iron levels and CMD) do not necessarily imply a direct causal relationship. Additionally, caution should be exercised against generalizations, where findings from studies conducted in specific populations might not be universally applicable across different populations. Eventually, the simplified dichotomy of high or low iron levels leading to specific outcomes, requires a balanced understanding that considers individual variability and metabolic complexity, as the physiological reality is often more nuanced.

## 7. Conclusion

Numerous epidemiological studies have consistently shown that premenopausal women exhibit lower rates of cardiometabolic diseases compared to their male counterparts, a disparity that tends to diminish post-menopause. While the prevailing hypothesis attributes this variance primarily to differences in estrogen levels, recent research has begun to challenge this view, suggesting the need for a more nuanced understanding. Notably, the role of iron metabolism, which undergoes significant changes in women during menopause, emerges as a compelling factor that may contribute to these epidemiological patterns. This hypothesis is grounded in the observation that menstruation serves as a major route for iron loss in premenopausal women, potentially impacting cardiometabolic risk factors. If substantiated through rigorous scientific investigation, this perspective on iron's influence could revolutionize our understanding of gender disparities in cardiometabolic diseases and potentially unveil novel therapeutic interventions. Such explorations are essential for advancing our comprehension of cardiometabolic health and could be particularly relevant in the field of molecular epidemiology, offering new avenues for research and public health strategies.

## Author contributions

NSA: Wrote the first draft of the manuscript, which all authors read, contributed to, and approved for submission. TM, PMV and NSA: conceptualization. TM and PMV: supervision. EL: generated the figures.

## Ethics approval and consent to participate

Not applicable.

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## Conflicts of interest

The authors declare no conflict of interest.

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