Title

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Journal

ESC Heart Failure, 11(3)

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Publication Date

2024-06-01

DOI

10.1002/ehf2.14724

ESC HEART FAILURE
ESC Heart Failure 2024; **11**: 1435–1442
Published online 26 February 2024 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.14724

ORIGINAL ARTICLE

Iron Deficiency and Incident Heart Failure in Older Community-Dwelling Individuals

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Abstract

Aims Among persons with prevalent heart failure (HF), iron deficiency has been linked to HF admissions, and intravenous iron replacement improves HF outcomes. Recent studies in persons with chronic kidney disease (CKD) demonstrate that iron deficiency is associated with incident HF. This study aimed to determine the relationship of iron status with incident HF in community-dwelling older adults irrespective of their kidney function.

Methods In this case-cohort study, 1,006 Cardiovascular Health Study participants (785 from the random sub-cohort [including 193 HF cases] and 221 additional HF cases [N = 414 total HF cases]) aged ≥ 65 years without HF (41% with CKD), we used weighted Cox models to evaluate associations of iron status with incident HF. Participants were categorized based on quartiles of transferrin saturation and ferritin as "iron replete" (27.3%), "functional iron deficiency" (7.7%), "iron deficiency" (11.8%), "mixed iron deficiency" (5.6%), "high iron" (9.3%) and "non-classified" (38.1%), consistent with prior studies.

Results Compared to older persons who were iron replete, those with iron deficiency were at higher risk of incident HF (HR 1.47; 1.02–2.11) in models adjusting for demographics, HF risk factors, and estimated glomerular filtration rate. Other iron categories did not associate with incident HF. The relationship of iron deficiency with incident HF did not differ by CKD status (interaction *P* value 0.2).

Conclusions Among community-dwelling elders, iron deficiency is independently associated with incident HF, an association that was similar irrespective of CKD status. Our findings support conduct of clinical trials of iron replacement for prevention of HF in older adults with iron deficiency.

Keywords Iron; Heart failure; Left ventricular ejection fraction; Left ventricular mass

Received: 7 June 2023; Revised: 1 December 2023; Accepted: 24 January 2024
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Introduction

Iron is an essential trace element and tight control of its concentrations and cellular distribution is required for health. On the one hand, excess iron participates in Fenton-type chemical reactions promoting cytotoxicity.[1] On the other, iron deficiency may impair oxidative metabolism, cellular energetics, and immune mechanisms that may cause structural and functional changes in the tissues.[2] In the myocardium, this resulting diminution in mitochondrial oxidative capacity can lead to left ventricular (LV) dysfunction.[3,4]

Patients with prevalent heart failure (HF) and iron deficiency have lower ability to increase their cardiac output from rest to peak exercise compared to non-iron deficient HF patients.[5] In prevalent HF patients, iron deficiency has been associated with poor exercise tolerance,[5] and mortality risk.[6] Multiple randomized clinical trials have tested iron replacement in patients with prevalent HF. These trials have shown improved exercise capacity, quality of life, alleviated HF symptoms, and reduced hospitalizations for HF exacerbations.[7–9] Intravenous (IV) iron treatment has also been associated with improved myocardial functional

parameters and cardiac dimensions in patients with anemia and chronic kidney disease (CKD).[10]

Less is known about the relationship of iron deficiency with incident HF risk. However, a recent analysis in a large cohort of persons with CKD demonstrated that iron deficiency was associated with incident HF in this setting.[11] Older persons are at particularly high risk of HF[12]; and iron deficiency is common in this population,[13] amenable to repletion. While clinical trial data suggest that iron parameters may be modifiable and translate to improved clinical outcomes in persons with prevalent HF, the relationship of iron deficiency with cardiac structural abnormalities in persons without prevalent HF, and the relationship of iron deficiency with incidence of HF in community-dwelling older persons have not been evaluated. Thus, the primary goal of the present study was to evaluate the association of iron status with risk of incident HF in community-dwelling older adults.

Methods

Study participants and setting

The Cardiovascular Health Study (CHS) design, objectives, sampling strategies, and examination techniques have been described in detail elsewhere, previously.[14] Briefly, eligibility required age ≥65 years, to not be institutionalized, be expected to remain in the area for 3 years after recruitment, and to not be receiving active cancer treatment. Between 1989 and 1990, 5,201 participants were recruited from 4 US communities using Medicare eligibility lists. An additional 687 individuals predominantly of African American race were recruited in 1992 and 1993. In-person examinations were performed annually through 1998 and 1999, and again in 2005 and 2006. Telephone interviews alternated with in-person visits every 6 months from 1989 to 1999 and occurred semiannually thereafter.

Study Design

For this analysis, we used a case-cohort design focused on incident HF. Among the 3,107 individuals who participated and provided blood samples at the 1996 to 1997 visit, we randomly selected a sub-cohort (N = 861). From this, we excluded those with prevalent HF at the 1996–97 visit (N = 76), resulting in 785 participants in our random subcohort. Of these, 193 participants developed incident HF during subsequent follow-up. To increase power, per usual case-cohort design we identified additional cases of incident HF among the 3,107 who were not selected as part of the subcohort (N = 221). Therefore, the final number of participants in this study (sub-cohort + additional incident HF cases) were 1,006 and total number of cases were 193 + 221 = 414 cases.

HF Ascertainment

Participants were followed for incident HF, which was centrally adjudicated against prespecified criteria by the CHS Events Committee. Methods used to assess cardiovascular events, including HF, have been reported previously in detail.[15–17] Potential clinical events were identified at semi-annual contacts. Self-report of a physician diagnosis of HF was followed by confirmatory review of the participant's medical records. The presence of HF was determined based on diagnosis of HF by a physician, consistent symptoms or signs, treatment of HF (i.e., a current prescription for a diuretic agent and either digitalis or a vasodilator) and imaging findings supportive of HF. Follow-up and adjudication continued until 2015.

Clinical Parameters and Biomarker Measurements

Iron status measures

We measured iron, total iron binding capacity, and ferritin in this case-cohort sample.[18] Ferritin concentrations were measured in serum using an Ortho Vitro 950 Chemistry analyzer. The assay uses colorimetric reflectance spectrophotometric measurement. The analytic range is 1 to 2,500 ng/mL and intra-assay and inter-assay CVs were $< 5\%$. Iron and total iron binding capacity were measured using serum specimens on the same analyzer. The analytic range for total iron binding capacity is 50 to 600 ng/mL and intra-assay and inter-assay CVs were $< 5\%$. Transferrin saturation (TSAT) was calculated using ratio of measured iron and total iron binding capacity.

Covariates

Information on baseline confounders was obtained at the 1996 to 1997 study visit,[14] including age, gender, race/ethnicity, education (> high school vs. less), clinic site, lifestyle factors (current smoking, alcohol consumption), and HF risk factors including hypertension (systolic blood pressure; SBP ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or use of antihypertensive medications), impaired fasting glucose (fasting glucose 100 to 125 mg/dL), diabetes (fasting glucose ≥ 126 mg/dL or use of anti-glycemic medications), smoking (current, former, or never), body mass index (BMI), total cholesterol, use of lipid-lowering medications, and C-reactive protein (CRP) concentrations. Cystatin C concentrations were measured using a BN II nephelometer (Siemens) and subsequently estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation.[19] A random morning urine sample was obtained and measured for urine albumin by rate nephelometry and creatinine using a Kodak Ektachem 700 Analyzer, and urinary albumin to creatinine ratio (ACR) was calculated (mg/g). NT-proBNP levels were

previously measured from samples at year 9 using serum specimens using immunoassay from Roche Diagnostics Corporation (Roche Diagnostics Elescys proBNP Assay, Indianapolis, Ind) on the Elescys instrument.[8]

Echocardiogram Assessment

Transthoracic echocardiography was performed in study participants at the 1994–1995 visit, predating iron measures by approximately 2 years. Standardized M-mode, 2D and Doppler images were acquired for central interpretation, which included determination of LV mass and LV ejection fraction, as detailed elsewhere.[20] Our two outcome measures for the secondary echocardiographic analysis were reduced LV systolic function, previously classified as LV ejection fraction <55%, and continuous LV mass indexed to sex, height and weight, as described previously.[21] We conducted analyses on echo measures within the random sub-cohort only, to minimize bias due to oversampling persons who would develop incident HF during follow-up.

Statistical analyses

We defined categories of iron status based on quartiles of ferritin and TSAT in the sub-cohort, as described in prior studies.[11] The final cohort was categorized into 6 iron status groups: "Iron Replete"- quartile 2 and 3 of both ferritin and TSAT, "Functional Iron Deficiency"- quartiles 3 & 4 of ferritin and quartile 1 of TSAT, "Iron Deficiency"- quartile 1 of both ferritin and TSAT, "Mixed Iron Deficiency"- quartile 2 of ferritin and quartile 1 of TSAT, "High Iron" - quartile 4 of both ferritin and TSAT and "Non-classified" - all remaining uncategorized participants (*Table 1*).

We used modified Cox models to account for the case-cohort design, using inverse probability weights for the sampling probability.[12,22] Sub-cohort participants (HF/non-cases and sub-cohort cases before the occurrence of event) were weighted by the inverse of the sampling fraction. Cases that arose outside the sub-cohort were not weighted before their incident HF occurred. All cases (irrespective of whether they arose in the sub-cohort) were assigned a weight of 1 at the time of the HF event. Robust variance estimators were computed. Furthermore, to account for the competing risk of death, we employed the Lunn & McNeil method[23] to evaluate the association between iron status groups and incident HF.

We used logistic regression to determine the semi cross-sectional association of iron categories (1996–97) with LV ejection fraction (1994–95) and linear regression with LV mass index. Confounders for all the final models were selected *a priori* and included age, gender, race, education, clinical site, SBP, antihypertensive medication use, BMI, total cholesterol, smoking, eGFR and ACR. We also used linear regression to determine the cross-sectional association between baseline NT-proBNP and iron deficiency among 785 participants included in the sub-cohort in companion analyses.

Finally, we assessed for effect modification by baseline CKD status (eGFR $<$ 60 mL/min/1.73 m^2 vs greater). All analyses were performed using R Core Team (2019) (R Foundation for Statistical Computing) and Stata statistical software (Stata SE version 17.1 (College Station, TX). A 2-sided P value $<$ 0.05 was considered statistically significant for all analyses including interaction terms.

Results

Among the 785 participants in the sub-cohort of older community-dwelling individuals without prevalent HF evaluated, the mean age was 78 ± 5 years, 61% were women, mean eGFR was 63 ± 18 mL/min/1.73 m^2, and median urine ACR was 9 mg/g (interquartile range [IQR], 5–20 mg/g). The median ferritin concentration was 104 ng/mL (IQR, 58–184 ng/mL), and the mean TSAT was 31% ± 10%. *Table 1* presents iron categories according to quartiles of ferritin and TSAT. Participants were categorized as "iron replete" (27.3% of participants; referent group), "functional iron deficiency" (7.7%), "iron deficiency" (11.8%), "mixed iron deficiency" (iron indices between the iron deficiency and functional iron deficiency groups; 5.6%), "high iron" (9.3%) and "non-classified" (38.1%), consistent with prior studies.[11]

Table 2 depicts the distribution of demographics, kidney function, and cardiovascular risk factors based on baseline iron status in the sub-cohort. Among those with iron deficiency, there was a greater percentage of participants identifying as female and current smokers. Iron-deficient individuals reported lower educational attainment compared

Table 1 Classification of Iron Status According to Quartiles of Ferritin and Transferrin Saturation

	Transferrin Saturation, %			
Ferritin, ng/ml	Quartile 1 (≤ 23.7)	Quartile 2 (23.8–29.4)	Quartile 3 (29.5–36.4)	Quartile 4 (≥36.5)
Quartile 1 (<57)	4 = Iron deficiency; N = 119	6 = Not classified1; N = 130		
Quartile 2 (58–100)	2 = Mixed; N = 57	1 = Iron replete; N = 275		7 = Not classified2; N = 121
Quartile 3 (101–179)	3 = Fxn iron deficiency; N = 78			
Quartile 4 (≥180)		8 = Not classified3; N = 132		5 = High iron; N = 94

Fxn, Functional.

Table 2 Demographics and Clinical Characteristics by Categories of Iron Status

Variable	Iron Deficient	Remaining Sub-cohort	Complete Sub-Cohort
Number of Participants	90	695	785
Demographics			
Age (years)	78 (5)	78 (5)	78 (5)
Female	65 (72)	428 (62)	493 (63)
Black	13 (14)	101 (15)	114 (15)
Education			
< High School	16 (18)	97 (14)	113 (14)
High School graduate	42 (47)	273 (39)	315 (40)
Postsecondary	32 (36)	323 (47)	355 (45)
Site			
Bowman Gray	20 (22)	174 (25)	194 (25)
Davis	16 (18)	194 (28)	210 (27)
Hopkins	16 (18)	165 (24)	181 (23)
Pittsburgh	38 (42)	162 (23)	200 (26)
Cardiovascular Risk Factors			
Smoking status			
Never	45 (52)	349 (51)	394 (51)
Former	29 (33)	292 (43)	321 (42)
Current	13 (15)	41 (6)	54 (7)
Alcohol Consumption			
Never/former	59 (66)	389 (56)	448 (57)
7 or fewer drinks per week	23 (26)	230 (33)	253 (32)
>7 drinks per week	8 (9)	71 (10)	79 (10)
Body Mass Index (kg/m^2)	27.6 (5.7)	26.9 (4.5)	27.0 (4.7)
Diabetes	10 (11)	90 (13)	100 (13)
Prevalent CHD	20 (22)	136 (20)	156 (20)
Systolic Blood Pressure (mmHg)	139 (21)	137 (21)	137 (21)
Diastolic Blood Pressure (mmHg)	68 (14)	70 (10)	70 (11)
HTN meds	49 (54)	362 (52)	411 (52)
Total Cholesterol (mg/dL)	197 (37)	204 (39)	203 (38)
Statin use	8 (9)	73 (11)	81 (10)
Laboratory Indices			
C-reactive protein (mg/L)	2.51 [1.31, 6.35]	2.27 [1.02, 4.77]	2.29 [1.03, 4.90]
Cystatin C (mg/L)	1.19 (0.34)	1.12 (0.32)	1.13 (0.33)
eGFR_cysC (ml/min/1.73m^2)	60 (18)	65 (18)	64 (18)
eGFR_cysC < 60	46 (51)	263 (38)	309 (39)
Urine Albumin/Creatinine ratio (mg/g)	8 [5, 23]	8 [5, 18]	8 [5, 18]
UACR ≥ 30 mg/g	16 (18)	113 (16)	129 (16)
NT-proBNP (pg/ml)	201 [108, 464]	174 [98, 321]	179 [98, 343]
Ferritin (ng/ml)	28 [20, 42]	117 [71, 191]	102 [57, 179]
Transferrin Saturation, TSAT(%)	18 (5)	32 (9)	31 (10)
Echocardiographic Indices (from Y7)			
LVEF %, N = 704			
Normal (≥50%)	76 (93)	579 (93)	655 (93)
mild/mod/severe decrease (<50%)	6 (7)	43 (7)	49 (7)
LV mass index (g/m^2)** N = 521	1.14 (0.33)	1.11 (0.29)	1.11 (0.29)

**LV mass = (e4.47 + 0.1[male] X height-0.64 X weight0.28).

to the remaining participants. Participants who were iron-deficient also had a greater burden of CKD, higher median levels of CRP and NT-proBNP compared to the remaining participants.

Associations of Iron Deficiency with Incident HF

The median follow-up time was 9.18 (SD 4.08) years. In the unadjusted analysis, iron deficiency was associated with incident HF relative to the iron replete reference group, but this finding did not reach statistical significance (HR 1.50; 0.93, 2.44). However, once adjusted for demographics, traditional risk factors and kidney function, the iron-deficient group was at statistically significant higher risk of incident HF with a similar hazard ratio as before (HR 1.47; 1.02–2.11; *Figure 1*). The other iron categories were not associated with incident HF in either unadjusted or adjusted models (*Table 3*). The relationship of iron deficiency with incident HF did not differ by CKD status (interaction *P* value = 0.2). The results were essentially unchanged after competing risk analysis, considering death as a competing risk to future HF.

Associations of Iron Deficiency with LV Measures

Next, we evaluated the association between iron categories and LV measures obtained two years prior to baseline, at

Figure 1 Incident Heart Failure Event Rate Per Year Among Categories of Iron Status; Iron-deficient group has a higher rate of incident HF compared to the other categories of iron status; HF, Heart Failure.

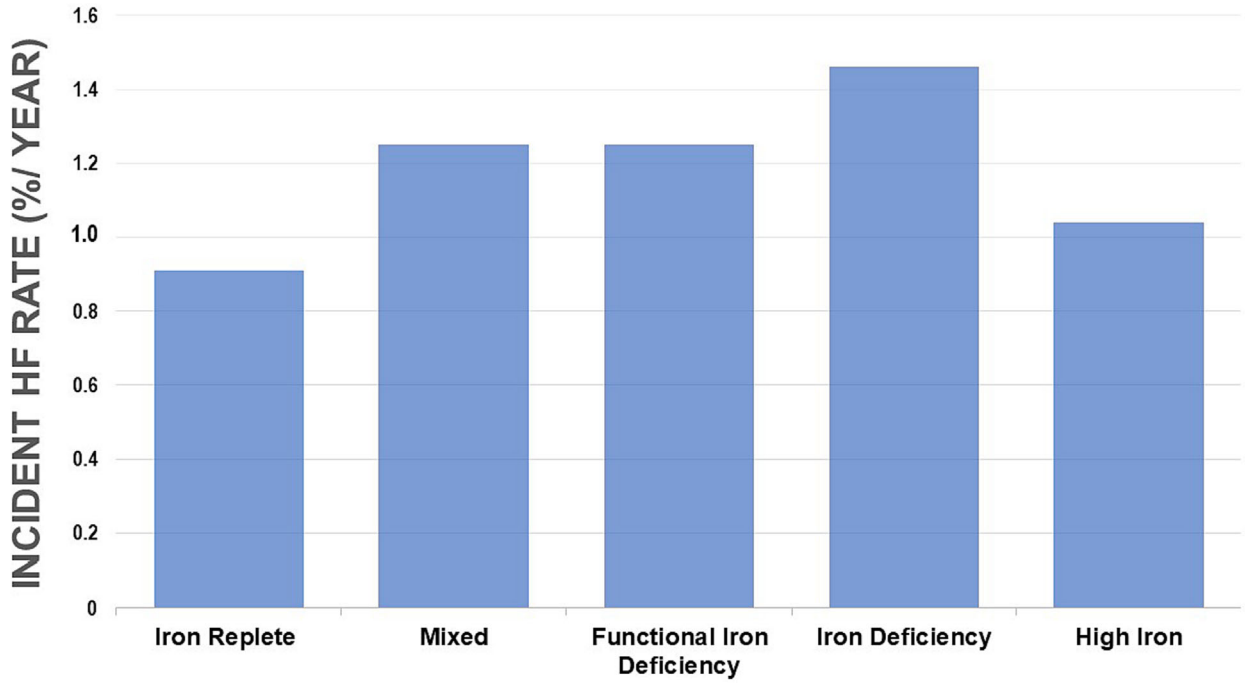

Table 3 Association of Iron Status Categories with Incident Heart Failure in Community-Dwelling Older Adults

	Sub-cohort		Additional Incident HF cases	Univariate Model	Multivariate Model*
	# HF Events	# Participants		HR (95% CI)	HR (95% CI)
Iron Replete	42	211	64	1.00 (ref)	1.00 (ref)
Mixed	17	47	10	1.29 (0.71, 2.36)	0.72 (0.42, 1.26)
Functional Iron Deficiency	9	51	27	1.29 (0.75, 2.23)	1.08 (0.72, 1.63)
Iron Deficiency	31	90	29	1.50 (0.93, 2.44)	**1.47 (1.02, 2.11)**
High Iron	16	72	22	1.07 (0.63, 1.82)	1.42 (0.91, 2.19)

*Final Model adjusted for demographics, SBP, BP medication use, BMI, diabetes, prevalent CHD, total cholesterol, smoking, alcohol consumption, CRP, eGFR and UACR; BP, Blood pressure; BMI, Body mass index; CHD, Coronary Heart Disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HF, Heart Failure; SBP, Systolic Blood Pressure; UACR, Urine albumin creatinine ratio.

the visit where echocardiographic data were available. Among the 785 participants without prevalent HF that were included in the random sub-cohort, 704 had echocardiographic data for LVEF and 521 had data for LV mass. Demographics and clinical characteristics of these participants were similar to the sub-cohort (*Table S1*). In both unadjusted and fully adjusted models, the iron deficiency group did not have statistically significant differences in odds of LV systolic dysfunction or mean LV mass index relative to the iron-replete group. In the unadjusted analysis, the functional iron deficiency iron group had a significantly higher LV mass index. However, once adjusted for demographics, traditional risk factors and kidney function, this association was no longer statistically significant (*Table 4*).

As echocardiograms were not available concurrent with the baseline visit, we also evaluated the association between iron deficiency and NT-proBNP concentrations in cross-section among 785 participants included in the sub-cohort. In the unadjusted model, iron deficiency was associated with greater NT-proBNP concentrations (β: 0.24; 95% CI 0.01 to 0.48; P = 0.04). However, once adjusted for demographics, traditional risk factors and kidney function, this association was no longer statistically significant (β: 0.16; 95% CI -0.05 to 0.36; P = 0.14).

Table 4 Association of Iron Status Categories with LV Echo Dimensions

	Univariate		Multivariate*	
LVEF (≥55% vs <55%) (Reference category is Iron Replete) N = 704	***OR (95% CI)***	***P value***	***OR (95% CI)***	***P value***
Mixed	0.87 (0.22, 3.36)	0.84	0.92 (0.22, 3.78)	0.91
Functional Iron Deficiency	1.51 (0.53, 4.27)	0.43	1.45 (0.48, 4.38)	0.51
Iron Deficiency	0.89 (0.32, 2.48)	0.83	0.81 (0.26, 2.45)	0.71
High Iron	1.16 (0.41, 3.25)	0.77	0.95 (0.32, 2.87)	0.93
LV mass index (Reference category is Iron Replete) N = 521	***Beta (95% CI)***		***Beta (95% CI)***	
Mixed	7.01 (−10.72, 24.72)	0.43	1.80 (−13.94, 17.55)	0.82
Functional Iron Deficiency	18.35 (3.01, 33.70)	**0.02**	8.58 (−5.26, 22.44)	0.22
Iron Deficiency	5.17 (−8.52, 18.87)	0.45	4.33 (−7.82, 16.51)	0.48
High Iron	12.28 (−1.92, 26.48)	0.09	1.31 (−11.48, 14.11)	0.84

*Multivariate is adjusted for age, gender, race, site, education, SBP, BP medication use, BMI, diabetes, prevalent CHD, total cholesterol, smoking, alcohol consumption, CRP, eGFR and UACR; BP, Blood pressure; BMI, Body mass index; CHD, Coronary Heart Disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; SBP, Systolic Blood Pressure; UACR, Urine albumin creatinine ratio.

Discussion

In a cohort of community-dwelling older individuals without HF at baseline, we demonstrate that iron deficiency is independently associated with incident HF, an association that is similar irrespective of CKD status. We also examined the cross-sectional relationship of iron deficiency with LV structure and function measures by echocardiography and NT-pro BNP concentrations in a subset. Despite the association of iron deficiency with incident HF, we did not find associations of iron deficiency with reduced LV ejection fraction, LV mass index, or NT-proBNP.

In persons admitted with acute HF, randomized trial evaluating IV iron therapy versus placebo demonstrate reduced risk of HF re-admissions,[24] improved functional capacity measured by 6-minute walk test distance,[9] and reductions in HF hospitalization and cardiovascular death.[25] A meta-analysis of randomized trials in prevalent HF demonstrated that iron therapy reduces the composite of recurrent hospitalizations for heart failure or cardiovascular death.[26] While our results need to be confirmed, in the context of these prior studies, our findings open the door to clinical trials designed to evaluate whether iron status testing, and repletion for those that are deemed iron-deficient, may reduce risk of HF in older adults without HF.

Based on the association of iron deficiency and risk of incident HF in CKD populations, we hypothesized that iron deficiency may have similar relationships in older community dwelling populations, even among those without CKD. Indeed, iron status was associated with incident HF irrespective of CKD status in our study. While our findings are novel for the setting and the specific outcome of incident HF, they are supported by other studies in the general population. For example, Stack et al. found that TSAT levels <23.7% were independently associated with cardiovascular and all-cause mortality in the general population after adjustment for multiple confounders, including kidney function and hemoglobin levels.[27] Schrage et al. examined persons from multiple European population-based cohorts, and found absolute iron deficiency (defined by ferritin <100 ug/L) to be associated with incident coronary heart disease and severe iron deficiency (ferritin <30 ug/L) to be associated with all-cause mortality.[28]

While we found an association between iron deficiency and incident HF, reduced LV ejection fraction and LV mass index appeared similar irrespective of iron status in a subset of our population. The reasons underlying these findings are uncertain, but several possibilities may be at play. First, the echo data were obtained 2 years before iron levels were measured. It is possible that echo parameters or iron status may have changed in the two years prior to iron measurement. However, an analysis of iron status with NT-proBNP measured concurrently was also null. Second, as the echo data were available only among a subset, it is possible that we were underpowered to detect differences in cardiac structures. Finally, we did not have state-of-the-art measures to permit up-to-date assessment of LV diastolic function or LV strain, which might have afforded more sensitive evaluation of preclinical cardiac disease than possible from our original analog echocardiograms. Finally, iron deficiency may predispose to HF by decreasing the threshold whereby HF becomes clinically manifest, or by changing cellular function as demonstrated in animal models,[29] rather than impair cardiac structure or function directly. Future studies are required to address these questions.

Iron deficiency anemia is the most common nutritional deficiency worldwide, and its common causes in the general population include gastrointestinal bleeding, decreased dietary iron, decreased gut iron absorption and menstruation in women.[30] Currently, an evidence-based definition of iron deficiency is lacking in both the general population as well as specific patient groups including HF. WHO uses a ferritin cut off <15ug/L in healthy individuals and < 70ug/L in individuals with infection or inflammation.[31] However, the limitations of diagnosing iron deficiency based on ferritin alone have been reported.[32,33] We utilized both ferritin and TSAT quartiles for defining categories of iron status, consistent with prior studies.[11]

This study has several strengths. We evaluated a well-characterized cohort of older community-dwelling adults

with long-term follow-up data, a population with high event rates, and nearly half had CKD. Thus, the study had substantial statistical power that provided the opportunity to test our hypotheses with considerable precision, and to evaluate consistency in subgroups with and without CKD. Finally, the CHS cohort specifically adjudicated HF events, and provided detailed ascertainment of risk factors, covariates, and outcomes.

This study has important limitations. We did not have hemoglobin levels available, and as whole blood was not stored; we are unable to measure hemoglobin levels in stored samples. Thus, our results were not adjusted for the potential co-occurrence of anemia. However, clinical trials suggest that treating iron deficiency is beneficial to patients with HF independent of hemoglobin levels. In addition, there is lack of evidence supporting restoration of hemoglobin levels using erythropoietin stimulating agents to improve clinical outcomes in HF.[34] Next, our analyses were observational and there remains the possibility of residual confounding. We do not have echo data at a later time point and are unable to explore the relationship of iron status and LV measures at the time iron status was assessed or at the time of incident HF presentation. Classification of iron status is challenging. We used a previously published classification but results may vary if other classifications are used.[11] Last, subclassification of incident HF events as preserved versus reduced ejection fraction was not possible in almost half the cases, leaving insufficient numbers for assessing relationships with these subtypes.

In conclusion, among older community-dwelling persons, iron deficiency is independently associated with incident HF, an association that was similar irrespective of CKD status. Based on prior randomized trials demonstrating clinical benefits of iron supplementation in prevalent HF, future studies should determine if iron replacement strategies could prevent incident HF in older persons with iron deficiency.

Acknowledgements/Sources of funding

This work was supported by National Institute of Diabetes and Digestive Kidney Diseases (NIDDK) Grants R01DK119528 and K24DK110427 (J.H.I). Veterans' Health Administration IK2-CX002195 (SS).

Cardiovascular health study was supported by contracts HHSN268201200036C, HHSN268200800007C, HHSN268201800001C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086, 75N92021D00006, and grants U01HL080295 and U01HL130114 from the National Heart, Lung, and Blood Institute (NHLBI), with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided by R01AG023629 from the National Institute on Aging (NIA). A full list of principal CHS investigators and institutions can be found at CHS-NHLBI.org.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Conflict of interest

Dr. Ix is principal investigator of an investigator-initiated research grant from Baxter International, serves as a data safety monitoring board member for Sanifit International, and has served on advisory boards for Alpha Young, AstraZeneca, Ardelyx Inc., and Bayer. Dr. Kizer reports stock ownership in Abbott, Bristol Myers Squibb, Johnson & Johnson, Medtronic, Merck and Pfizer.

Remaining authors have declared no relevant conflicts of interest.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Demographics and Clinical Characteristics of Sub-cohort who had Echocardiographic Data available.

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