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RESEARCH ARTICLE

Serum ferritin and risk for new-onset heart failure and cardiovascular events in the community

IJsbrand T. Klip [1], Adriaan A. Voors [1], Dorine W. Swinkels [2], Stephan J.L. Bakker [3], Jenny E. Kootstra-Ros [4], Carolyn S. Lam [5], Pim van der Harst [1],

Table 2 Multivariable regression beta-coef cients between cardiovasular risk factors and serum ferritin in men and women (selected after bootstrapping)

Variables	Men (*n* = 3145)			Women (*n* = 3241)		
	Standardized *β*	*T*	*P*-value	Standardized *β*	*T*	*P*-value
Menstruation (yes vs. no)	…	…	…	Š0.129	Š7.4	<0.001
BMI (per kg/m^2)	0.090	5.4	<0.001	…	…	…
Smoking (yes vs. no)	…	…	…	Š0.035	Š2.6	0.011
Haemoglobin (per g/dL)	0.108	6.5	<0.001	0.071	4.1	<0.001
MCV (per fL)	0.099	6.0	<0.001	0.124	7.6	<0.001
Log 2 hepcidin (nmol/L)	0.680	38.6	<0.001	0.625	30.4	<0.001
TSAT (per 5%)	0.094	5.	<0.001	0.1		

Table 3 Levels of ferritin and hepcidin and risk for incident heart failure with all-cause mortality as a competing risk

Ferritin (per doubling)	sHR	95% CI	Harrell's C	*P*-value
Total population (n = 6386)[a]				
Univariable	1.48	1.30–1.69	0.64	<0.001
Model 1	1.24	1.05–1.46	0.83	0.011
Model 2	1.06	0.89–1.26	0.88	0.45
Men (n = 3145)				
Univariable	1.00	0.81–1.23	0.52	0.98
Model 1	1.06	0.87–1.29	0.82	0.54
Model 2	0.92	0.75–1.14	0.87	0.45
Women (n = 3241)				
Univariable	2.07	1.63–2.63	0.74	<0.001
Model 1	1.57	1.20–2.05	0.83	0.001
Model 1A	1.69	1.26–2.26	0.79	<0.001
Model 2	1.35	1.02–1.79	0.87	0.038
Model 3	1.39	1.05–1.86	0.87	0.024
Hepcidin (per doubling)	**HR**	**95% CI**	**Harrell's C**	***P*-value**
Total population (n = 6386)[b]				
Univariable	1.45	1.23–1.72	0.61	<0.001
Model 1	1.20	0.98–1.45	0.83	0.07
Model 2	1.09	0.92–1.30	0.88	0.39
Men (n = 3145)				
Univariable	0.96	0.79–1.16	0.54	0.76
Model 1	1.00	0.81–1.25	0.82	0.94
Model 2	0.95	0.74–1.21	0.87	0.49
Women (n = 3241)				
Univariable	2.10	1.63–2.70	0.75	<0.001
Model 1	1.59	1.17–2.17	0.84	0.003
Model 1A	1.68	1.19–2.37	0.79	0.003
Model 2	1.44	1.03–2.05	0.87	0.039
Model 3	1.60	1.09–2.37	0.88	0.018

CI, confidence interval; HR, hazard ratio; sHR, subhazard ratio.
[a]*P* for interaction ferritin, sex, and new-onset heart failure = 0.032.
[b]*P* for interaction hepcidin, sex, and new-onset heart failure = 0.045.
Model 1 is adjusted for age (per 10 years) and sex (in total population).
Model 1A is adjusted for menstrual state instead of age.
Model 2 is adjusted for model 1 + cardiovascular and heart failure risk factors: body mass index, current smoking, the presence of diabetes, hypertension, hypercholesterolaemia, history of myocardial infarction or stroke, left ventricular hypertrophy, renal function, and levels of haemoglobin, erythropoietin, high-sensitivity C-reactive protein, and urinary albumin excretion.
Model 3 is adjusted for model 2 + time-varying incident cardiovascular events.

pathway determining cardiomyocyte damage. Production of ROS causes lipid peroxidation and DNA damage, leading to cell death, fibrosis, and eventually cardiac dysfunction. However, iron overload is only observed when the binding capacity of transferrin is fully saturated and non-transferrin bound iron is formed. Interestingly, joint analyses showed an association between serum ferritin and new-onset HF in all TSAT tertiles, suggesting that another pathway linking increased ferritin levels with cardiomyocyte damage may be involved.

Iron-mediated cell damage does not only occur under conditions of iron overload. It has been proposed that iron maldistribution among organs, tissues, and cellular compartments can also attenuate cell integrity and cell life. Dysmetabolic hyperferritinaemia, meaning elevated ferritin levels with normal TSAT, is commonly observed in clinical practice and has been associated with insulin resistance, obesity, hypertension, and other manifestations of the metabolic syndrome[26]. During circumstances of subclinical systemic inflammation, iron efflux in organs may be halted due to increased hepcidin production and subsequent internalization and degradation of its receptor, the iron exporter ferroportin[27]. Therefore, elevated ferritin levels (and hepcidin) might be a reflection of a low-grade inflammatory response to another pathophysiological process (e.g. metabolic syndrome), causally responsible for the development of HF[28]. Supporting this hypothesis is the fact that

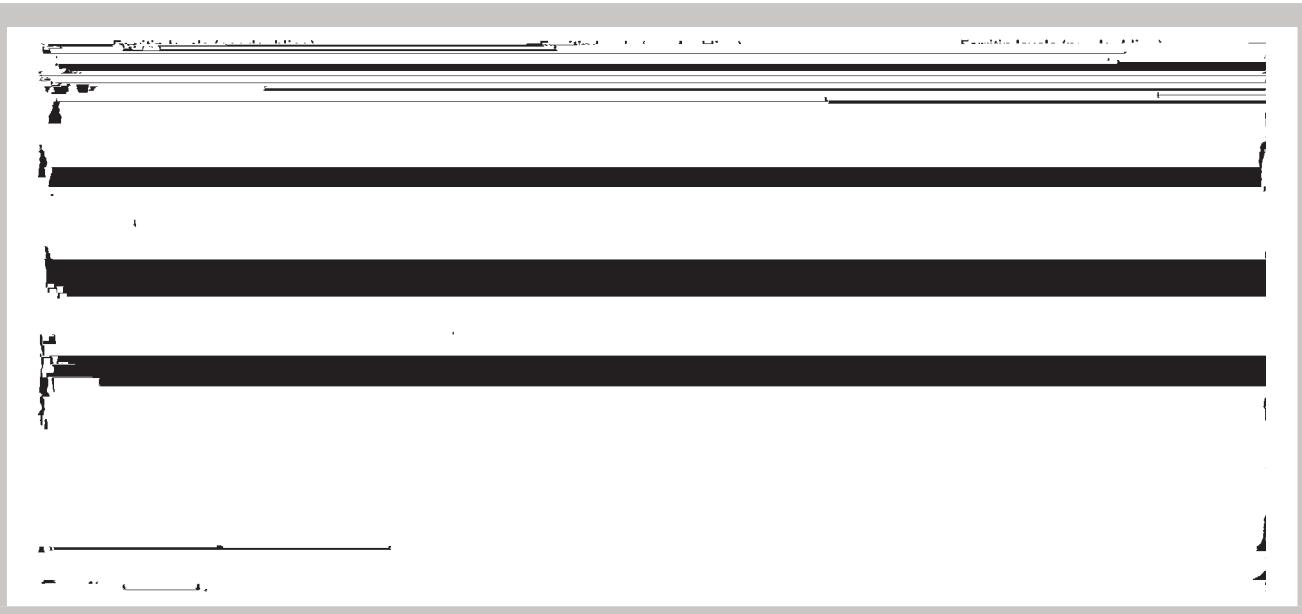

Figure 2 Sex-strati ed risk for new-onset heart failure according to the joint classi cation of ferritin levels and tertiles of transferrin saturation (TSAT;A), hepcidin (B), high-sensitivity C-reactive protein (CRP;C), body mass index (BMI;D), glucose (E), or systolic blood pressure (F).

events or all-cause mortality in multivariable analyses. It has been hypothesized that both elevated and decreased markers of iron status enhance the risk for CV disease.[34,35] However, con icting results have also been reported.[36] Furthermore, studies in haemodialysis patients or women from the general population have suggested a role for elevated hepcidin levels in the pathogenesis of atherosclerosis.[37–39] In contrast, Kautz and colleagues did not detect any increase in hepatic hepcidin expression during progression of atherosclerosis or atherosclerotic plaque size in mice with elevated macrophage iron.[6] A recently published population-based study also found no relationship between hepcidin or the hepcidin-to-ferritin ratio and prevalent carotid atherosclerosis or incident CV events.[7] Future population-based studies are needed to establish nally whether an abnormal iron homeostasis is associated with the development of CV events in the general population.

Implications for clinical practice

Although the present associations do not prove causality between iron stores and incident HF, the present study provides evidence that increased ferritin levels may directly or indirectly be associated with the pathogenesis of new-onset HF in women. Identi cation of subjects at risk for HF using biomarkers alongside clinical characteristics has gained interest over the years. Markers of iron homeostasis may provide additional information to the clinician regarding aetiology, clinical risk (in our case HF), and disease severity. Secondly, ferritin is a widely available routine marker and a relatively inexpensive measurement. Finally, elimination of iron may confer a bene cial effect. Iron removal, by means of phlebotomy, improved coronary vascular function in patients with type 2 diabetes and endothelial function in patients with known CAD.[40,41] Still, the ndings of this study need to be validated in other population-based studies.

Strengths and limitations

The large size of this contemporary, prospective community-based cohort, long follow-up period, and thorough validation of outcome parameters are strengths of this study. Furthermore, all blood samples were taken in the morning, minimizing the in uence of circadian rhythm on markers of iron status. The present study is limited by the fact that the subjects from the PREVEND study are predominantly Caucasian and our results cannot therefore be extrapolated to subjects from other ethnicities. Secondly, our analyses rely on one baseline measurement of iron markers and hepcidin, which is used as a proxy for the concentration in the years before and after this measurement. Therefore, we cannot comment on the effects of changes in markers over time. More population-based studies with serial measurements over time are warranted. Thirdly, long-term storage at Š80 C might be associated, to some extent, with less precise measurements of hepcidin. A recent paper by Laarakkers and co-workers investigated the stability of hepcidin during long-term storage.[42] The authors concluded that hepcidin results are not changed during 2 years of storage at Š80 C. However, after 2 years of storage at Š80 C, hepcidin results may become less precise. Although we believe that average results for a population may not be affected, perhaps existing differences in hepcidin levels between groups, or correlations of hepcidin with other parameters might be more dif cult to assess. Finally, the PREVEND cohort is enriched for increased UAE. For this reason, we corrected for study design by conducting a design-based analysis. Furthermore,

compared with the Framingham cohort, UAE was not higher in PREVEND.[43]

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