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*Published in:*  
Circulation. Genomic and precision medicine

*DOI:*  
[10.1161/CIRCGEN.119.002544](https://doi.org/10.1161/CIRCGEN.119.002544)

**IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.**

*Document Version*  
Publisher's PDF, also known as Version of record

*Publication date:*  
2020

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Grote Beverborg, N., Said, M. A., van der Wal, H. H., Verweij, N., van der Meer, P., & van der Harst, P. (2020). Genetically Determined High Levels of Iron Parameters Are Protective for Coronary Artery Disease. *Circulation. Genomic and precision medicine*, 13(1), 36-38. Article e002544. <https://doi.org/10.1161/CIRCGEN.119.002544>

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## RESEARCH LETTER

# Genetically Determined High Levels of Iron Parameters Are Protective for Coronary Artery Disease

Niels Grote Beverborg, MD, PhD; M. Abdullah Said, Bsc; Haye H. van der Wal, MD; Niek Verweij, PhD; Peter van der Meer, MD, PhD; Pim van der Harst, MD, PhD

The observation that premenopausal women have a relatively low incidence of heart disease led in the 1980s to the hypothesis that iron deficiency protects against heart diseases.<sup>1</sup> These early observations were followed up by conflicting epidemiological data.<sup>2</sup> To confer causal relationships from epidemiological data is challenging as results can be influenced by residual confounding or reverse causation. For bias reduction, an alternative analysis strategy utilizing single-nucleotide polymorphisms (SNPs) as instrumental variables (Mendelian Randomization) has been developed. A recent study using 3 iron status associated SNPs suggested a protective effect of a higher iron status on the development of coronary artery disease (CAD).<sup>3</sup> With a larger set of SNPs covering different components of iron metabolism, we aimed to provide a reliable answer to this lingering question.<sup>4</sup>

We studied the association of 11 SNPs previously associated with serum markers levels of iron status with CAD<sup>4</sup> in 408 659 participants (age [mean±SD] 57±8 years, 45.9% males) of the UK Biobank cohort. Subjects of the original cohort (n=502 653) were excluded in case of nonwhite British ethnicity (n=92 653), or genetic and reported sex mismatch, high missingness, or excess heterozygosity (n=1341). Combined Mendelian Randomization estimates were obtained using a random effects model. Pleiotropy in the univariable model was assessed with MR-EGGER and MR-PRESSO. Sensitivity analyses were performed when necessary. All analyses were adjusted for age, sex, genotyping-array, relatedness by clustering, and the first 30 principal components. Two-sided *P* values <0.005 were considered statistically

significant. Data are available upon request at: <https://www.ukbiobank.ac.uk/>. Individual informed consent and institutional review committee approval were obtained.

Twenty nine thousand one hundred eighty-five (7.1%) participants had CAD reported in their medical history or during a median of 6.2 (IQR, 5.5–6.7) years of follow-up. All individual SNPs were associated with a protective or neutral effect of a genetically determined higher iron status on CAD, except for rs9990333 (Transferrin Receptor, TFRC). The small effect reported between rs9990333 and iron status, the relatively large effect of the SNP on CAD and a positive MR-PRESSO test for horizontal pleiotropy, suggest an iron status independent pathway. Removing rs9990333 from the model did not significantly alter the results. No significant pleiotropy was observed in any model according to MR-EGGER. The weighted combined estimates associated higher iron levels with lower risk of CAD, see Figure. Each SD increase in genetically determined iron level was associated with a 11% lower risk of CAD ([95% CI, 5%–16%]; *P*<0.001). Genetically determined log-transformed ferritin levels were suggestively associated with a 19% lower risk of CAD ([95% CI, 5%–31%]; *P*=0.009). These findings were confirmed in meta-analysis with CARDIoGRAMplusC4D (16% [95% CI, 7%–23%]; *P*<0.001) and 8% [95% CI, 4%–11%; *P*<0.001], for ferritin and iron, respectively).<sup>5</sup> Separate analyses in CARDIoGRAMplusC4D significantly confirmed log ferritin (17% [95% CI, 6%–27%]; *P*=0.003) but not iron (6% [95% CI, –2% to 13%]; *P*=0.162) as an associate of CAD. Correction for phenotypic systolic blood pressure and/or LDL cholesterol in multivariable analyses

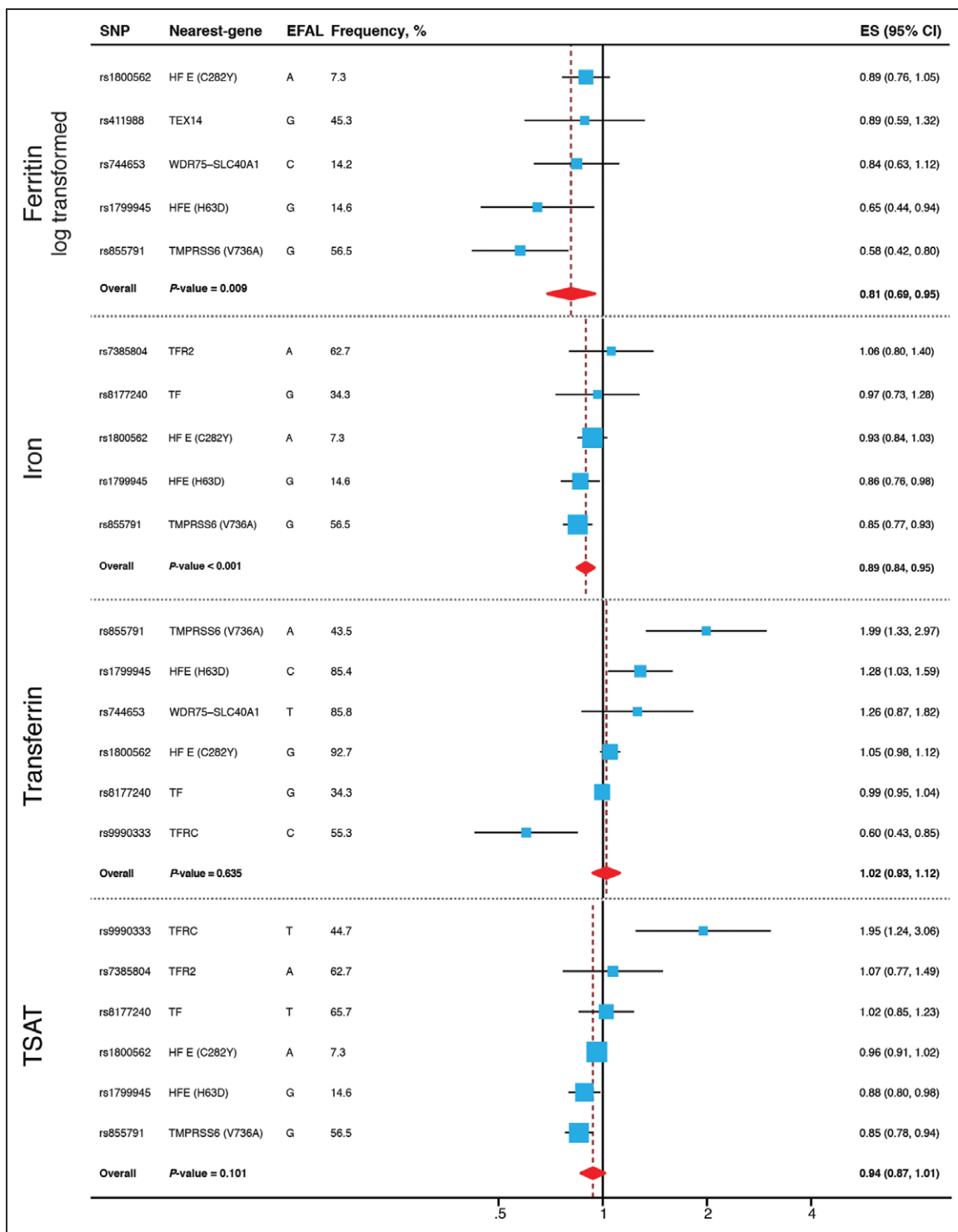
**Key Words:** coronary artery disease ■ ferritins ■ heart diseases ■ incidence ■ iron

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For Sources of Funding and Disclosures, see page 38.

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**Figure. Genetically determined iron marker levels and risk of coronary artery disease.**

Forest plot depicting the single-nucleotide polymorphism (SNP) and overall effect (random effects meta-analysis) on the risk of coronary artery disease (CAD). MR effect size (ES; odds ratios) with 95% CIs relate to a change per SD change in iron parameter. Ferritin and iron have an ES<1.0, reflecting a lower risk of CAD in subjects with higher genetically determined iron or ferritin levels. EFAL indicates effect allele; and TSAT, transferrin saturation.

did not notably affect the results, while inclusion of HbA1c significantly depressed the reported associations.

We observed a protective effect of a genetically determined higher iron status on CAD. Mechanistically, a high

iron state could protect from CAD through increasing hemoglobin and subsequently lowering the HbA1c level, supported by our findings in multivariable analyses. These analyses do introduce the potential risk of collider bias;

potential mechanisms will therefore require further investigation. Independent assessment of the different iron markers with outcome was unfortunately hampered by the large overlap in genetic determinants. Although SNPs showing clear pleiotropy were excluded from the analyses and the included SNPs are near genes involved in iron metabolism, residual pleiotropy cannot be excluded. In conclusion, we report novel and independent evidence for the hypothesis that higher levels of iron parameters might protect from the development of clinical manifestations of CAD. These findings warrant further validation and support the study of iron supplementation in the prevention CAD.

## ARTICLE INFORMATION

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### Acknowledgment

This research has been conducted using the UK Biobank resource under application number 15031.

## Sources of Funding

None.

## Disclosures

Dr Beverborg received personal fees from Vifor Pharma. Dr van der Meer received consultancy fees and an unrestricted grant from Vifor Pharma. The other authors report no conflicts.

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