9 Genetically determined low ferritin and iron levels are causally linked to coronary artery disease

Niels Grote Beverborg, Abdullah Said, Haye van der Wal, Niek Verweij, Pim van der Harst, Peter van der Meer

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In 1981, Sullivan introduced the iron hypothesis.[1] He proposed that iron deficiency was the reason premenopausal women have relatively low rates of heart disease. These preliminary observations could not be confirmed by the majority of subsequent epidemiological studies nor large meta-analyses. To the contrary, a significant negative association was reported between transferrin saturation (TSAT), a measure of systemic iron availability, and coronary artery disease (CAD) in different reports.[2,3] Epidemiological data do not provide evidence for causality as the results are often influenced by residual confounding or reverse causation. To minimalize the impact of these factors, we applied a Mendelian Randomization approach to assess potential causality between iron levels and CAD using our previously reported genetic variants associated with iron status.[4]

We studied the association of 11 independent single nucleotide polymorphisms (SNPs) that were previously associated with one or more serum markers levels of iron status reflecting both iron storage (ferritin) and functional availability (iron, transferrin and TSAT) with CAD in the UK Biobank cohort.[4] The UK Biobank is a population-based cohort of 40-69-year-old inhabitants of the UK recruited between 2006-2010. Individual SNPs were weighted for their reported effect size. Combined Mendelian Randomization estimates were obtained for each iron marker using a random effects model. 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.

Of the 408.659 subjects, 34,541 (8.7%) had CAD, either in their medical history or during follow-up. All individual SNPs had an effect consistent with a protective or neutral effect of a genetically determined higher iron status, except for rs9990333, see *Figure*. The T allele of this variant was associated with higher iron status (higher levels of TSAT, lower levels of transferrin) and a higher risk of CAD. The small β1 reported between rs9990333 and iron status, and the large effect of the SNP on CAD, inconsistent with the other SNPs, suggested an iron status independent pathway. The estimates of the single SNPs combined associated higher ferritin and iron levels with lower risk of CAD. Each standard deviation increase in logarithmic transformed ferritin levels was associated with a 15% lower risk of CAD (95% confidence interval: 5 – 24%). Each standard deviation increase in iron level was associated with a 6% lower risk of CAD (95% confidence interval: 1 – 11%).

High iron levels are believed to be associated with increased oxidative stress and thereby an increased risk of atherosclerosis and CAD.[1] However, contradictory results have been reported, which has been accounted to residual confounding by, among others, systemic inflammation.[2,3] The first evidence for a causal association was recently reported in the CARDIoGRAM (CAD Genome-Wide Replication and Meta-Analysis) study. Using

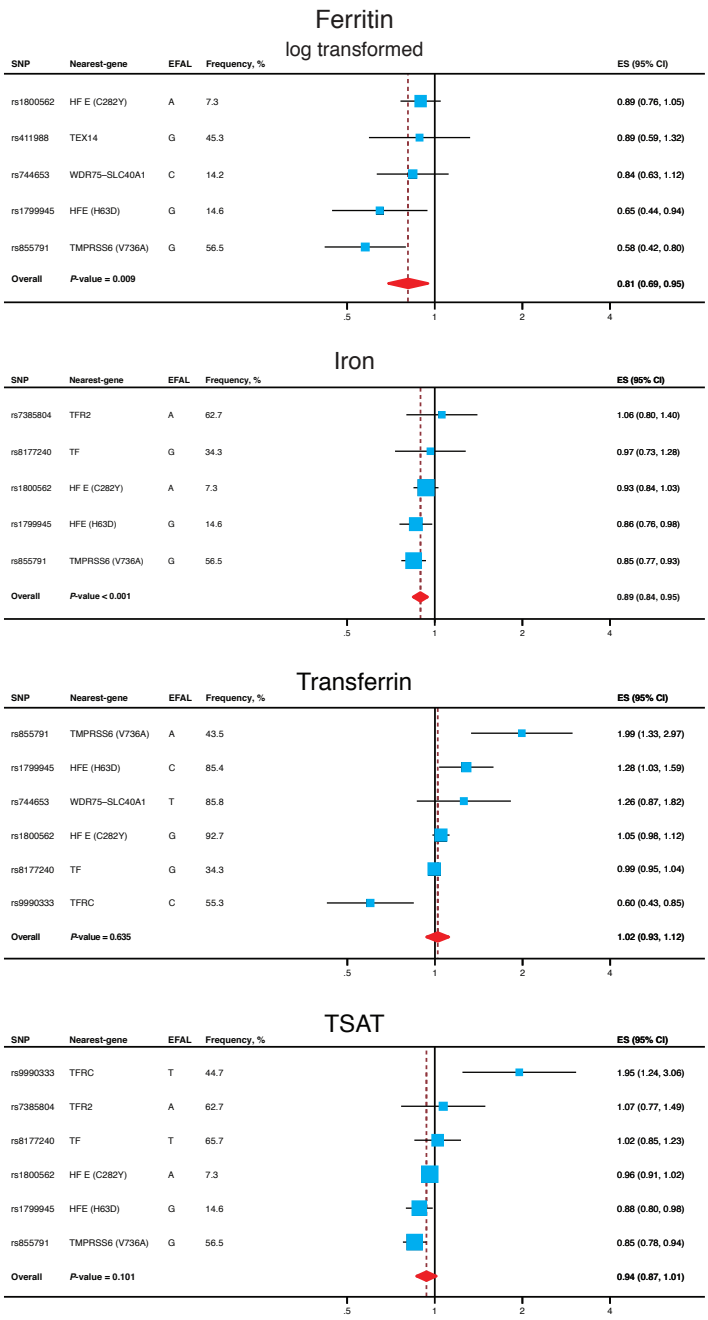

Figure 1 - Genetically determined iron marker levels and risk of coronary artery disease. The genetically determined levels of iron markers and risk of coronary artery disease. Overall effect is obtained using the summation of all single SNPs in a random effects meta-analysis. Odds ratios (OR) with 95% confidence intervals (CI) relate to a change per SD change in iron parameter.

3 SNPs (rs1800562, rs1799945 and rs855791), a protective effect of higher iron marker levels on CAD was reported. Similar to our results, this effect was most pronounced for ferritin (OR 0.85, 95% confidence interval 2 – 27%).[5] Using additional instrumental variables in an independent dataset, we provide further support for the hypothesis that higher levels of iron are causally linked with CAD. Since it is possible to intervene with iron status by oral or intravenous iron supplementation, this finding could be of clinical relevance.

In conclusion, we report evidence for a causal relationship between higher levels of ferritin and iron and a protective effect on coronary artery disease in the UK Biobank.

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