Supplementary information for:

Genome-wide meta-analysis of iron status biomarkers and the effect of iron on all-cause mortality in HUNT

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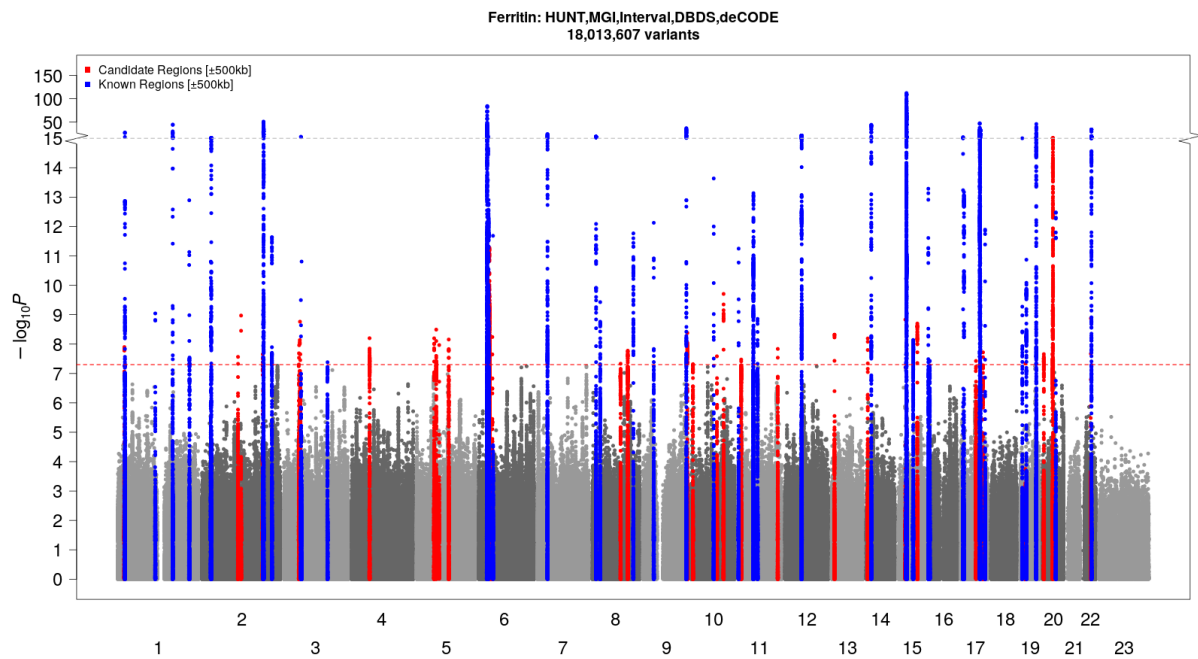
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Supplementary Figures

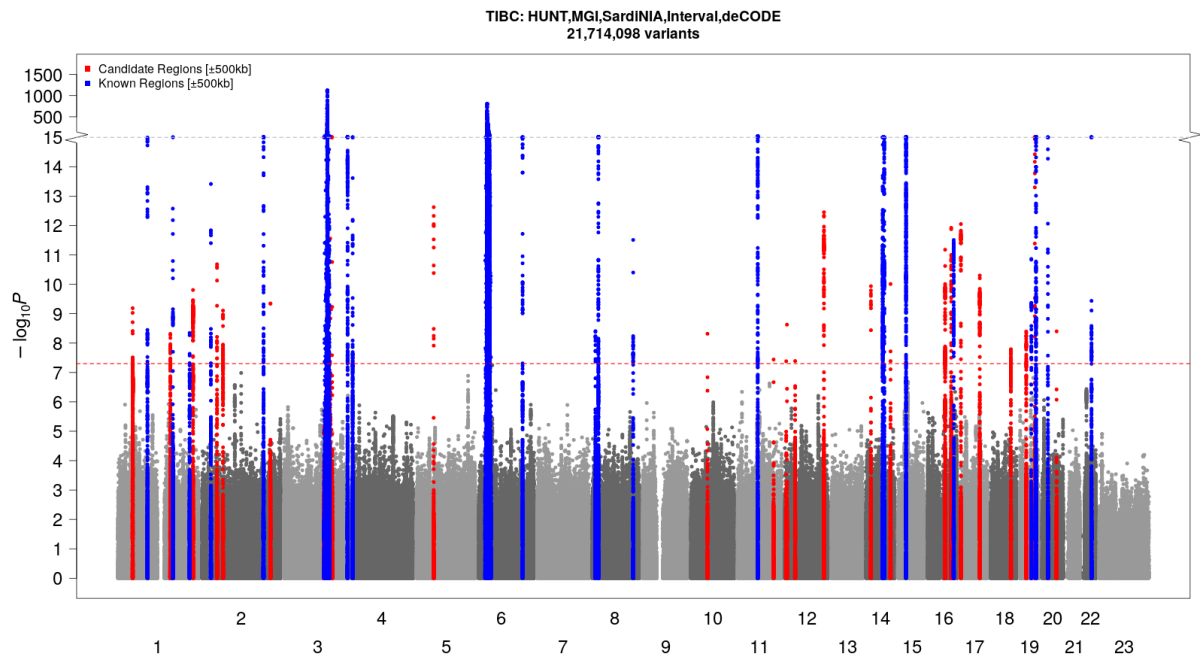## *Supplementary Figure 1: Manhattan Plot - Serum Ferritin*

Manhattan plot of the serum ferritin meta-analysis of the HUNT, MGI, deCODE, DBDS and Interval studies: The x-axis gives the chromosomes and chromosomal positions, and the y-axis gives -log10(p-value) for the association of the genetic variants with ferritin. Known (blue) and novel candidate (red) regions for any iron status biomarker.

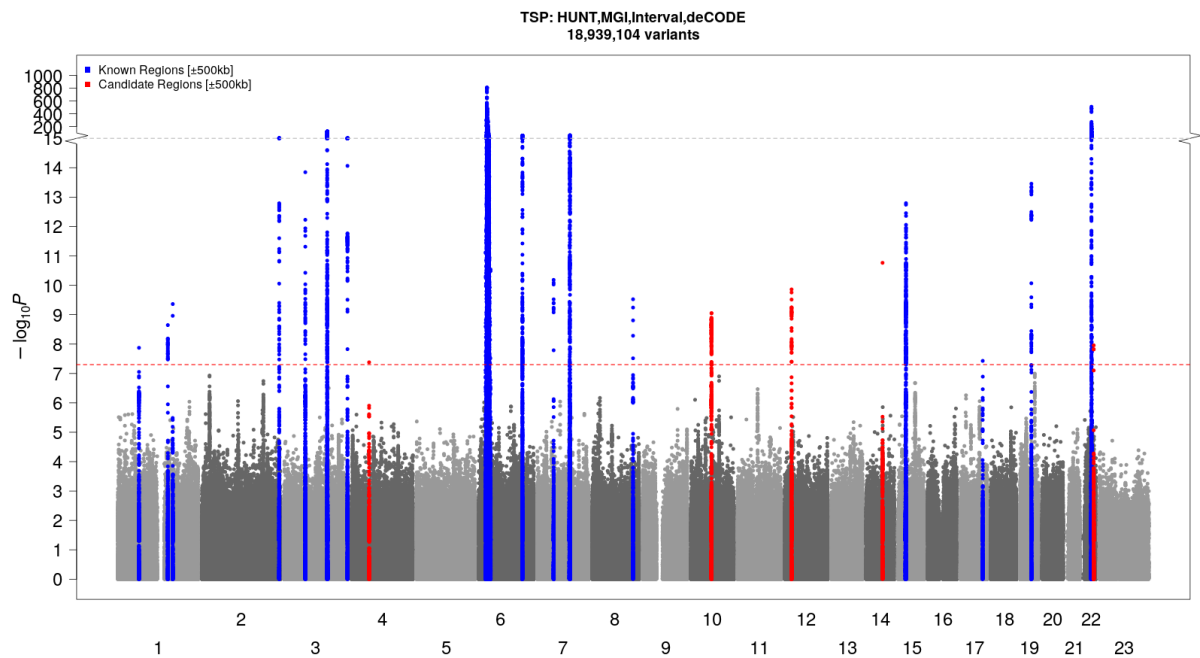## *Supplementary Figure 2: Manhattan Plot - Serum Iron*
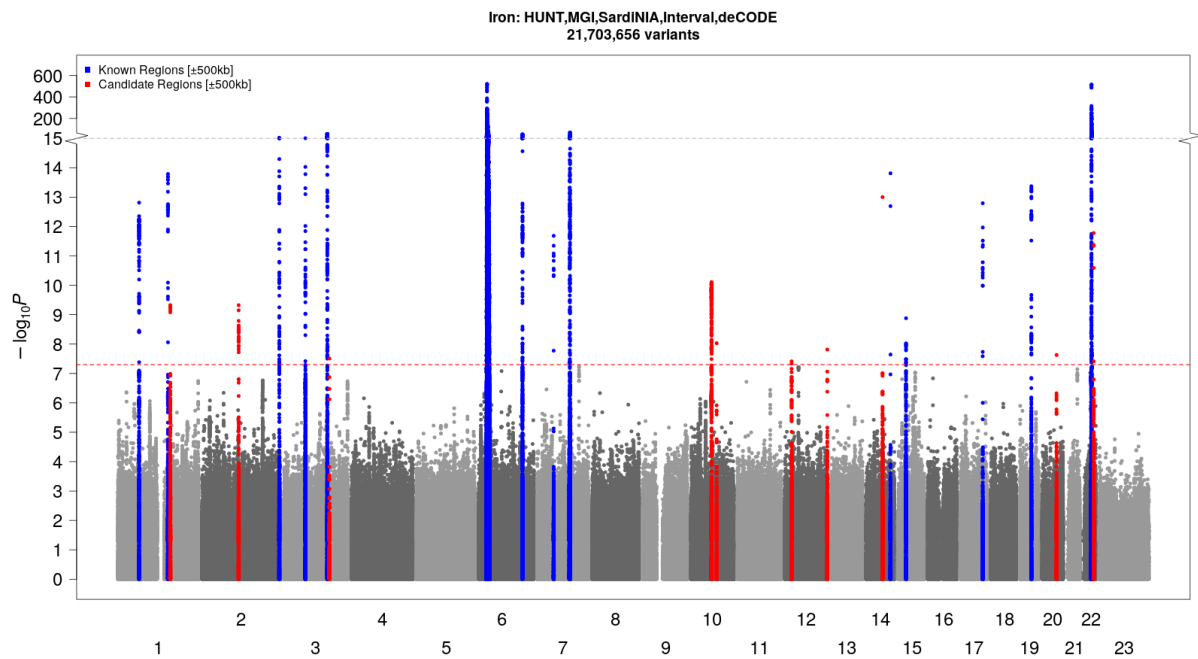
Manhattan plot of the serum iron meta-analysis of the HUNT, MGI, SardiNIA, deCODE and Interval studies: The x-axis gives the chromosomes and chromosomal positions, and the y-axis gives -log10(p-value) for the association of the genetic variants with serum iron. Known (blue) and novel candidate (red) regions for any iron status biomarker.

**Supplementary Figure 3: Manhattan plot - Total Iron Binding Capacity**

Manhattan plot of the total iron binding capacity (TIBC) meta-analysis of the HUNT, MGI, SardiNIA, deCODE and Interval studies: The x-axis gives the chromosomes and chromosomal positions, and the y-axis gives -log10(p-value) for the association of the genetic variants with TIBC. Known (blue) and novel candidate (red) regions for any iron status biomarker.

Supplementary Figure 4: Manhattan plot - Transferrin Saturation Percentage

Manhattan plot of the transferrin saturation percentage (TSP) meta-analysis of the HUNT, MGI, deCODE and Interval studies: The x-axis gives the chromosomes and chromosomal positions, and the y-axis gives -log10(p-value) for the associations of the genetic variants with TSP. Known (blue) and novel candidate (red) regions for any iron status biomarkers.

Supplementary Figure 5: Non-linear Mendelian randomization post-hoc sensitivity analysis
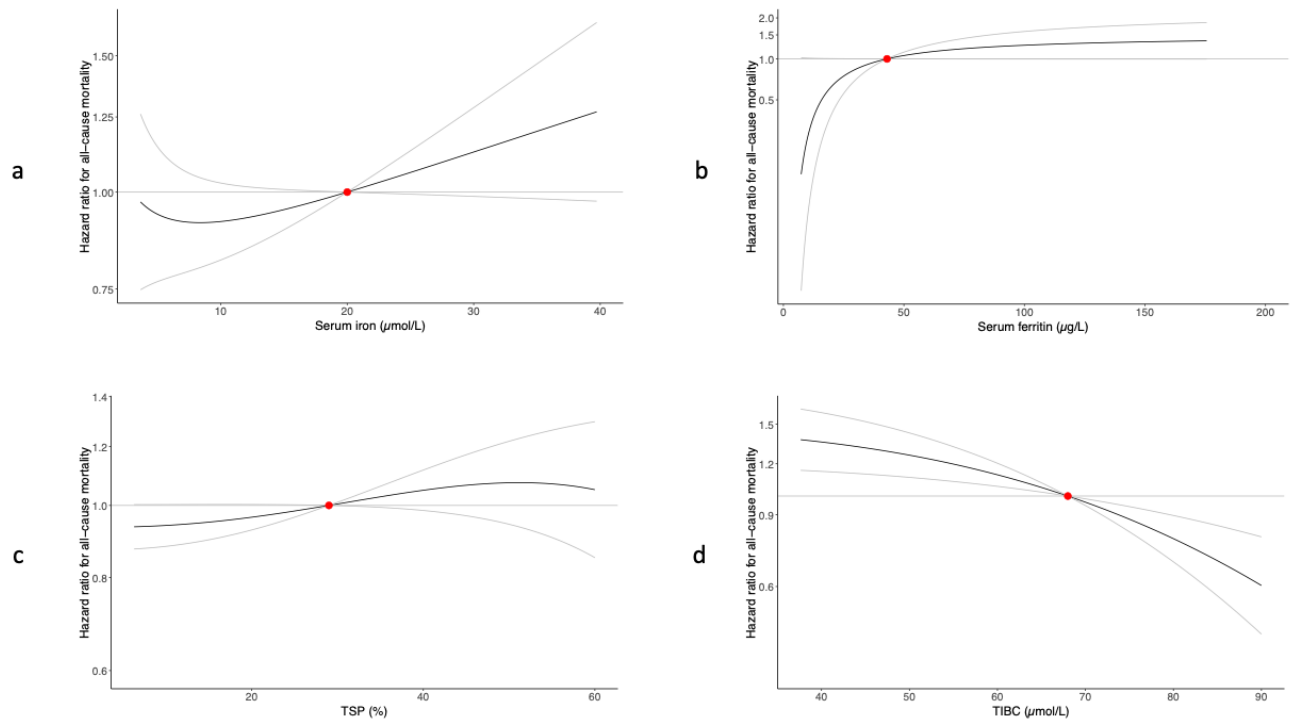
Dose-response curves (black) between iron traits and all-cause mortality in HUNT (gray lines give 95% confidence interval) using a GRS consistent with systemic iron status. The x-axis gives a: serum iron levels (μmol/L), b: serum ferritin (μg/L), c: transferrin saturation (%) and d: total iron binding capacity (TIBC) (μmol/L). The y-axis gives the hazard ratios for all-cause mortality with respect to the reference values (red dot), which represent the established target values (iron, TIBC, TSP)[51] or median value (ferritin) for the traits. The curve gradients represent the localized average causal effect at each point.

Supplementary Notes

Supplementary Note 1: Some novel intronic and intergenic associations reached p-value < 5×10^{-8} in the meta-analysis of deCODE, Interval and DBDS[21], but they were not detected because the previous study design used a consequence specific p-value cut-off prioritizing high-impact variants.

Supplementary Note 2: Genetic variants excluded from GRS-PheWAS because they were not imputed in the UK Biobank reference data: rs374974760 (iron), rs35945185, rs7165401 (TSP), rs551459670, rs142350264, rs536826368, rs7009973, rs189899297, rs681099, 9:133264504:G:GAAACTGCC, rs10685744, rs141253118, rs192331981, rs6088374 (ferritin). Genetic variants excluded from single variant PheWAS because they were not imputed in the UK Biobank reference data: rs142350264, 9:133264504:G:GAAACTGCC (ferritin).

Supplementary Note 3: Genetic variants excluded from the GRSs validation because they were not imputed in HUNT: rs35945185 (iron), rs748587164 (iron, TSP, TIBC), rs773570300 (iron, TSP), rs551459670 (ferritin), rs762752083 (ferritin), rs750717575 (ferritin), rs745795585 (ferritin), rs143041401 (ferritin) and two deletions on chromosomes 9 and 12 (ferritin).

Supplementary Note 4: Genetic variants selected for GRS used in post-hoc sensitivity non-linear Mendelian randomization analyses: rs75965181, rs10801913, rs6025, rs13007705, rs1799945, rs1800562, rs9399136, rs4841429, rs13253974, rs2954029, rs57659670, rs34523089, rs2005682, rs855791. The directions of effect for these genetic variants were consistent with systemic iron status (increasing iron, TSP, ferritin, decreasing TIBC). Further, they were GWAS significant for at least one iron related biomarker and at least nominally significant for the other three biomarkers.