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## Exploring the causal link between iron levels and pernicious anaemia: A mendelian randomisation study

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Pernicious anaemia (PA) is characterised by vitamin B<sub>12</sub> deficiency due to autoimmune-mediated destruction of gastric parietal cells and the consequent loss of intrinsic factor, a specific transporter for the intestinal uptake of vitamin B<sub>12</sub>. The aetiology of PA remains largely unknown, although genetic and environmental factors have been proposed to underpin the onset of PA<sup>(1)</sup>. A significant proportion of PA patients exhibit iron deficiency, with approximately 50% of PA patients presenting with it before or at diagnosis and 61% subsequently, suggesting an association between the two<sup>(2)</sup>. However, findings from traditional epidemiological studies are subject to confounding and reverse causality. For instance, these associations do not clarify whether iron deficiency contributes to the development of PA or is a consequence of the disease process. Given the profound prevalence of iron deficiency at diagnosis, we hypothesised that reduced iron levels may play a causal role in the onset of PA. We used a Mendelian randomisation (MR) approach to test the causal relationship between iron status and PA.

MR leverages the naturally randomised allocation of genetic variants among the population as instrumental variables to gauge the causal effect of an exposure on an outcome of interest<sup>(3)</sup>. We conducted two-sample MR analyses to assess the association between genetically predicted iron levels and PA risk. We obtained genetic association data on iron status from the deCODE study<sup>(4)</sup>. PA genetic association data was sourced from the R10 release of FinnGen as our main analysis. The participant data consisted of 3,694 cases of PA and 393,684 controls. Our primary MR analysis method was the inverse-variance weighted approach with additional sensitivity analyses, including leave-one-out, Egger and weighted median analyses.

Four single nucleotide polymorphisms (SNPs) were strongly associated with systemic iron status and used as genetic instruments to proxy iron status in two-sample MR analyses. We found that genetically predicted higher iron status was not significantly associated with risk of PA (odds ratio per 1 standard deviation increase in serum iron: 1.12, 95% confidence interval 0.80 to 1.57,  $P = 0.49$ ). Sensitivity analyses had consistent results, indicating that MR assumptions were not violated and that no single SNP drove the association.

This is the first study to test the hypothesis that iron deficiency is causally associated with an increased risk of PA. Our results show that genetically predicted lower iron levels were not associated with an increased risk of PA among individuals of Finnish ancestry. Further investigation is required to understand the manifestation of iron deficiency in PA. Iron deficiency may only be a consequence of PA due to the loss of parietal cells, which produce hydrochloric acid necessary for iron absorption. The frequent presence of iron deficiency before or at diagnosis may also reflect delays in diagnosing PA.

### References

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