# Iron Deficiency and the Development of Celiac Disease

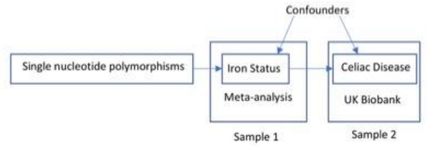
Isabel A. Hujoel, MD[1]; Margaux L.A. Hujoel, PhD[2]
[1]University of Washington, [2]Brigham and Women's Hospital and Harvard Medical School

## Introduction

- The development of celiac disease depends on the presence of **genetic factors** and **environmental triggers**.
- The **incidence of celiac disease has been increasing** over the past few decades, with one meta-analysis estimating a pooled average of 7.5% increase per year.
- The reasons behind this increase are not known, but are thought to be **secondary to environmental exposure**.
- Many environmental exposures have been suggested, but evidence in support of these exposures is conflicting.
- Iron status has been one suggested environmental trigger for the development of celiac disease.
- We aimed to use **Mendelian Randomization** to evaluate the relationship between iron status and celiac disease.
- Mendelian randomization capitalizes on the random allocation of **single nucleotide polymorphisms** at conception, and as long as certain assumptions hold, can suggest causality.

## Methods and Materials

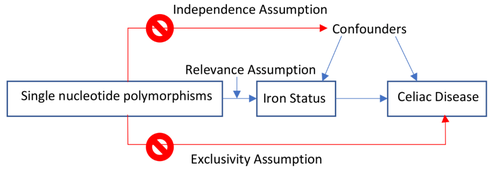
- **Two-sample** Mendelian randomization study




- **Exposure** of interest: **iron status** (serum iron, ferritin, transferrin, transferrin saturation biomarkers)
  - Sample 1: **meta-analysis** of 3 genome-wide association studies which identified 4 single nucleotide polymorphisms
- **Outcome** of interest: **celiac disease**
  - Sample 2: **UK Biobank** summary statistics
    - 336,638 white British individuals; 1,855 with celiac disease (based on ICD coding))

## Methods and Materials

**Assumption Testing**




- Plausibility of independence assumption: we analyzed the association between genetic instruments for iron status and risk factors for celiac disease (sex and age).
- Plausibility of exclusion assumption: we reviewed the single-nucleotide polymorphism-phenotype associations for secondary phenotypes associated with the single-nucleotide polymorphisms and conducted an MR Egger test for pleiotropy.
- Relevance assumption: we looked for single-nucleotide polymorphisms that were strongly associated with iron status.

We used **serum iron levels** to quantify the genetic associations of the instruments with systemic iron status. We used the **inverse-variance weighted (IVW)** method to combine information from multiple independent genetic variants into one causal estimate.

**Sensitivity Analyses**

- Leave-one-out test.
- We obtained the MR estimate through a weighted median estimator (WME) (a consistent estimator if at least 50% of weight comes from variants that satisfy the assumptions).
- We obtained an MR estimate through MR-Egger (provides a valid test of the null causal hypothesis and consistent estimate even if all variants fail the assumptions).
- We investigated using the other 3 biomarkers (aside from serum iron levels).

## Results

**Relevance Assumption:**

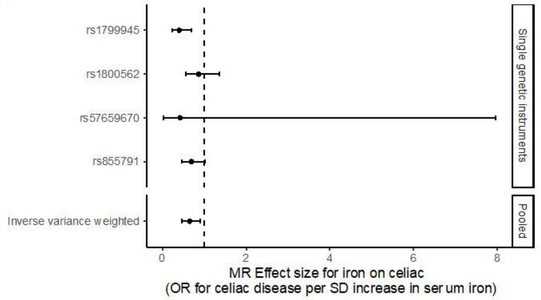
- 4 independent and strongly associated SNPs for iron status: rs1800562 and rs1799945 in the hemochromatosis (HFE) gene, rs855791 in the transmembrane protease serine 6 (TMPRSS6) gene, and rs57659670 predicted to affect the Dual Oxidase 2 (DUOX2) gene.
- The two variants in HFE are in low linkage disequilibrium.
- All instruments have high F-statistics (F>10).

**Independence and Exclusion Assumptions:**

- No evidence of directional pleiotropy.
- No SNPs associated with known risk factors for celiac disease.

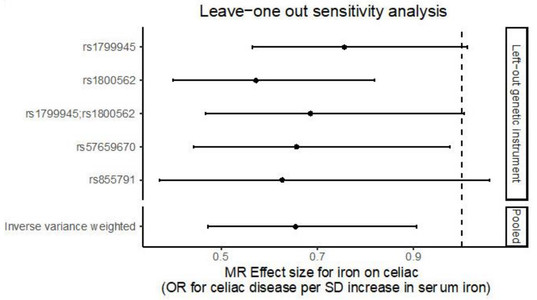
**Findings**

- A higher iron status was negatively associated with risk of celiac disease.
- Odds ratio per 1 standard deviation increase in serum iron: 0.65 (95% CI 0.47-0.91; p=0.01).




## Sensitivity Analyses

- No one variant appeared to be driving this association.
- WME approach had similar findings as IVW estimate (odds ratio: 0.71; 95% CI 0.52-0.98; p-value 0.037).
- MR-Egger estimate was non-significant; however this approach is less efficient than IVW or WME.
- The other 3 biomarkers were limited by low power.




## Conclusions

- Genetically higher iron levels are associated with s decreased risk of having celiac disease.
- If the assumptions of Mendelian Randomization hold, this suggests a causal effect of iron deficiency on celiac disease development.
- Several possible pathogenic roles of iron deficiency in celiac disease:
  - The transferrin receptor 1, which is upregulated in iron deficiency, has been demonstrated to transport intact gliadin across enterocytes.
  - Iron's impact on the innate immune system, infection risk, and microbiome.

## Contact

Isabel Hujoel
University of Washington
isabelh@uw.edu

## References

1. King J, Jeong J, Underwood F, et al. Incidence of Celiac Disease Is Increasing Over Time: A Systematic Review and Meta-analysis. *Am J Gastroenterol*. 2020;115(4):507-525.
2. Stordal K, Haugen M, Brantsaeter AL, Lundin K, Stene L. Association Between Maternal Iron Supplementation During Pregnancy and Risk of Celiac Disease in Children. *Clin Gastroenterol Hepatol*. 2014;12(4):624-631.
3. Ludvigsson J, Murray J, Adams P, Elmberg M. Does hemochromatosis predispose to celiac disease? A study of 29,096 celiac disease patients. *Scand J Gastroenterol*. 2013;48(2):176-182.
4. Davies N, Holmes M, Smith G. Reading Mendelian randomisation sudies: a guide, glossary, and checklist for clinicians. *BMJ*. 2018;362(k601).
5. Bell S, Rigas AS, Magnusson MK, et al. A genome-side meta-analysis yields 46 new loci associating with biomarkers of iron homeostasis. *Commun Biol*. 2021;4(1):156.
6. Matysiak-Budnik T, Moura I, Arcos-Fajardo M, et al. Secretory IgA mediates retrotranscytosis of intact gliadin peptides via the transferrin receptor in celiac disease. *J Exp Med*. 200899;205(1):143-154.