# Celiac Disease Triggers

***Using Mendelian Randomization to infer causality***

The largest conducted Mendelian Randomization screening


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**DATE**
Wednesday, January
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# PREFACE

# ABSTRACT

# ABBREVIATIONS

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# INTRODUCTION

Celiac is a autoimmune disorder that has the possibility to occur genetically in predisposed people where the ingestion of gluten cause damage in the small intestine. When people with celiac disease digest gluten their body triggers an immune response that attacks the small intestine. This causes damage to the villi that are lined up in the small intestine for nutrient absorption.[1] Celiac disorder affects up to two percent of the European population, and it is hereditary. People with a first-degree relative with celiac disease have a risk of developing celiac disease. The inheritance model of the disease is oligogenic, a phenotypic outcome that is determined by more than on gene. In this model, HLA-DQ2 is a genetic variant in the major histocompatibility complex (MHC) region that accounts for 40% of the inheritable risk. But, this genetic variant is not sufficient enough to develop celiac disease. 30% of the Europeans are carriers of the variant, however 3% are affected by the celiac disease.[2]

The aim of this study is the identification of factors that cause or protect against celiac disease, and to quantify the impact of the causal or protective relationship. To determine potential causal or protective relationships more than 440.000 public available clinical parameters and molecular mechanisms will be screened with the Mendelian Randomization (MR) approach. MR is an approach that uses genetic variants associated with a phenotype of interest to estimate a causal or protective relationship between this phenotype and a relevant medical outcome.[3] This study uses two-sample MR[4] methods; Inverse-Variance Weighted[5] (IVW) method and MR-Egger method[5].

Here briefly an overview of the mechanism of celiac disease will be discussed. This report will discuss what MR is, how it works and how it can be deployed. The opportunities and challenges from the methods from two-sample MR that are used in this research will be discussed.

# ORGANISATION

# THEORY

## CELIAC DISEASE

Celiac disease is an autoimmune disorder that has the possibility to occur genetically in predisposed people where the ingestion of gluten cause damage. When people with celiac disease digest gluten their body triggers an immune response that attacks the small intestine.[1] This is characterized by small intestinal damage with the loss of function from the villi to take up nutrients, which leads to malabsorption.[6]

## MENDELIAN RANDOMIZATION

MR refers to the process of random segregation and assortment of alleles from an ancestor to offspring, that occur during gamete formation.[3]

This process gives us the advantage of using these genetic variants in observational settings to predict causal relationships between exposure and outcome.[4] This process is comparable to Randomized Controlled Trials (RCT).

## ONE-SAMPLE MR

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## TWO-SAMPLE MR

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### *INVERSE-VARIANCE WEIGHTED METHOD*

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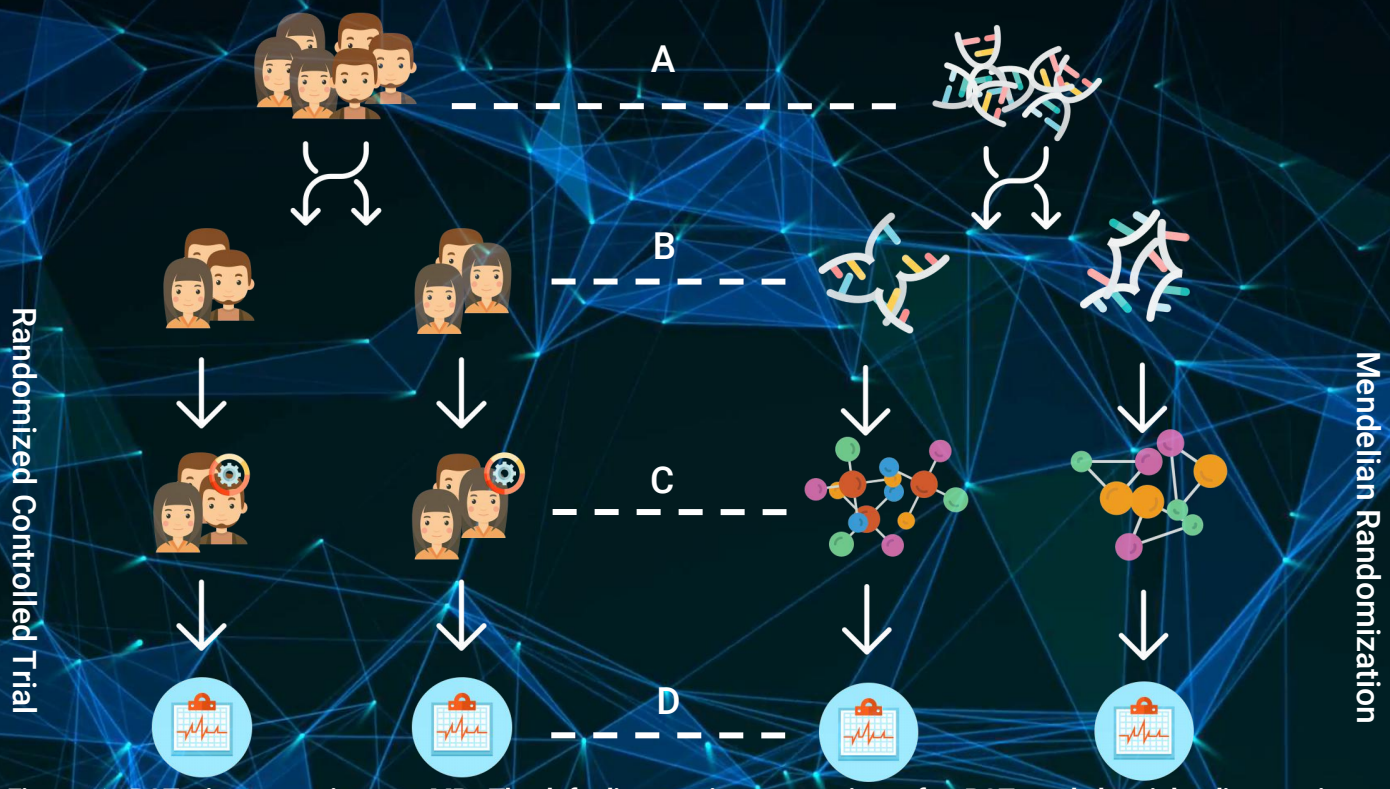


**Figure 1: RCTs in comparison to MR. The left diagram is an overview of a RCT, and the right diagram is an overview of a MR. (A) describes the random allocates and segregation of alleles in MR, and in RCT the random distribution of the population into two arms. At stage (B); here in RCT there will be a case group and a control group, and for MR there will be two different genotypes. After that, stage (C); for RCT here will take place different target effects for one of the arms, for MR there will be two different products from the genotype which in turn in stage (D) give rise to a different effect, as does this take place for RCT. And these differences in arms can be studied.**

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### *MR-EGGER METHOD*

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# MATERIAL & METHODS

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# RESULTS

# DISCUSSION

# CONCLUSIONS

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# APPENDIX

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