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Orignal Article

Celiac Disease and Nephrotic Syndrome: A Two-Sample Mendelian Randomization Study

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Abstract:

Background: Celiac disease is a chronic immunodeficiency disorder that affects multiple organs, primarily the small intestine.Nephrotic syndrome encompasses a range of diseases characterized by structural and functional abnormalities of the glomerular filtration membrane in the kidneys.This study employed Mendelian randomization to investigate the potential causal relationship between celiac disease and nephrotic syndrome.

Methods: We obtained whole-genome association study data on celiac disease and nephrotic syndrome in the European population from the IEU GWAS database. Relevant single nucleotide polymorphisms (SNPs) were selected for analysis. The causal relationship between celiac disease and nephrotic syndrome was assessed using the MR-Egger, weighted median, and IVW methods. Heterogeneity and pleiotropy were evaluated using weighted median and MR-Egger regression methods, as well as Cochran's Q test.

Results: Our study revealed a significant association between celiac disease and nephrotic syndrome ($P < 0.05$). Sensitivity analyses showed no evidence of horizontal pleiotropy or heterogeneity ($P > 0.05$).

Conclusion: Our findings provide evidence of an association between celiac disease and nephrotic syndrome, enhancing our understanding of their relationship and contributing to our knowledge of their pathogenesis and prevention.

Keywords Celiac disease; Nephrotic syndrome; Mendelian randomization

Introduction

Celiac disease is a chronic immunodeficiency disorder that affects multiple organs, primarily the small intestine. It is a globally prevalent condition, with a prevalence of approximately 1% worldwide,[1] although there are considerable variations across different countries and regions.[2] Celiac disease is more commonly observed in genetically susceptible populations, with individuals having a family history of celiac disease showing a lifetime risk ranging from 10% to 15%.[3] The primary etiology of celiac disease lies in gluten, a protein present in wheat, rye, and barley that can lead to varying degrees of intestinal damage .[4] Upon consumption of gluten-containing foods, individuals with celiac disease exhibit an aberrant immune response toward gluten, resulting in the generation of antibodies that actively target gluten, thereby causing mucosal injury within the intestines. Moreover, the pathogenesis of celiac disease is also influenced by genetic factors. Celiac disease is almost exclusively detected in individuals harboring specific human leukocyte antigen (HLA) alleles, such as HLA-DQ2 and HLA-DQ8 .[5] While these genes play a pivotal role in the onset of celiac disease, their presence alone does

not necessarily guarantee the manifestation of the disease, as additional genetic and environmental factors contribute to its development.

Nephrotic syndrome encompasses a range of diseases characterized by structural and functional abnormalities of the glomerular filtration membrane in the kidneys. Its primary hallmark is diffuse glomerular damage, leading to the excretion of significant protein (proteinuria) in the urine, accompanied by symptoms such as hypoalbuminemia and edema. Typically, protein excretion in the urine exceeds 3.5 grams per day. The pathogenesis of nephrotic syndrome primarily involves glomerular filtration membrane injury and increased permeability. Nephrotic syndrome has diverse etiologies, including primary glomerular diseases, secondary diseases (such as systemic lupus erythematosus, diabetes, etc.), as well as factors like medications and infections. The majority of nephrotic syndrome cases stem from primary renal conditions.[6] Spontaneous resolution of nephrotic syndrome symptoms is rare. Relief can usually be achieved through the elimination of causative factors (such as medications or infections) or through immunosuppressive therapy.[7]

There may be a connection between celiac disease and the occurrence of nephrotic syndrome. Studies have indicated that the incidence of celiac disease in patients diagnosed with nephrotic syndrome is 2% .[8] Furthermore, there is an increased risk of celiac disease patients progressing to end-stage kidney disease. Additionally, research has shown that as the symptoms of celiac disease improve, nephrotic syndrome gradually subsides .[9] The association between celiac disease and nephrotic syndrome could be attributed to the abnormal deposition of immunoglobulin A (IgA), which is triggered by celiac disease and contributes to the development of IgA nephropathy. However, the specific mechanisms underlying the connection between celiac disease and nephrotic syndrome still require further investigation. More studies are needed to explore this relationship and gain a deeper understanding of the impact of celiac disease on the kidneys and the associated pathological and physiological effects.

Mendelian randomization (MR) is a statistical method that leverages the random distribution of genetic variations in nature to simulate experimental designs akin to randomized controlled trials, aiming to explore the causal relationship between observed exposure effects and outcomes. By utilizing genetic variations as instrumental variables (IVs), MR can offer stronger causal evidence. Furthermore, MR can harness the extensive application of genome-wide association studies (GWAS) databases, enabling access to large-scale samples and rich genetic data, thereby enhancing the statistical power and reliability of research. Consequently, Mendelian randomization has emerged as a commonly employed statistical method in modern medical research.

Two-sample Mendelian randomization analysis is a widely used approach in Mendelian randomization studies. By comparing the results of Mendelian randomization estimation between two distinct samples, it enhances the robustness of causal inference. Consequently, the two-sample Mendelian randomization analysis offers a versatile method to conduct causal inference research on a broader scale of data.

In this study, we performed a two-sample Mendelian randomization analysis utilizing the GWAS database to investigate the association between celiac disease and nephrotic syndrome.

Material and Methods:

Data Sources:

Based on single nucleotide polymorphisms (SNPs) connected to Celiac disease, genetic instrumental factors were chosen. Summary statistics for celiac disease were obtained from the IEU-GWAS, involving 11812 clinically diagnosed cases and 229 controls from European populations. SNPs associated with NS were also derived from the IEU-GWAS in a sample of 775 cases and 475255 controls from Europe. From the IEU GWAS database (https://gwas.mrcieu.ac.uk/datasets/), all datasets may be downloaded.

Importantly, neither patient consent nor ethical approval were needed in this investigation because the data used in our MR analysis was completely based on summary statistics reported previously.

Selection of the Genetic Instruments:

Legitimate genetic instrumental variables (GIVs) must adhere to three fundamental presumptions in order to be considered legitimate :[10] GIVs must (i)

be intimately linked to Celiac disease; (ii) solely have an impact on Celiac disease in order to alter NS; and (iii) have no other confounding effects.

To filter eligible genetic IVs that fulfill the three core MR assumptions, we performed a set of quality control techniques. Firstly, we selected independent SNPs that were strongly associated with celiac disease with p-value less than 5×10-8. Then, to exclude SNPs that were in strong linkage disequilibrium (LD), we performed the clumping procedure with R2 < 0.001. SNPs with a lower p value would be kept among SNP pairings with an LD R2 greater than the stated threshold. We utilized these carefully chosen SNPs as the final genetic IVs for the subsequent MR analysis.

MR Analysis:

Taking advantage of the MR-Egger, weighted median, and IVW methods, the causal relationship between celiac disease and nephrotic syndrome was established in this study. Meta-analyzing the Wald ratios of each SNP used in our primary statistical analysis technique was defined as the method of IVW. It is about exposure and outcome using the random-effect inverse-variance approach, weighting each ratio through its standard error deviation while measurably taking into account potential heterogeneity.

Social Sensitivity Analysis:

Leave-one-out analyses were satisfactorily performed to aggressively investigate whether IVW estimates may be biased or accurately determined by single SNPs. Based on this, IVW results were re-run and meta-analyzed on account of the remaining SNPs each time through consecutive omissions of 1 SNP. Additionally, weighted median and MR-Egger regression methods were intentionally used to indirectly test whether Celiac disease-associated IVs could just have an influence on the nephrotic syndromes through their profound impact on Celiac disease. To test for directional pleiotropy, MR-Egger regression was properly used, obtaining the successful intercept and its p-value naturally. In addition, because of the heterogeneity in the random estimate based on the IVW and MR-Egger estimates, to identify SNPs accurately, MR nonuniformity tests were conducted by executing Cochran's Q tests. And for MR and sensitivity analyses, the "standard Two Sample MR" package in R was intentionally used.

Results:

The significant genetic correlations between celiac disease and nephrotic syndrome were demonstrated convincingly in our comparative analysis. Three methods known as MR Egger, WM, and IVW were used for the feasibility study of the causal effect of Celiac disease on the nephrotic syndrome. It indicated significant associations among the three modern MR methods properly based on the remarkable consistency (MR Egger OR: 1.029, 95% CI: [0.961, 1.103], P = 0.415; WM OR: 1.039, 95% CI: [0.981, 1.101], P = 0.194; IVW OR: 1.058, 95% CI: [1.012, 1.107], P = 0.013).

Table 1 provides additional information regarding the analysis mentioned.

id.exposure	id.outcome	outcome	exposure	method	nsnp	b	se	pval	lo_ci	up_ci	or	or_lci95	or_uci95
ebi-a-GCST005523	ebi-a-GCST90018884	Nephrotic syndrome || id:ebi-a-GCST90018884	Celiac disease || id:ebi-a-GCST005523	MR Egger	38	0.029066	0.035272	0.415347	-0.04007	0.098199	1.029492	0.960724	1.103183
ebi-a-GCST005523	ebi-a-GCST90018884	Nephrotic syndrome || id:ebi-a-GCST90018884	Celiac disease || id:ebi-a-GCST005523	Weighted median	38	0.038159	0.029401	0.194328	-0.01947	0.095786	1.038897	0.980721	1.100524
ebi-a-GCST005523	ebi-a-GCST90018884	Nephrotic syndrome || id:ebi-a-GCST90018884	Celiac disease || id:ebi-a-GCST005523	Inverse variance weighted	38	0.056752	0.02304	0.01377	0.011594	0.10191	1.058394	1.011662	1.107284
ebi-a-GCST005523	ebi-a-GCST90018884	Nephrotic syndrome || id:ebi-a-GCST90018884	Celiac disease || id:ebi-a-GCST005523	Simple mode	38	0.056584	0.059542	0.348119	-0.06012	0.173287	1.058215	0.941652	1.189207
ebi-a-GCST005523	ebi-a-GCST90018884	Nephrotic syndrome || id:ebi-a-GCST90018884	Celiac disease || id:ebi-a-GCST005523	Weighted mode	38	0.041027	0.024861	0.107365	-0.0077	0.089755	1.04188	0.992328	1.093906

Next, we provide more relevant details on the relationship between heterogeneity and pleiotropy. No horizontal pleiotropy or heterogeneity can be concluded from the desired results of the negative (P > 0.05) hypnotic MR-Egger regression. To make the results undoubtedly more intuitive and visible, methods about scatter plots, funnel patches, leave-one-out plots, and forest plots were taken as supplementary materials **(Fig. 1)**.

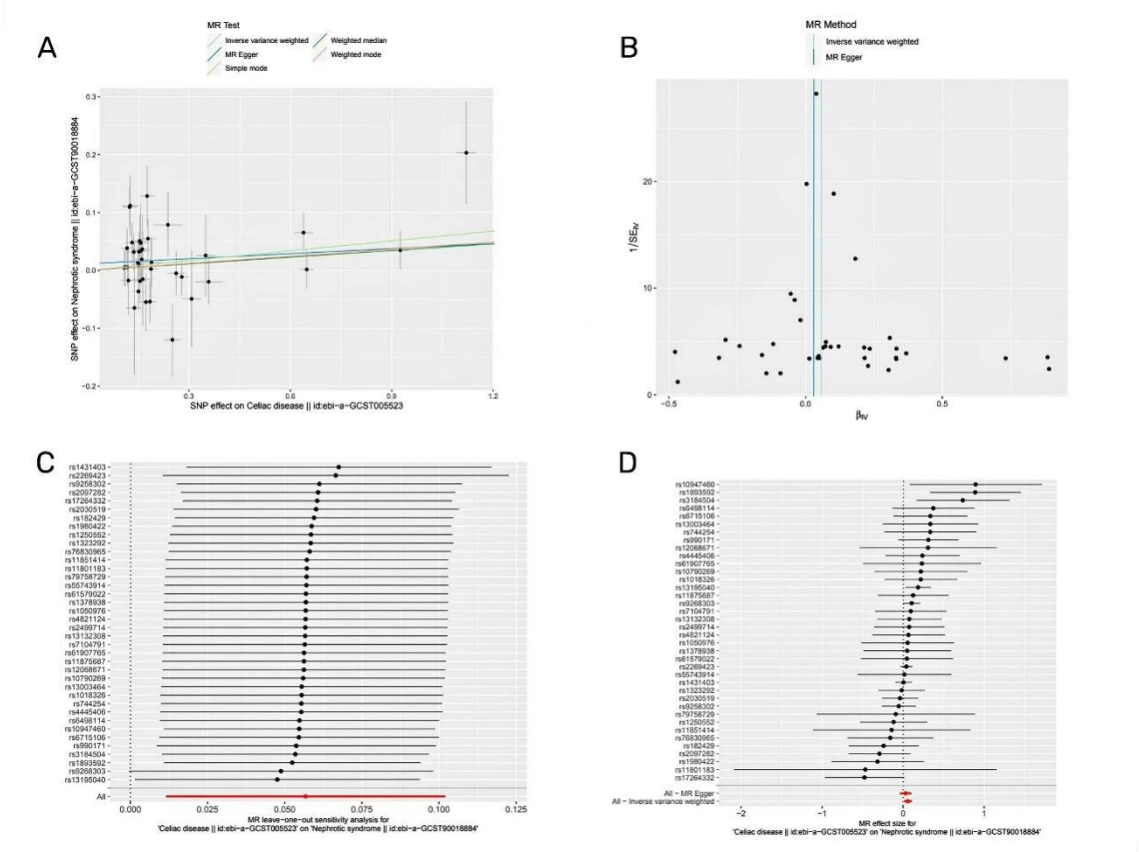

Figure 1 methods about scatter plots, funnel patches, leave-one-out plots, and forest plots were taken as supplementary materials

Discussion:

In this two-sample MR study, we have identified a significant genetic correlation between celiac disease and nephrotic syndrome. After conducting a sensitivity analysis, we can conclude that these results are reliable.

Celiac disease is an autoimmune disorder that is triggered by the ingestion of gluten by genetically susceptible individuals. Its development depends on complex immune responses to gluten proteins, involving both adaptive and innate mechanisms. [3] According to surveys, the global prevalence of celiac disease is approximately 1%. [11] The most common symptoms of celiac disease are related to the gastrointestinal tract, but the disease can also present with a variety of systemic manifestations outside the intestines. [12] Multiple studies have demonstrated that extraintestinal manifestations of celiac disease can occur in various organs and systems, including the oral cavity, reproductive health, lungs, pancreas, spleen, heart, liver, kidneys, and more. [13]

Nephrotic syndrome is a kidney disease characterized by the breakdown of the glomerular filtration barrier, leading to proteinuria, hypoalbuminemia, edema, and hyperlipidemia. [14] The most common causes of nephrotic syndrome are minimal change disease, primary and secondary membranous nephropathy, and focal segmental glomerulosclerosis. [15] Clinical manifestations, urine, and blood biochemical Clinical manifestations, urine and blood biochemical tests, a kidney biopsy, and genetic testing are important diagnostic tools for nephrotic syndrome. [16]

In recent years, an increasing number of studies have suggested a potential association between celiac disease and nephrotic syndrome. Celiac disease is the most common and classical autoimmune disorder caused by gluten proteins. Studies have shown that the global seroprevalence of celiac disease is 1.4%, and it is increasing year by year. [17] Gluten proteins that trigger intestinal autoimmunity in celiac disease can promote the abnormal deposition of immunoglobulin A (IgA) in the kidneys, while IgA nephropathy is characterized by the mesangial and/or capillary loop deposition of IgA or predominantly IgA-containing immune complexes in the glomeruli. [18] A study based on patients recruited at Tampere

University Hospital between 1970 and 2015 showed an increased risk of kidney disease (HR 1.85, 95% CI 1.12–3.03), glomerulonephritis (HR 3.37, 95% CI 1.64-6.95), and IgA nephropathy (HR 18.98, 95% CI 2.29–157.63) associated with celiac disease. [19] In a Swedish general population cohort study, Jonas In a Swedish general population cohort study, Jonas F. Ludvigsson and colleagues found that CD was associated with an increased risk of any form of glomerulonephritis (hazard ratio (HR) = 1.64; 95% confidence intervals (CI) = 1.01–2.66; P = 0.046; 89 events). [19]

This is the first time that Mendelian randomization analysis has been used to examine the causal relationship between celiac disease and nephrotic syndrome. This study has several notable strengths. Firstly, this is a two-sample study with a Mendelian randomization design. This can effectively avoid confounding factors and their effects, as well as the influence of reverse causality and other bias variables, and accurately determine the direction of causal relationships, thereby improving the accuracy of causal inference results. Secondly, we used genetic variation as a tool variable to avoid retrospective bias and assess causal relationships that are difficult to intervene in, making the study more reliable. Finally, we used the GWAS dataset to explore exposure and outcome, selected SNPs with high F statistics, effectively addressed potential weak instrument bias, and improved the ability to detect causal relationships.

However, our study also has certain limitations. Firstly, there may be limitations in terms of the population studied. The two-sample MR analysis requires that the study subjects belong to the same or similar populations, which may limit the generalizability of the results to other populations. Secondly, there may be some unmeasured confounding factors. When performing MR analysis, we assume that there are no confounding factors that affect the instrumental variable or the outcome. However, in reality, there may be influencing factors that interfere with the causal relationship between the instrumental variable and the outcome. Finally, our study sample size was relatively small compared to other population-based observational studies.

Conclusion

In summary, our MR analysis suggests a causal relationship between celiac disease and NS. The pathophysiological interaction between celiac disease and NS warrants further investigation.

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None.

Declarations

Ethics approval and consent to participate: None.

Consent for publication: Not applicable.

Availability of data and materials: The data used to support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests: All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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