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RESEARCH SUBMISSIONS

Migraine, inflammatory bowel disease and celiac disease: A Mendelian randomization study

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Abstract

Objective: To assess whether migraine may be genetically and/or causally associated with inflammatory bowel disease (IBD) or celiac disease.

Background: Migraine has been linked to IBD and celiac disease in observational studies, but whether this link may be explained by a shared genetic basis or could be causal has not been established. The presence of a causal association could be clinically relevant, as treating one of these medical conditions might mitigate the symptoms of a causally linked condition.

Methods: Linkage disequilibrium score regression and two-sample bidirectional Mendelian randomization analyses were performed using summary statistics from cohort-based genome-wide association studies of migraine (59,674 cases; 316,078 controls), IBD (25,042 cases; 34,915 controls) and celiac disease (11,812 or 4533 cases; 11,837 or 10,750 controls). Migraine with and without aura were analyzed separately, as were the two IBD subtypes Crohn's disease and ulcerative colitis. Positive control analyses and conventional Mendelian randomization sensitivity analyses were performed.

Results: Migraine was not genetically correlated with IBD or celiac disease. No evidence was observed for IBD (odds ratio [OR] 1.00, 95% confidence interval [CI] 0.99–1.02, $p = 0.703$) or celiac disease (OR 1.00, 95% CI 0.99–1.02, $p = 0.912$) causing migraine or migraine causing either IBD (OR 1.08, 95% CI 0.96–1.22, $p = 0.181$) or celiac disease (OR 1.08, 95% CI 0.79–1.48, $p = 0.614$) when all participants with migraine were analyzed jointly. There was some indication of a causal association between celiac disease and migraine with aura (OR 1.04, 95% CI 1.00–1.08, $p = 0.045$), between celiac disease and migraine without aura (OR 0.95, 95% CI 0.92–0.99, $p = 0.006$), as well as between migraine without aura and ulcerative colitis (OR 1.15, 95% CI 1.02–1.29, $p = 0.025$). However, the results were not significant after multiple testing correction.

Abbreviations: CI, confidence interval; FDR, false discovery rate; GI, gastrointestinal; GWAS, genome-wide association study; IBD, inflammatory bowel disease; IHGC, International Headache Genetics Consortium; IVW method, inverse-variance weighted method; LD, linkage disequilibrium; MA, migraine with aura; MO, migraine without aura; MR, Mendelian randomization; OR, odds ratio; r_G, genetic correlation; SE, standard error; SNP, single-nucleotide polymorphism.

Conclusions: We found no evidence of a shared genetic basis or of a causal association between migraine and either IBD or celiac disease, although we obtained some indications of causal associations with migraine subtypes.

KEYWORDS
celiac disease, gastrointestinal disease, genetic correlation, inflammatory bowel disease, Mendelian randomization, migraine

BACKGROUND

Migraine is a highly prevalent brain disorder characterized by recurrent headache attacks, often accompanied by symptoms such as photophobia, phonophobia, nausea and vomiting.[1] Migraine is two to three times more prevalent in women than in men, and the peak incidence is in the mid-20s for both sexes.[2] In one-third of patients, attacks are preceded by an aura, which underlies the distinction between migraine with aura (MA) and migraine without aura (MO).[1] There is a well-known bidirectional comorbidity between migraine and a variety of disorders, including major depression, epilepsy, and stroke.[3] Less known is the observation from epidemiological studies that migraine is linked to gastrointestinal (GI) disorders, including inflammatory bowel disease (IBD)[4–7] and celiac disease.[4,8–10]

Crohn's disease and ulcerative colitis, collectively known as IBD, are characterized by chronic inflammation of the GI tract with various intestinal and extraintestinal manifestations.[11] The prevalence of IBD, based on US data, is 1.3% in adults.[12] The age of onset for IBD peaks between the ages of 15 and 30 years,[13] with Crohn's disease being most frequently diagnosed in patients in their 20s and ulcerative colitis in patients in their 30s.[12] Crohn's disease is more common in females (female-to-male ratio 1.8:1), whereas the prevalence of ulcerative colitis is equal in males and females.[13] Celiac disease is an immune-mediated disorder involving dietary gluten intolerance, leading to GI problems such as diarrhea. In addition, celiac disease has been reported to be associated with several neurological disorders, including cerebellar ataxia, epilepsy, and headaches.[14] Celiac disease has a global prevalence of ~1.4%, is more common in women than men, and typically occurs before the age of 10 years.[15]

Many GI disorders, to a certain extent, share disease characteristics with migraine, namely that they predominantly affect females and start at a relatively young age.[2,12,13] Furthermore, in both migraine and GI disorders, the rate of psychiatric comorbidities, such as depression, is higher than in the general population.[16,17] The interaction between the brain and the gut, commonly referred to as the gut–brain axis, has been proposed as relevant in both migraine and GI disorders.[18,19] Hence, it is conceivable that migraine and GI disorders might share etiological mechanisms and might be causally linked. Obtaining information on whether the link is causal could have clinical implications, as treating GI symptoms could help mitigate migraine symptoms or vice versa. One approach to inferring causality is conducting a Mendelian randomization (MR) analysis, in which genetic variants associated with an exposure are identified and regressed upon an outcome measurement. Given the random assortment of alleles at gametogenesis, this method is less likely to suffer from issues with confounding and reverse causation than methods used in conventional observational epidemiological studies.[20]

In this study, we first aimed to assess whether the observed associations between migraine and IBD and celiac disease might be explained by a shared genetic basis using genetic correlation analyses. Based on the associations reported between these conditions in epidemiological studies, we hypothesized that migraine would be genetically correlated with both IBD and celiac disease. Next, we investigated whether migraine may be causally linked to either IBD or celiac disease using a bidirectional MR approach. Considering the typical ages of onset of the different conditions, we hypothesized that celiac disease might be more likely to cause migraine than vice versa, and that migraine might be more likely to cause IBD than vice versa.

METHODS

Mendelian randomization assumptions

For an MR analysis to be valid, three key assumptions need to be fulfilled:[21] (i) There needs to be an association between the genetic variants used as instruments and the exposure; (ii) the genetic variants must *only* be associated with the outcome through the exposure; and (iii) the genetic variants used as instruments should not be associated with confounders.

In the present study, the first assumption was ensured by only including genetic variants that were associated with the exposure at a genome-wide significance level ($p \leq 5 \times 10^{-8}$) in the exposure genome-wide association study (GWAS).[20] Factors that may lead to violation of the second assumption include population stratification, variants within linkage disequilibrium (LD) and horizontal pleiotropy.[21] The risk of population stratification was reduced by only including participants of European ancestry, and the risk of problems due to LD was reduced by clumping. To assess the presence of horizontal pleiotropy, several sensitivity analyses were performed (see "Mendelian randomization analyses" section). Admittedly, the third assumption is difficult to assess when using summary statistics without access to individual-level data.

Summary statistics

Summary statistics from a GWAS meta-analysis of migraine were obtained with permission from the International Headache Genetics Consortium (IHGC) and 23andMe, Inc. The meta-analysis is based on 22 GWAS from 33 population-matched case–control samples and includes 59,674 migraine cases and 316,078 controls, all of European descent.[22] The summary statistics for migraine regardless of subtype (referred to as "any migraine") included data from participants with self-reported migraine from 23andMe. Many of the cohorts assessed their participants' migraine diagnoses using the second edition of the *International Classification of Headache Disorders*.[23] For migraine subtype analyses, which require detailed information on aura status, only genetic information from clinical cohorts from dedicated headache centers was used. For MO, data from 8348 cases and 139,622 controls were used, whereas for MA, data from 6332 cases and 144,883 controls were available. As there were no genome-wide significant loci detected for MA in the study by Gormley et al.,[22] MA was only used as an outcome and not as an exposure in the MR analyses. Further details on the cohorts included in the migraine GWAS are provided in the Supplementary Methods section (Supplementary Table A). As only summary statistics were used (i.e., only aggregate *p* values and association data for each variant) and not individual-level data, no complete descriptive statistics or information on missing samples and missing genetic variants can be provided. Instead, we refer to the original publication.[22] Some information on missing data in the separate cohorts is provided in the Supplementary Note of the original publication. The analyses used in this study were all secondary analyses of previously collected data and were thus post hoc analyses.

For IBD, publicly available summary statistics from the largest GWAS to date were used, covering 25,042 cases and 34,915 controls.[24] In this GWAS, separate summary statistics for Crohn's disease (12,194 cases and 28,072 controls) and ulcerative colitis (12,366 cases and 33,609 controls) were available. The study consisted of a new GWAS as well as a meta-analysis of previously published summary statistics, all based on patients with IBD of European ancestry, diagnosed using endoscopic, histopathologic and radiologic criteria.[24,25] Information on the cohorts included in the GWAS is provided in the Supplementary Methods section (Supplementary Table B). Given that we used summary statistics data, we refer to the original publication for any information on the exclusion of samples or variants.[24]

When celiac disease constituted the exposure in the MR analyses, the most recent GWAS of celiac disease was used, containing publicly available summary statistics from 11,812 cases and 11,837 controls of European ancestry.[26] The genetic variants that were strongly associated with migraine were absent from this GWAS. Therefore, publicly available summary statistics from a previous, partially overlapping GWAS of celiac disease, based on 4533 cases and 10,759 controls of European ancestry, were used in the MR analyses in which celiac disease constituted the outcome.[27] Celiac disease was diagnosed using clinical, serologic, and histopathologic criteria. Information on some of the cohorts included in the GWAS is provided in the Supplementary Methods section (Supplementary Table C). In the most recent GWAS, the percentage of missing genotype calls was 0.008%. Given that we used summary statistics data, we refer to the original publication for any further information on the quality control procedures used.[26] For the sake of consistency, both sets of summary statistics for celiac disease were used in the genetic correlation analyses.

A summary of the sample sizes of the datasets employed and the number of single-nucleotide polymorphisms (SNPs) included in each MR analysis are provided in Figure 1.

Statistical analyses

Genetic correlation analyses

Linkage Disequilibrium Score Regression (LDSC, version 1.0.1) was used to calculate genetic correlations (r_G) between migraine and IBD, including Crohn's disease and ulcerative colitis, as well as between migraine and celiac disease, using default settings.[28,29] Further details on the genetic correlation analyses are provided in the Supplementary Methods section.

Positive control analyses

Positive control analyses were used to assess the suitability of the genetic instruments used in the MR analyses. As positive controls, outcome traits known to be causally linked to the exposures (the various disease traits) were selected.[30]

For IBD and its two subtypes, publicly available summary statistics from a GWAS on ankylosing spondylitis were used in the positive control analyses,[31] thus partially replicating the results of Cui et al.[32] All participants had a definite diagnosis of ankylosing spondylitis, based on the modified New York criteria.[31] For celiac disease, following a "gluten-free diet" was chosen as a positive control trait, using publicly available summary statistics based on UK Biobank and obtained through the Integrative Epidemiology Unit (IEU) GWAS database.[33] This trait was based on self-reported information; UK Biobank participants were asked if they followed a special diet, and "gluten-free" was one of the available options.[34] For migraine, self-reported alcohol consumption was used as a positive control trait, as employed by Daghlas et al.[35] Specifically, being a current alcohol drinker in UK Biobank was selected as the outcome trait instead of alcohol intake frequency, as the latter is a continuous trait and the remaining analyses all have binary outcome traits. The summary statistics used in this analysis were also obtained from the Integrative Epidemiology Unit GWAS database.[33]

Mendelian randomization analyses

The MR analyses were conducted using the TwoSampleMR package (version 0.5.6) in R (version 4.0.2).[33,36] All genetic variants reaching

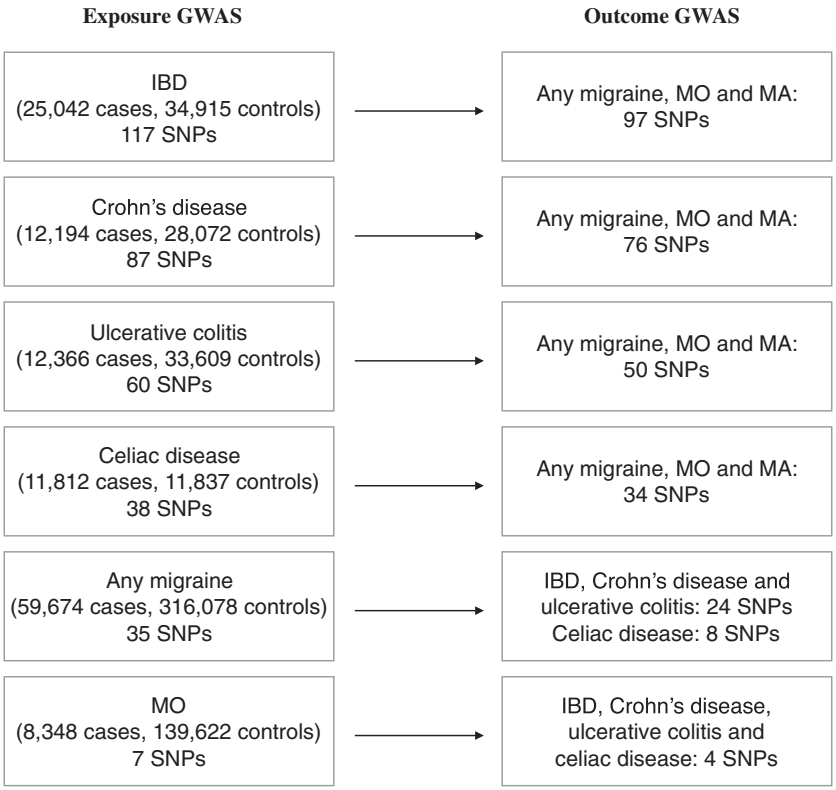

FIGURE 1 Overview of genetic instruments. The number of genome-wide significant SNPs available from each exposure GWAS is presented in the left column. The number of overlapping SNPs from each outcome GWAS is presented in the right column. GWAS, genome-wide association study; IBD, inflammatory bowel disease; MA, migraine with aura; MO, migraine without aura; SNPs, single-nucleotide polymorphisms.

a genome-wide significance level of $p \leq 5 \times 10^{-8}$ were extracted from each GWAS to obtain the genetic instruments. Subsequently, independent SNPs were selected via clumping with an LD r^2 threshold of 0.001 and a distance of 10,000 kilobases, using the default 1000 genomes European LD reference panel.[37] The corresponding genetic variants were then extracted from each outcome GWAS, and the effect alleles were harmonized. Any variants that could not be harmonized were removed from further analysis. Additional details on data harmonization are provided in the Supplementary Methods section.

The main analysis method used was the inverse-variance weighted (IVW) method (for more information, see Section 3.2 in the Supplementary Methods section). As this method assumes the absence of horizontal pleiotropy, several sensitivity analyses were employed. A Cochran's Q $p < 0.05$ was considered an indication of possible heterogeneity. A test of the MR Egger intercept for each of the analyses was used to detect the presence of directional pleiotropy, i.e., horizontal pleiotropic effects that bias the IVW estimate.[38,39] In addition to MR Egger effect estimates, simple mode, weighted mode, and weighted median effect estimates were generated for the main analyses, as well as for the positive control analyses. More information on sensitivity analyses is included in Section 3.3 in the Supplementary Methods section. All significance testing was two-tailed.

To account for multiple testing, a maximum false discovery rate (FDR) of 0.05 was used to calculate significance thresholds for the 20 tests that constituted the main analyses. These FDR-adjusted thresholds are included in Figures 3 and 4. The term "nominally significant" is used for p values below the conventional significance level of 0.05. Further information on multiple testing correction is provided in the Supplementary Methods section. As only summary statistics from previously collected GWAS data were used, no statistical power calculation was conducted prior to the study. The sample size was based on the available data.

RESULTS

Genetic correlation analyses

Using LD score regression to estimate genetic correlations, migraine was not correlated with either IBD in general ($p = 0.110$) or with either of its two subtypes, Crohn's disease ($p = 0.621$) or ulcerative colitis ($p = 0.577$) (Table 1). Similarly, there were no significant genetic correlations between migraine and celiac disease using either set of summary statistics for celiac disease ($p = 0.742$ and $p = 0.846$, respectively) (Table 1). The lack of a genetic correlations between migraine and the GI diseases in question does not preclude the use of an MR approach, as specific SNPs may still be used as genetic instruments to assess causality between the exposure and outcome traits.

TABLE 1 Genetic correlations between gastrointestinal conditions and migraine.

Gastrointestinal condition	r_G	SE	Z	p	Intercept	SE
IBD	0.05	0.03	1.60	0.110	0.01	0.01
Crohn's disease	0.01	0.01	0.50	0.621	0.00	0.00
Ulcerative colitis	0.02	0.36	0.56	0.577	0.01	0.01
Celiac disease[26]	−0.02	0.67	−0.33	0.742	0.01	0.03
Celiac disease[27]	0.01	0.06	0.19	0.846	0.00	0.01

Note: Genetic correlations based on results from linkage disequilibrium score regression analyses. For celiac disease, two separate sets of summary statistics were used. The references to these publications are provided using superscript numerals. The intercept for the genetic covariance and its SE are also provided. The intercept is expected to be zero in the absence of confounding factors affecting both traits.

Abbreviations: IBD, inflammatory bowel disease; r_G, genetic correlation; SE, standard error; Z, Z score.

FIGURE 2 Positive control analyses. Forest plot of two-sample Mendelian randomization effect estimates for IBD, celiac disease and migraine on positive control traits based on the inverse-variance weighted method. CI, confidence interval; IBD, inflammatory bowel disease; MO, migraine without aura; OR, odds ratio; SNPs, single-nucleotide polymorphisms.

Positive control analyses

The results from all positive control analyses were significant (Figure 2). Results from the sensitivity analyses of the positive controls are provided as Tables S1–S7. The results from the positive control MR analyses indicated that the genetic instruments used for IBD, celiac disease and migraine were strong enough for expected associations to be confirmed.

Forward MR: GI diseases on migraine

In total, 97 SNPs were used as instruments for assessing causality between IBD and migraine (Figure 1, Tables S15A–C). In addition, 76 SNPs were used to assess the effect of Crohn's disease on migraine (Figure 1, Tables S16A–C), and 50 SNPs were used to assess the effect of ulcerative colitis on migraine (Figure 1, Tables S17A–C). Based on the results from the IVW method, no causality could be detected between IBD and any migraine ($p = 0.703$), MO ($p = 0.637$) or MA ($p = 0.814$) (Figure 3). Furthermore, neither Crohn's disease nor ulcerative colitis had a significant effect on the risk of any migraine ($p = 0.626$ and $p = 0.174$, respectively), or on MO ($p = 0.621$ and $p = 0.506$, respectively), or on MA ($p = 0.813$ and $p = 0.581$, respectively) (Figure 3). Results from Cochran's Q tests were on some occasions significant, which indicates that issues with heterogeneity are present in the analyses, specifically for the effect of IBD on any migraine and Crohn's disease on any migraine (Table S8). In addition, the MR Egger intercept indicated the presence of directional pleiotropy in the analysis of the effect of liability to ulcerative colitis on MA (Table S11). Given the presence of directional pleiotropy, the second MR assumption has been violated and the results from the IVW method cannot be interpreted. The remaining sensitivity analyses for the effect of IBD or Crohn's disease on migraine and its subtypes were not significant (Tables S9 and S10). Scatter plots of the SNP effects on IBD and migraine (as well as disease subtypes) depending on the analysis method used are provided in Figures S1–S9.

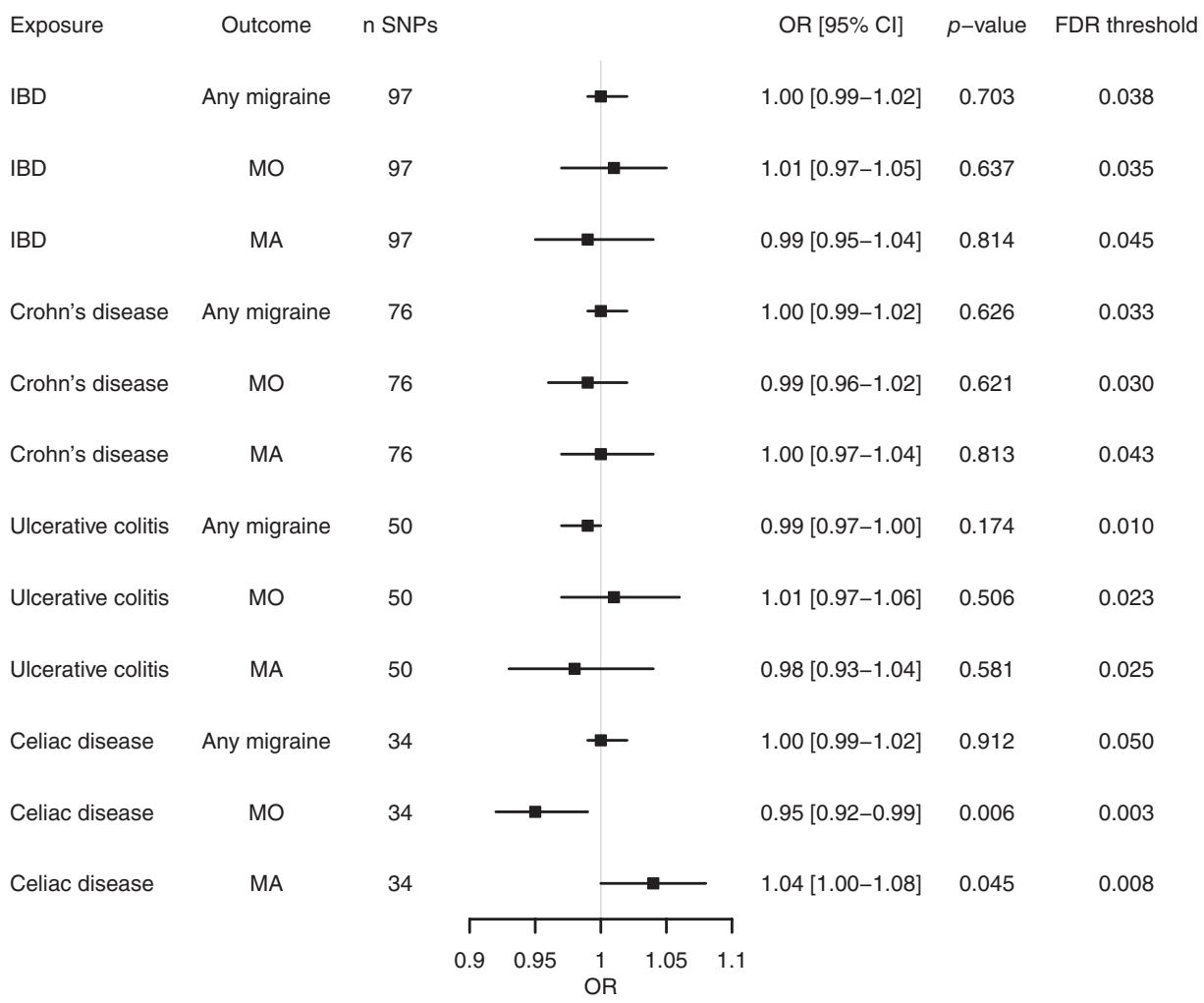

FIGURE 3 Effects of genetic liability to gastrointestinal conditions on migraine. Forest plot of two-sample Mendelian randomization effect estimates for IBD (including subtype analyses for Crohn's disease and ulcerative colitis) and celiac disease on migraine (including subtype analyses for MO and MA) based on the inverse-variance weighted method. CI, confidence interval; FDR, false discovery rate; IBD, inflammatory bowel disease; MA, migraine with aura; MO, migraine without aura; OR, odds ratio; SNPs, single-nucleotide polymorphisms.

For assessing causality between celiac disease and migraine, 34 genetic variants were used (Figure 1, Tables S18A–C). We observed no causal effect of celiac disease on any migraine ($p = 0.912$), but nominally significant results for the effect of celiac disease on MO and MA in opposite directions. Whereas celiac disease had a nominally significant protective effect on MO (odds ratio [OR] 0.95, 95% confidence interval [CI] 0.92–0.99, $p = 0.006$), it had a nominally significant causal effect on MA (OR 1.04, 95% CI 1.00–1.08, $p = 0.045$). However, these results were no longer significant when using an FDR-adjusted threshold (Figure 3). There was no evidence of heterogeneity, as assessed by Cochran's Q tests, in any of the analyses (Table S8). Similarly, the MR Egger intercepts did not significantly differ from zero (Table S12). The effect estimates of the MR Egger, weighted median, simple mode, and weighted mode methods were all in the same direction as that of the IVW method when MO or MA was used as the outcome (Table S12). Scatter plots of the SNP effects on celiac disease and migraine (as well as migraine subtypes) depending on the analysis method used are provided in Figures S10–S12.

Reverse MR: Migraine on GI diseases

To assess whether any migraine had a causal effect on IBD and its subtypes, 24 SNPs were used (Figure 1, Tables S19A–C). In addition, eight SNPs were used to assess the effect of migraine on celiac disease (Figure 1, Table S20). In the subtype analyses of the effect of MO on IBD or celiac disease, four SNPs were used (Figure 1, Tables S21A–C and 22). There was no evidence of effects of genetic liability to any migraine on IBD ($p = 0.181$), Crohn's disease ($p = 0.325$), ulcerative colitis ($p = 0.257$) or celiac disease ($p = 0.614$) (Figure 4). Similarly, there were no causal effects for MO on IBD ($p = 0.235$), Crohn's disease ($p = 0.878$) or celiac disease ($p = 0.745$) (Figure 4). However, we did find a nominally significant result for MO on ulcerative colitis (OR 1.15, 95% CI 1.02–1.29, $p = 0.025$), but this result was no longer significant when using an FDR-adjusted threshold (Figure 4). MA was not used as an exposure, as there were no significant SNPs for this subtype based on the summary statistics from Gormley et al.[22] Cochran's Q tests revealed problems with heterogeneity when any

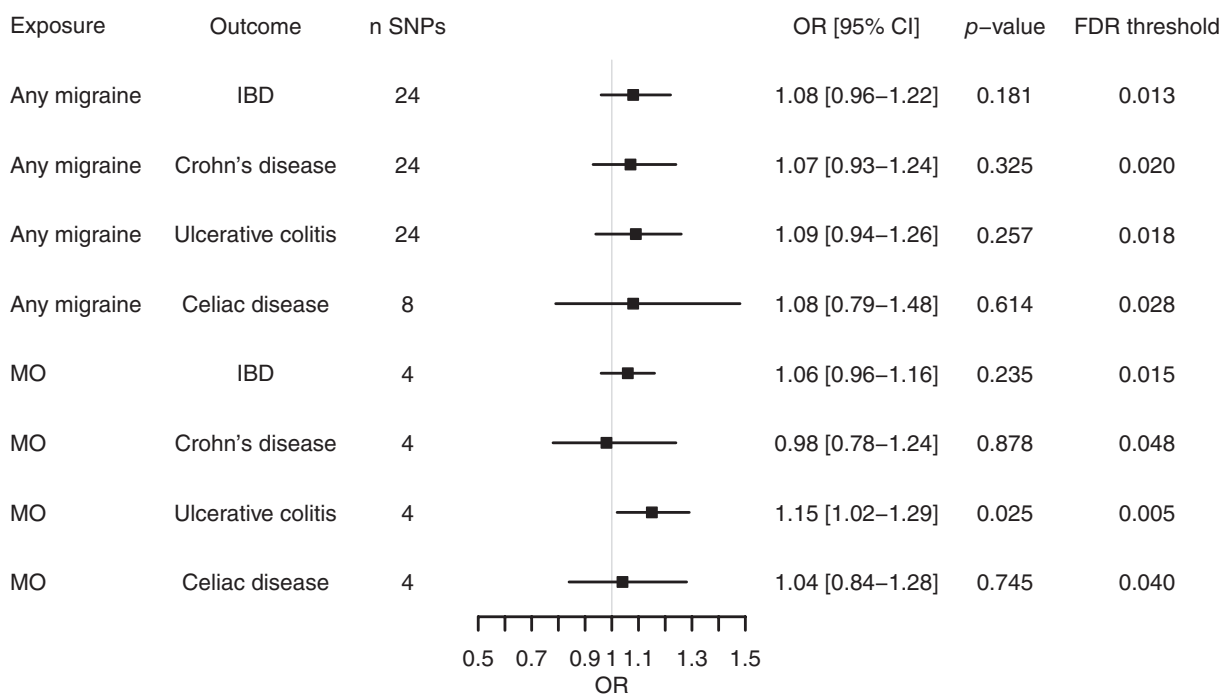

FIGURE 4 Effects of genetic liability to migraine on gastrointestinal conditions. Forest plot of two-sample Mendelian randomization effect estimates for migraine (including subtype analyses for MO and MA) on IBD (including subtype analyses for Crohn's disease and ulcerative colitis) and celiac disease based on the inverse-variance weighted method. CI, confidence interval; FDR, false discovery rate; IBD, inflammatory bowel disease; MO, migraine without aura; OR, odds ratio; SNPs, single-nucleotide polymorphisms.

migraine was used as the exposure in two analyses (any migraine on IBD and any migraine on ulcerative colitis), as well as when MO was used as the exposure and Crohn's disease was used as the outcome (Table S8). However, there was no indication of directional pleiotropy as assessed using the MR Egger intercept (Table S13). In the sensitivity analyses, the MR Egger, weighted median, simple mode, and weighted mode analyses yielded similar estimates of the effect of migraine on IBD and celiac disease (Tables S13 and S14). Scatter plots of the SNP effects on migraine and both IBD and celiac disease (as well as migraine and IBD subtypes) depending on the analysis method used are provided in Figures S13–S20.

DISCUSSION

This is the first study exploring the possible causal relationship between migraine and IBD and celiac disease. We found no genetic correlations between migraine and either IBD or celiac disease. In addition, we assessed whether the associations between migraine and IBD and celiac disease might be causal, using a bidirectional two-sample MR analysis approach. In the forward MR analyses, no significant effects of either IBD or celiac disease on any migraine were observed, although the results for ulcerative colitis on MA could not be interpreted due to directional pleiotropy. However, we did find some indication of celiac disease having a potential protective effect on MO and a causal effect on MA, even though the results did not withstand multiple testing correction. Similarly, when reversing the analyses, neither any migraine nor MO had a causal effect on either IBD or celiac disease. Again, some of the analyses may have been affected by heterogeneity and the results should therefore be interpreted with caution. Our results did indicate the presence of a causal effect of MO on ulcerative colitis, but this effect was not significant after correcting for multiple testing. Taken together, we found no overlapping genetic etiology between migraine and either IBD or celiac disease. Furthermore, no clear-cut causal bidirectional relationship between migraine and IBD or celiac disease was identified, although the effect of celiac disease on migraine subtypes, as well as that of MO on ulcerative colitis, may warrant further exploration.

Most of the evidence in favor of an association between migraine and IBD to date has come from small-scale epidemiological studies,[4,5] except for a recent study based on 60,000 participants.[6] Of note, this latter study investigated a mixed group of participants with migraine and severe headaches; whether migraine was independently associated with IBD was thus not established. In a previous study by our group based on the UK Biobank cohort, no statistically significant associations were found between migraine and either Crohn's disease or ulcerative colitis.[40] This is supported by the lack of significant causal effects or genetic correlations in the present study. Instead, the previously observed association between migraine and IBD could be mediated by hitherto unidentified confounding factors.

The evidence in favor of a link between migraine and celiac disease is stronger, as one meta-analysis[8] and two population-based studies[9,10] all demonstrated an association. Results from the present study indicate that this association is not likely to arise from shared genetic underpinnings or from a causal effect of celiac disease on any migraine

or vice versa. Still, celiac disease had a nominally significant protective effect on MO and a nominally significant causal effect on MA before FDR adjustments were applied. One can envisage that the opposite effects of celiac disease on MO and MA may be canceled out when analyzing all participants with migraine (any migraine) jointly. Future studies may be needed to shed light on the complex but potentially interesting association between celiac disease and migraine.

A strength of the present study is that the MR method enables assessments of potential bidirectional causality between migraine and both IBD and celiac disease. In addition, multiple assessments according to disease subtypes were performed, as well as genetic correlation analyses. Given that previous studies on the link between migraine and IBD have primarily relied on small sample sizes, the fact that the present study is based on large-scale summary statistics is an additional advantage. The findings of our positive control analyses were consistent with expectations, adding to the validity of our genetic instruments.

Several limitations must, nevertheless, also be considered. First, no genome-wide significant SNPs were detected for MA in the study by Gormley et al.,[22] thus preventing analyses on whether liability to MA is causally linked to celiac disease or IBD. Second, there was a small sample overlap between the migraine GWAS and the celiac disease GWAS, as they included data from the same 925 participants of the Health 2000 cohort. This corresponds to a sample overlap of ~0.2%, which could theoretically bias the estimate.[41] However, as only strong genetic instruments were used, the small sample overlap is not expected to have resulted in considerable bias. Third, tests of Cochran's *Q* indicated the presence of heterogeneity in some of the analyses, necessitating a cautious interpretation of these results. Fourth, a general limitation that affects MR studies based on summary statistics is the difficulty in assessing the crucial assumption that the genetic variants used should not be associated with confounders. To assess this assumption, access to individual-level data is needed, which was not possible for the present study. Hence, the term "causality" should be interpreted with caution. Fifth, although positive control analyses demonstrated that the instruments were strong enough for expected associations to be observed, the migraine subtype analyses relied on few genetic variants and may have suffered from weak statistical power. Sixth, to reduce the risk of population stratification, only summary statistics derived from participants of European descent were used. Consequently, the results from the present study may not be applicable to groups of other ethnicities.

CONCLUSIONS

No genetic correlation was observed between migraine and either IBD or celiac disease in the present study. In addition, no clear bidirectional causal relationship between the two disease types was identified. Nevertheless, some indications of GI diseases affecting migraine subtypes, and vice versa, were detected. Stronger genetic instruments may be required to explore these associations further.

AUTHOR CONTRIBUTIONS

Study concept and design: Jessica Mwinyi, Nike Zoe Welander. *Analysis and interpretation of data*: Nike Zoe Welander, Gull Rukh, Mathias Rask-Andersen, Aster V. E. Harder, Arn M. J. M. van den Maagdenberg, Helgi Birgir Schiöth, Jessica Mwinyi. *Drafting of the manuscript*: Nike Zoe Welander. *Revising it for intellectual content*: Gull Rukh, Mathias Rask-Andersen, Aster V. E. Harder, Arn M. J. M. van den Maagdenberg, Helgi Birgir Schiöth, Jessica Mwinyi. *Final approval of the completed manuscript*: Nike Zoe Welander, Gull Rukh, Mathias Rask-Andersen, Aster V. E. Harder, Arn M. J. M. van den Maagdenberg, Helgi Birgir Schiöth, Jessica Mwinyi.

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CONFLICT OF INTEREST

Jessica Mwinyi, **Helgi Birgir Schiöth**, **Arn M. J. M. van den Maagdenberg**, **Aster V. E. Harder**, **Mathias Rask-Andersen**, **Gull Rukh**, and **Nike Zoe Welander** have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The GWAS summary statistics for migraine are available upon request from the International Headache Genetics Consortium as well as from 23andMe. GWAS summary statistics for the 23andMe discovery data set are available through 23andMe to qualified researchers under an agreement with 23andMe that protects the privacy of the 23andMe participants. Please visit https://research.23andme.com/collaborate/#dataset-access/ for more information and to apply to access the data. Summary statistics for IBD, celiac disease and ankylosing spondylitis were downloaded from the NHGRI-EBI GWAS Catalog[42] for studies GCST004131 (IBD),[24] GCST005523 (celiac disease, Trynka et al.),[26] GCST00612 (celiac disease, Dubois et al.)[27] and GCST005529 (ankylosing spondylitis),[31] downloaded on July 7, 2020.

ETHICS STATEMENT

As only summary statistics and no individual-level data were used in the analyses, ethical approval was not required for this study. Each GWAS from which summary statistics were used obtained written informed consent from their participants and the separate studies included were approved by local research ethics committees or institutional review boards.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX

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