Assessing the impact of blood pressure in the development of inflammatory bowel disease

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Abstract
The purpose of this study is to investigate the potential causal relationships between blood pressure and inflammatory bowel disease (IBD) by using the bidirectional Mendelian randomization (MR) approach. Summary-level data for blood pressure was extracted from the hitherto largest genome-wide study (GWAS) with 759,601 participants of European descent. We used 56 single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) for blood pressure. Summary statistics for IBD were derived from a GWAS with an overall 59,957 participants of European ancestry, of which 109 IVs were selected. Several robust analytical methods, including inverse-variance weighted (IVW) method, weighted-median method, MR-Egger regression, MR-PRESSO test, maximum likelihood method, “leave-one-out” and multivariable MR analysis were used to evaluate the causal associations between blood pressure and IBD. Genetically predicted higher systolic blood pressure (SBP) was associated with an increased risk of IBD (odds ratio (OR) = 1.05, 95% confidence interval (CI): 1.02–1.08, P = .001 by IVW). Subgroup analysis showed that higher SBP was positively associated with Crohn’s disease (CD) (OR = 1.06, 95% CI: 1.03–1.09, P = 9.18 × 10−5) and ulcerative colitis (UC) (OR = 1.05, 95% CI: 1.01–1.09, P = .017) risk, respectively. In reverse-direction MR analysis, the authors observed no evidence for the causal effect of IBD on blood pressure. Our findings suggested that high SBP was associated with an increased risk of IBD (for both UC and CD). Further studies are required to clarify the underlying mechanism of this causal association.

KEYWORDS
diastolic blood pressure, inflammatory bowel disease, Mendelian randomization, pulse pressure, systolic blood pressure
1 | INTRODUCTION

Inflammatory bowel disease (IBD) is a group of chronic idiopathic inflammatory diseases occurring in the gastrointestinal tract, which includes ulcerative colitis (UC) and Crohn’s disease (CD). The prevalence of IBD remains high worldwide, and there were approximately 4.9 million prevalent cases, resulting in 41 000 deaths in 2019. The etiology of IBD is related to the abnormal immune imbalance in the intestine, which is caused by the interaction of multiple factors, including genetic and environmental factors. However, the exact mechanism of the development of IBD is still unclear, and more study is required to detect potential causal risk factors for IBD.

Recently, several epidemiological studies have uncovered the link between blood pressure and IBD. For example, two recent retrospective studies pointed out an improved disease outcome in IBD patients treated with angiotensin-converting-enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB). Moreover, a population-based experimental study involving 300 IBD patients with and without hypertension also demonstrated that antihypertensive drugs (renin-angiotensin system inhibitors) exert a protective effect on the overall course of IBD. However, due to bias such as residual confounding and reverse causation, evidence from observational epidemiological studies is limited for causal inference. Moreover, given the sparse evidence from experimental studies, the potential relationship between blood pressure and the risk of IBD still needs much greater exploration.

As an emerging approach, Mendelian Randomization (MR) uses genetic variants as instrumental variables (IVs) to investigate the potential causal relationship between the exposure and the outcome. The validity of this approach relies on inherited genetic variation fixed at birth and the random assortment of genetic alleles at gametogenesis, and therefore it is not modifiable by environmental factors. This method is now extensively used to infer causal relationships in health research due to its potential causal relationship between the exposure and the outcome. We performed a two-sample MR analysis to investigate the potential causal association between blood pressure and IBD (Table S1).

2 | MATERIAL AND METHODS

2.1 | Study design

The study design is shown in Figure 1. In brief, we conducted a bidirectional two-sample MR analysis to investigate the potential causal associations between three phenotypes of blood pressure and IBD, respectively.

2.2 | Source of outcome

Summary-level data for IBD was obtained from a previous GWAS meta-analysis published by de Lange and coworkers. In this study, a total of 25 042 IBD patients (including 12 194 CD and 12 366 UC) and 34 915 controls were included. All the participants were of European ancestry from the UK Inflammatory Bowel Disease Genetics (UKIBDGC) and UK10K consortia. Using 1000 Genomes Project Phase 3 v5 and a standard-error-weighted meta-analysis method, nine million genetic variants were tested for their association with CD and UC. The GWAS analysis was adjusted for principal components.

We used the largest published genome-wide meta-analyses of blood pressure from the UK Biobank and the International Consortium of Blood Pressure–Genome Wide Association Studies (ICBP), which was conducted in 757 601 participants of European descent. The descriptive characteristics of the summary-level data for blood pressure and IBD are provided in the Table S1.

2.3 | Instrumental variables selection

We identified the genetic variants associated with blood pressure at the genome-wide significance threshold (P < 5 × 10^-8) from a GWAS on blood pressure consisting of 152 249 European individuals. In this GWAS, the mean age of participants was 56.8 years old, with 54.2% females, and the rate of hypertension was 53.5%. The corresponding effect estimates of SNP on blood pressure (including SBP, DBP, and PP) had been adjusted for sex, age, body mass index (BMI), the top ten principal components and genotyping chips. We clumped all SNPs in linkage disequilibrium (LD) (r^2 < 0.1) and retained SNPs with the lowest P-value for exposures. To avoid the interference of horizontal pleiotropy, we searched individual SNPs in the GWAS Catalog (https://www.ebi.ac.uk/gwas/) for their associated traits. After excluding SNPs associated with secondary phenotypes at genome-wide significance, 14 SNPs associated with SBP, 20 SNPs associated with DBP, and 22 SNPs associated with PP were used as IVs in subsequent MR analysis, respectively. Detailed information about these IVs is displayed in Table S2.

IVs associated with IBD and two subtypes were selected from the GWAS involving 59 957 participants of European ancestry. In this study, 215 distinct loci associated with IBD were discovered, of which 109 SNPs (including 78 SNPs associated with IBD, 17 SNPs associated with CD and 14 SNPs associated with UC) reached genome-wide significance and were used as IVs for IBD in the reverse-direction MR analysis (Table S3).

2.4 | Statistical analysis

To assess the strength of the association between the genetic variants and the exposure, we calculated F-statistic. It was approximately calculated by using the following equation: \(F = \frac{R^2(n-k-1)}{k(1-R^2)}\), where \(R^2\) is variance of exposure explained by selected IVs; \(n\), sample size; and \(k\), number of IVs. The F-statistic > 10 was considered to be unlikely to suffer from weak instrumental bias.

For MR analysis, the inverse-variance weighted (IVW) model was used as the main analysis, which combines Wald estimates for each
SNP (ie, SNP-exposure over SNP-outcome estimate) by a meta-analysis approach to get the overall estimates of the effect of blood pressure on the risk of IBD.\textsuperscript{13} To assess the heterogeneity, Cochran’s Q test was also performed. A P-value < .05 was considered to have significant heterogeneity, and therefore, the random-effects IVW model was adopted. Otherwise, a fixed-effects model was used. Moreover, the weighted median, MR-Egger regression, the maximum likelihood, “leave-one-out” analysis and MR pleiotropy residual sum and outlier (MR-PRESSO) test were conducted as supplementary analyses to assess the robustness of findings from the main analysis. Specifically, the weighted median method can reduce the bias of causal effects compared with IVW, when more than 50% of the instrumental variables are invalid.\textsuperscript{14} The intercept of MR-Egger regression was used to judge whether directional pleiotropy has an influence on the causal estimates.\textsuperscript{14} In addition, the maximum likelihood method was also performed, in which the causal effect estimates are obtained by assuming a linear relationship between the exposure and the outcome.\textsuperscript{15,16} To identify potentially influential SNPs, we performed “leave-one-out” analyses where the MR is reran but leaving out each SNP in turn. Finally, we conducted the MR-PRESSO test to determine and eliminate the pleiotropic effects caused by outliers by using the observed and expected distributions of the tested variants.\textsuperscript{17}

Considering the effects of BMI, smoking, and alcohol consumption on IBD, we further performed a multivariate Mendelian randomization (MVMR) analysis for the statistically significant association in the main MR analysis.\textsuperscript{18} We used summary statistics for BMI from Locke and coworkers,\textsuperscript{19} for smoking and alcohol consumption from Liu and coworkers.\textsuperscript{20} We restricted the MVMR analysis to significant independent SNPs that were clumped on $r^2 < 0.1$.

All statistical analyses were conducted using R software version 3.6.2, with the “MendelianRandomization,” “MRPRESSO” and “TwoSampleMR” packages. An observed P-value < .017 (0.05/3) was considered as statistically significant evidence for a causal association.

### 3 | RESULTS

#### 3.1 | Causal effect of blood pressure on IBD

For the IVs used in this study, all the F-statistics were above 10, and the median F-statistic was 37.00 for SBP, 42.28 for DBP, and 52.51 for PP, respectively.

As shown in Figure 2 and Figure S1, the result from the IVW method supported that genetically predicted higher SBP was associated with an increased risk of IBD (odds ratio (OR) = 1.05, 95% confidence interval (CI): 1.02–1.08, P = .001). In sensitivity analyses, the weighted median method and the maximum likelihood method produced similar effect estimates (OR = 1.04, 95% CI: 1.01–1.08, P = .009 by the weighted median method; OR = 1.05, 95% CI: 1.02–1.08, P = .001 by the maximum likelihood method). Additionally, MR-Egger regression did not suggest statistically significant evidence of horizontal pleiotropy ($P_{\text{intercept}} = 0.201$, OR = 0.97, 95% CI: 0.95–1.10, P = .617). No outliers are detected by the MR-PRESSO test, and the OR for the association between SBP and IBD was 1.05 (95% CI: 1.02–1.08, P = .005). Results from “leave-one-out” analysis also demonstrated that high SBP was associated with an increased risk of IBD, and no SNPs were found that had a large effect on the outcome effect (Figure S2). In MVMR analysis, we found that genetically predicted higher SBP retained its association with an increased risk of IBD, and no SNPs were found that had a large effect on the outcome effect (Figure S2). In MVMR analysis, we found that genetically predicted higher SBP retained its association with an increased risk of IBD, and no SNPs were found that had a large effect on the outcome effect (Figure S2). In MVMR analysis, we found that genetically predicted higher SBP retained its association with an increased risk of IBD, and no SNPs were found that had a large effect on the outcome effect (Figure S2).
No evidence for a potential causal association of DBP or PP with the risk of IBD was observed (DBP: OR = 0.98, 95% CI: 0.93–1.02, P = .319; PP: OR = 1.01, 95% CI: 0.99–1.03, P = .403, by IVW) (Figure 2). There was also no indication of pleiotropy by using the MR-Egger regression (DBP: P intercept = 0.694; PP: P intercept = 0.301). The findings from MR-PRESSO test showed no evidence of outliers (DBP: OR = 0.98, 95% CI: 0.93–1.02, P = .331; PP: OR = 1.01, 95% CI: 0.99–1.03, P = .420) (Figure 2). The leave-one-out analysis also confirmed no evidence of association (Figure S2). Similarly, there is also no evidence that DBP or PP associated with the risk of CD (DBP: OR = 0.97, 95% CI: 0.92–1.02, P = .220; PP: OR = 1.03, 95% CI: 1.00–1.06, P = .112, by IVW) and UC (DBP: OR = 0.98, 95% CI: 0.93–1.04, P = .506; PP: OR = 1.00, 95% CI: 0.97–1.03, P = .840, by IVW) (Figure S3).

3.2 Causal effect of IBD on blood pressure

As demonstrated from the results of the IVW, genetically predicted IBD, CD and UC had no causal effects on the risk of SBP (IBD: OR = 1.00, 95% CI: 0.84–1.20, P = .970), as well as CD and UC (CD: OR = 1.01, 95% CI: 0.57–1.78, P = .984; UC: OR = 1.00, 95% CI: 0.78–1.29, P = .977) (Figure 3 and Figure S4). Similarly, no evidence of causal- ity was observed between IBD, CD or UC and the risk of DBP (IBD: OR = 1.04, 95% CI: 0.90–1.20, P = .585; CD: OR = 0.95, 95% CI: 0.67–1.35, P = .775; UC: OR = 1.05, 95% CI: 0.94–1.18, P = .362) and PP (IBD: OR = 0.97, 95% CI: 0.90–1.04, P = .400; CD: OR = 1.07, 95% CI: 0.83–1.37, P = .627; UC: OR = 0.96, 95% CI: 0.83–1.12, P = .640). Besides, consistent results were obtained from other sensitivity analyses (Figure 3 and Figure S5). There was little evidence of directional pleiotropy for all models, except IBD for both SBP (MR-Egger intercept P = .015) and DBP (MR-Egger intercept P = .022).

4 DISCUSSION

In the present study, we performed bidirectional two-sample MR analyses to identify the potential causal relationships between blood pressure and IBD. The findings of this study demonstrated that genetically predicted higher SBP had a potential causal effect on the risk of IBD, for both UC and CD. In reverse-direction MR analysis, consistent evidence showed that no effect of IBD on the risk of blood pressure.

Limited studies that have evaluated the link between blood pressure and the risk of IBD. Only two epidemiological studies have suggested that the use of ACEI and ARB may have a substantial protective effect on the prognosis of IBD, hinting at the potential role of blood pressure on the development of IBD. Specifically, a cross-sectional study has reported that the IBD patients taking ACEI/ARB had fewer hospitalizations (OR = 0.26, 95% CI: 0.10–0.70, P < .01), operations (OR = 0.08, 95% CI: 0.01–0.67, P = .02), and corticosteroid prescriptions (OR = 0.50, 95% CI: 0.30–0.82, P = .01) compared to those without. Additionally, Garg and coworkers noted that compared with health controls, patients with IBD had a higher level of circulating renin (mean 25.4 vs. 18.6 mIU/L, P = .026) and higher ratio of angiotensin converting enzyme 2 (ACE2) to ACE (mean 0.92 vs. 0.69, P = .015). Consistent with these prior observational epidemiological studies, our findings supported the hypothesis that higher blood pressure, especially SBP, may be causally associated with an increased risk of IBD.
One potential mechanism for the relationship of hypertension with IBD may be that higher blood pressure could alter the tight junction proteins and gut permeability in the intestine, and thereby increased the risk of IBD. For example, the increased level of Zonulin, a gut epithelial tight junction protein regulator, was found to be strongly correlated with SBP ($r^2 = 0.530, P < .0001$), and can cause the contents of the cavity to pass through the epithelial barrier, leading to the release of proinflammatory cytokines in the intestine. Additionally, previous studies have shown that compared with healthy controls, patients with hypertension had altered microbial compositions in the gastrointestinal tract, like butyrobacter. The decrease of butyrobacter could reduce the concentration of butyrate and weakens its ability to mitigate chronic inflammatory responses, which resulted in the disorders of intestinal epithelial. Furthermore, high blood pressure can active the proliferation, mobilization, and differentiation of hematopoietic stem cells, and thus increase peripheral and neuroinflammation, which may induce the development of IBD.

Despite the relationship between SBP and IBD, we did not observe the causal effect of DBP or PP on the risk of IBD. This may be because the gut microbiota can be altered in different settings of hypertension. A previous study showed that several gut bacteria, such as Christensenellaceae, consistently depleted in individuals with IBD, and were only found to be negatively associated with SBP. An additional possible explanation for the lack of causal associations may be the insufficient statistic power in the present MR study. Thus, the

![FIGURE 3 A Forest plot of the potential causal association of inflammatory bowel disease with the risk of blood pressure. Abbreviations: CI, confidence interval; CD, Crohn’s disease; DBP, diastolic blood pressure; IBD, inflammatory bowel disease; IVW, inverse-variance weighted; OR, odds ratio; PP, pulse pressure; SNP, single nucleotide polymorphism; SBP, systolic blood pressure; UC, ulcerative colitis; WM, weighted-median](image-url)
nonsignificant associations of DBP and PP with IBD should be further clarified in future studies with larger independent populations.

To the best of our knowledge, this was the first study using MR design to elaborate the association between blood pressure and IBD, which minimized potential bias due to confounding and reverse causation. Additionally, we have excluded the genetic variants associated with other traits to avoid the presence of horizontal pleiotropy in the MR analysis. Furthermore, the F-statistics were greater than 10 in our analysis, hinting at the small possibility of weak IV’s bias. Finally, the consistent causal effect estimates obtained from sensitivity analyses using alternative MR methods suggested the robustness of our results.

Nevertheless, several limitations of our study need to be considered. First, due to data availability, we restricted the populations to individuals of European ancestry. Therefore, generalization of the findings of the present study to other populations needs to be cautious. Second, though we identified potential pleiotropic SNPs by searching the GWAS Catalog, it is difficult to completely exclude the influence of potential horizontal pleiotropy. However, by using MR-Egger regression and several other sensitivity analyses, we did not note any evidence of horizontal pleiotropy. Finally, GWAS may lead to overestimation of genetic effect sizes owing to the “winner’s curse” and bias MR results.41 Thus, further study is needed to confirm our findings.

5 | CONCLUSIONS

The present study suggests that high SBP may increase the risk of IBD, including CD and UC. There was no clear evidence of a causal link between blood pressure and IBD of reverse causation. Further research is still required to clarify the underlying mechanism of blood pressure on the development of IBD.

ACKNOWLEDGMENT

The authors sincerely thank the researchers and participants of the original GWASs for the collection and management of the large-scale data resources. This work was supported by grants from the National Natural Science Foundation of China (82103936), the Natural Science Foundation of Zhejiang Province (LQ21H260001, LQ20H260008), the Talent Project of Zhejiang Association for Science and Technology (2018YCGC003).

CONFLICT OF INTEREST

The author reports no conflicts of interest in this work.

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How to cite this article: Xu X, Ye D, Liu B, et al. Assessing the impact of blood pressure in the development of inflammatory bowel disease. J Clin Hypertens. 2022;24:566–572. https://doi.org/10.1111/jch.14477