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ABOUT COVER

Peer Review of *World Journal of Diabetes*, Erkan Gokce, MD, Professor, Department of Radiology, Tokat Gaziosmanpasa University, School of Medicine, Tokat 60100, Türkiye. drerkangokce@gmail.com

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ORIGINAL ARTICLE

Clinical and Translational Research

Does type 1 diabetes serve as a protective factor against inflammatory bowel disease: A Mendelian randomization study

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Abstract

BACKGROUND

The impact of type 1 diabetes (T1D) on inflammatory bowel disease (IBD) remains unclear.

AIM

To analyze the causal relationship between T1D and IBD using Mendelian randomization (MR).

METHODS

Single nucleotide polymorphisms were sourced from FinnGen for T1D, IBD, ulcerative colitis (UC) and Crohn's disease (CD). Inverse variance-weighted, MR-Egger, and weighted median tests were used to assess exposure-outcome causality. The MR-Egger intercept was used to assess horizontal pleiotropy. Cochran's *Q* and leave-one-out method were used to analyze heterogeneity and sensitivity, respectively.

RESULTS

Our MR analysis indicated that T1D was associated with a reduced risk of IBD [odds ratio (OR): 0.959; 95% confidence interval (CI): 0.938-0.980; $P < 0.001$] and UC (OR: 0.960; 95%CI: 0.929-0.992; $P = 0.015$), with no significant association observed in terms of CD risk (OR: 0.966; 95%CI: 0.913-1.022; $P = 0.227$). The MR-

Egger intercept showed no horizontal pleiotropy ($P > 0.05$). Cochran's Q and leave-one-out sensitivity analyses showed that the results were not heterogeneous ($P > 0.05$) and were robust.

CONCLUSION

This MR analysis suggests that T1D serves as a potential protective factor against IBD and UC but is independent of CD.

Key Words: Type 1 diabetes; Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Mendelian randomization

Core Tip: Type 1 diabetes (T1D) is an autoimmune disease characterized by the destruction of pancreatic beta cells. As research progresses, the potential relationship between T1D and inflammatory bowel disease (IBD) has attracted an increasing amount of attention. The study analyzed the causal relationship between T1D and IBD using Mendelian randomization. Our findings indicate that T1D serves as a potential protective factor against IBD and ulcerative colitis but is independent of Crohn's disease.

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INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic, recurrent, nonspecific inflammatory disorder of the intestines[1]. Epidemiological data indicate that approximately 1.5 million people in North America are affected by IBD[2], and that 25% of individuals with IBD develop the condition before the age of 25[3]. The pathogenesis of IBD is not fully understood; however, it is generally believed to be linked to environmental factors acting on genetically predisposed individuals, triggering an uncontrolled inflammatory response mediated by the immune system[4]. The chronic inflammatory response in patients with IBD heightens the risk of cardiovascular diseases, including heart failure and atrial fibrillation, and often necessitates surgeries and frequent hospitalizations[5,6] that can significantly affect the quality of life in patients [7]. Ulcerative colitis (UC) and Crohn's disease (CD) represent the two most prevalent forms of IBD[8]. UC is a chronic idiopathic disease characterized by predominant inflammatory changes localized to the large intestine[9], with clinical manifestations that include bloody diarrhea and a sense of rectal urgency[10]. CD is a refractory inflammatory disease characterized by abdominal pain, fever, intestinal obstruction, and diarrhea, accompanied by the accumulation of blood and mucus[11]. Irregular diet, physical inactivity, and smoking are considered major risk factors for IBD[12-14]. Controlling these risk factors can help to reduce the risk of IBD[4,15]. As research has progressed, researchers have recognized the potential link between type 1 diabetes (T1D) and IBD, suggesting a possible involvement of T1D in IBD induction[16].

T1D is an autoimmune and endocrine disease characterized by endogenous insulin deficiency resulting from the destruction of pancreatic beta cells by the adaptive immune system[17,18]. Epidemiological data show that approximately 542000 children worldwide have T1D[19], and its annual incidence is increasing by 2%-5%[20]. Persistent hyperglycemia in T1D is associated with an elevated risk of cardiovascular and cerebrovascular diseases, as well as kidney disease and retinopathy[21], which significantly affects both health and quality of life in affected patients[22]. Several clinical studies have reported a higher prevalence of IBD in patients with T1D, suggesting that T1D represents a potential risk factor for IBD[23]. However, genetic studies have indicated that genes associated with a high risk of T1D have protective effects against IBD[24]. The effect of T1D on IBD remains unclear, and some related controversies and shortcomings remain unresolved.

Mendelian randomization (MR), a means of analyzing the causal effect of exposure on outcomes through genetic variants, is an emerging method in epidemiological research[25]. Since genotypes are randomly assigned, MR is unlikely to be affected by confounding factors, thus providing better reliability and accuracy[26,27]. We analyzed the causal relationship between T1D and IBD using MR, based on analysis of large-scale genetic data and clinical information.

MATERIALS AND METHODS

Study design

The MR protocol was based on three basic assumptions[28] (Figure 1). The assumption of association requires that a single nucleotide polymorphism (SNP) is closely related to the exposure variable. The independence assumption requires

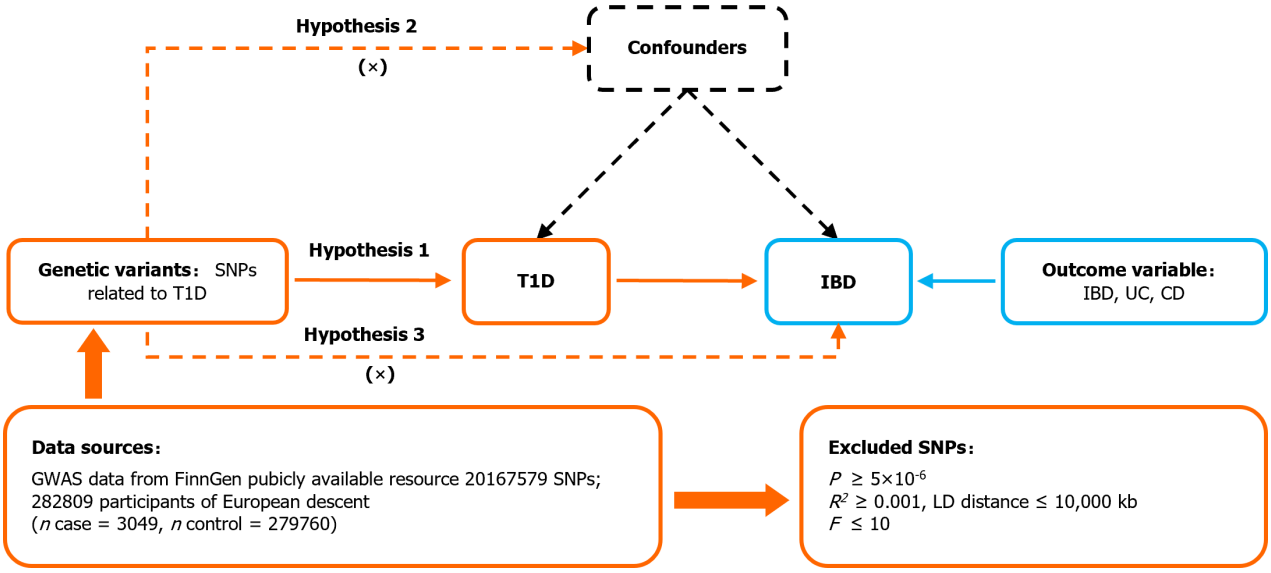

Figure 1 Mendelian randomization design for causal analysis of type 1 diabetes and inflammatory bowel disease. CD: Crohn's disease; IBD: Inflammatory bowel disease; SNP: Single nucleotide polymorphism; T1D: Type 1 diabetes; UC: Ulcerative colitis.

that the SNP is not influenced by confounding variables. The exclusivity assumption requires that the SNP acts only on the outcome, through the exposure, and not through any other pathways.

Data sources

FinnGen (www.finngen.fi/fi) is a publicly available genetic database, originating in Finland, that provided the datasets from Europeans with T1D, IBD, UC, and CD for this study. The database is open; therefore, ethical approval was not required.

Selection of genetic instrument variables

First, $P < 5 \times 10^{-6}$ was used as the restriction when searching for SNPs strongly linked to T1D to fulfill the association assumption. Second, we limited *kb* to 10000 and R^2 to < 0.001, to exclude the interference of linkage disequilibrium. Third, SNPs with strong correlations were searched for with a threshold of $F > 10$, where $F = [R^2/(1\text{-}R^2)] \times [(N\text{-}K\text{-}1)/k]$, with R^2 representing the cumulative explained variance, N representing the total number of samples, and K denoting the number of paired samples. Fourth, SNPs with confounding factors were excluded using PhenoScanner and Google Scholar, to fulfill the independence assumption. Fifth, the nonmatching SNPs were excluded based on effect allele frequency when the direction of exposure and outcome alleles were adjusted. Finally, the MR-pleiotropy residual sum and outlier (MR-PRESSO) approach was used to eliminate outlier SNPs ($P < 1$) to ensure correct causal inference.

Data analysis

STROBE-MR was used as the guiding method[29]. The "TwoSampleMR (0.5.7)" package for R 4.3.1 was used to perform all operations of the MR analysis. Inverse variance-weighted (IVW) was set as the primary assessment tool[30], as it is capable of achieving unbiased causal analysis in the absence of pleiotropy. The weighted median, which is sensitive to outliers, and MR-Egger, which can analyze data in the presence of pleiotropy, were used as secondary assessment tools. The MR-Egger intercept was also used to assess horizontal pleiotropy, which was required to satisfy the exclusivity assumption ($P \geq 0.05$). Cochran's Q and leave-one-out tests were used to analyze heterogeneity and sensitivity, respectively. No heterogeneity was observed in the results at $P \geq 0.05$, and the results were robust when no significant changes were noted in the combined effect sizes.

RESULTS

Genome-wide association studies data on the exposure

The T1D data included 282809 Europeans (Dataset No. finngen _R8_T1D_STRICT1). After association, independence, and exclusivity tests, we included a total of 43 SNPs for T1D in the remainder of our analysis (Supplementary Table 1). Mismatched and outlier SNPs were excluded based on the effects of allele frequency and MR-PRESSO, respectively. Supplementary Tables 2-4 presents the final included SNPs.

Genome-wide association studies data on outcomes

For IBD, UC, and CD, data were acquired from FinnGen (www.finngen.fi/fi), and included 377277 Europeans on IBD (Dataset No. finngen_R9_K11_IBD_STRICT); 364454 Europeans on UC (Dataset No. finngen_R9_ULCERNAS); and

Table 1 Details of the genome-wide association studies included in the Mendelian randomization

Year	Trait	GWAS ID	Population	Sample size	Web source
2022	T1D	finngen_R8_T1D_STRICT1	European	282809	www.finngen.fi/fi
2023	IBD	finngen_R9_K11_IBD_STRICT	European	377277	www.finngen.fi/fi
2023	UC	finngen_R9_ULCERNAS	European	364454	www.finngen.fi/fi
2023	CD	finngen_R9_CHRONNAS	European	361934	www.finngen.fi/fi

CD: Crohn's disease; GWAS: Genome-wide association studies; IBD: Inflammatory bowel disease; T1D: Type 1 diabetes; UC: Ulcerative colitis.

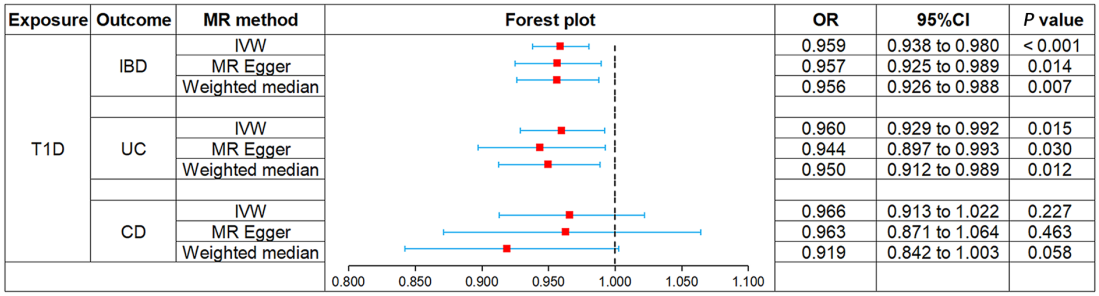

Figure 2 Forest plot of Mendelian randomization analysis on the causal relationship between type 1 diabetes and inflammatory bowel disease. 95%CI: 95% confidence interval; CD: Crohn's disease; IBD: Inflammatory bowel disease; IVW: Inverse variance-weighted; MR: Mendelian randomization; OR: Odds ratio; T1D: Type 1 diabetes; UC: Ulcerative colitis.

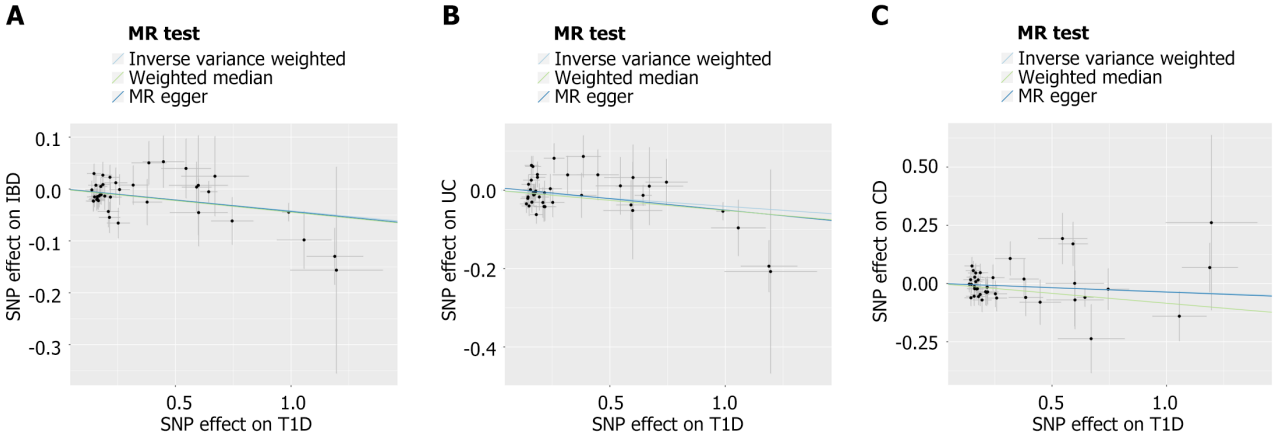

Figure 3 Scatter plot of Mendelian randomization analysis on the causal relationship between type 1 diabetes and inflammatory bowel disease. A: Type 1 diabetes (T1D) on inflammatory bowel disease; B: T1D on ulcerative colitis; C: T1D on Crohn's disease. MR: Mendelian randomization; SNP: Single nucleotide polymorphism; UC: Ulcerative colitis; IBD: Inflammatory bowel disease; T1D: Type 1 diabetes; CD: Crohn's disease.

361934 Europeans on CD (Dataset No. finngen_R9_CHRONNAS). Table 1 provides more detailed information on patient characteristics.

MR analysis

MR analysis was used to assess the causal effects of the exposure factors (T1D) on the outcome variables (IBD). Figure 2 presents a forest plot of this relationship, while Figure 3 displays a scatter plot. The MR-Egger intercept was used to assess the horizontal pleiotropy of the results (Supplementary Table 5).

Causal relationship between T1D and IBD: Our MR analysis showed that T1D was associated with a reduced risk of IBD for IVW [odds ratio (OR): 0.959; 95% confidence interval (CI): 0.938-0.980; $P < 0.001$], MR-Egger (OR: 0.957; 95%CI: 0.925-0.989; $P = 0.014$), and weighted-median (OR: 0.956; 95%CI: 0.926-0.988; $P = 0.007$) approaches. No horizontal pleiotropy was observed ($P = 0.857$).

Causal relationship between T1D and UC: Our MR analysis showed that T1D was associated with a reduced risk of UC, in terms of IVW (OR: 0.960; 95%CI: 0.929-0.992; $P = 0.015$), MR-Egger (OR: 0.944; 95%CI: 0.897-0.993; $P = 0.030$), and

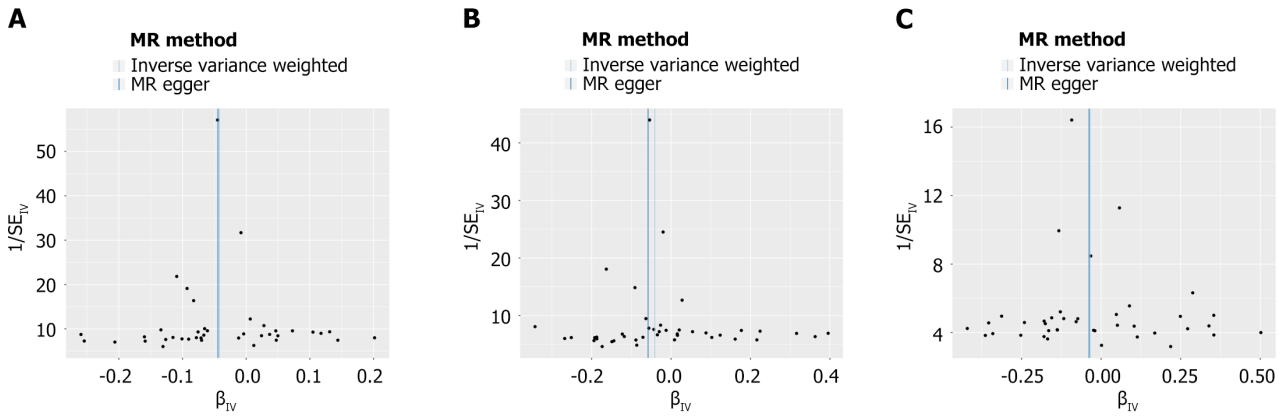

Figure 4 Funnel plot of heterogeneity analysis on the causal relationship between type 1 diabetes and inflammatory bowel disease. A: Type 1 diabetes (T1D) on inflammatory bowel disease; B: T1D on ulcerative colitis; C: T1D on Crohn's disease. MR: Mendelian randomization.

weighted-median (OR: 0.950; 95%CI: 0.912-0.989; P = 0.012) results. No horizontal pleiotropy was observed (P = 0.390).

Causal relationship between T1D and CD: All three analysis methods showed no causal relationship between T1D and CD: IVW (OR: 0.966; 95%CI: 0.913-1.022; P = 0.227), MR-Egger (OR: 0.963; 95%CI: 0.871-1.064; P = 0.463), and weighted-median (OR: 0.919; 95%CI: 0.842-1.003; P = 0.058). No horizontal pleiotropy was observed (P = 0.941).

Heterogeneity and sensitivity analysis

Cochran's Q test revealed an absence of heterogeneity in all of the MR analysis results ($P \geq 0.05$), as shown in Figure 4 and Supplementary Table 6. Our sensitivity analysis confirmed the robustness of the MR analysis, as shown in Figure 5.

DISCUSSION

As a disease that cannot be completely cured[31], IBD increases the risk of bowel cancer, cardiovascular disease, and mental disorders in patients[32-34]. This places significant burdens on healthcare systems, economies, and societies in general[35]. Individualized treatment and close monitoring are crucial for the management of IBD[36,37]. Smoking, high-sugar and high-fat diets, vitamin D deficiency, and the use of antibiotics and nonsteroidal anti-inflammatory drugs are considered major risk factors for IBD, and controlling these risk factors can help reduce the risk of the disease[38-40]. As research on the subject progresses, some studies have found an association between T1D and an increased risk of IBD [41], suggesting it may represent a potential risk factor for the condition. However, there is little evidence for this, and some genetic studies have even shown that T1D risk genes are protective against CD and UC[24]. The causal effect of T1D on IBD remains a controversial and intriguing topic. To the best of our knowledge, this was the first study to use MR to assess the causal relationships between these two. In this MR analysis, we observed that T1D was associated with a reduced risk of IBD and UC but not CD. Given the absence of pleiotropy and heterogeneity, our MR analysis results were deemed to be reliable.

Few studies have examined the effect of T1D on the risk of developing CD. The only clinical study in the literature to date, an epidemiological survey conducted by Jasser-Nitsche *et al*[16] in Germany and Austria, showed that the risk of CD in patients with T1D < 18 years of age was 1.06 × higher than that in the general population within the same age group [relative risk (RR): 2.06; 95%CI: 1.17-3.65]. Although that clinical study supported T1D as a potential risk factor for CD, genetic studies offer a markedly different perspective. Wang *et al*[24] showed that T1D risk alleles at the protein tyrosine phosphatase nonreceptor type 22 (*PTPN22*), interleukin 27 (IL-27), IL-18 receptor accessory protein, and IL-10 loci have opposing roles in CD, sometimes protecting against it. *PTPN22* is involved in both T1D and CD[42]. Studies have shown that T1D-susceptible children with the *PTPN22* 1858T allele have a significantly increased risk of developing T1D after the appearance of their first pancreatic beta-cell autoantibody [hazard ratio (HR): 1.68; 95%CI: 1.09-2.60][43]. This effect may be achieved by reducing insulin tolerance and increasing the expression of proinflammatory T cells[44]. Interestingly, the presence of the *PTPN22* gene has been associated with an increased risk of T1D, whereas its absence is associated with an increased risk of CD. Under normal circumstances, the intestinal immune system is tightly controlled by the balance between proinflammatory and anti-inflammatory factors. CD occurrence is closely linked to the disruption of this balance, as well as an increase in proinflammatory factors. The deletion of the *PTPN22* gene promotes the activation of inflammatory signaling and increases the secretion of T helper 17 (Th17)-associated inflammatory factors, which further induces the occurrence of CD by promoting Th17 and Th1 differentiation[45]. The absence of *PTPN22* also leads to an increase in p38 mitogen-activated protein kinase and a decrease in signal transducer and activator of transcription 1 (STAT1) and STAT3 expression, resulting in an increase in IL-6 and IL-17 levels, as well as a decrease in T-box-expressed-in-T-cells, intercellular adhesion molecule-1, monocyte chemoattractant protein-1, IL-2, IL-8, and IL-12p40 levels, ultimately inducing the development of CD[42,45]. The roles of common genes, represented by *PTPN22*, are

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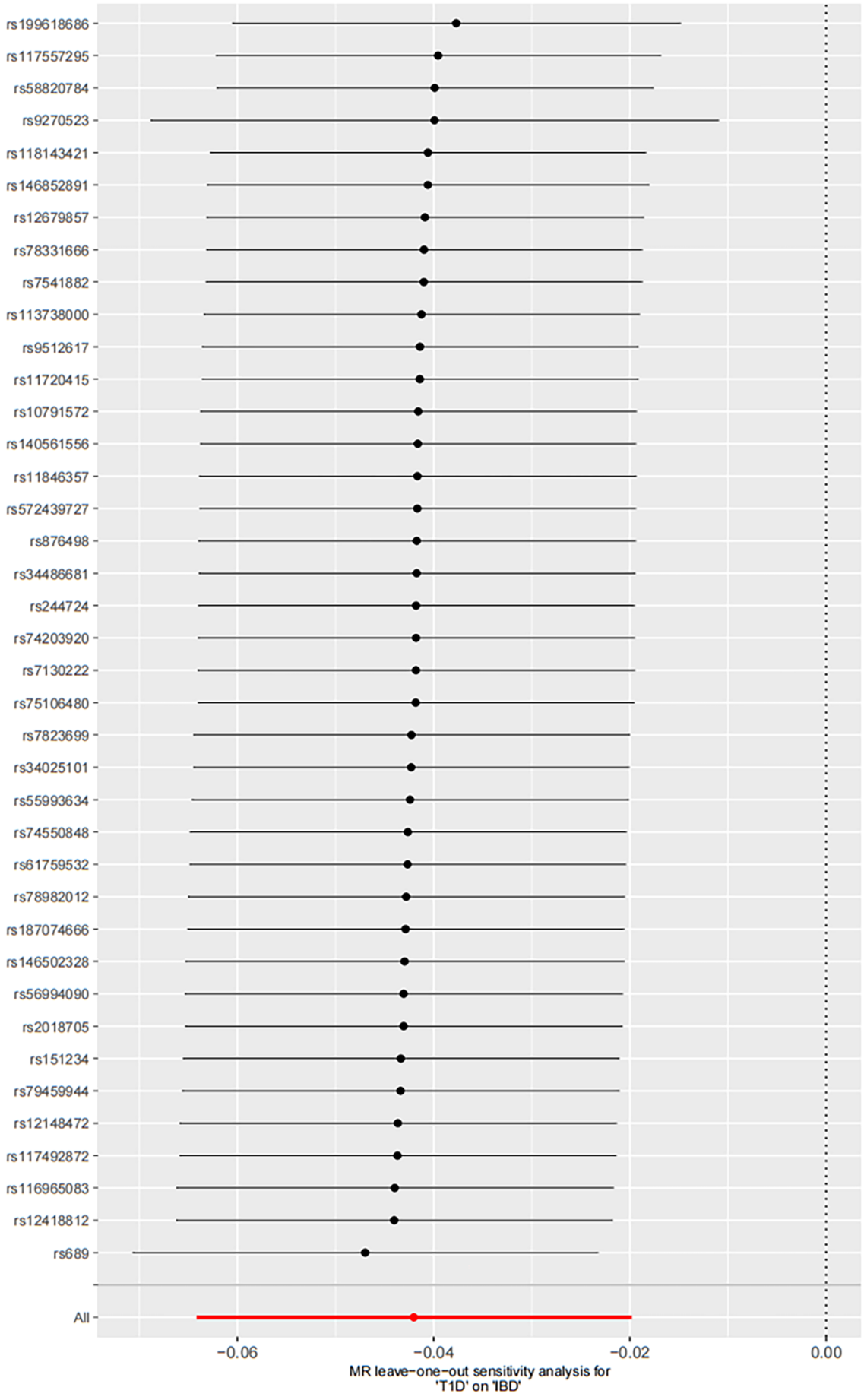
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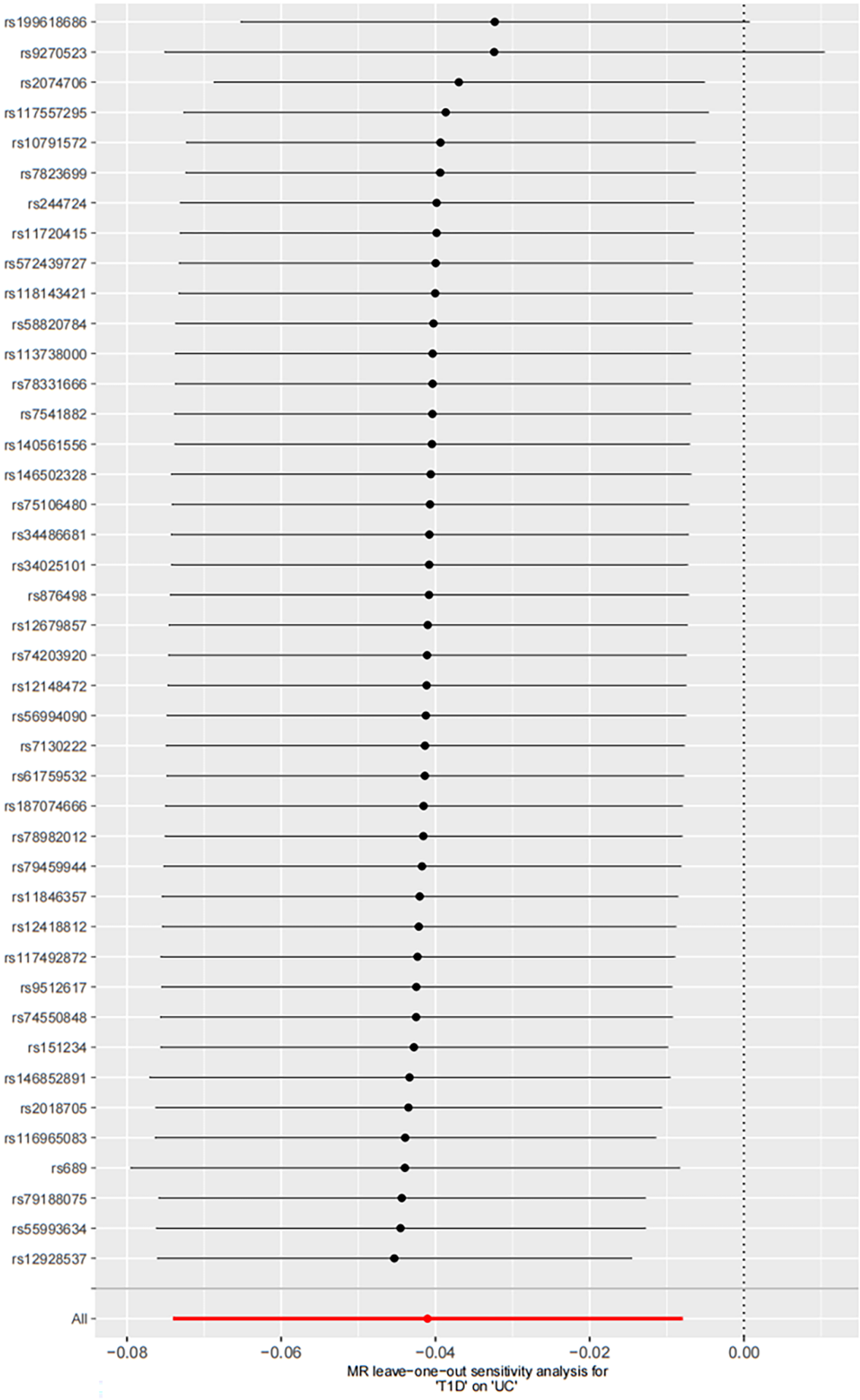
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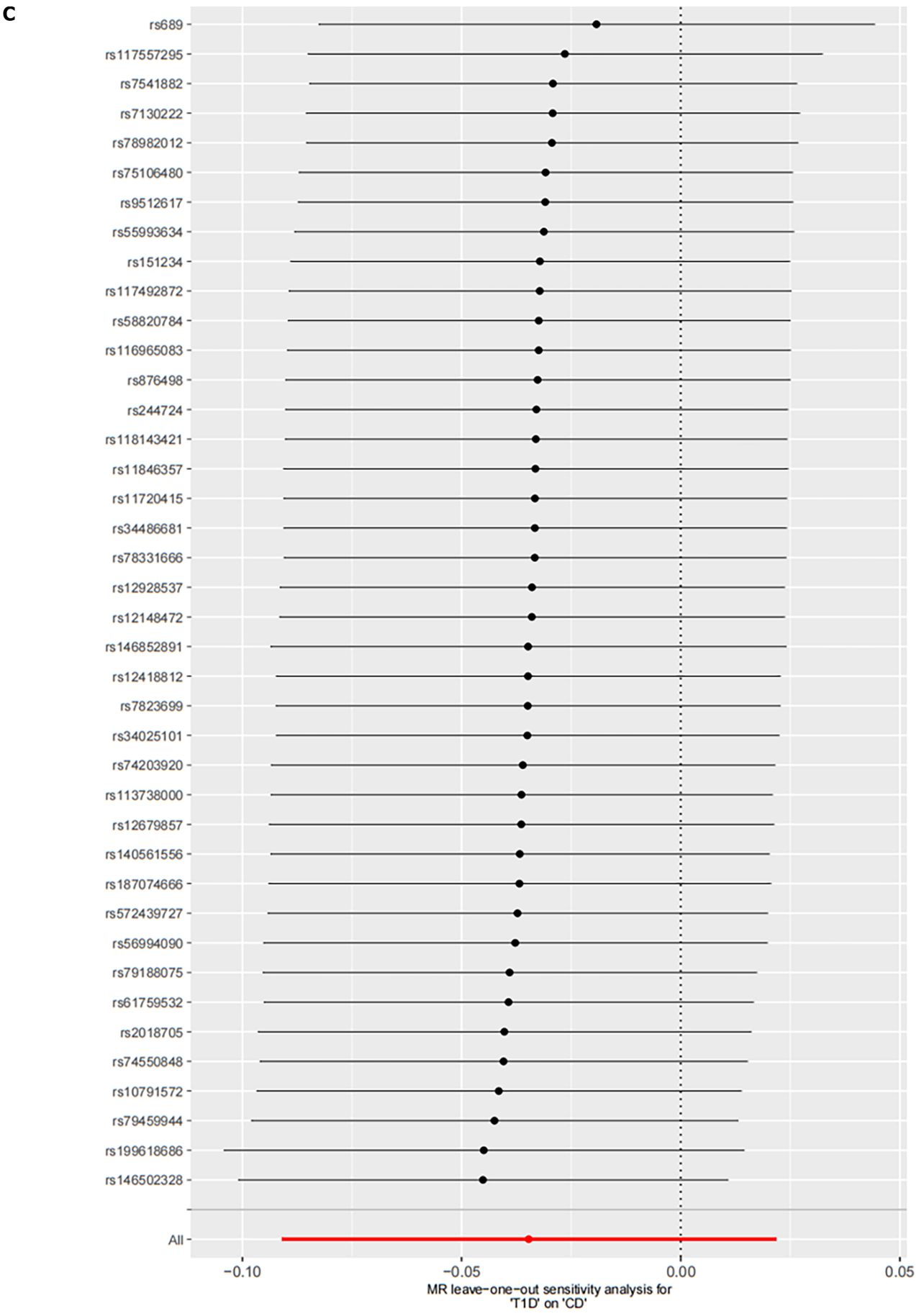

Figure 5 Leave-one-out sensitivity analysis on the causal relationship between type 1 diabetes and inflammatory bowel disease. A: Type 1 diabetes (T1D) on inflammatory bowel disease; B: T1D on ulcerative colitis; C: T1D on Crohn's disease. UC: Ulcerative colitis; IBD: Inflammatory bowel disease; T1D:

Type 1 diabetes; CD: Crohn's disease.

opposite in T1D and CD, suggesting that T1D may be associated with a low risk of CD. However, our study indicated that T1D was not associated with CD risk, supporting neither the risk factors that have been reported in previous clinical studies, nor the protective factors that have been reported in genetic ones. Due to the paucity of current evidence, the relationship between T1D and CD risk remains unclear and merits further exploration.

Current clinical studies predominantly support the association between T1D and increased risks of IBD and UC. A UK clinical study that included 662 patients with T1D and 602 randomly selected individuals showed that the patients with T1D had a higher prevalence of IBD (1.5% *vs* 0.3%)[41]. In an epidemiological survey in Germany and Austria, Jasser-Nitsche *et al*[16] found that the risks of IBD and UC in patients with T1D under the age of 18 years were 2.25 × (RR: 3.25; 95%CI: 2.17-4.88) and 3.67 × (RR: 4.67; 95%CI: 2.35-9.26) higher, respectively, compared to those in the general age-matched population. Although these pieces of evidence suggest that T1D is a potential risk factor for IBD and UC, the quality of these studies is limited by their small and specific patient samples. By contrast, our MR analysis unexpectedly identified T1D as a protective factor against both IBD and UC. Some genetic studies support our findings, confirming that T1D risk genes may have protective effects against IBD and UC. As a gene shared by T1D and UC, human leukocyte antigen (HLA) plays diametrically opposing roles in T1D and UC[46,47]. Studies have shown that individuals with the HLA genotypes (DR3-DQ8 and DR4-DQ2) have a higher risk of developing T1D[47]. The risk of T1D in those with high-risk HLA genotypes is 1.9 × higher than that in individuals with low-risk genotypes (HR: 2.9; 95%CI: 1.0-8.0)[48]. However, the strongest T1D risk allele, rs9275383, which is located between HLA-DQB1 and HLA-DQA2, has been shown to protect against UC (P = 1.9 × 10^{-9}; OR: 0.53)[24]. These genetic studies suggest that T1D may represent a potential protective factor against UC, which is consistent with our findings. Notably, the results of gene-based predictions are strikingly different from those of clinical studies. Considering the extreme paucity of current clinical evidence, determining the specific effects of T1D on UC risk is difficult for now. More research is expected to further explore this controversy in the future.

Although this MR analysis increased the genetic evidence surrounding T1D and IBD, it was nevertheless subject to certain limitations worth noting. First, the data were from European patients; therefore, our findings cannot be extrapolated to elucidate the relationship between T1D and IBD in other ethnic groups. Second, despite strict adherence to the STROBE-MR guideline, the results of this MR analysis differed from those reported in clinical studies, necessitating further research to elucidate the reasons behind these inconsistent results. Third, there may be unrecognized confounding factors between the exposure factors and outcome indicators that increased the risk of bias in our MR results. Acknowledging these limitations, we anticipate that future studies will continue to enrich the database of genome-wide association studies, aiming for ethnically diverse MR research and the promotion of health equity. Moreover, multicenter, large-sample clinical studies are warranted to provide higher-quality clinical evidence investigating the correlation between T1D and IBD.

CONCLUSION

This MR analysis suggests that T1D serves as a potential protective factor against IBD and UC, independent of CD. Nevertheless, clinical evidence supporting this result is currently insufficient, and further studies are warranted to explore the intrinsic link between T1D and IBD.

FOOTNOTES

Author contributions: Tong KK and Yu YF conceived and designed the study; Yu YF and Yang XY participated in data processing and statistical analyses; Tong KK, Yu YF, Yang XY, and Wu JY drafted the manuscript; Yu R and Tan CC supervised the review of the study; All authors revised and approved the final manuscript. Tong KK and Yu YF have made equal contributions to this work as co-first authors for two reasons. First, Tong KK and Yu YF made contributions of equal significance throughout the research process. The choice of these researchers as co-first authors acknowledges and respects this equal contribution. Second, the research was a collaborative effort, and co-first authorship accurately reflects the distribution of responsibilities and the substantial time and effort invested in completing the study and the resulting paper. In summary, designating Tong KK and Yu YF as co-first authors is appropriate for our manuscript as it faithfully reflects our team's collaborative ethos, equal contributions, and diversity. In addition, Tan CC and Yu R have made equal contributions to this work as co-corresponding authors. Their work spanned the entire process, collectively guiding the conception, drafting, revision, and finalization of the manuscript, which is indispensable to the completion of this manuscript.

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