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Association between diabetes mellitus and giant cell arteritis: a bidirectional 2-sample mendelian randomization study

Si Chen^{1†}, Xiaoli Zeng^{1†}, Xu Ma¹, Haixia Luan¹, Rui Nie¹, Yan Wang¹, Hua Liao², Lili Pan^{2*} and Hui Yuan^{1*}

Abstract

Objective Recent studies have indicated a potential association between giant cell arteritis (GCA) and diabetes mellitus, encompassing both type 1 diabetes (T1D) and type 2 diabetes (T2D). However, the exact nature of this relationship requires further investigation to be fully elucidated.

Methods Genetic links between T1D/T2D and GCA were explored using data from genome-wide association studies available to the public, focusing on populations of European ancestry. We applied a bidirectional mendelian randomization (MR) approach to assess the potential association between these diseases. Confirmatory analyses, including additional datasets and a comprehensive meta-analysis, were utilized. The inverse-variance-weighted (IVW) method was applied to pinpoint heterogeneity and pleiotropy, while subsequent sensitivity analyses aimed to trace the origins of any heterogeneity.

Results Initial analysis demonstrated a correlation between T1D and an elevated likelihood of developing GCA (IVW odds ratio = 1.33, with a 95% confidence interval of 1.22–1.46, and a *P*-value of 9.42E–10). The causal association was verified through four validation datasets and meta-analysis (all *P*-value < 0.001). However, the reverse MR analysis was unable to detect any genetic basis for the increased risk of T1D due to GCA. Furthermore, we could not establish any causal links between T2D and GCA.

Conclusion T1D patients may have a higher risk of developing GCA, whereas an inverse causal relationship was not evident. Furthermore, no causal relationship was detected between T2D and GCA. These insights shed light on the possible pathological mechanisms underlying GCA and may influence the future clinical handling of both T1D and GCA.

Keywords Diabetes mellitus, Giant cell arteritis, Mendelian randomization, Type 1 diabetes, Type 2 diabetes

Background

Giant cell arteritis (GCA) is a type of vascular inflammation characterized by granulomatous swelling within the medium to large arteries, notably the temporal artery, and predominantly affects individuals over the age of 50 [1]. This condition manifests through symptoms such as persistent headaches, pain in the jaw when chewing, and tenderness of the scalp, in addition to increased levels of inflammatory markers like C-reactive protein and the erythrocyte sedimentation rate [2]. While Temporal artery biopsy (TAB) remains the standard for diagnosing GCA, less invasive techniques such as Doppler

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ultrasound, PET-CT, and MRI are progressively being adopted in diagnostics [3–5]. GCA has been traditionally treated using substantial doses of glucocorticoids (GCs), which come with a spectrum of potential side effects. Tocilizumab, an inhibitor to the interleukin-6 (IL-6) receptor, is a promising alternative that may lower the reliance on glucocorticoids [6, 7].

Diabetes mellitus (DM) refers to a group of chronic conditions marked by inadequate regulation of blood glucose levels due to insufficient insulin production and/or inefficient insulin action. If left unmanaged, the chronic hyperglycemic state arising as a result can cause various complications affecting the cardiovascular, nervous, and renal systems [8]. Type 1 diabetes (T1D) is characterized by an autoimmune attack on the insulin-secreting beta cells in the pancreas, and typically develops in younger populations [9]. On the other hand, type 2 diabetes (T2D) usually arises from insulin resistance and is more common among adults and the elderly [10]. Both types of diabetes pose significant health risks if not properly managed, including cardiovascular complications, kidney disease, and nerve damage.

The correlation between GCA and blood glucose levels is ambiguous. Population-based cohort studies have shown an inverse correlation between the incidence of GCA and increased levels of fasting blood glucose [11]. Moreover, several studies have reported lower glycated hemoglobin (HbA1c) levels and prevalence of diabetes among individuals diagnosed with GCA [12, 13]. However, Esen et al. [14] demonstrated increased baseline glucose levels in GCA patients compared to the general population, although no differences were observed in HbA1c levels. In a case report of a male T1D patient, acute upper respiratory infection was followed by the development of biopsy-proven GCA [15], which underscores the complex interactions between autoimmune diseases and infections. The interrelation between T2D and GCA is similarly multifaceted, with some studies suggesting a potential protective effect of T2D against developing GCA [16], Abel et al. [17] found that T2D increased the risk of GCA by 100% among the beneficiaries of Medicare. In addition, high-dose (GC) treatment of GCA increases the body mass index (BMI), which in turn can elevate the risk of T2D [18–20].

Case studies and observational analyses are often restricted by various factors, such as potential confounding influences, limited participant numbers, and variations across population ethnicities, which hinders the ability to firmly establish causative links. Consequently, the nature of the association between DM and GCA—whether causative, coincidental, or a one-way or two-way relationship—remains to be clarified. Mendelian randomization (MR) leverages genetic variants as

instrumental variables to sidestep limitations inherent in observational studies, and therefore can offer more definitive insights. MR utilizes the single nucleotide polymorphisms (SNPs) sourced from extensive genome-wide association studies (GWAS) to elucidate the relationship between an exposure and its outcome, while minimizing the confounding effects [21–23]. As SNPs assort independently according to Mendelian inheritance during gamete formation, MR analyses are generally less susceptible to reverse causation and lingering bias [24]. The aim of this study was to examine a possible causal link between DM and GCA using bi-directional MR analyses based on data collated in GWAS.

Materials and methods

Study design

Several key hypotheses were made: (1) Appropriateness of IVs: the selected instrumental variables (IVs) are appropriate because they have strong correlations with exposure (T1D/T2D or GCA). These IVs are well-documented in existing research for their strong association with exposure (T1D/T2D or GCA), making them suitable for the analysis. (2) Independence from confounders: the IVs used are not influenced by confounding variables in the T1D/T2D and GCA relationship. The IVs known to be independent of confounding factors were selected to ensure a clear causal pathway. (3) Exogeneity of IVs regarding outcome: the IVs affect outcome (GCA or T1D/T2D) through mechanisms unrelated to exposure (T1D/T2D or GCA). Causality was investigated with diabetes as the influencing factor and GCA as the outcome, followed by an inverse assessment with GCA as the influencer and diabetes as the outcome (Fig. 1).

Data sources

The inclusion criteria for data were as follows: (1) The data must be from articles published within the last three years. (2) The included data should represent either the largest or one of the largest sample sizes currently available. (3) The number of SNPs in the data must reach 10^7 . The exclusion criteria for data were as follows: (1) Data from articles published a long time ago. (2) Data with a relatively small sample size. (3) Data with a small number of SNPs. (4) Data for which the original datasets are not accessible. The data for T1D was obtained from five GWASs. The discovery T1D GWAS data was sourced from FinnGen Release 10 [25], using the phenocode “T1D_STRICT2” for identification. In addition, four validation T1D datasets (GCST90014023 [26], GCST90018925 [27], GCST90013891 [28], and GCST90013941 [28]), along with one T2D dataset (GCST90018926 [27]), were accessed from the IEU OpenGWAS database, located

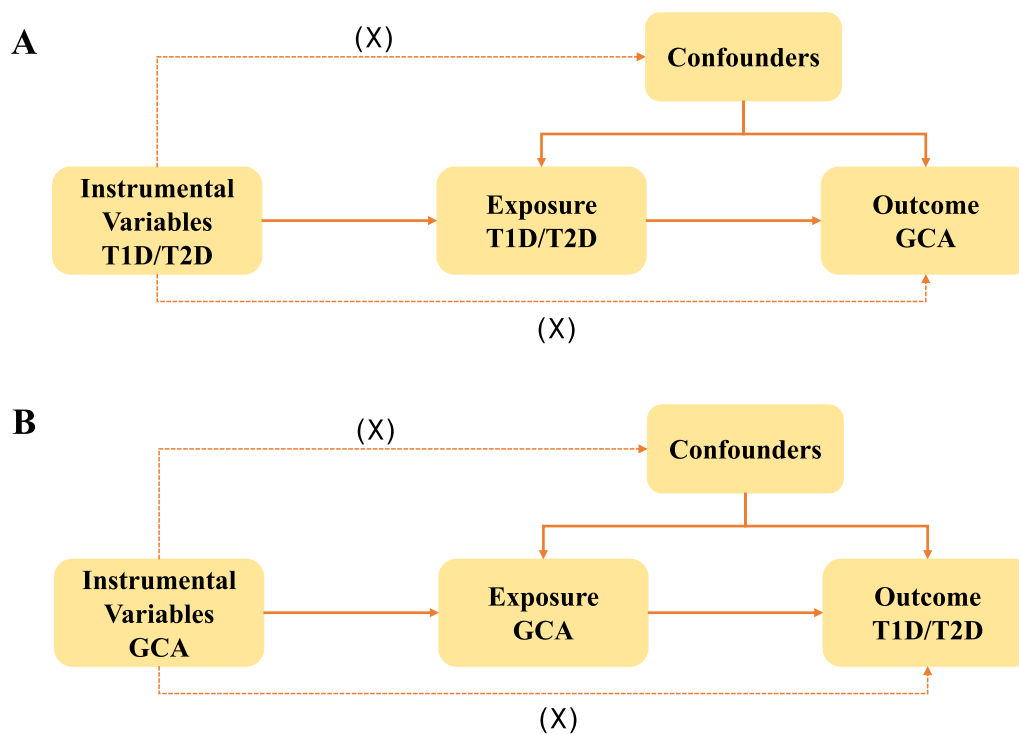


Fig. 1 Overview of the MR analysis. **(A)** T1D/T2D-related SNPs were used as instrumental variables (IVs) to investigate the potential causal effect of T1D/T2D on GCA. **(B)** GCA-related SNPs were used as IVs to investigate the potential causal effect of GCA on T1D/T2D. Solid lines: instrumental variables (SNPs) that are linked to the exposure and can solely affect the outcome through exposure. Dotted lines: instrumental variables (SNPs) that are unrelated to any confounding factors and are between the exposure and the outcome. The confounding factors included exposure to environmental toxins, radiation, infectious agents, chemical substances, smoking, and prior pregnancy

at <https://gwas.mrcieu.ac.uk/>. Furthermore, aggregate GCA genetic insights were also derived from FinnGen Release 10, earmarked with the phenocode “M13_GIANTCELL”. All GWAS data were retrieved by December 31, 2023. Comprehensive GWAS datasets pertaining to T1D, T2D, and GCA are delineated in Table 1.

Selection of IVs

Genome-wide association significance for the SNPs was set as P value $< 5 \times 10^{-8}$, the independence of all selected SNPs was within 10,000 kb, and linkage disequilibrium threshold r^2 was less than 0.001 when T1D/T2D (GCST90014023, GCST90018925, and GCST90018926) was taken as the exposure. When T1D (T1D_STRICT2, GCST90013891, and GCST90013941) was the exposure, the significance threshold for the SNPs was P

Table 1 The detailed information on included GWAS data

Disease	GWAS ID	Sample size (N)	Cases (N)	Controls (N)	Population	Number of SNPs	Year	Median age (years)	Author	PMID
T1D	T1D_STRICT2	331,094	105	330,989	European	N/A	N/A	12.38	N/A	N/A
T1D	GCST90014023	520,580	18,942	501,638	European	59,999,551	2021	N/A	Chiou J	34012112
T1D	GCST90018925	457,695	6447	451,248	European	24,182,422	2021	N/A	Sakaue S	34594039
T1D	GCST90013891	407,746	N/A	N/A	European	11,039,126	2021	N/A	Mbatchou J	34017140
T1D	GCST90013941	407,746	N/A	N/A	European	11,035,542	2021	N/A	Mbatchou J	34017140
T2D	GCST90018926	490,089	38,841	451,248	European	24,167,560	2021	N/A	Sakaue S	34594039
GCA	M13_GIANTCELL	400,421	1066	399,355	European	N/A	N/A	69.81	N/A	N/A

GCA giant cell arteritis; T1D type 1 diabetes; T2D type 2 diabetes; GWAS genome-wide association studies; N number; N/A not available

value $< 1 \times 10^{-6}$, the independence of all selected SNPs was within 1000 kb, and linkage disequilibrium threshold r^2 was 0.01. In scenarios where GCA served as the exposure, SNP significance was defined by a P value of less than 1×10^{-5} , LD coefficient cap set at $r^2 < 0.01$, and LD search span restricted to 10,000 kb. The F-statistic of each SNP was ascertained to confirm robustness, requiring an F-value above 10. The SNP dataset was further refined to exclude SNPs that were palindromic or could not be unambiguously interpreted. To guard against possible pleiotropic effects, IVs tied to confounding factors or recognized GCA risk factors, like exposure to other autoimmune disorders, were screened out using the PhenoScanner V2 tool (available at <http://www.phenoscaner.medschl.cam.ac.uk/>).

MR analyses

The primary methodology adopted for MR analysis was the inverse variance weighted (IVW) method, which can mitigate pleiotropic variations and produce dependable outcomes. To further evaluate causation under varying conditions, MR-Egger regression was employed alongside the calculation of a weighted median [29–31]. The findings were articulated as odds ratios (ORs) along with their 95% confidence intervals (CIs). A p value threshold of less than 0.05 was determined to denote statistical significance. The statistical computations were performed using the TwoSampleMR package (version 0.5.7) of R version 4.3.1 [32].

Sensitivity analysis

The MR-Egger intercept was employed to probe for horizontal pleiotropy, where the IVs might influence the outcome through several distinct channels. The presence of horizontal pleiotropy was visualized using scatter plots. Heterogeneity among the IVs was quantified using Cochran's Q test, with P values below 0.05 indicating significant variance. Funnel plots were used to visualize heterogeneity and validate the stability of the results. The results were further verified through the leave-one-out sensitivity analysis, which involves sequential omission of each SNP. Moreover, the MR pleiotropy residual sum and outlier test was applied to scrutinize the direct influence of the IVs on the outcomes, and to evaluate any residual horizontal pleiotropy.

Results

Causal relationships between T1D and GCA

We use the rigorously screened T1D dataset (T1D_STRICT2) as the exposure data for the discovery stage. Based on the IVW approach, T1D was associated with a significant increase in the risk of GCA (OR=1.33, 95% CI 1.22–1.46, $P=9.42E-10$) (Table 2). Therefore, we

selected the GWAS data of four European T1D datasets (GCST90013891, GCST90013941, GCST90014023, and GCST90018925) with a current sample size of over 400000 as the exposure data for the validation phase, and observed that T1D increased the risk of GCA development (IVW: all P -value < 0.05) (Table 3, Supplementary Figs. 1–4). Additionally, a meta-analysis of the IVW method was conducted on these four datasets, which also revealed a significant increase in the GCA risk due to T1D ($P < 0.0001$; Fig. 2). We then performed reverse MR analysis to explore the effect of GCA on five T1D GWAS data. However, there was no indication of a reverse causal link with the IVW technique (Table 2 and Supplementary Table 1). Furthermore, the MR-Egger intercept test (scatter plots shown in Fig. 3A, Supplementary Figs. 1A, 2A, 3A and 4A), sensitivity analysis (forest plots shown in Fig. 3B, Supplementary Figs. 1B, 2B, 3B and 4B), leave-one-out analysis (Fig. 3C, Supplementary Figs. 1C, 2C, 3C and 4C), and Cochran's Q statistics (funnel plots shown in Fig. 3D, Supplementary Figs. 1D, 2D, 3D and 4D) did not indicate any significant heterogeneity in the impact of T1D on GCA risk. We also did not detect any directional pleiotropy (Table 2 and Table 3), and the robustness of the data was confirmed by the leave-one-out analyses. The analysis revealed a lack of significant heterogeneity or directional pleiotropy when evaluating the influence of GCA on T1D, as demonstrated by the MR-Egger intercept, Cochran's Q test, and further corroborated by leave-one-out and sensitivity analyses (Supplementary Table 1 and Figs. 5–9).

Causal links between T2D and GCA

To elucidate the potential causal links between T2D and GCA, a bidirectional MR approach was employed. As indicated in Table 1, the analysis did not establish any causal link between T2D and GCA. Furthermore, the sensitivity tests, including the MR-Egger intercept and Cochran's Q statistics, along with the leave-one-out method, consistently found no notable heterogeneity or directional pleiotropy (Supplementary Figs. 10 and 11).

Discussion

This study is possibly the first to apply a bidirectional MR framework to uncover a causative link between DM and GCA. Our results confirm a significant correlation between genetically predicted T1D and a greater risk of GCA. However, reverse MR analysis did not indicate that a genetic predisposition to GCA increased the risk of developing T1D. In addition, no causal relationship was detected between T2D and GCA.

GCA, an inflammatory disease of large and medium-sized blood vessels, is characterized by granulomatous inflammation affecting, and mainly occurs in the elderly

Table 2 Causal association between T1D/T2D and GCA in MR analysis during the discovery stage

Exposure/Outcome	Methods	SNPs (n)	OR (95% CI)	P-value	Test of heterogeneity		Test of pleiotropy			MRPRESSO (P-value)
					Q	P-value	Intercept	SE	P-value	
T1D/GCA	MR Egger	6	1.71 (1.39–2.11)	7.42E–03	2.12	0.71	–0.31	0.12	0.07	0.284
	Weighted median	6	1.29 (1.16–1.43)	2.87E–06						
	IVW	6	1.33 (1.22–1.46)	9.42E–10	8.26	0.14				
	Simple mode	6	1.41 (1.16–1.71)	0.018						
	Weighted mode	6	1.22 (1.07–1.39)	0.031						
GCA/T1D	MR Egger	35	1.21 (0.66–2.23)	0.54	38.23	0.23	–0.07	0.13	0.61	0.212
	Weighted median	35	1.18 (0.75–1.85)	0.48						
	IVW	35	1.06 (0.78–1.43)	0.71	38.88	0.26				
	Simple mode	35	0.56 (0.20–1.60)	0.29						
	Weighted mode	35	0.48 (0.16–1.42)	0.20						
T2D/GCA	MR Egger	167	1.24 (0.98–1.57)	0.08	174.78	0.29	–0.015	8.83E–03	0.10	0.261
	Weighted median	167	1.05 (0.87–1.28)	0.61						
	IVW	167	1.04 (0.93–1.17)	0.50	177.67	0.25				
	Simple mode	167	1.44 (0.97–2.12)	0.07						
	Weighted mode	167	1.05 (0.84–1.31)	0.69						
GCA/T2D	MR Egger	16	1.00 (0.95–1.05)	0.97	13.87	0.46	1.29E–03	8.74E–03	0.89	0.492
	Weighted median	16	1.00 (0.97–1.03)	0.89						
	IVW	16	1.00 (0.98–1.02)	0.79	13.90	0.53				
	Simple mode	16	0.98 (0.93–1.03)	0.51						
	Weighted mode	16	0.98 (0.95–1.03)	0.65						

GCA giant cell arteritis; T1D type 1 diabetes; T2D type 2 diabetes; MR mendelian randomization; IVW inverse variance weighted; SNPs single nucleotide polymorphisms; OR odds ratio; CI confidence intervals; SE standard error

[1]. In addition to specific symptoms like headaches, jaw claudication, limb claudication and vision loss, patients frequently experience non-specific manifestations such as fever and weight loss [2]. Previous studies have reported abnormalities in blood glucose and HbA1c levels in patients with GCA [11, 12, 14]. However, there are no documented cases of GCA patients developing T1D. This is not surprising given that GCA is more common in individuals older than 50 years [1], while T1D primarily manifests in adolescence due to a genetic predisposition [9]. Nevertheless, T1D and GCA share a few susceptibility genetic variations, such as PTPN22 1858C/T polymorphism and STAT4 rs7574865, which provide indirect evidence of an association between the two diseases [33, 34]. Furthermore, several inflammatory factors are elevated during T1D and GCA, such as interleukin 21 [35]. There is however one reported case of late GCA onset in a 62-year-old patient with T1D, who developed biopsy-confirmed GCA after suffering an acute upper respiratory infection. Serological tests revealed concomitant *Streptococcus pneumoniae* infection. The clinical signs of vasculitis disappeared in a month without any immunosuppressive therapy, and no relapse was noted during the ensuing 12 months [18]. The natural course of GCA

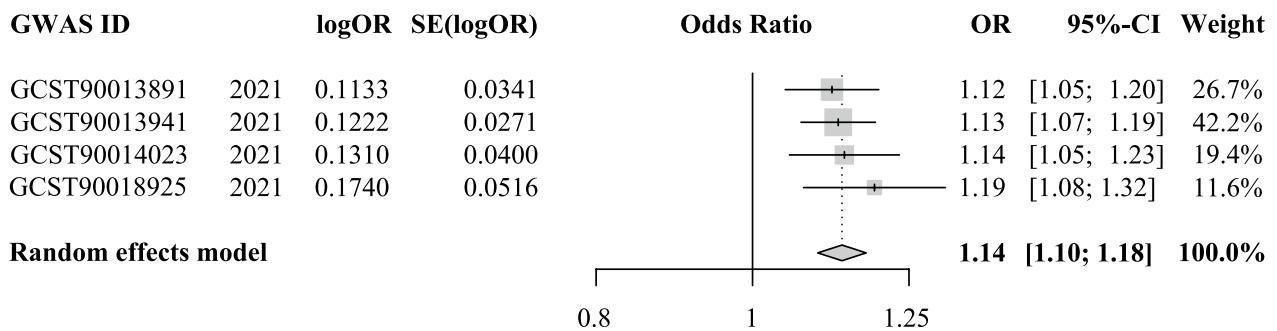
is still unknown, and the respiratory infection may have contributed to its development. In fact, some recent studies have demonstrated an indirect link between infection and GCA development [36, 37]. However, the aforementioned individual case reports do not clearly establish a causal relationship between T1D and GCA. Furthermore, there is a lack of large-scale and comprehensive genetic studies investigating the relationship between the two conditions. In this study, we used the latest five GWAS datasets for both T1D and GCA, and applied rigorous selection criteria to T1D as the exposure variable. Subsequently, four sets of T1D GWAS data were used for validation, and a meta-analysis was also conducted. Therefore, our findings regarding the causal relationship between T1D and GCA are reliable and highly representative, and consistently indicate that T1D can increase the risk of developing GCA. Conversely, there is no genetic evidence of GCA influencing the development of T1D.

T2D, a common chronic metabolic disorder in the elderly population, is often caused by the development of insulin resistance, which gradually impairs the ability of pancreatic beta cells to secrete sufficient levels of insulin. Several studies have suggested a potential protective influence of T2D against GCA [19, 38, 39], and

Table 3 Causal association between T1D (exposure) and GCA (outcome) in MR analysis during the validation stage

GWAS ID	Methods	SNPs (n)	OR (95% CI)	P-value	Test of heterogeneity		Test of pleiotropy			MRPRESSO (P-value)
					Q	P-value	Intercept	SE	P-value	
GCST90013891	MR Egger	12	1.18 (0.98–1.43)	0.097	10.58	0.39	−0.035	0.06	0.59	0.465
	Weighted median	12	1.16 (1.07–1.27)	7.76E−04						
	IVW	12	1.12 (1.05–1.20)	3.43E−04	10.91	0.45				
	Simple mode	12	1.12 (0.97–1.29)	0.15						
	Weighted mode	12	1.17 (1.05–1.30)	0.018						
GCST90013941	MR Egger	15	1.13 (1.00–1.28)	0.069	18.54	0.14	−3.25E−04	0.05	0.99	0.195
	Weighted median	15	1.13 (1.06–1.21)	4.02E−04						
	IVW	15	1.13 (1.07–1.19)	2.58E−06	18.54	0.18				
	Simple mode	15	1.11 (0.99–1.24)	0.10						
	Weighted mode	15	1.13 (1.03–1.23)	0.023						
GCST90014023	MR Egger	71	1.16 (1.04–1.29)	8.02E−03	83.25	0.12	−3.36E−03	0.01	0.76	0.118
	Weighted median	71	1.08 (0.96–1.21)	0.23						
	IVW	71	1.14 (1.06–1.24)	5.48E−04	83.36	0.13				
	Simple mode	71	1.04 (0.82–1.31)	0.76						
	Weighted mode	71	1.11 (1.00–1.23)	0.05						
GCST90018925	MR Egger	17	1.25 (1.05–1.50)	0.027	10.00	0.82	−0.016	0.024	0.51	0.84
	Weighted median	17	1.24 (1.08–1.42)	1.90E−03						
	IVW	17	1.19 (1.07–1.31)	8.60E−04	10.46	0.84				
	Simple mode	17	1.23 (0.96–1.58)	0.12						
	Weighted mode	17	1.25 (1.08–1.44)	7.07E−03						

GCA giant cell arteritis; T1D type 1 diabetes; MR mendelian randomization; IVW inverse variance weighted; SNPs single nucleotide polymorphisms; OR odds ratio; CI confidence intervals; SE standard error



Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.79$

Fig. 2 Forest plot of the causal association between T1D and GCA in the meta-analysis by the IVW method. GCA giant cell arteritis; T1D type 1 diabetes; IVW inverse variance weighted; GWAS genome-wide association studies; OR odds ratio; CI confidence intervals

the proposed mechanisms include aberrant cytokine secretion, weakened T cell response, and decreased dendritic cell activity due to high antigen glycosylation [19, 38, 39]. Furthermore, a new study reported lower incidence of biopsy-positive GCA in T2D patients, along with less prevalence of T2D in subjects with positive TAB as opposed to those with a negative TAB [19]. However, another study conducted on a single-center large

cohort showed that T2D patients older than 68 years had a higher chance of being diagnosed with GCA [20]. A possible explanation is that the cell-mediated immune dysfunction in T2D and GCA exhibit similar abnormalities. GCA patients often experience a reduction in the circulating regulatory T cells (Tregs), which has not been observed in T2D patients [40, 41]. Therefore, the presence of functional Tregs in T2D patients may increase

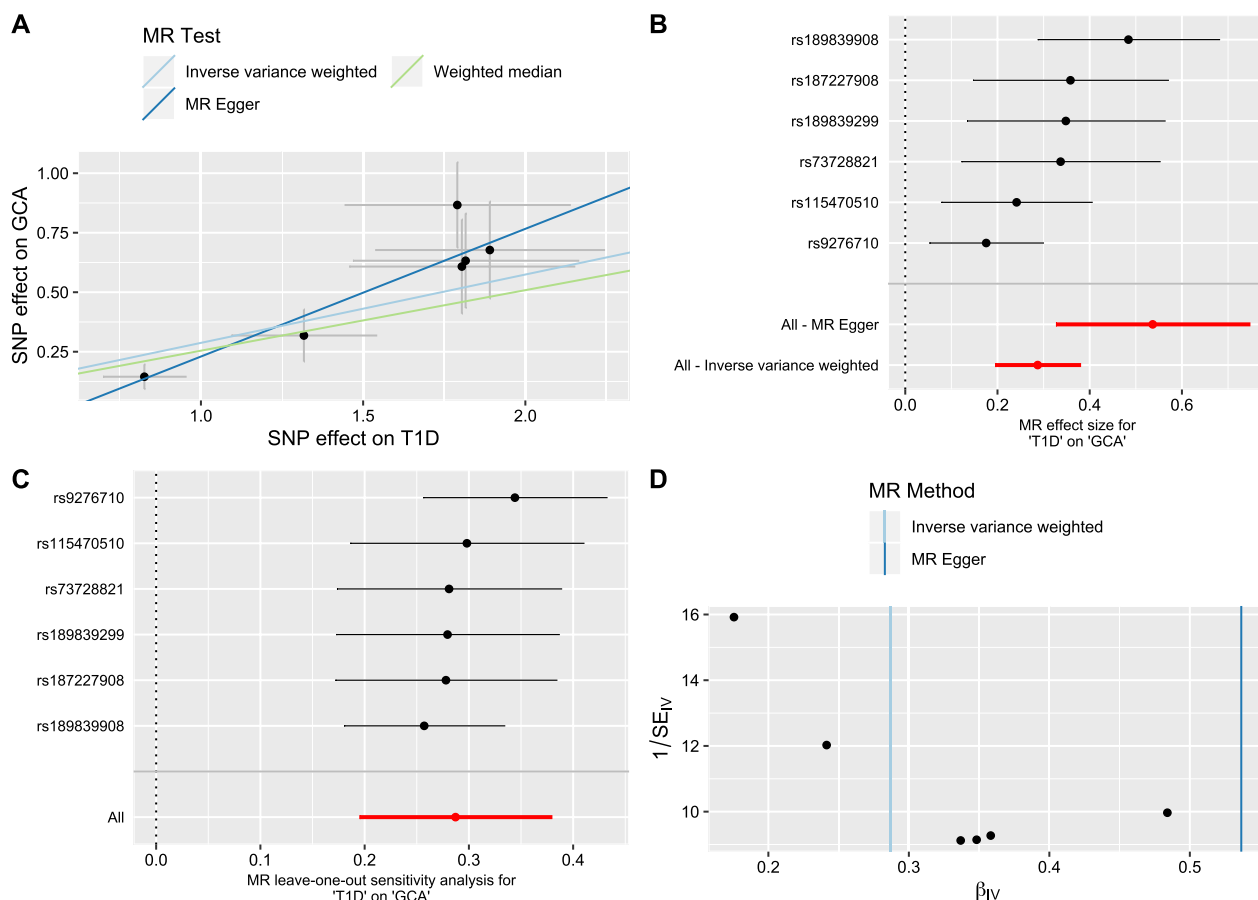


Fig. 3 Assessment of the influence of discovery T1D data (T1D_STRICT2) on GCA. **(A)** Scatter plot of the MR-Egger intercept test. **(B)** Forest plot of sensitivity analysis. **(C)** Forest plot of leave-one-out analysis. **(D)** Funnel plot of Cochran's Q statistic. MR Mendelian randomization

the risk of GCA. The primary treatment for GCA entails high doses of orally administered GCs [42]. However, prolonged GC exposure can lead to severe adverse events, notably T2D [18–20]. The average daily dose of oral GC has been linked to hyperglycemia, glucose intolerance, and the initiation of new T2D. Furthermore, up to 50% of GCA patients experience worsening of underlying T2D in response to GC treatment, although it may not always correspond with the average daily GC dose [43–46]. However, these observational studies and individual case reports do not clearly establish a causal relationship between T2D and GCA. The complex relationship between these two conditions needs to be validated through large-scale, extensive, and comprehensive genetic studies. We used the most recent GWAS datasets for T2D and GCA for the present MR analysis. The GWAS for T2D included 38,841 cases and 451,248 controls from the IEU OpenGWAS database, and the GWAS for GCA had 1066 cases and 399,355 controls from the FinnGen database. Our results indicated lack of any causal connections between T2D and GCA.

The present study is the first to employ a 2-sample bidirectional MR approach to dissect the possible bidirectional causality between GCA and T1D/T2D. Currently, most of the research on the relationship between T1D/T2D and GCA consists of observational studies or individual case reports. Reverse causation, confounding, and inaccurate non-differentially assessed exposures are less common with MR analysis compared to observational studies or individual case reports. We also employed several MR framework methodologies to conduct sensitivity analyses on these causal links, which verified the consistency of point estimates both before and after outlier removal, and successfully reduced heterogeneity. Furthermore, we employed an extensive summary-level available GWAS dataset to obtain all the relevant genetic data.

There are several limitations in this study that ought to be considered. First, the modest number of SNPs included as IVs decreased the total statistical power, even though there was minimal possibility of moderate IV bias affecting our findings (all F-statistics were

larger than 10). Therefore, additional subjects need to be included in future MR analyses. Second, the publicly available GWAS data for GCA are currently limited to populations of European ancestry. The lack of GWAS datasets for GCA in the Asian, Black, or Middle Eastern populations limits our ability to study the causal relationship between T1D/T2D and GCA in these populations. Therefore, caution should be exercised when extrapolating the findings of this study to non-European populations. To ensure broader applicability and understand the potential differences in genetic predispositions, further studies are needed that include diverse populations. This will help validate the findings in a more comprehensive manner and explore any potential variations in the causal relationship between T1D/T2D and GCA across different ethnic groups. Third, MR studies are essentially statistical constructs, which overlook the intricate interactions between genetic and environmental factors in autoimmune illnesses like GCA and DM. Therefore, the causal factors identified through this approach should be applied with caution in clinical settings. Given the steady increase in both the number and size of GWASs, future studies will likely involve larger samples and more comprehensive patient data.

Conclusion

This study pioneers the use of MR to dissect the bidirectional causality between DM and GCA. The evidence we have gathered indicates an increased risk of GCA in patients with T1D, but not a reciprocal causal effect. Furthermore, our study did not establish any causal links between T2D and GCA. These outcomes underscore the need for a more comprehensive investigation into the mechanisms underlying the causal association between DM and the occurrence of GCA.

Abbreviations

GCA	Giant cell arteritis
TAB	Temporal artery biopsy
DM	Diabetes mellitus
T1D	Type 1 diabetes
T2D	Type 2 diabetes
GC	Glucocorticoid
MR	Mendelian randomization
IVs	Instrumental variables
SNPs	Single nucleotide polymorphisms
GWAS	Genome-wide association studies
IVW	Inverse variance weighted
ORs	Odds ratios
CIs	Confidence intervals

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s43042-024-00561-y>.

Supplementary Material 1.
Supplementary Material 2.

Supplementary Material 3.
Supplementary Material 4.
Supplementary Material 5.
Supplementary Material 6.
Supplementary Material 7.
Supplementary Material 8.
Supplementary Material 9.
Supplementary Material 10.
Supplementary Material 11.
Supplementary Material 12.

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Author contributions

Conceptualization, S.C. and X.Z.; methodology, S.C.; software, S.C.; validation, L.H., X.M.; formal analysis, R.N.; investigation, Y.W.; resources, R.N.; data curation, H.L.; writing—original draft preparation, S.C.; writing—review and editing, L.P. and H.Y.; visualization, S.C.; supervision, X.Z.; project administration, L.H.; funding acquisition, X.Z. and H.Y. All authors have read and agreed to the published version of the manuscript.

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Availability of data and materials

This study utilized publicly available datasets, which were obtained from the IEU OpenGWAS database (<https://gwas.mrcieu.ac.uk/>) and the FinnGen consortium (<https://www.finnngen.fi/>).

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors read and approved the final manuscript. And agree to the publication of the manuscript.

Competing interests

The authors declare no competing interests.

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