Bidirectional causal association between type 1 diabetes and autoimmune diseases: a Mendelian randomization study

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Abstract

Introduction: It has been reported that individuals with type 1 diabetes (T1D) are at a higher risk of concomitant occurrence of other autoimmune diseases (AIDs). Currently, there is a lack of research investigating the causal relationship between T1D and other AIDs. A comprehensive Mendelian randomization (MR) study was conducted using debiased inverse-variance weighted (dIVW) and inverse-variance weighted (IVW) estimators to examine the bidirectional causal relationship between T1D and 12 AIDs.

Material and methods: Genome-wide association study (GWAS) summary statistics datasets related to T1D or 12 AIDs were obtained from the FinnGen study or other published cohort studies. Pruned SNPs in linkage disequilibrium (LD)-clumped single-nucleotide polymorphisms (SNPs) were used as instrumental variables. For the dIVW analysis, no genome-wide significance threshold was applied for SNP selection.

Results: For each 1-unit increase in the log-transformed odds ratio (OR) of patients with primary biliary cholangitis (PBC) or rheumatoid arthritis (RA), the ORs of T1D were 1.123 (95% CI: 1.094–1.151) and 1.133 (95% CI: 1.100–1.167), respectively. Conversely, for each 1-unit increase in the log-transformed OR of T1D, the OR of RA was 1.383 (95% CI: 1.213–-1.578). No bidirectional associations were found between T1D and other AIDs.

Conclusions: Patients with RA or PBC have a higher risk of developing T1D, and those with T1D also have an increased risk of developing RA. These findings highlight the importance of regular screening for individuals with T1D, RA, or PBC.

Key words: primary biliary cholangitis, rheumatoid arthritis, causal inference, etiological studies, epidemiology.

Introduction

Type 1 diabetes (T1D) is a common chronic autoimmune disease (AID) characterized by persistent insulin deficiency and high blood sugar, resulting from the destruction of β-cells in the pancreas by the autoimmune process [1–3]. T1D accounts for 10% of all diabetes cases and affects 30 million people worldwide [4]. In the United States, the incidence of T1D among children and adolescents is gradually increasing [5]. Similarly, surveys from several provinces and municipalities in China indicate a continuous increase in the incidence of T1D [6–8]. This suggests an ongoing upward trend in the prevalence of T1D nationwide in China, despite the lack of direct survey data at the national level. At present, T1D cannot be completely cured, and exogenous insulin remains the cornerstone of treatment [9]. New therapies are continuously being explored, including biologics that exert immunomodulatory effects targeting specific cells or cytokines, as well as non-immunomodulatory small molecules, such as the promising sodium-glucose cotransporter (SGLT) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists [10]. However, these novel therapies are challenging to use in isolation for the management of T1D. In light of this, long-term management of T1D patients is crucial, with an emphasis on addressing complications as an essential component of their ongoing care.

According to several observational studies, a minority of T1D patients will develop another AID during their lifetime [11]. Compared to the general population, individuals with T1D have a higher risk of developing other AIDs such as rheumatoid arthritis (RA), inflammatory bowel disease (IBD), autoimmune thyroid disease (AIT), and celiac disease (CeD) [12–14]. The clustering of AID occurrence may be attributed to sharing common immunopathogenic mechanisms and risk factors [15].

The co-occurrence of T1D and AIDs can have implications for the management of both diabetes and AIDs [16, 17]. Therefore, it is important to identify early on whether individuals with AIDs also have other AID conditions. Establishing a causal relationship between T1D and other AIDs would guide clinicians toward better screening practices.

However, this task is challenging. As mentioned above, while many observational studies have found associations between T1D and various AIDs, the limitations of observational research, such as reverse causality and residual or unknown confounding factors, prevent results from providing sufficient evidence of causal or reverse causal relationships. Additionally, the low prevalence of AIDs in the general population adds to the difficulty of conducting relevant observational studies [18].

Compared to observational study methods and randomized-controlled trials, Mendelian randomization (MR) is a more effective and convenient approach for causal inference [19–22]. MR utilizes genetic variations associated with the exposure of interest as instrumental variables (IVs) to infer causal associations with the outcome, without the need to fully account for confounding factors. Mainstream MR methods, such as MR-Egger and inverse-variance weighted (IVW), employ statistical inference using single nucleotide polymorphisms (SNPs) strongly correlated with the exposure as the IVs. Recently, more powerful MR estimators have been developed, including debiased inverse-variance weighted (dIVW), robust adjusted profile score (RAPS), and penalized inverse-variance weighted (pIVW), enabling more robust causal estimation using instruments that are weakly correlated with the exposure but are more numerous [23–25]. The objective of this study was to comprehensively investigate the bidirectional causal associations between T1D and 12 other AIDs by integrating both mainstream and newly developed MR approaches.

Material and methods

Study design

This study aimed to comprehensively examine the potential bidirectional causal relationships between T1D and 12 AIDs by employing robust MR estimators and an adequate number of IVs. The genome-wide association study (GWAS) summary statistics datasets used in this study were derived from the FinnGen study and other publicly available large cohorts [26]. All cohorts were designed for European populations, with no overlaps. Ethical approval was obtained before the commencement of all studies, and participants provided informed consent. We employed a comprehensive approach, utilizing all available SNPs, including those weakly associated with the exposure, primarily focusing on the results provided using the dIVW method. When dIVW was not applicable (due to the presence of average horizontal pleiotropy), we relied on IVW to report causal associations. The main analytical workflow of this study is illustrated in Figure 1.

Genetic association datasets for T1D

The GWAS data of T1D used in this study were derived from large cohort studies based on European populations. The summary statistics dataset used for the primary analysis includes 9,266 T1D patients and 15,574 controls [27]. Additionally, the summary statistics dataset used for the sensitivity analysis consists of 7,467 T1D patients and 10,218 controls [28].

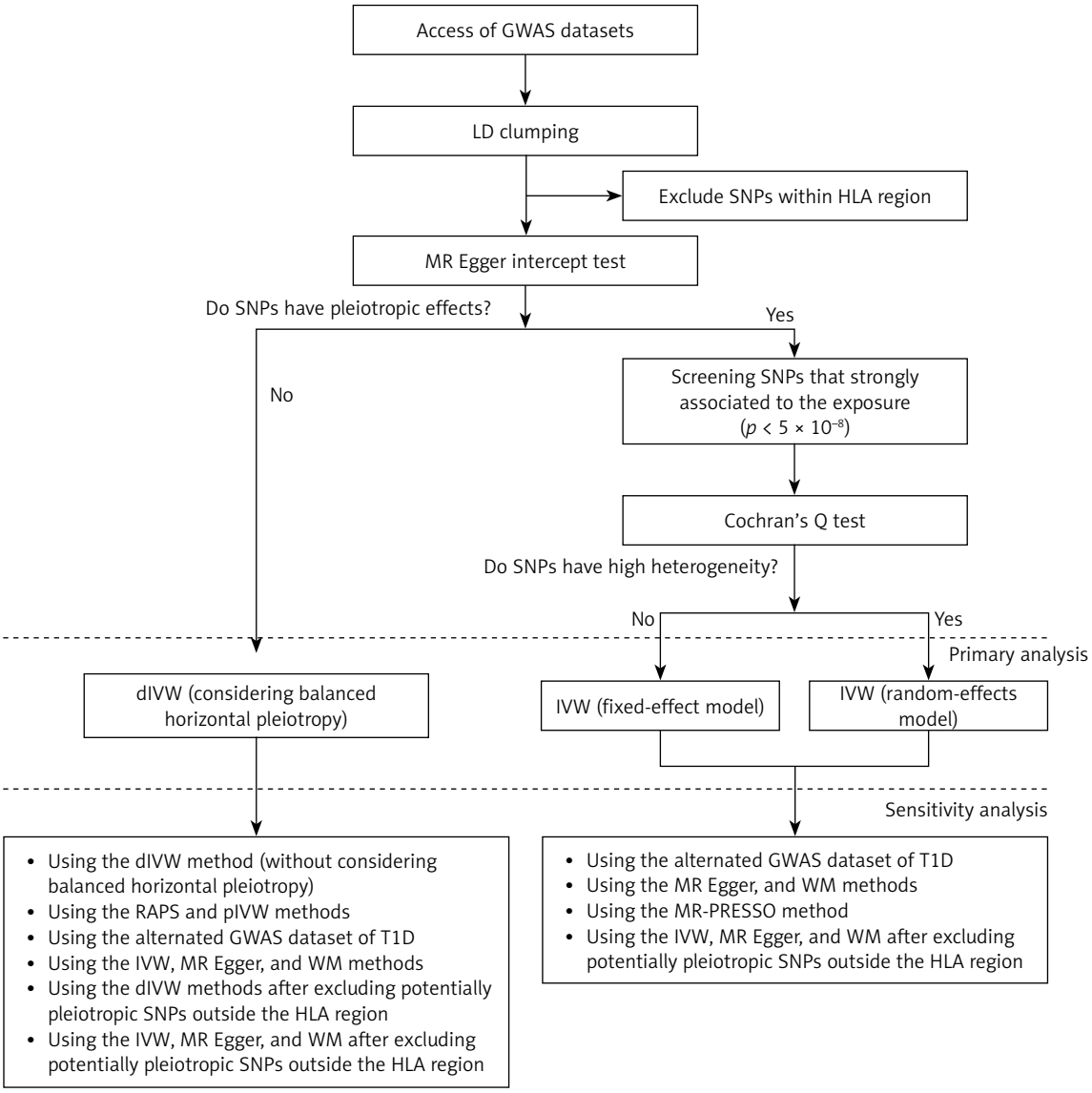

Figure 1. Analytical workflow of the study

GWAS – genome-wide association studies, LD – linkage disequilibrium, SNPs – single nucleotide polymorphisms, HLA – human leukocyte antigens, MR – Mendelian randomization, dIVW – debiased inverse-variance weighted, IVW – inverse-variance weighted, RAPS – robust adjusted profile score, pIVW – penalized inverse-variance weighted, T1D – type 1 diabetes, WM – weighted median, MR-PRESSO – Mendelian Randomization Pleiotropy RESidual Sum and Outlier.

Genetic association datasets for 12 AIDs

Twelve AIDs were included in this study. The GWAS data for IBD, ulcerative colitis (UC), Crohn's disease (CD), systemic lupus erythematosus (SLE), ankylosing spondylitis (AS), Graves' disease (GD), AIT, and multiple sclerosis (MS) were obtained from the FinnGen study, including a minimum of 1,023 cases and 281,127 controls. Data on the remaining four diseases, namely CeD, PBC, RA, and sarcoidosis, were sourced from large cohort studies specific to each disease. Detailed information on the sources of GWAS data for the 12 AIDs is provided in Supplementary Table SI.

Selection of genetic IVs

A series of procedures were performed to identify the potential genetic IVs; the specific details are presented in Figure 1. First, PLINK was used to calculate the linkage disequilibrium (LD) between each exposure-associated SNP based on the 1000 Genomes European panel. Only the independent SNPs (defined as $r^2 > 0.001$ within a 10,000 kb window) were retained for further analysis. There were no restrictions on the genome-wide significance level of SNP-disease exposure association when evaluating statistical inference using dIVW, RAPS, or pIVW. However, the associations of SNPs and diseases were restricted to genome-wide statistically significant levels ($p < 5 \times 10^{-8}$) when us-

ing IVW, MR-Egger and WM. The SNPs used in this study are provided in Supplementary Table SII. The PhenoScanner v2 database was queried to identify and remove all SNPs located within the human leukocyte antigen (HLA) region (chr6: 27,477,797–34,448,354, hg19/GRCh37) to mitigate their potential effects [29].

Statistical analysis

First, the MR-Egger intercept test was conducted to assess the presence of average horizontal pleiotropy for all independent SNPs. If no significant balanced horizontal pleiotropy was detected, the advanced MR estimator, dIVW, was used as the primary analysis to estimate the causal associations between T1D and other AIDs. Conversely, if the SNPs used in the analysis exhibited significantly balanced horizontal pleiotropy, further SNP filtering was performed to ensure genome-wide correlation between the SNPs and disease exposure ($p < 5 \times 10^{-8}$). After restricting the SNPs to those with genome-wide correlations with disease exposure, Cochran's Q test was employed to assess heterogeneity among the instruments. If $I^2 < 50\%$, indicating low heterogeneity, the fixed-effect model of the IVW method was used for primary MR analysis. Conversely, if $I^2 \geq 50\%$, indicating substantial heterogeneity, the random-effect model of the IVW method was employed.

Multiple sensitivity analyses were further conducted. The following steps were performed for the sensitivity analysis of results from dIVW. First, we utilized GWAS data for T1D from a different source than the primary analysis and conducted corresponding analyses. Second, we attempted to use alternative MR estimators, such as pIVW or RAPS, which can also effectively infer causality even with weak IVs. Third, we considered the analysis without accounting for balanced horizontal pleiotropy when using the dIVW estimator. Fourth, the results of classical MR methods, including IVW, MR-Egger, and WM, were compared with those obtained from the dIVW method. If necessary, Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) was used for further supplementary analysis when using classical MR methods [30]. Fifth, we excluded SNPs located within genes such as PTPN22, AFF3, CTLA4, TNFAIP3, and TAGAP to further eliminate the potential influence of non-HLA region SNPs on the level of pleiotropy [31–33]. This decision was made based on previous studies demonstrating that some SNPs associated with these genes shared risk loci between T1D and other AIDs, including RA, PBC, GD, and CeD.

We employed the following approaches for the sensitivity analysis of results from the IVW estimator. First, we conducted a sensitivity analysis using the MR-Egger and WM methods. Then, we performed a similar analysis using GWAS data for T1D from an alternative source. We also conducted a supplementary analysis using MR-PRESSO to identify and remove potential outlier SNPs. Lastly, the same analysis procedure was followed as in the primary analysis, but excluding SNPs located within genes such as PTPN22, AFF3, CTLA4, TNFAIP3, and TAGAP.

Results from Benjamini correction was the primary criterion used to assess significance. Associations with a corrected p-value < 0.05 were considered significant, and those with a corrected p-value > 0.05 but a nominal p-value < 0.05 were considered suggestive. Except for the LD-based result clumping procedure, which utilized PLINK 1.9, all other analyses were conducted using R 4.2.0. The following R packages related to MR analysis were used: mr.divw (version: 0.1.0), mr.raps (version: 0.4.1), TwoSampleMR (version: 0.5.7), MendelianRandomization (version: 0.6.0), and MR-PRESSO (version: 1.0) [34, 35].

Results

Estimation of average horizontal pleiotropy in instrumental variable SNPs

Firstly, after LD clumping, the remaining SNPs were accessed using the PhenoScanner v2 database to determine whether they were located within the HLA region or any of the gene regions including PTPN22, AFF3, CTLA4, TNFAIP3, and TAGAP. A total of 86 SNPs were found to be located within the HLA region, and 10 SNPs were found to be located within the regions of the PTPN22, AFF3, CTLA4, and TNFAIP3 genes (Supplementary Tables SIII, SIV). None of the SNPs was found within the TAGAP gene locus. Subsequently, the presence of average horizontal pleiotropy was examined for the SNPs via the MR-Egger intercept test, as shown in Supplementary Table SV. Only when the outcomes were CD, PBC, and RA did the SNPs exhibit overall horizontal pleiotropy. Therefore, IVW was used instead of dIVW for the corresponding primary analysis. However, for the remaining analyses, we continued to use the dIVW method as the primary analysis approach as the IVs did not demonstrate average horizontal pleiotropy.

Results from dIVW support an association between PBC, RA and increased risk of T1D

In the analysis using the dIVW method, the results showed that PBC or RA led to a higher risk of T1D, while the other 10 AIDs exhibited no influence (Table I). Our analysis revealed that for a 1-unit increase in the log-transformed odds of PBC or RA, the odds ratios (ORs) for T1D were

Table I. Estimating the bidirectional associations between T1D and 12 AIDs using the dIVW method

Exposure	Outcome	β	SE	OR (95% CI)	*P*-value	Adjusted *p*-value
T1D	IBD	0.008	0.005	1.008 (0.999, 1.018)	0.080	0.965
	UC	0.004	0.006	1.004 (0.993, 1.015)	0.433	1
	CeD	0.030	0.015	1.030 (1.000, 1.061)	0.0484	0.580
	SLE	–0.013	0.012	0.987 (0.965, 1.009)	0.249	1
	AS	–0.007	0.011	0.993 (0.971, 1.014)	0.496	1
	GD	–0.010	0.008	0.990 (0.976, 1.005)	0.200	1
	AIT	–0.009	0.017	0.991 (0.958, 1.025)	0.613	1
	MS	–0.010	0.008	0.990 (0.974, 1.007)	0.253	1
	Sarcoidosis	–0.016	0.028	0.984 (0.932, 1.039)	0.562	1
IBD	T1D	1.310×10^{-4}	0.012	1.000 (0.976, 1.025)	0.992	1
UC		–0.016	0.011	0.984 (0.964, 1.005)	0.125	1
CD		–0.008	0.006	0.992 (0.980, 1.004)	0.171	1
CeD		0.004	0.005	1.004 (0.993, 1.015)	0.445	1
PBC		0.116	0.013	1.123 (1.094, 1.151)	<0.001	<0.001
RA		0.125	0.015	1.133 (1.100, 1.167)	<0.001	<0.001
SLE		-5.48×10^{-5}	0.005	1.000 (0.990, 1.010)	0.991	1
AS		0.003	0.005	1.003 (0.994, 1.013)	0.508	1
GD		–0.009	0.008	0.991 (0.975, 1.007)	0.256	1
AIT		–0.007	0.004	0.993 (0.985, 1.000)	0.057	0.687
MS		-2.76×10^{-4}	0.006	1.000 (0.987, 1.012)	0.966	1
Sarcoidosis		0.006	0.003	1.006 (1.001, 1.011)	0.013	0.160

T1D – type 1 diabetes, AID – autoimmune disease, dIVW – debiased inverse-variance weighted, SE – standard error, OR – odds ratio, CI – confidence interval, IBD – inflammatory bowel disease, UC – ulcerative colitis, CeD – celiac disease, SLE – systemic lupus erythematosus, AS – ankylosing spondylitis, GD – Graves' disease, AIT – autoimmune thyroiditis, MS – multiple sclerosis, CD – Crohn's disease, PBC – primary biliary cirrhosis, RA – rheumatoid arthritis.

1.123 (95% CI: 1.094–1.151; $p < 0.001$) and 1.133 (95% CI: 1.100–1.167; $p < 0.001$), respectively. The associations remained after adjusting for multiple testing corrections. No significant associations were found between T1D and the risk of IBD, UC, CeD, SLE, AS, GD, AIT, MS, or sarcoidosis. Similarly, no significant associations were found between IBD, UC, CD, CeD, SLE, AS, GD, AIT, MS, or sarcoidosis and the risk of T1D.

Sensitivity analyses were conducted using the dIVW method without considering balanced horizontal pleiotropy, the pIVW method, or the RAPS method. The results of these sensitivity analyses consistently aligned with the positive findings of the primary analysis (Supplementary Tables SVI–SVIII). However, in the sensitivity analysis using GWAS data of T1D from another, smaller-scale T1D cohort, it was found that T1D increased the risk of CeD while decreasing the risk of GD (Supplementary Table SIX). Similarly, GD also reduced the risk of T1D.

When performing supplementary MR analyses using the IVW, MR-Egger, and WM methods, average horizontal pleiotropy was observed only in SNPs where UC, PBC, or RA served as the exposure and T1D as the outcome (Supplementary Table SX). The MR estimates from IVW and WM were consistent with the positive findings of the primary analysis (Supplementary Table SX). However, the results from MR-Egger did not support an association between PBC and T1D. Additionally, it is noteworthy that classical methods yielded several positive results that were reported as negative in the primary findings. IVW, MR-Egger, and WM all suggested an association between T1D and a lower risk of AIT, and these associations remained stable after multiple testing corrections. Apart from the association between T1D and AIT, one or two of the methods (IVW, MR-Egger, or WM) indicated an association between T1D and a lower risk of GD and SLE, susceptibility to SLE and a lower risk of T1D, and susceptibility to AS and a higher risk of T1D. However, these associations did not remain significant after the multiple correction test (Supplementary Table SX). Due to the persistent association between T1D and a lower risk of AIT in the results obtained using the classical MR method, an MR-PRESSO test was conducted. The results of MR-PRESSO revealed the presence of 2 outlier SNPs out of 32 SNPs. After removing these outliers, a potential association between T1D and AIT was observed, but the association was not sig-

nificant after the multiple correction test (Supplementary Table SXI).

The results of the primary and sensitivity analyses revealed a bidirectional relationship between PBC and T1D; however, outside the HLA region, SNPs were considered shared loci for T1D and other AIDs, particularly PTPN22. To address the potential horizontal pleiotropy effects caused by IV, 10 SNPs located outside the HLA region that may introduce horizontal pleiotropy were further removed, and sensitivity analyses were repeated using the dIVW, IVW, MR-Egger, and weighted median (WM) methods (Supplementary Tables SXII, SXIII). The MR results using the dIVW method, after excluding the 10 SNPs, showed that the SNPs had an average horizontal pleiotropy in the analysis with RA as the exposure (Supplementary Table SXII). Therefore, the MR results with RA as the exposure should be interpreted while considering the results from IVW, MR-Egger, and WM, rather than relying solely on the dIVW results. After excluding the 10 SNPs, the dIVW MR results supported the association of PBC with T1D risk, with OR and 95% CI values closely resembling those from the primary analysis (Supplementary Table SXII). The IVW and WM results also supported the association between RA and increased T1D risk. Although the MR-Egger results suggested no association between RA and T1D, the MR-Egger intercept test indicated a lack of average horizontal pleiotropy for the IVs (Supplementary Table SXIII). Interestingly, despite the IVW results suggesting an association between PBC and with T1D after excluding the 10 SNPs, the MR-Egger estimation did not support a correlation between the two, and the MR-Egger intercept test indicated overall pleiotropy of SNPs (Supplementary Table SXIII).

Results from IVW support an association between T1D and increased risk of RA

As mentioned above, the IVW method was used to perform a primary analysis of the association between genetic susceptibility to T1D and the risk of CD, PBC, and RA. All SNPs used in the analysis exhibited high heterogeneity. The results from IVW suggested a positive association between T1D and an increased risk of RA (OR = 1.383, 95% CI: 1.213–1.578; $p < 0.001$) (Table II). This association remained significant after the multiple correlation test. The association between T1D and the risk of RA was consistently observed even after a series of sensitivity analyses, including analysis using alternative datasets, the MR-Egger or WM methods, and MR-PRESSO (Supplementary Table SXIV). It is worth noting that although the MR-Egger results do not support an association between T1D and RA after excluding potentially pleiotropic SNPs, the results from IVW and WM still support this association. Considering that the standard error of MR-Egger estimates is generally much larger than that of IVW, it is appropriate to rely on the results from IVW (Supplementary Table SXIII).

In the primary analysis, no significant association was found between genetic susceptibility to T1D and an increased or decreased risk of CD or PBC, except for a potential association between genetic susceptibility to T1D and the risk of CD (Table II). However, in sensitivity analyses using the alternative T1D GWAS data, the results using the IVW and WM methods indicated an association between T1D and an increased risk of PBC (Supplementary Table SXV). Furthermore, sensitivity analysis using MR-PRESSO suggested a significant association between T1D susceptibility and an increased risk of CD and PBC after removing two and three SNPs, respectively. However, a possible association between T1D and CD was observed after the multiple correlation test (Supplementary Table SXVI). Finally, the sensitivity analysis, after excluding the 10 SNPs that could potentially introduce horizontal pleiotropy, yielded consistent results with the primary analysis, indicating that the IVs used in the primary analysis did not include these 10 SNPs (Supplementary Table SXVII).

Discussion

In this bidirectional two-sample MR study, we utilized genetic variants as IVs and employed the advanced and robust dIVW estimator to evaluate

Table II. Estimating the associations between T1D and risks of CD, PBC and RA using the random-effects IVW methods

Exposure	Outcome	Q	I^2	Cochran's Q test, *p*-value	β	SE	OR (95% CI)	*P*-value	Adjusted *p*-value
T1D	CD	59.981	50.0%	< 0.001	0.077	0.042	1.080 (0.994, 1.173)	0.070	0.837
	PBC	150.990	88.1%	< 0.001	0.147	0.084	1.158 (0.982, 1.366)	0.081	0.977
	RA	498.681	94.8%	< 0.001	0.324	0.067	1.383 (1.213, 1.578)	< 0.001	< 0.001

T1D – type 1 diabetes, CD – Crohn's disease, PBC – primary biliary cirrhosis, RA – rheumatoid arthritis, IVW – inverse-variance weighted, SE – standard error, OR – odds ratio, CI – confidence interval.

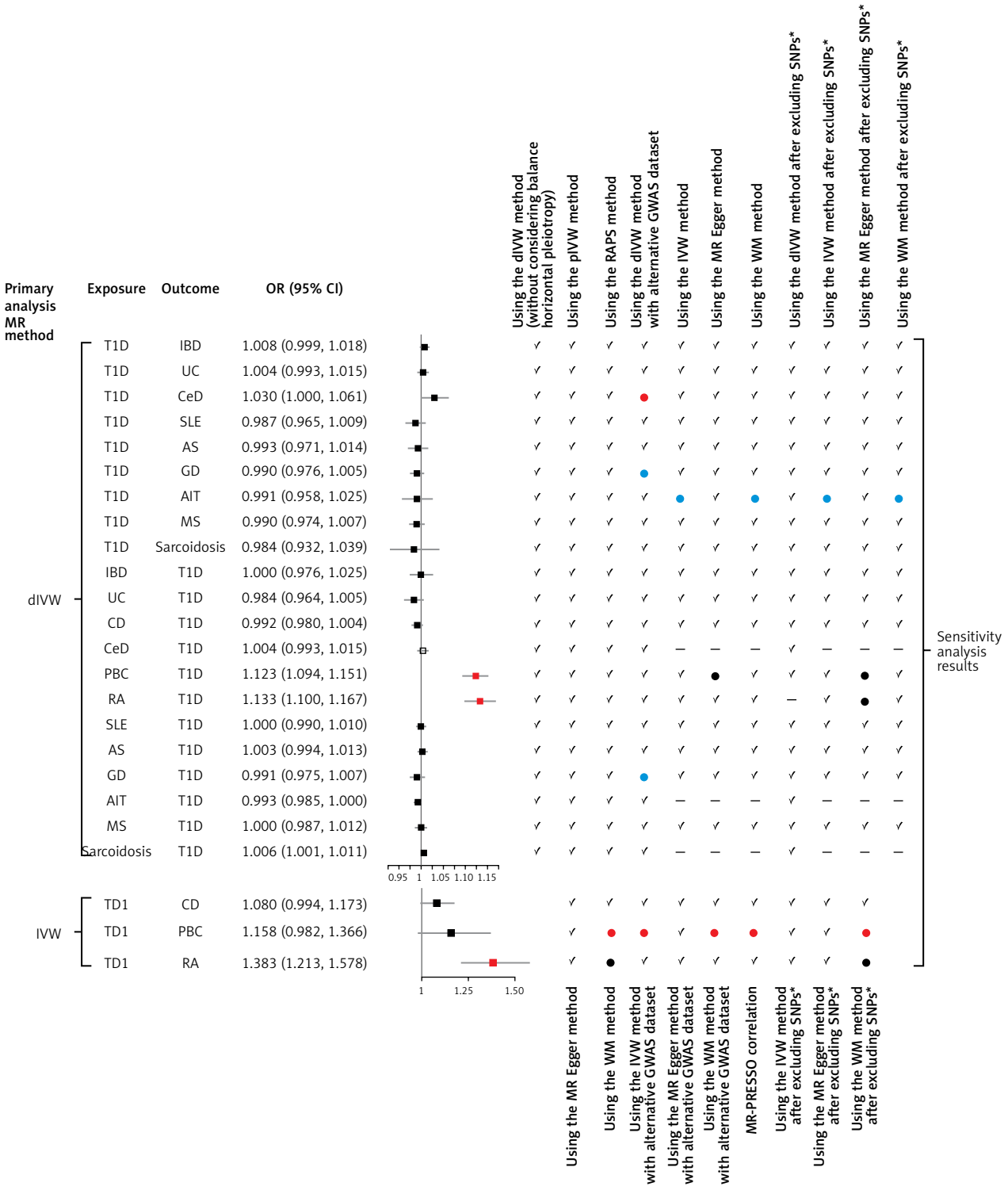

Figure 2. Summary of results in the study from the primary analysis and sensitivity analysis. The forest plot and the left side of the forest plot displaying OR and 95% CI represent the results of the primary analysis, while the matrix on the right side of the forest plot represents the results of the sensitivity analysis. Red, blue and black indicate that the 95% CI of the OR value after multiple comparison corrections is greater than 1, less than 1, crosses 1, respectively. In the results of sensitivity analysis, checkmarks are used instead of dots if the significance and direction of the OR value after multiple comparison corrections are consistent with the results of the primary analysis

OR – odds ratio, CI – confidence interval, MR – Mendelian randomization, dIVW – debiased inverse-variance weighted, pIVW – penalized inverse-variance weighted, RAPS – robust adjusted profile score, IVW – inverse-variance weighted, WM – weighted median, T1D – type 1 diabetes, IBD – inflammatory bowel disease, UC – ulcerative colitis, CD – Crohn's disease, CeD – celiac disease, PBC – primary biliary cirrhosis, RA – rheumatoid arthritis, SLE – systemic lupus erythematosus, AS – ankylosing spondylitis, GD – Graves' disease, AIT – autoimmune thyroiditis, MS – multiple sclerosis – MR-PRESSO – Mendelian Randomization Pleiotropy RESidual Sum and Outlier. The asterisk (*) indicates the results of the analysis conducted after the removal of SNPs within the HLA region or any of the gene regions including PTPN22, AFF3, CTLA4, TNFAIP3, and TAGAP.

the bidirectional causal associations between 12 common AIDs involving the digestive system, connective tissues, thyroid, nervous system, etc., and T1D. We confirmed the association between T1D and increased risk of RA using mainstream MR estimators such as IVW. By incorporating additional genetic variants as IVs and employing the dIVW method for MR estimation, we discovered associations between PBC and RA with higher risk of T1D. These associations were consistently observed in sensitivity analyses. A summary of the results from the primary analysis and sensitivity analysis is provided in Figure 2.

Our study also revealed potential associations between T1D and certain AIDs. The results from the dIVW analysis indicated that T1D may be associated with a higher risk of CeD and a lower risk of GD. GD may also be associated with a lower incidence of T1D. These associations were only significant in sensitivity analyses using a smaller-scale summary statistics dataset of T1D. Furthermore, although the results of sensitivity analysis using the IVW and WM methods suggested a decreased risk of AIT associated with T1D, no significant association between T1D and AIT was found through further examination using MR-PRESSO after removing outlier SNPs and adjusting for multiple comparisons. The results from MR-PRESSO indicated significant heterogeneity in the SNPs used in the IVW and WM analyses. Therefore, these results tend to align with the results from dIVW, suggesting no association between T1D and AIT. In conclusion, it is essential to treat this unexpected result with caution and to seek further confirmation through future observational studies.

Consistent with our study findings, previous observational studies have supported the association between T1D and RA, as well as PBC. A case–control study involving 1,419 RA patients in Europe found that patients with T1D, but not T2D, had a higher risk of RA. A meta-analysis of multiple case–control studies also indicated an increased risk of T1D among RA patients [12]. A study examining cases from the large clinical cohort of the UK Biobank also found an elevated risk of T1D among PBC patients, although this study included only 345 PBC patients [18]. However, there is currently a lack of observational studies investigating whether T1D patients have a higher risk of developing PBC. In our MR study, the analysis using a larger-scale GWAS dataset of T1D suggested that T1D does not increase the risk of PBC; however, an increased risk was indicated in the analysis after removing outlier SNPs. In contrast, the findings from another, relatively small-scale GWAS dataset of T1D suggested that T1D can increase the risk of PBC. Therefore, further research is warranted to confirm whether there is an association.

Genetic factors, including specific HLA and non-HLA genotypes, may be one of the underlying causes of the onset of T1D, PBC, and RA. In addition to genetic factors, immune and metabolic dysregulation may be common etiological factors between T1D and other AIDs. The association between PBC and T1D may primarily be mediated by abnormalities in blood glucose levels and disruptions in bile acid metabolism. Diabetes has also been linked to more severe liver fibrosis in PBC, suggesting that abnormal blood glucose levels may exacerbate biliary damage [36]. Thus, hyperglycemia in T1D patients could be one of the triggers for PBC. In patients with PBC, the disorder of bile acid circulation leads to a reduction in bile acids entering the intestine and the blood [37]. Bile acids have a protective function against endoplasmic reticulum (ER) stress in β-cells, and decreased circulating levels may promote ER stress in these cells [38]. It has been confirmed that ER stress can induce β-cell apoptosis through various pathways, including the regulation of β-cell autoantigen expression, and the induction of oxidative stress, autophagy, and cellular senescence, all of which are closely linked to the onset and progression of T1D [39, 40]. Therefore, the disorder of bile acid circulation in PBC patients may promote β-cell apoptosis, leading to β-cell destruction and ultimately triggering T1D.

Abnormalities in the immune system represent another important link between T1D and other AIDs. Helper T cells are abnormally activated in the early stages of both RA and T1D, contributing to inflammation in the joints and pancreatic islets, respectively [41, 42]. Furthermore, the B-cell-targeting biologic agent rituximab has been shown to improve the conditions of both RA and T1D, suggesting that B-cell-mediated humoral immunity also plays a role in both diseases [43, 44]. The immune dysregulation observed in RA and T1D patients is systemic, indicating that the abnormal activation of B cells and T cells may simultaneously contribute to damage in the pancreatic islets of RA patients, and vice versa for T1D patients. Furthermore, the composition and function of immune cells can change with age. For instance, immune regulatory functions decline in the early years of T1D, and immune cell senescence may further disrupt the immune system as individuals age, thereby increasing the risk of developing AIDs [45, 46]. Therefore, age may influence the occurrence of T1D or other AIDs by affecting the immune system; however, there is a paucity of clinical research on this aspect. In addition, at the level of cytokines, inflammatory factors such as tumor necrosis factor (TNF) and interleukin (IL)-1β

derived from macrophages can promote the β-cell presentation of modified antigens and induce cell death, ultimately contributing to the development of T1D [47]. TNF and IL-1β are also active in the joint local and systemic blood of patients with RA [48]. Therefore, elevated levels of inflammatory cytokines may be significant shared pathogenic factors in RA and T1D. Notably, sex differences may also influence the risk of T1D patients developing other AIDs, suggesting a partial role of sex hormones in this process [49]. However, the specific molecular mechanisms underlying this relationship remain unknown.

Despite several observational studies suggesting that T1D patients are more prone to developing AIDs such as IBD, MS, CeD, hypothyroidism, and hyperthyroidism, these findings are not entirely consistent with the conclusions of this study [50–53]. The estimation of GWAS data of T1Ds from different populations in this study revealed that T1D may predominantly contribute to the development of other AIDs. One possible reason for the inconsistency is that age and sex have been reported to be associated with the prevalence of other A1Ds in T1D patients, with older age and female T1D patients having a higher proportion of concurrent AIDs. However, there may be variations in the age distribution of the populations included in the T1D GWAS datasets used in this study, which could influence the causal estimates between T1Ds and other AIDs.

Several MR studies have attempted to demonstrate causal associations between individual AIDs and T1D; however, these studies have some limitations in their methodology or interpretation of results. Su *et al.* and Zhang *et al.* reported an increased risk of SLE and AS, respectively, associated with T1D [54, 55]. Moreover, a non-peer-reviewed MR study found a negative association between T1D and IBD [56]. However, these studies did not explicitly address the potential horizontal pleiotropy from genetic variants, such as SNPs located in the HLA region. Furthermore, although Zhang *et al.*'s MR study reported a positive association between T1D and AS, the OR was very close to 1, indicating that this statistically significant association has a minimal clinical impact.

The primary goal of universal T1D screening is to reduce the incidence of life-threatening diabetic ketoacidosis at diagnosis. Currently, there are several public health studies focused on screening for T1D in the general population [57]. Estimates suggest that even a 20% reduction in diabetic ketoacidosis incidence through screening and follow-up is cost-effective [57]. Therefore, for many AIDs, screening at-risk populations for chronic conditions facilitates early diagnosis and treatment, which often translates to better prognoses, longer life expectancy, and lower societal expenditures [57–59]. Despite often being overlooked by clinicians and not addressed in relevant clinical guidelines, our study suggests that regular serological screening for RA in T1D patients is necessary, as well as periodic screening for islet autoantibodies in PBC and RA patients. However, due to methodological limitations, it is challenging to compare the differences in the risk of developing other AIDs or T1D among patients of different sexes or age groups. Consequently, this hinders the ability to perform more refined risk stratification and targeted clinical screening for AIDs patients. Preventing the onset of other AIDs through lifestyle changes is essential. For patients with RA or PBC, reducing risk factors associated with T1D – such as avoiding exposure to mumps virus, vitamin D deficiency, unhealthy diets, and obesity – can help lower the risk of developing T1D [60]. For T1D patients, minimizing exposure to tobacco smoke, occupational dust, air pollution, and low vitamin D intake, as well as reducing sodium, red meat, and iron consumption, can help decrease the risk of developing RA [61].

Strengths and limitations. Compared to traditional cohort and case–control studies, using MR to reveal causal associations between AIDs offers advantages, particularly because the overall incidence of AIDs in the population is relatively low. The application of MR estimation methods including dIVW has several advantages in exploring causal relationships between diseases. Firstly, more accurate point estimates of ORs and narrower CIs can be obtained through the use of thousands of genetic variants as IVs, thereby increasing the precision of causal estimation. For example, in our study, dIVW yielded an OR of 1.133 with a narrow 95% CI (95% CI: 1.100, 1.167) for the risk of RA and T1D. In comparison, IVW and MR-Egger provided point estimates of ORs as 3.334 and 1.683, respectively, accompanied by higher 95% CIs. Moreover, dIVW and other methods may more likely detect positive results compared to classical MR methods, as the assumption of MR's instrumental variable relevance requires the exclusion of most SNPs, which can lead to selection bias due to over-selection of SNPs, known as the "winner's curse" [62]. When analyzing the association between PBC and T1D risk by excluding 10 SNPs that could introduce horizontal pleiotropy using the classical MR method, the MR-Egger intercept test revealed the presence of horizontal pleiotropy in the SNPs, and the results suggested no causal association between PBC and T1D. In contrast, dIVW, which involves incorporation of more IVs, continued to yield positive results.

This study has several limitations. First, the age of onset and sex in T1D may influence the risk

of developing other AIDs. However, the impact of age and gender on the association between T1D and the development of other AIDs could not be considered further due to limitations in the GWAS data. Second, it was not possible to use dIVW estimation to assess the risk of CD, PBC, and RA associated with T1D due to the presence of horizontal pleiotropy. Thus, the results obtained using classical MR methods may be less accurate. Third, a previous observational study suggested that T1D is only associated with anti-cyclic citrullinated peptide (anti-CCP)-positive RA patients [12]. However, we could not further investigate the association between T1D and subgroups of RA with different serological features due to limitations in the summary statistics dataset. Fourth, although the results are generally consistent, there are slight differences in the results from summary statistics datasets obtained from different T1D cohorts, which primarily involve the estimates of T1D and the risk of CeD and GD, as well as the estimate of GD risk for T1D. Future clinical research should further investigate the causal associations between T1D and these diseases. Lastly, the generalizability of our study results to other populations is limited as we only included individuals of European ancestry, primarily from Finnish cohorts, in the GWAS datasets, and the genetic structure and disease prevalence can vary across populations. In summary, the results obtained through MR analysis have certain limitations, and the causal associations between diseases require further confirmation through extensive observational studies. However, our research provides a reference for the direction of future observational studies.

In conclusion, our study revealed an increased risk of RA associated with T1D, with an OR of 1.383 (95% CI: 1.213–1.578). Associations of PBC and RA with higher risk of T1D were also observed, with ORs of 1.123 (95% CI: 1.094–1.151) and 1.133 (95% CI: 1.100–1.167), respectively. These findings enhance our understanding of the etiology of AIDs and highlight the importance of early screening and preventive lifestyle interventions for individuals with T1D, PBC, and RA. However, given the limitations of our study due to sample diversity, the generalizability of these results may be restricted. Future research should explore these associations in diverse populations to validate the findings and investigate underlying mechanisms.

Data availability

All raw data used in this study were obtained from GWAS summary statistics, which were publicly released by the FinnGen research consortium or GWAS Catalog database.

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Ethical approval

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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