In summary, we have not documented evidence of a lessebo effect in an experimental therapeutic scenario of disease modification in PD. The current findings call for alternative approaches to study the impact of expectation of benefit on efficacy outcome in clinical trials and prospectively measure the lessebo effect in future therapeutic development in PD. ●

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Potential Protective Link Between Type I Diabetes and Parkinson's Disease Risk and Progression

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ABSTRACT: Background: Epidemiological studies suggested an association between Parkinson's disease (PD) and type 2 diabetes, but less is known about type 1 diabetes (T1D) and PD.

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Objective: This study sought to explore the association between T1D and PD.
Methods: We used Mendelian randomization, linkage disequilibrium score regression, and multi-tissue transcriptome-wide analysis to examine the association between PD and T1D.
Results: Mendelian randomization showed a potentially protective role of T1D for PD risk (odds ratio [OR], 0.97; 95% confidence interval [CI], 0.94–0.99; $P = 0.039$), as well as motor (OR, 0.94; 95% CI, 0.88–0.99; $P = 0.044$) and cognitive progression (OR, 1.50; 95% CI, 1.08–2.09; $P = 0.015$). We further found a negative genetic correlation between T1D and PD (rg = −0.17; $P = 0.016$), and we identified eight genes in cross-tissue transcriptome-wide analysis that were associated with both traits.
Conclusions: Our results suggest a potential genetic link between T1D and PD risk and progression. Larger comprehensive epidemiological and genetic studies are required to validate our findings. © 2023 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: Parkinson's disease; Mendelian randomization; type 1 diabetes; insulin; genetic correlation

Introduction

Multiple lines of evidence suggest an association between type 2 diabetes (T2D) and Parkinson's disease (PD).[1-4] T2D is associated with both increased PD risk and worse progression, measured by cognitive and motor scales.[4] Moreover, drugs targeting T2D may reduce the risk for PD and potentially could be repurposed to modify PD progression.[5]

Less is known about the link between PD and type 1 diabetes (T1D). T1D is an autoimmune disorder characterized by the destruction of islets of Langerhans in the pancreas.[6] The pathophysiology of T1D is different from T2D; nonetheless, both diseases have a strong genetic correlation and shared biological pathways.[7] PD is a complex disease with multiple pathways involved in its development,[8] including pathways related to immune response and inflammation.[9] Most observational studies did not differentiate between T1D and T2D when defining diabetes as a risk factor,[10-12] because T1D is much less prevalent than T2D. One report suggested a potential increased risk for PD in patients with T1D.[13]

Mendelian randomization (MR) uses genetic variants such as single-nucleotide polymorphisms (SNPs) associated with an exposure of interest (in our case, T1D) as proxies for causal inference about the association between that exposure and an outcome. In this study, we performed MR to estimate whether a relationship between T1D or other autoimmune traits and PD risk and progression may exist. Furthermore, we conducted genetic correlation analysis and transcriptome-wide association study (TWAS) to assess potential shared genetic architecture.

Subjects and Methods

Mendelian Randomization

We selected publicly available genome-wide association studies (GWASs) for T1D and PD risk and progression with participants of European ancestry and no overlapping samples. We used SNPs from the selected GWASs that were significant at the GWAS level ($P < 5 \times 10^{-8}$) to construct a genetic instrument for the exposure (T1D) and examine its effects on two categories of outcomes: PD risk and PD progression. For the exposure, we selected a recent T1D study (n cases = 13,458; n = 20,143 control subjects)[14] downloaded from the GWAS catalog,[15] with only samples of European ancestry being included. For the outcome, we selected the most recent PD GWAS (n = 33,674 cases; n = 449,056 control subjects).[16] UK Biobank participants were included in the PD GWAS, but not in the selected T1D study, to avoid potential bias.

To study the genetically estimated effect of T1D on PD motor progression, measured by Unified Parkinson's Disease Rating Scale (UPDRS) Part III, and on PD cognitive progression, measured by Montreal Cognitive Assessment (MoCa) and Mini-Mental State Examination (MMSE), we selected the largest publicly available GWASs of these continuous traits.[17] The GWAS on PD progression is a meta-analysis of several studies, with a different number of participants for each phenotype. It means that results for different SNPs correspond different numbers of cases. Therefore, to calculate the sample sizes for PD progression studies, we calculated the means of patients included in each analysis across all SNPs. The mean sample sizes included in the GWASs of PD progression traits were n = 1398 for UPDRS Part III, n = 1329 for MMSE, and n = 1000 for MoCA.

We also performed MR analyses among 10 additional immune and inflammatory disorders and PD. The full list of studies included in the analysis can be found in Table S1 in Data S1.

To perform MR, we used the two-sample MR R package.[18,19] We used the default clumping window of 10,000 kb with r^2 cutoff of 0.001. We applied Steiger filtering to exclude SNPs that explain more variance in the outcome than in the exposure.[19] We used inverse variance weighted (IVW) meta-analysis, which combines results from individual Wald ratios together. We used MR Egger, which likewise combines separate

Wald ratios into metaregression to obtain an estimate that is unbiased in the presence of directional pleiotropy.[20] Considering that some of our inverse variances could be invalid, we also used weighted median based estimate to account for it.[21] To further explore potential pleiotropy, we applied a variety of sensitivity analyses, including Cochran's Q test in the IVW, MR-Egger methods, and global MR-PRESSO.[22] We calculated power to detect an equivalent effect size of OR 1.2 on PD risk and progression using an online MR power calculation (https://sb452.shinyapps.io/power/).[23]

Genetic Correlation

We examined genetic correlations between PD and T1D using linkage disequilibrium (LD) score regression (LDSC) as previously described.[24,25] LDSC considers LD structure to estimate potential genetic overlap between two traits. MR analyses and genetic correlation were done after the exclusion of SNPs within the major histocompatibility complex region because of the biased LD structure.

Transcriptome-wide Association Analysis

To calculate cross-tissue gene-expression associations in T1D and PD, we used the Unified Test for Molecular Signatures (UTMOST) software.[26] In this analysis, we included the largest publicly available T1D summary statistics, which also includes UK biobank (UKBB; n = 18,942 cases; n = 501,638 control subjects).[27] However, our results should not be biased because we independently conducted the analysis on the two summary statistics and compared only the output. UTMOST is a multi-tissue TWAS method that can provide a powerful prediction of gene-trait associations. As a first step, we used a precalculated matrix with tissue-specific TWAS weights that was created using grouped penalized regression. The predicted gene expression levels were then used as input for the subsequent association tests. In the second step, we used UTMOST to conduct single-tissue TWASs across 44 tissues available in GTEx (V6p; Table S2 in Data S1).[28] Subsequently, we used UTMOST to identify genes associated with T1D and PD across all tissues by combining the single-tissue test results with Generalized Berk-Jones test.[26] This was done using a unified statistical framework that integrates information across multiple tissues and accounts for correlation between gene expression and the trait. UTMOST outputs a *P* value for each gene-trait association. Notably, this statistical framework enables gene-trait associations to have different directions across tissues. Finally, we applied false discovery rate correction and performed head-to-head comparisons of genes significant for both PD and T1D. We created heatmaps for genes significant in our multi-tissue analysis selecting several tissues that are relevant for T1D and/or PD (basal ganglia, frontal cortex, pancreas, and Epstein-Barr virus (EBV)-transformed lymphocytes).

Results

Evidence for a Modest Protective Effect of T1D on PD Risk and Progression

The instruments in all analyses had sufficient strength as demonstrated by F-statistics > 10 (Table 1). The number of GWAS significant SNPs before clumping in the exposure (T1D) GWAS was 30,938. There were 71 SNPs after clumping. We excluded the human leukocyte antigen locus and conducted the analysis on 63 remaining SNPs. The PD risk GWAS had 100% statistical power to detect causal effect with an OR of 1.2. However, the PD progression GWASs could be underpowered to detect causal associations (Table 1). We found weak evidence of a modest protective effect of T1D on PD risk (IVW: OR, 0.97; 95% CI, 0.94–0.99; $P = 0.039$; weighted median: OR, 0.95; 95% CI, 0.90–0.99; $P = 0.026$; Table 1; Fig. S1A in Data S1). We studied the effects of T1D on motor and cognitive progression. UPDRS3 is a motor performance scale,

TABLE 1 *MR analysis between exposure to T1D and outcome of PD risk and progression*

				Inverse variance weighted		MR Egger	
Outcome	**N, SNPs included**	**Power, %**	**F-statistics**	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
PD risk	58	100	22	0.97 (0.94–0.99)	**0.039**	0.96 (0.91–1.01)	0.115
UPDRS3	42	32.8	34	0.94 (0.88–0.99)	**0.044**	1.03 (0.88–1.20)	0.721
MMSE	39	31.4	37	1.11 (0.99–1.25)	0.060	1.13 (0.85–1.50)	0.418
MoCA	38	24.8	39	1.50 (1.08–2.09)	**0.015**	2.00 (0.85–4.72)	0.121

Note: Significant *P*-values are highlighted in bold.
Abbreviations: MR, Mendelian randomization; PD, Parkinson's disease; T1D, type 1 diabetes; SNP, single-nucleotide polymorphism; OR, odds ratio; 95% CI, 95% confidence interval; UPDRS3, Unified Parkinson's Disease Rating Scale part III; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment.

meaning that higher scores indicate poorer performance. MMSE and MoCA are cognitive scales, and higher scores signify better performance. We observed potentially protective effects of T1D on motor progression measured by UPDRS3 (IVW: OR, 0.94; 95% CI, 0.88–0.99; $P = 0.044$; Table 1; Fig. S1B in Data S1) and on cognitive progression as measured by both MMSE (IVW: OR, 1.11; 95% CI, 0.99–1.25; $P = 0.060$) and MoCA (IVW: OR, 1.50; 95% CI, 1.08–2.09; $P = 0.015$; Table 1; Fig. S1C,D in Data S1). We found that rs7110099 near *INS-IGF2* (Insulin-Insulin like growth factor 2) and rs56994090 near *MEG3* (Maternally expressed gene 3) have potential protective effects on PD risk (Wald ratio OR, 0.95; 95% CI, 0.89–1.00; $P = 0.055$; and OR, 0.67; 95% CI, 0.46–0.96; $P = 0.03$, respectively). Another SNP next to *MEG3*, rs4900384, might have a protective effect for cognitive progression as measured by MoCA (Wald ratio OR, 17.25; 95% CI, 1.86–159.50; $P = 0.010$). We did not find pleiotropy in any sensitivity analysis (Table S3 in Data S1). Furthermore, we applied MR-PRESSO analysis and did not find either general pleiotropy or specific pleiotropic SNPs (Table S3 in Data S1).

MR Analysis Between Additional Autoimmune/Inflammatory Traits and PD Did Not Reveal Any Novel Causal Association

We investigated the potential causal relationship among 10 additional autoimmune or inflammatory traits with PD (Table S1 in Data S1). The instruments in all studies had sufficient strength as demonstrated by F-statistics > 10. As previously reported, and after correction for multiple comparisons, we found a protective effect for rheumatoid arthritis in PD (IVW; beta = −0.072; SE = 0.021; $P = 4.7E{-}04$),[29] but not for any other trait. We repeated the analysis after the exclusion of SNPs within the human leukocyte antigen locus and did not find any additional associations between any of the studied traits and PD.

Shared Expression for Genes Related to Autophagy and Lysosomal Pathways between T1D and PD

We found evidence for some negative genetic correlation between T1D and PD using LDSC (rg = −0.17; $P = 0.016$). We then performed TWASs on T1D and PD in multiple tissues and selected significant genes across all tissues for both traits after false discovery rate correction. We demonstrated eight significant genes for PD, as well as for T1D (*CTSB*, *LAT*, *LRRC37A*, *LRRC37A2*, *R3HDM1*, *RAB7L1*, *RNF40*, *WNT3*; Table 2), suggesting potential pleiotropy that was not detected by the MR tools. We performed tissue-specific comparisons of four selected tissues relevant to PD, T1D, or the immune system (basal ganglia, frontal cortex, pancreas, and EBV-transformed lymphocytes; Fig. S2 in Data S1). Of the nominated genes, *RNF40* and *CTSB* showed differential expression between the traits. Although other genes showed similar patterns of expression across the tissues, genes within the *MAPT* locus (*LRRC37A*, *LRRC37A2*, and *WNT3*) displayed markedly different levels of expression, with PD showing twice the level of expression compared with T1D.

TABLE 2 *Genes associated with both T1D and PD in cross-tissue transcriptomic gene-trait association analysis*

Gene	T1D, Pfdr	PD, Pfdr
CTSB	8.06E−05	0.028
LAT	0.026	0.009
LRRC37A	5.25E−04	0.0001
LRRC37A2	8.21E−04	4.36E−08
R3HDM1	0.046	0.001
RAB7L1	0.001	1.65E−05
RNF40	0.027	0.002
WNT3	0.010	2.24E−08

Abbreviations: T1D, type 1 diabetes; PD, Parkinson's disease; Pfdr, *P* value after false discovery rate correction.

Discussion

In this analysis, we demonstrated a potential protective effect of T1D on PD risk and progression. We did not find obvious pleiotropy or heterogeneity in any of our MR analyses, using a variety of sensitivity methods. However, our genetic correlation analysis suggested that there is some potential pleiotropy, with negative genetic correlation between the two traits (ie, variants that are associated with reduced risk of one trait are associated with increased risk of the other traits). This suggests that the association seen in the MR analysis is due to residual pleiotropy that was not identified by the MR tools, because they are only able to detect potential pleiotropic GWAS significant SNPs in the exposure, whereas genetic correlation relies on LD structure unrelated to the significance level of the SNPs. Our TWAS also supports the notion that the association seen in the MR is due to residual pleiotropy and not a true causative association.

We demonstrated potential protective effects of SNPs near *IGF2* and *MEG3* for PD. Previously, a neuroprotective effect of *IGF2* was reported in cell and mouse models of PD,[30] and its downregulation was shown in PD patients' blood.[31] Moreover, overexpression of *IGF2* resulted in a neuroprotective effect.[32] Similarly, downregulation of *MEG3* was

recently reported in patients with PD,[33] and its overexpression could be protective for PD through negative regulation of LRRK2.[33]

Using the conjunction false discovery rate method, some pleiotropy between PD and T1D in two loci was previously reported (*CXCR4* and *MAPT*).[34] In our analysis, we also found pleiotropic genes in these regions (Table S4 in Data S1) and detected several novel pleiotropic loci. Inflammatory and autoimmune pathways play an important role in the development of T1D.[35] Accumulating evidence suggests lysosomal dysfunction as a prevalent mechanism in the pathogenesis of PD.[36] We showed that *CTSB* and *RAB7L1* were associated in cross-tissue TWAS analysis with both PD and T1D. These genes are playing an important role in the autophagy-lysosome pathway, suggesting a role for lysosomal function in both traits and potential pathway overlap. Recently, a similar protective effect was demonstrated in an MR study for another autoimmune disease, rheumatoid arthritis.[29] This finding was also replicated in our MR analysis. The authors also highlighted the hypothesis that the protective effect of autoimmune conditions of PD could be driven by some variants in genes involved in the lysosomal-autophagy pathway.[29] We suggest that a protective association could be driven by pleiotropy, particularly in lysosomal genes, as demonstrated by the genetic correlation and TWAS in our analyses.

The casual effect between T2D and PD has a different direction, because T2D may increase the risk for PD and accelerate its progression as we previously reported.[4] This difference could be because of several reasons. First, T1D and T2D are genetically distinct disorders; therefore, different effects on PD risk are possible. Second, as we have demonstrated here with several lines of evidence, the associated between T1D and PD is likely due to pleiotropy, whereas the association between T2D and PD may be a true causative effect.

Our study has several limitations. First, we included only samples of European ancestry, because large GWASs in other populations do not exist; therefore, our findings cannot be generalized to the population at large. Second, the GWASs on PD progression parameters are underpowered (<80%). Thus, additional replication is required when larger GWASs on PD progression will be made available. In addition, we used GWAS on PD progression with a limited number of individuals with data on MMSE (n = 1329) and MoCA (n = 1000).[17] It is also likely that the associations with MMSE and MoCA were not adjusted for years of education. Therefore, our analyses on MMSE and MoCA should be interpreted with caution. Another limitation is the potential effect of survival bias, which can arise in MR studies when the exposure of interest (in this case, T1D) is associated with premature mortality. This can lead to spurious associations between the exposure and the outcome (in this case, PD) because individuals who died prematurely are excluded from the analysis. Consequently, the association between the exposure and outcome may be either increased or reduced. In our case, for a survival bias to have a major effect, it would require that there would be numerous patients with T1D who were developing PD but did not survive before the analysis of the PD GWAS had been performed. MR also could be influenced by the quality of selected GWASs that are used for the MR analysis. We, therefore, used different GWASs for exposure and nonoverlapping cohorts in the outcome to partially account for this limitation. Lastly, TWAS can improve the statistical power, allowing for the detection of additional gene-trait associations. However, it is important to note that TWAS may still yield false-positive signals, and therefore further genetic and functional studies are necessary to validate associations nominated by TWAS.

To conclude, our results support a protective effect of T1D on PD risk and progression, which could be driven by potential pleiotropy. Larger comprehensive epidemiological studies are required to further explore this association. ■

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Data Availability Statement

We used only publicly available data in the current study. References for GWASs and packages for analysis are detailed in the Methods section. All results are reported in the tables or attached in the Supplementary data.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Differences Among Native Hawaiian, Asian, and White Patients with Progressive Supranuclear Palsy

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