

Causal Association Between Diabetes, Body Mass Index and Lichen Sclerosus: A Bidirectional Two-Sample Mendelian Randomization Analysis

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Background: Previous observational studies have found that lichen sclerosis (LS) is associated with metabolic statuses, such as diabetes mellitus (DM) and body mass index (BMI). However, there are also some studies showing that LS is not related to DM and BMI. The mechanism behind observational results is still unclear. Therefore, the causality of this relationship remains unknown. In this study, a bidirectional two-sample Mendelian randomization (MR) was conducted to investigate the correlation between DM, BMI, and LS.

Methods: The instrumental variables related to DM (including type 1 and type 2 diabetes), and BMI were identified from genome-wide association studies (GWAS) and a GWAS meta-analysis. The GWAS data for LS was from obtained the eighth edition of the FinnGen biological database released in 2022. Inverse variance weighted (IVW), weighted median, and MR-Egger methods were used to conduct a bidirectional two-sample MR analysis. Thereafter, the heterogeneity and horizontal pleiotropy were examined to determine whether the results were affected by a single-nucleotide polymorphism (SNP).

Results: We found a lack of evidence for the causal association of DM, and BMI on LS in inverse variance weighted (type 1 diabetes, OR=0.97, 95% CI=0.91–1.04, p=0.429; type 2 diabetes, OR=0.91, 95% CI=0.82–1.00, p=0.0511; BMI, OR=0.92, 95% CI=0.73–1.15, p=0.4554). In the other direction, the results also showed that LS had no significant causal effect on DM and BMI.

Conclusion: This MR analysis demonstrated no significant causal relationship between DM and BMI with LS in both directions, which contradicts previous observational studies reporting a positive association. Potential confounding factors may contribute to previously observed associations, and further research is necessary.

Keywords: lichen sclerosis, diabetes mellitus, body mass index, Mendelian randomization

Introduction

Lichen sclerosis (LS) is a chronic inflammatory skin disease with a complex etiology that mainly affects the anal and genital regions. It can occur in men and women of any age, but usually affects more women than men, manifesting in a bimodal fashion in pre-pubertal children and middle-aged adults.^{1,2} LS mainly occurs in the genital region, with a typical clinical manifestation of white atrophic plaques. External genital lichen sclerosis can occur in areas such as the neck, shoulder, upper torso, thigh, and mouth. Genital lichen sclerosis is often accompanied by persistent itching and sexual pain, which can develop into anatomical malformations of the vulva, phimosis, and urinary and sexual dysfunction. The condition seriously affects the quality of life of patients and increases the risk of localized skin malignancies.^{3–6} Unlike genital lichen sclerosis, extragenital lichen sclerosis usually has no obvious symptoms, progresses slowly, and generally does not undergo malignant transformation.⁷ Observational studies have shown a correlation between DM, BMI, and LS.^{8–14} There are also studies indicating that LS is not related to diabetes and BMI.^{13,15} However, observational research may be limited by reverse causality and confounding factors. Understanding the causal relationship between DM, BMI and LS can help us better understand the pathogenesis of LS. At the same time, it can also guide doctors on whether to conduct relevant disease screening for patients, achieving early diagnosis and intervention of the disease.

MR analysis uses a genetic variation, known as single nucleotide polymorphism (SNP), as a tool variable to assess the causal relationship between risk factors for complex diseases. Due to the random allocation of alleles during gamete formation, MR analysis reduces confounding and enhances exposure-outcome associations with the exponential growth and widespread availability of genotype data. Therefore, MR analysis is considered a “natural” RCT, overcoming the limitations of observational research such as confounding factors and reverse causal relationships.^{16–18}

In view of the uncertain causality of the relationships between DM, BMI, and LS, the present study applied MR to evaluate their correlation using data from the large Genome-Wide Association Study (GWAS).

Methods

Study Design

This study employed a bidirectional two-sample Mendelian randomization (MR) analysis method to study the causal relationship between DM, BMI, and LS. First, single-nucleotide polymorphisms (SNPs) related to DM (including type 1 and type 2 diabetes) and BMI were used to evaluate their causal impact on LS. Then, SNPs related to the LS were used as instrumental variables (IVs) to check for causal relationships in the other direction in order to rule out reverse causal relationships. Sensitivity analysis was conducted to test for heterogeneity and horizontal pleiotropy. In order to screen suitable IVs for dual sample bidirectional MR analysis, the following three key assumptions were adopted. Firstly, IVs used as a tool must be associated with the exposure of interest; secondly, IVs should not be associated with confounding factors; thirdly, genetic variation must not be associated with results independently of the exposure.¹⁹ The flowchart is shown in Figure 1.

Data Source

Diabetes

Summary-level data were acquired from a GWAS meta-analysis of type 2 diabetes (T2D), which aimed to identify functional genes and infer the possible mechanism of T2D.²⁰ This study included 62,892 cases of T2D and 596,424 controls, with 5,030,727 SNPs. A meta-analysis of three GWAS datasets of European descent was conducted: DIAbates

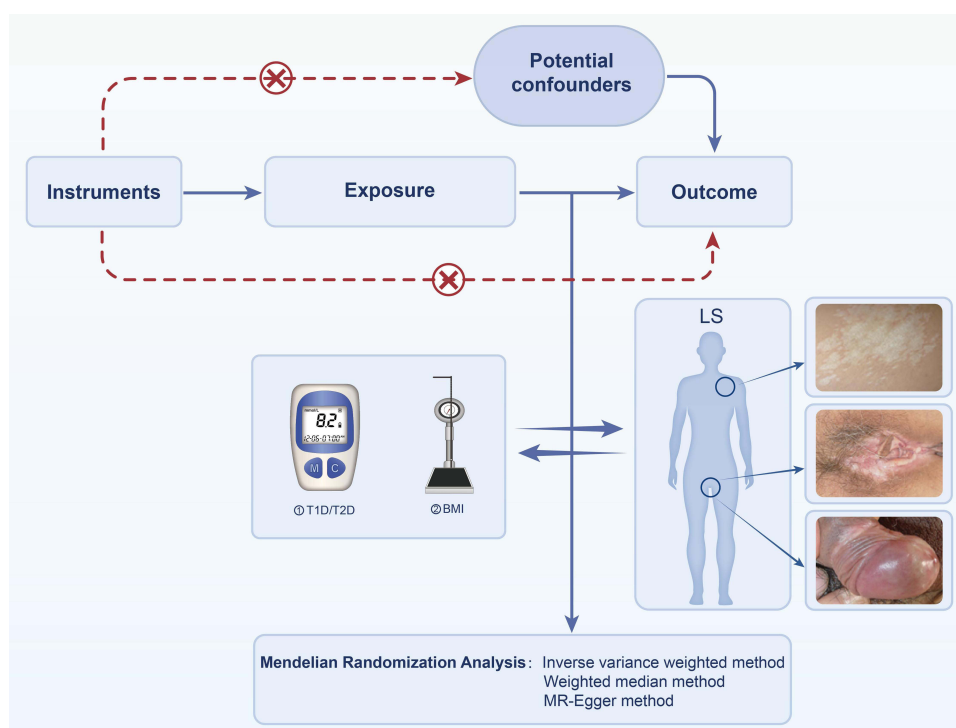


Figure 1 Workflow of Mendelian randomization study in this study.

genetic replication and meta-analysis (DIAGRAM, N=149821), the Genetic Epidemiology of Aging Study (GERA, N=53888), and the British Biological Bank (UKB, N=455607). Summary-level data on type 1 diabetes (GWAS ID: ebi-a-GCST010681) were obtained from a GWAS conducted in 2020, which aimed to identify new rare sites exerting a significant impact on the risk of type 1 diabetes (T1D).²¹ The study included 9358 cases of T1D and 15,705 controls, covering 12,783,129 SNPs from 12 European cohorts.

BMI

BMI data (GWAS ID: ieu-b-40) were obtained from a GWAS meta-analysis conducted by Yengo et al²² in 2018, in which a meta-analysis of previous GWAS of the Genetic Investigation of ANthropometric Traits (GIANT) consortium studies was performed with new GWAS of height and BMI in ~450,000 participants of the UK Biobank (UKB), yielding a total sample size of ~700,000. The BMI dataset included 461,460 European male and female descendants with 9,851,867 SNPs, significantly increasing the number of GWAS related to BMI. This provided a larger GWAS sample size, enabling more discoveries.

Lichen sclerosis

The GWAS data for LS was obtained from the eighth edition of the FinnGen biological database released in 2022 (https://storage.googleapis.com/finngen-public-data-r8/summary_stats/finngen_R8_L12_LICHENSCLERATROPH.gz). In total, 1984 cases of LS and 321,903 controls were included, with 20,169,015 SNPs. The patients in this data include both males and females. However, the data does not specify whether the site of the disease is located in the genital area or outside the genital area. The FinnGen research project was launched in 2017, combining genomic information with digital healthcare data from Finnish participants. FinnGen's research plan used 500,000 unique samples collected from the Finnish National Biobank Network to improve human health through genetic research.²³

Since all data used were already in the public domain, no additional ethical approval was required. The genetic background of the study population was derived from people of European descent to avoid bias due to racial-related confounding factors (Table 1).

Instrumental variable

Criteria for selecting instrumental variables: (1) SNP meets the genome-wide significance criteria ($p < 5 \times 10^{-8}$). However, when LS was exposed to T2D and BMI, no SNP met this standard, so the cut-off p-value was set to 5×10^{-6} ; (2) The parameter r^2 threshold was set to 0.001 and the kilobase pair (kb) to 10,000 to minimize interference from linkage disequilibrium (LD);²⁴ (3) F-statistic of each SNP was limited to greater than 10 to avoid weak tool bias. (4) We used PhenoScanner V2 to detect and remove genetic variations that exhibit significant associations with different phenotypes, in order to prevent potential horizontal pleiotropy. Finally, effective SNPs significantly related to exposure factors were obtained as IVs (Supplementary Tables 1–7).

Mendelian randomization analysis

The “TwoSampleMR” package in R version 4.1.2 was used for MR analysis. The inverse variance weighting (IVW) method used in this study mainly applies the reciprocal of the variance of each IV as a weight for weighted calculation. This process was conducted under the premise of ensuring that all IVs were valid, in order to evaluate horizontal multiple validity.²⁵ The

Table 1 Details of GWAS Used for Exposures and Outcomes.

Variables	Sample size	Case	Control	No. SNPs	Participates	Year Of Release	PMID/Source
T1D	25,063	9358	15,705	1,27,83,129	European	2020	32,005,708
T2D	6,59,316	62,892	5,96,424	50,30,727	European	2018	30,054,458
BMI	681275	NA	NA	2336260	European	2018	30,124,842
Lichen sclerosis	323,887	1984	321903	2,01,69,015	European	2022	FinnGen biobank(R8)

MR-Egger regression rule used the reciprocal of the outcome variance as the weight to perform a fitting, adding an intercept term.²⁶ WME was defined as the median of a weighted empirical density function of ratio estimates.²⁷

Sensitivity analysis

In this study, Cochran’s Q test was used to assess the heterogeneity between individual genetic variations. Heterogeneity was defined by Cochran’s Q test $P<0.05$, indicating that the relationship between exposure and outcome was affected by confounding factors. Therefore, the final Mendel randomization results used the IVW random effect model as the gold standard.²⁸ In the Egger intercept method of horizontal pleiotropy, the cutoff value estimates whether genetic variation significantly affects outcomes through pathways other than exposure. In the current study, $P<0.05$ represented the presence of horizontal pleiotropy, indicating that the selected IV significantly affected outcomes through pathways other than exposure, which violates assumptions 2 and 3.²⁹ The Leave-one-out method is mainly used to determine whether any one of the final SNPs is an outlier by individually eliminating each IV.³⁰ Moreover, the stability of the results was also checked by observing the asymmetry in the funnel diagram. A crossover in the Leave-one-out method would suggest that the positive result was not stable. The RadialMR method was employed to identify and remove abnormal SNPs.

Results

Diabetes and Lichen Sclerosus

Causal Effects of Diabetes on Lichen Sclerosus

In total, 29 SNPs related to T1D were used, and the IVW results showed no significant association with LS ($OR=0.97$, 95% $CI=0.91-1.04$, $p=0.429$) (Table 2). The Leave-one-out method result was shown in [Supplementary Figure 1A](#). The scatter plot of MR analysis was shown in [Figure 2A](#). Using 122 T2D-related SNPs, the IVW result was statistically significant ($OR=0.88$, 95% $CI=0.78-0.99$, $p=0.031$), but there was a crossover in the Leave-one-out method result ([Supplementary Figure 1B](#)), which indicated that the potential causal effect of T2D on LS was unstable. Furthermore, the P value of MR Egger obtained by the Cochran Q test was 2.10×10^{-5} and the IVW p value was 1.16×10^{-5} , indicating heterogeneity ([Supplementary Table 8](#)). The scatter plot of MR analysis was shown in [Figure 2B](#). Subsequently, 10 outliers were identified by the RadialMR method. After removing the 10 outliers (rs10087241, rs10169613, rs1063355, rs11925227, rs16988333, rs1899951, rs2307111, rs2857605, rs576674, and rs753270), MR analysis was reapplied to evaluate the relationship between T2D and LS ([Supplementary Figure 2A-D](#)). The IVW results showed no significant

Table 2 The Causal Effect of (A) T1D, (B) T2D, and (C) BMI on Lichen Sclerosus.

Exposures	Outcomes	Methods	No. SNPs	OR (95% CI)	P-value
T1D	Lichen sclerosus	IVW	29	0.97(0.91–1.04)	0.4294
		MR Egger		1.02(0.92–1.12)	0.766
		Weighted median		1.00(0.95–1.05)	0.9596
T2D		IVW	122	0.88(0.78–0.99)	0.031
		MR Egger		0.71(0.54–0.94)	0.0195
		Weighted median		0.81(0.69–0.94)	0.0049
T2D(After removing outliers)		IVW	112	0.91(0.82–1.00)	0.0511
		MR Egger		0.77(0.61–0.94)	0.0247
		Weighted median		0.81(0.69–0.95)	0.0082
BMI		IVW	436	0.92(0.73–1.15)	0.4554
		MR Egger		1.04(0.58–1.86)	0.895
		Weighted median		0.97(0.69–1.36)	0.8591

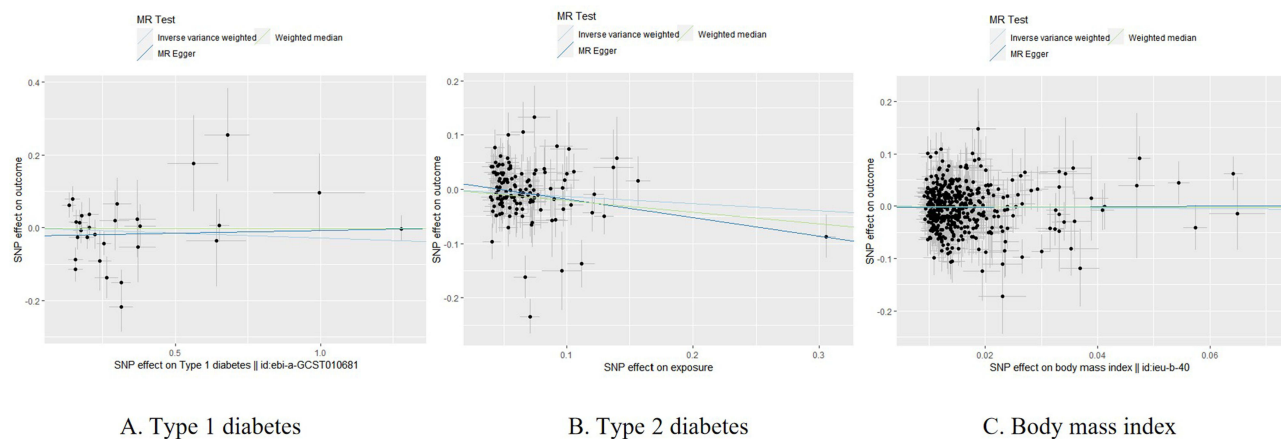


Figure 2 Scatter plots visualizing the Mendelian randomization (MR) estimates of the different exposures ((A): Type 1 diabetes; (B): Type 2 diabetes; (C): Body mass index) with the outcome (lichen sclerosis). Inverse-variance weighted (IVW), MR-Egger, and weighted median methods were the main estimators of the analysis.

correlation between T2D and LS (OR=0.91, 95% CI=0.82–1.00, $p=0.0511$), as shown in [Table 2](#). In addition, there was no significant evidence of intercept (intercept=0.008; SE=0.008, $p=0.113$), indicating the absence of directional pleiotropy ([Supplementary Table 9](#)). Therefore, no obvious causal relationship was observed between T2D and LS. The funnel plots were shown in [Supplementary Figure 3A](#) and [3B](#).

Causal Effects of Lichen Sclerosis on Diabetes

Four SNPs were significantly related to LS and were used as IVs; the IVW results showed no significant association between LS and T1D (OR=0.74, 95% CI=0.27–2.05, $p=0.5639$) ([Table 3](#)). The scatter plot of MR analysis was shown in [Figure 3A](#). Thereafter, 8 T2D-related SNPs ($p<5\times 10^{-6}$) were used, and the IVW results showed no causal relationship between LS and T2D (OR=0.97, 95% CI=0.92–1.03, $p=0.3979$) ([Table 3](#)). The scatter plot of MR analysis was shown in [Figure 3B](#). The Cochran Q test yielded an MR Egger P value of 0.005, while the IVW p value was 0.005 ([Supplementary Table 10](#)). However, the presence of heterogeneity did not affect the results as IVW can accept heterogeneity. The p-value obtained from the pleiotropic test was 0.45, indicating that IVs did not significantly affect outcomes through pathways other than exposure ([Supplementary Table 11](#)). The funnel plots were shown in [Supplementary Figure 4A](#) and [4B](#).

Table 3 The Causal Effect of LS on (A) T1D, (B) T2D, and (C) BMI.

Exposures	Outcomes	Methods	No. SNPs	OR (95% CI)	p-value
LS	DIM	IVW	4	0.74(0.27–2.05)	0.5639
		MR Egger		4.77(0.25–92.58)	0.4102
		Weighted median		1.56(1.26–1.93)	0.000031
	D2M	IVW	8	0.97(0.92–1.03)	0.3979
		MR Egger		1.10(0.82–1.47)	0.5632
		Weighted median		0.97(0.92–1.03)	0.3182
	BMI	IVW	6	0.99(0.96–1.01)	0.3144
		MR Egger		1.10(0.94–1.29)	0.2821
		Weighted median		1.01(0.99–1.02)	0.471

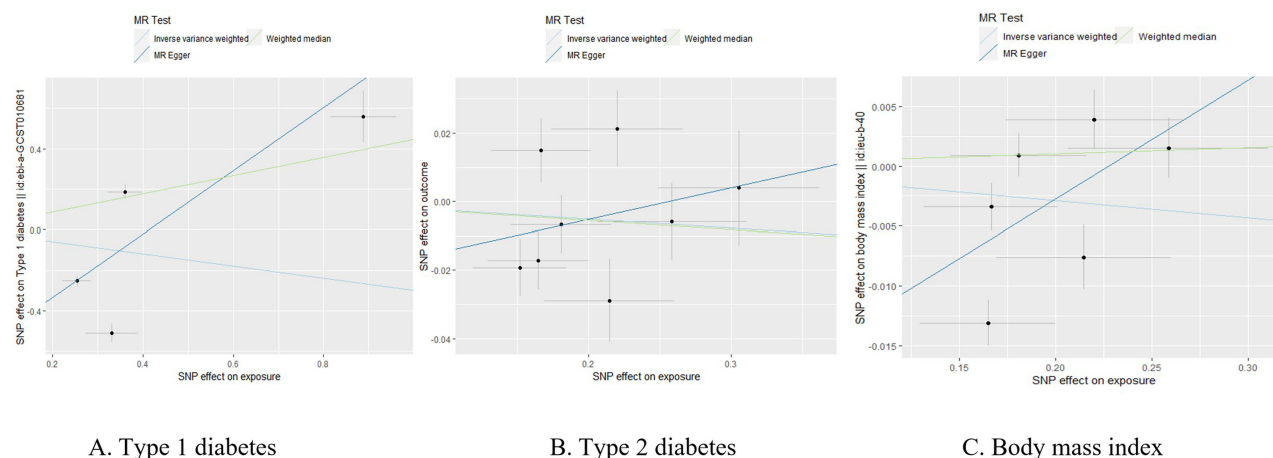


Figure 3 Scatter plots visualizing the Mendelian randomization (MR) estimates of the exposure (lichen sclerosus) with different outcomes ((A): Type 1 diabetes; (B): Type 2 diabetes; (C): Body mass index).

BMI and Lichen Sclerosus

Causal Effects of BMI on Lichen Sclerosus

In total, 436 SNPs related to BMI were identified, and the IVW, MR Egger, and weighted median methods used to estimate the causal relationship between BMI and LS did not show a significant correlation (IVW, OR=0.92, 95% CI=0.73–1.15, $p=0.4554$; MR Egger, OR=1.04, 95% CI=0.58–1.86, $p=0.8950$; weighted median, OR=0.97, 95% CI=0.69–1.36, $p=0.8584$) (Table 2). The scatter plot of MR analysis was shown in Figure 2C. The Leave-one-out method result was shown in Supplementary Figure 1C. The P value of MR Egger obtained by the Cochran Q test was 0.017, while the IVW p value was 0.018 (Supplementary Table 8). The presence of heterogeneity did not affect the results. The funnel plot was shown in Supplementary Figure 3C.

Causal Effects of Lichen Sclerosus on BMI

In this study, 6 LS-related SNPs were identified to estimate the causal relationship between LS and BMI. IVW, MR Egger, and weighted media methods did not show a significant correlation (IVW, $\beta=-0.01$, SE=0.014, $p=0.314$; MR Egger, $\beta=0.1$, SE=0.080, $p=0.282$; weighted median, $\beta=0.01$, SE=0.007, $p=0.444$) (Table 3). The scatter plot of MR analysis was shown in Figure 3C. The P value of MR Egger obtained by the Cochran Q test was 9.00×10^{-7} , with an IVW p value of 8.41×10^{-10} (Supplementary Table 10). The result was heterogeneous, therefore, IVW was used as the gold standard in the final result of the MR. The funnel plot was shown in Supplementary Figure 4C.

Discussion

The pathogenesis of LS involves genetic factors, immune factors, hormone levels, microbial infections, and other aspects.³¹ Sherman et al³² conducted a basic genetic study on family members of LS patients. The study found that 12% of family members of LS patients also had this disease, indicating the potential role of genetic components. Some studies have found that specific HLA types, especially DQ7, DQ8, and DQ9, are more common in LS patients.^{33–35} Studies also have found that the expression of estrogen receptors is increased in the external genitalia of LS patients.³¹ In this study, a bidirectional two-sample MR analysis was performed to determine the correlation between metabolic factors, including DM, BMI, and LS, revealing no correlation between them.

As early as 1988, García Bravo et al³⁶ first published a report on the correlation between LS and diabetes. Subsequently, many studies have reported the correlation between LS and metabolic factors, such as DM and BMI. A retrospective cohort study found that women with LS were associated with an increased risk of metabolic syndrome. That study observed a 1.49-fold increase in the risk of LS with T2DM compared to normal individuals. Another retrospective study also found that an increase in BMI and vulvar LS were associated.¹⁴

Hofer et al¹⁰ performed a case-control study and found an association between male LS and increased BMI and diabetes. The study aimed to identify potential comorbidity factors that may promote its development and persistence. Considering the correlation between obesity and diabetes, they believed that the etiology or development of LS may have metabolic or lifestyle components. Therefore, the authors hypothesized that LS may be caused by systemic changes that affect blood perfusion in terminal organs, and that LS may not be solely a skin disease. Metabolic and lifestyle factors may play a role in the development of LS. Edmonds et al³⁷ have also found that both adult and child patients with LS exhibited reduced regulation of cellular metabolism, and decreased physiological processes related to cellular metabolism. Moreover, Virgili's et al⁸ research results also indicated a higher incidence of overweight and obesity in patients with vulvar LS than in the general population. These findings suggest that metabolic factors and possibly a sedentary lifestyle may play a role in the pathogenesis of GLS in genetically susceptible patients. Despite some differences in the onset of symptoms, the risk profile is similar for men and women. Therefore, metabolic factors were hypothesized to be involved in the pathogenesis of LS. The article also mentioned that their observations only assumed causal relationships. Nevertheless, no histological confirmation of LS patients was performed in the study, and the study cohort included only caucasian patients, so the findings may not be generalized to other races.⁸

All previous observational studies were susceptible to confusing risk factors. In contrast, the present study applied MR methods to maximize the disclosure of causal relationships despite potential bias. The results revealed that diabetes was not a risk factor for LS, and LS was not a predisposing factor for diabetes. On the one hand, we believe that a large part of the high-risk population comprises menopausal women and middle-aged men, which also coincides with the onset age of T2D, potentially leading to a false combination of the two diseases.¹ On the other hand, the current diagnostic standard of LS states that pathology can not be necessary in cases with typical clinical manifestations, which makes the diagnosis of the disease subjective. In addition, patients with diabetes are prone to skin itching and eczema.^{1,38–42} Therefore, there is a possibility of misdiagnosis of vulvar LS in clinical practice. Due to LS occurring mostly in the genital area, it can cause discomfort in the external genitalia, leading to behavioral changes such as a decrease in overall activity levels. This may lead to a relatively high BMI in LS patients. The present study applied MR analysis and found no correlation between diabetes (including T1D and T2D), BMI, and LS. However, these findings do not elucidate whether controlling the metabolic factors of individuals already suffering from LS would reduce its progress. Therefore, managing these factors is still important to minimize their inherent negative health effects.

This research has several significant advantages. To our knowledge, this is the first study to explore the two-way causal relationship between DM, BMI, and LS through bidirectional two-sample MR analysis. Compared to observational studies, this analysis method is less susceptible to potential confounding, reverse causality, and non-differential measurement exposure errors. Secondly, the current results have been confirmed in various sensitivity analyses, and there was no sign of horizontal pleiotropy. Nevertheless, Mendelian randomized studies also have some limitations. First, the incidence of LS in men and women and its relationship to metabolic factors could not be determined as the FinnGen biological database did not include information on the gender of LS. Then, further stratification of the included population is not possible owing to the nature of GWAS summary statistics. Moreover, all GWAS data were collected from the European population, and whether the current findings can be extended to other populations remains to be investigated. Prospective studies with a larger sample size are also needed for further exploration.

Conclusions

In conclusion, our study suggests the lack of causal relationship between diabetes, BMI, and lichen sclerosus. Potential confounding factors may contribute to previously observed associations, and further research is necessary.

Abbreviations

LS, Lichen sclerosus; GLS, Genitalia lichen sclerosus; DM, Diabetes mellitus; T1D, Type 1 diabetes; T2D, Type 2 diabetes; BMI, Body mass index; MR, Mendelian randomization; GWAS, Genome-wide association studies; IVW, Inverse variance weighted; IV, Instrumental variable; SNP, Single-nucleotide polymorphism.

Data Sharing Statement

All analyses were conducted using publicly available data. The GWAS summary data for type 1 diabetes and BMI are available in GWAS catalog, at <https://gwas.mrcieu.ac.uk/>. The summary-level data of type 2 diabetes were acquired from a GWAS meta-analysis. The GWAS summary data for lichen sclerosis are available in FinnGen, at <https://www.finnngen.fi/en>.

Ethics Approval and Consent to Participate

According to Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Beings adopted by the National Science and Technology Ethics Committee of the People's Republic of China, ethical review can be exempted because the data used in this study do not cause any harm to human beings, do not involve any sensitive personal information or commercial interests, and the databases selected are open and legal. Therefore, approval from a new ethics review committee is not required.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare they have no conflicts of interest.

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