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The dual role of diabetes on oral potentially malignant disorders

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Abstract

Background Observational studies suggest a link between diabetes and oral potentially malignant disorders (OPMDs), such as oral lichen planus (OLP) and oral leukoplakia (OLK). The causal relationship, as well as the type of diabetes that promotes OPMDs development, remains unclear. This Mendelian randomization (MR) study estimated the causal effects of diabetes-related traits on OPMDs.

Methods Large-scale genome-wide association study data on type 1 diabetes (T1D), type 2 diabetes (T2D), fasting glucose (FG), fasting insulin (FI), glycated hemoglobin (HbA1c), OLP, OLK, and actinic cheilitis (AC) were used. Causal effects were assessed using inverse-variance weighted (IVW), weighted median, and MR–Egger methods. Multivariable MR analyses evaluated the independent roles of these traits, with extensive sensitivity analyses.

Results Genetic susceptibility to T1D (IVW OR = 1.09, 95% CI 1.02–1.17, $P = 0.007$) and T2D (IVW OR = 0.91, 95% CI 0.86–0.97, $P = 0.002$) showed protective effects against AC. T1D was associated with an increased risk of OLP (IVW OR = 1.09, 95% CI 1.02–1.17, $P = 0.007$). The effect of T1D on AC and OLP remained robust after adjusting for FI, FG, and HbA1c, while T2D's effect on AC was not significant when considering these glycemic traits. No potential pleiotropy was detected ($P > 0.05$).

Conclusions T1D may have a causal role in the development of OLP independent of glycemic traits, emphasizing the need for routine oral examinations in T1D patients. Conversely, genetically predicted T1D and T2D are significantly associated with a reduced risk of AC, challenging previous assumptions and offering new insights into the relationship between diabetes and OPMDs. Further extensive investigations are required to address the limitations of this study and to clarify these associations.

Keywords Mendelian randomization analysis, Oral lichen planus, Oral leukoplakia, Actinic cheilitis, Diabetes mellitus

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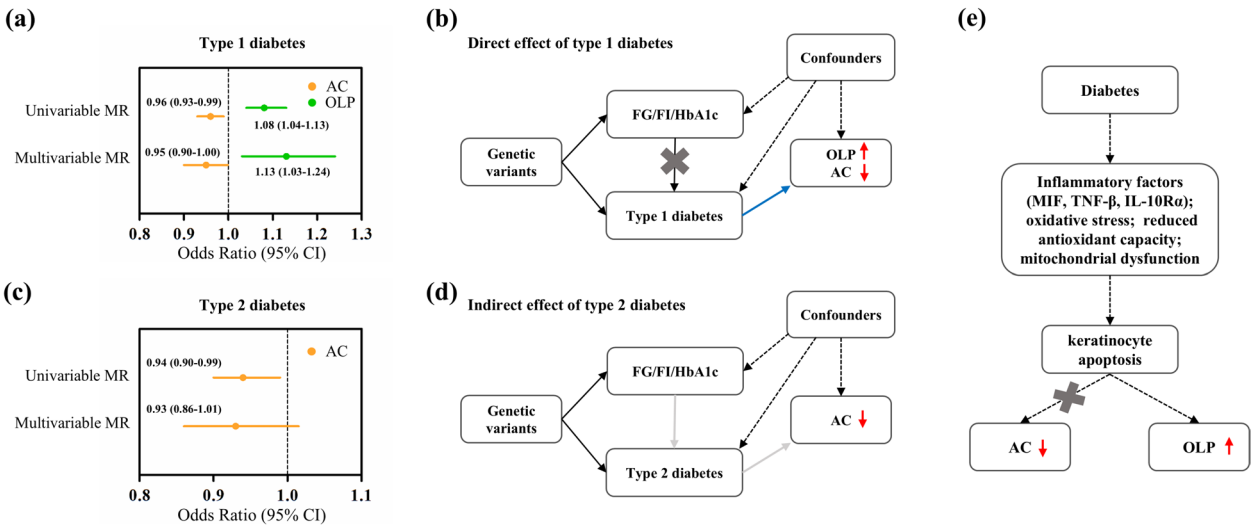
Graphical abstract



Introduction

Oral potentially malignant disorders (OPMDs) refer to oral mucosal lesions with an elevated risk of malignant progression, including conditions, such as oral leukoplakia (OLK), erythroplakia, oral lichen planus (OLP), actinic keratosis (including actinic cheilitis, AC), and oral graft-versus-host disease [1]. Approximately 80% of oral cancer cases are associated with OPMDs, which demonstrate an average malignant transformation rate of 7.9% [2, 3]. Despite advancements in oral cancer management, many cases are still diagnosed at advanced stages, where curative treatment options become limited and less effective [4]. Therefore, the early identification of OPMDs, particularly in high-risk groups, is essential for preventing their progression to malignancy.

Diabetes, characterized by chronic hyperglycemia due to insulin deficiency, resistance, or both, has been associated with an increased incidence of OPMDs, including OLP, OLK, and oral submucous fibrosis [5, 6]. Within diabetic populations, the reticular type of OLP is observed more frequently (83.3%) compared to atrophic and erosive forms (16.7%) [5]. In addition, individuals with type 1 diabetes (T1D) exhibit a higher prevalence of autoimmune diseases, including OLP, Sjogren's syndrome, systemic lupus erythematosus, and pemphigus vulgaris [7–9]. Factors such as trace element deficiencies, chronic inflammation, and psychological stress may enhance the vulnerability of diabetic patients to OPMDs [7]. Moreover, hyperglycemia can promote the M1 macrophage phenotype through the generation of excessive reactive oxygen species, which may contribute to the development of conditions, such as OLP, AC, and OLK [10–12]. As standard treatments for OPMDs, glucocorticoids intake may reversely elevate blood glucose and insulin levels [13, 14]. Consequently, establishing a clear causal connection between diabetes and OPMDs is complicated by potential biases, confounding factors, and the possibility of reverse causality inherent in observational studies.

Mendelian randomization (MR) has emerged as a powerful method for establishing causality by utilizing genetic variants linked to specific exposures [15]. Since genotypes are determined at conception and remain unaffected by subsequent disease progression, MR effectively mitigates the risk of reverse causality. Prior MR investigations have demonstrated causal relationships between diabetes and various oral health conditions, including dental caries, periodontitis, and oral cancers while identifying potential mediating factors within these associations [16–18]. The recent accessibility of genome-wide association study (GWAS) data on OPMDs enhances the capacity for MR analysis, addressing issues related to weak-instrument bias [19]. It is also essential to investigate the distinct impacts of different diabetes types on OPMDs, given the inconsistencies reported in existing literature [5]. T1D, resulting from the autoimmune destruction of β-cells leading to absolute insulin deficiency, contrasts with type 2 diabetes (T2D), characterized by metabolic dysfunction that results in progressive β-cell impairment and insulin resistance, which manifest chronic hyperglycemia in varied ways [6]. In addition,

the combination of other glycemic traits, such as fasting glucose (FG), glycated hemoglobin (HbA1c) and fasting insulin (FI), allows for a comprehensive understanding of the pathophysiology of T1D and T2D and their potential associations with OPMDs.

In light of the limited understanding of the causal effects of diabetes on OPMDs, this study utilized GWAS data to systematically investigate potential causal relationships through both univariable and multivariable MR approaches. We first employed human genetic data within the MR framework to examine the overall causal link between diabetes or glycemic traits and the risk of developing OLP, OLK, or AC. Subsequently, we assessed the specific effects of significant indicators on the likelihood of developing OPMDs. Our results not only elucidate the causal relationship between diabetes and OPMDs but also indicate a direct influence of T1D on the development of OLP or AC, providing valuable insights for clinical interventions.

Methods

The study design

This study follows the guidelines outlined in the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement for MR (Supplementary Table 1) and the study's design is depicted in Fig. 1.

Data sources

In this investigation, T1D, T2D, FI, FG, and HbA1c were utilized as indicators of diabetes. T1D data, including 6,808 cases, were obtained from the UK Genetic Resource Investigating Diabetes cohort, with 12,835 controls sourced from the British 1958 Birth Cohort, the UK National Blood Services collection, and the NIHR Cambridge Biomedical Research Centre Cambridge BioResource [20]. T1D cases were limited to individuals younger than 16 years without concurrent diseases or disorders within 6 months of starting insulin treatment. T2D summary statistics were derived from the latest GWAS, which included 62,892 cases and 596,424 controls from DIAbetes Genetics Replication

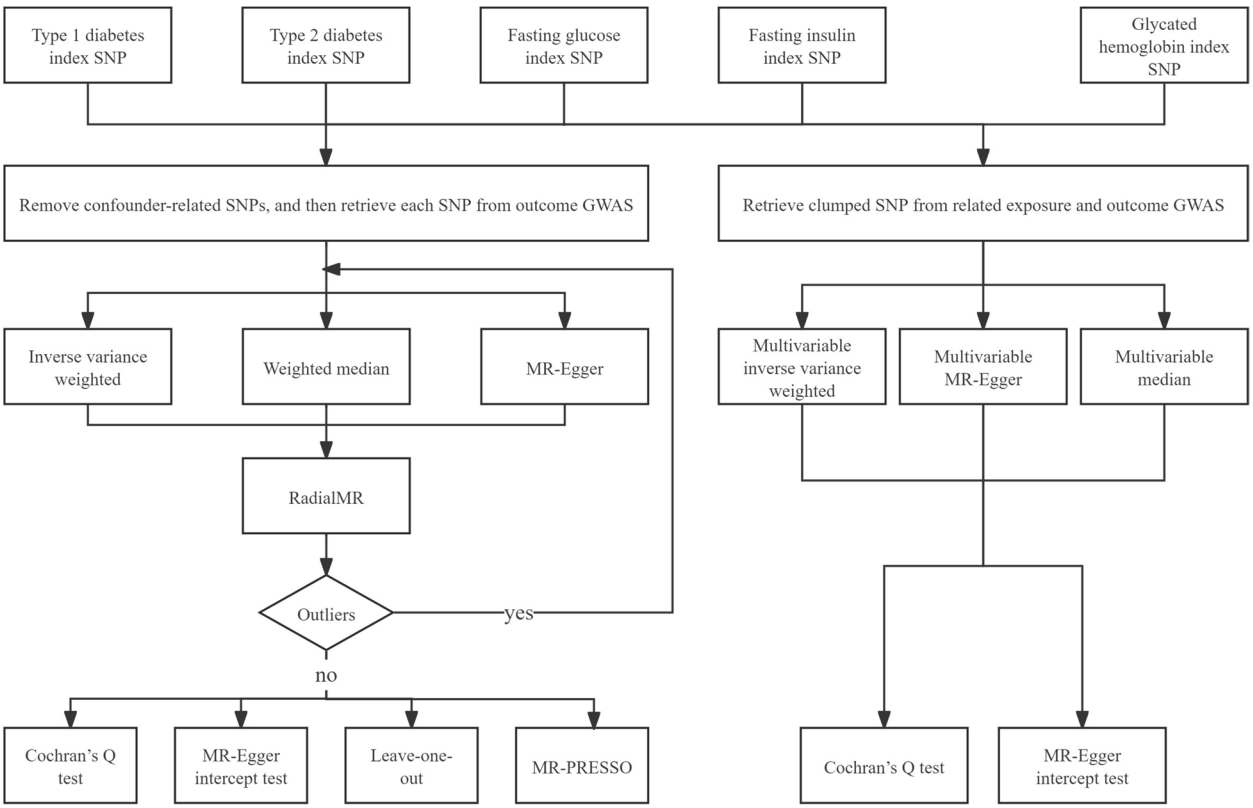


Fig. 1 Workflow of Mendelian randomization study revealing causality from diabetes on oral potentially malignant disorders. We first employed human genetic data within the Mendelian randomization framework to examine the overall causal link between diabetes or glycemic traits and the risk of developing oral potentially malignant disorders, such as oral lichen planus and oral leukoplakia and actinic cheilitis. Subsequently, we assessed the specific effects of significant indicators on the likelihood of developing oral potentially malignant disorders using multivariable Mendelian randomization analyses

and Meta-analysis, Genetic Epidemiology Research on Adult Health and Aging and the UK Biobank [21]. The T2D phenotype was identified through self-reports and the International Classification of Diseases 10th Revision (ICD-10) diagnoses. Data for FG, FI, and HbA1c were obtained from the Meta-Analyses of Glucose and Insulin-related traits Consortium, covering 200,622, 151,013, and 146,806 individuals, respectively [22]. Measurements of FG and FI taken from whole blood were adjusted to plasma levels using a constant factor 1.13 [23]. Individuals with T1D, T2D, or on diabetes-relevant medications were excluded. The details of the research consortium, research location, sample size, and data source are listed in Table 1.

To investigate whether the relationship between diabetes and OPMDs is influenced by gender, we obtained gender-stratified data on T2D from the DIAbetes Genetics Replication and Meta-analysis consortium. The data was divided into two categories: one with only females (30,053 T2D cases; 434,336 controls), and the other with only males (41,846 T2D cases; 383,767 controls) [24]. Unfortunately, the gender-stratified GWAS on T1D was unavailable.

FinnGen is a genomics medicine research project that has compiled and analyzed genomic and health data from 500,000 Finnish biobank donors to uncover the genetic basis of diseases. The latest GWAS data set release from December 2023 (R10 version) includes OPMDs, such as AC, OLK, and OLP, all classified according to the ICD-10 criteria (https://risteys.finregistry.fi/). This study utilized GWAS data comprising 12,094 cases of AC and 398,605 controls, 6411 cases of OLP and 405,770 controls, and 1652 cases of OLK and 410,529 controls. All GWAS data focused on European populations and were conducted with appropriate ethical approvals and participant consent. There was no overlap between diabetes-related and OPMDs samples in this MR study.

Instrument selection

The genetic variants were selected based on three key assumptions: they must be strongly associated with the exposure of interest, be genetically independent of confounding variables, and affect outcomes exclusively

Table 1 Details of the GWAS included in the Mendelian randomization

Phenotype	Research institution/ conductor	Sample size Total (cases/controls)	Research location	Ancestry	Source
T1D	Onengut-Gumuscu et al.	19,643 (6808/12,835)	United Kingd om	European	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST005536/
T2D	Xue et al.	659,316 (62,892/596,424)	United Kingdom and America	European	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST006867/
T2D-female	DIAGRAM	464,389 (30,053/434,336)	United Kingdom and America and Germany	European	https://diagram-consortium.org/
T2D-male	DIAGRAM	425,613 (41,846/383,767)	United Kingdom and America and Germany	European	https://diagram-consortium.org/
FG	MAGIC	200,622	America and Netherlands and Scandinavia and Denmark and Switzerland and Germany and Croatia and Spain and Sweden and Estonia and France and United Kingdom and Greece and Italy and Norway and Australia	European	https://magicinvestigators.org/downloads/MAGIC1000G_FG_EUR.tsv.gz
FI	MAGIC	151,013			https://magicinvestigators.org/downloads/MAGIC1000G_FI_EUR.tsv.gz
HbA1c	MAGIC	146,806			https://magicinvestigators.org/downloads/MAGIC1000G_HbA1c_EUR.tsv.gz
AC	FinnGen	410,699 (12,094/398,605)	Finland	European	https://storage.googleapis.com/finngen-public-data-r10/summary_stats/finngen_R10_L12_ACTINKERA.gz
OLP	FinnGen	412,181 (6411/405,770)	Finland	European	https://storage.googleapis.com/finngen-public-data-r10/summary_stats/finngen_R10_K11_LICHEN_PLANUS_WIDE.gz
OLK	FinnGen	412,181 (1652/410,529)	Finland	European	https://storage.googleapis.com/finngen-public-data-r10/summary_stats/finngen_R10_K11_ORAL_LEUCOPLAC_RELAT.gz

T1D type 1 diabetes, *T2D* type 2 diabetes, *FG* fasting glucose, *FI* fasting insulin, *HbA1c* glycated hemoglobin levels, *AC* actinic cheilitis, *OLP* oral lichen planus, *OLK* oral leukoplakia, *DIAGRAM* DIAbetes Genetics Replication And Meta-analysis, *MAGIC* the Meta-Analyses of Glucose and Insulin-related traits Consortium

through the exposure pathway [16]. The selection of single nucleotide polymorphisms (SNPs) for this MR study followed criteria series of steps to ensure reliable causal inferences [15]. SNPs were selected based on their association with the exposure of interest at a genome-wide significance level ($P < 5 \times 10^{-8}$). Linkage disequilibrium SNPs were eliminated ($r^2 \geq 0.001$, clumping window ≤ 10,000 kb) to ensure instrumental independence. The selected SNPs were then analyzed using the LDtrait website (https://ldlink.nih.gov/?tab=ldtrait) to exclude those associated with potential confounders (e.g., smoking behavior, alcohol consumption, psychosocial conditions and carcinoma) [25] and the outcome (thresholds r^2: 0.1 ± 500,000 base pair window). If exposure-related SNPs were not available in the outcome GWAS statistics, proxy SNPs significantly associated with the variant of interest were selected ($r^2 > 0.8$). Subsequently, SNP harmonization was performed to ensure consistency between the exposure and outcome SNPs while also removing any ambiguous or incompatible SNPs. Finally, the F-statistics were calculated to assess the strength of the remaining instruments, with F-statistics > 10 considered strong IVs.

Statistical analysis

Multiple MR methods were employed to ensure robust estimates, including inverse-variance weighted (IVW), the weighted median, and MR–Egger. IVW was the primary MR analysis method, combining all the Wald ratios for each SNP to provide a pooled estimate [15, 16]. Sensitivity analysis was crucial in detecting pleiotropy and heterogeneity in MR estimates. Horizontal pleiotropy was assessed using the MR–Egger intercept test, Mendelian randomized polymorphism RESidual Sum and Outlier (MR-PRESSO), and leave-one-out analyses. The Cochran *Q* test was performed to examine heterogeneity among genetic variations. Due to the significant heterogeneity observed, two modified methods were applied: a random-effect IVW model and RadialMR analyses using modified second-order weights to identify outliers [26]. Identified outliers were removed, and the analysis was repeated. Statistical significance for the MR effect estimate was defined with a false discovery rate (FDR) of < 5% to adjust for multiple testing.

In addition, multivariable IVW (MV-IVW) was used to determine whether the causal effects of specific diabetes types on OPMDs were independent of comprehensive glycemic traits. MVMR–Egger and MVMR-median methods were employed to validate the robustness of the MV-IVW results, with the *P* value of the MR–Egger intercept serving as an indicator of horizontal pleiotropy.

All MR analyses were conducted using R (version 4.3.0) through the TwoSampleMR package (version 0.5.6), MRPRESSO (version 1.0), RadialMR (version 1.1), and MendelianRandomization (version 0.7.0).

Results

Causal effects of diabetes-related traits on OPMDs

The specific characteristics of SNPs associated with diabetes, FI, FG, and HbA1c are detailed, including the steps for post-screening and the removal of potential confounders such as smoking (e.g., rs3184504, rs459193, rs2001945, rs12454712, rs2925979, rs7903146, rs1701704, and rs2867125), alcohol consumption (e.g., rs1260326, rs780094, rs10401969, rs2925979, rs9928094, rs1800562, rs13389219, rs2001945), worry conditions (e.g., rs6798941), and carcinoma (e.g., rs72928038, rs6679677, rs3184504, rs3087243, rs3217992, rs1758632, and rs174559) (Supplementary Tables 2, 3). The information on specific traits, sample details, PubMed IDs, and mapped genes related to confounders is provided in Supplementary Table 3. Data harmonization steps are provided in Supplementary Table 4. In total, 33 SNPs for T1D, 108 for T2D, 64 for FG, 33 for FI, and 69 for HbA1c were selected, all demonstrating F-statistic of 22.4 or higher.

IVW analysis indicated that T2D has a causal effect in reducing the risk of AC (OR = 0.91, 95% CI 0.86–0.97, $P = 0.002$, FDR $q = 0.031$) (Fig. 2). In contract, genetically predicted T1D was significantly associated with an increased risk of OLP (IVW: OR = 1.09, 95% CI 1.02–1.17, $P = 0.007$, FDR $q = 0.047$) and suggested a reduced risk of AC (IVW: OR = 0.96, 95% CI 0.92–0.99, $P = 0.021$, FDR $q = 0.121$) (Fig. 3). These findings were consistent across other MR methods. No significant causal relationship was identified between glycemic traits and AC, OLP, or OLK (Supplementary Figs. 1–3). Except for the influence of FG on OLP ($P = 0.040$), all MR–Egger intercept test *P* values were above 0.05 (Table 2). The *Q* test highlighted heterogeneity between diabetes-related traits and OPMDs.

Radial plots and regression analyses were employed to detect outliers and influential points within the IVW analysis (Supplementary Figs. 4–6). Following the removal of these outliers, significant causal associations were observed between T1D and OLP (OR = 1.08, 95% CI 1.04–1.13, $P < 0.001$, FDR $q = 0.003$), T2D and AC (OR = 0.94, 95% CI 0.90–0.99, $P = 0.014$, FDR $q = 0.031$), and T1D and AC (OR = 0.96, 95% CI 0.93–0.99, $P = 0.013$, FDR $q = 0.030$) (Figs. 2, 3). The findings were further corroborated by the ME–Egger and WM methods. Cochran's *Q* test did not reveal any significant heterogeneity (Table 2). In addition, no evidence of horizontal pleiotropy was detected through the MR–Egger intercept test or the MR-PRESSO global test, except for FG's impact on OLP (Egger intercept = 0.013, $P = 0.023$)

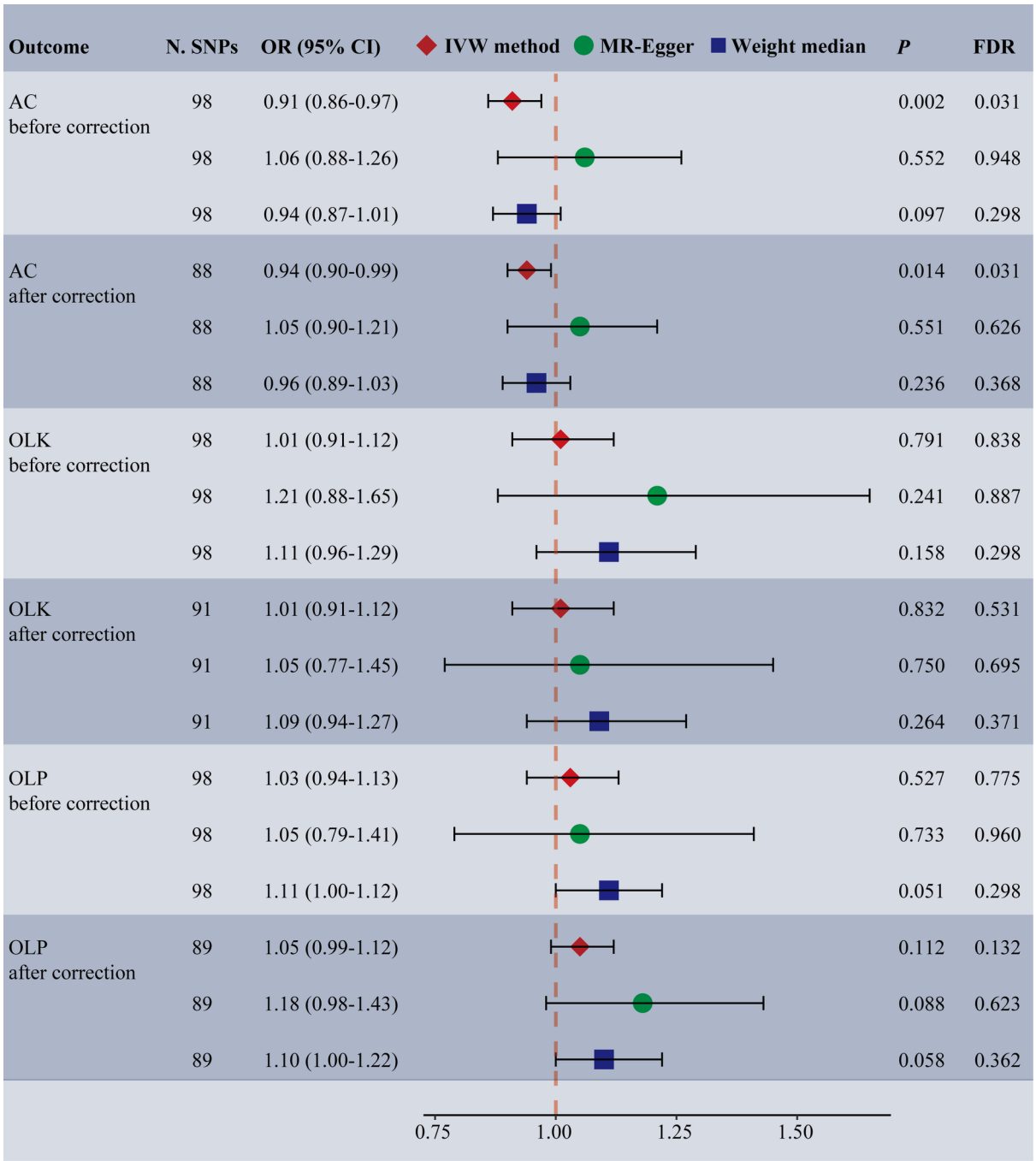


Fig. 2 Forest plot depicting MR results for the association of genetically proxied type 2 diabetes with oral potentially malignant disorders. The association between genetically proxied type 2 diabetes and oral potentially malignant disorders were assessed before and after removing outliers (detected by Radial MR). Odds ratios (ORs) with 95% CIs were calculated for the categorical outcomes. Inverse variance weighted analyses showed that genetically predicted type 2 diabetes is significantly associated with a reduced risk of actinic cheilitis. N. *SNPs* number of SNPs used in MR, *OR* odds ratio, *CI* confidence intervals, *IVW* inverse variance weighted, *AC* actinic cheilitis, *OLK* oral leukoplakia, *OLP* oral lichen planus, *FDR* false discovery rate

(Table 2; Supplementary Table 5). Funnel plots exhibited no asymmetry, suggesting an absence of pleiotropy (Supplementary Figs. 7–9). The leave-one-out analysis did not indicate any SNP significantly diverging from the overall effect of diabetes on OPMDs (Supplementary Figs. 10–12).

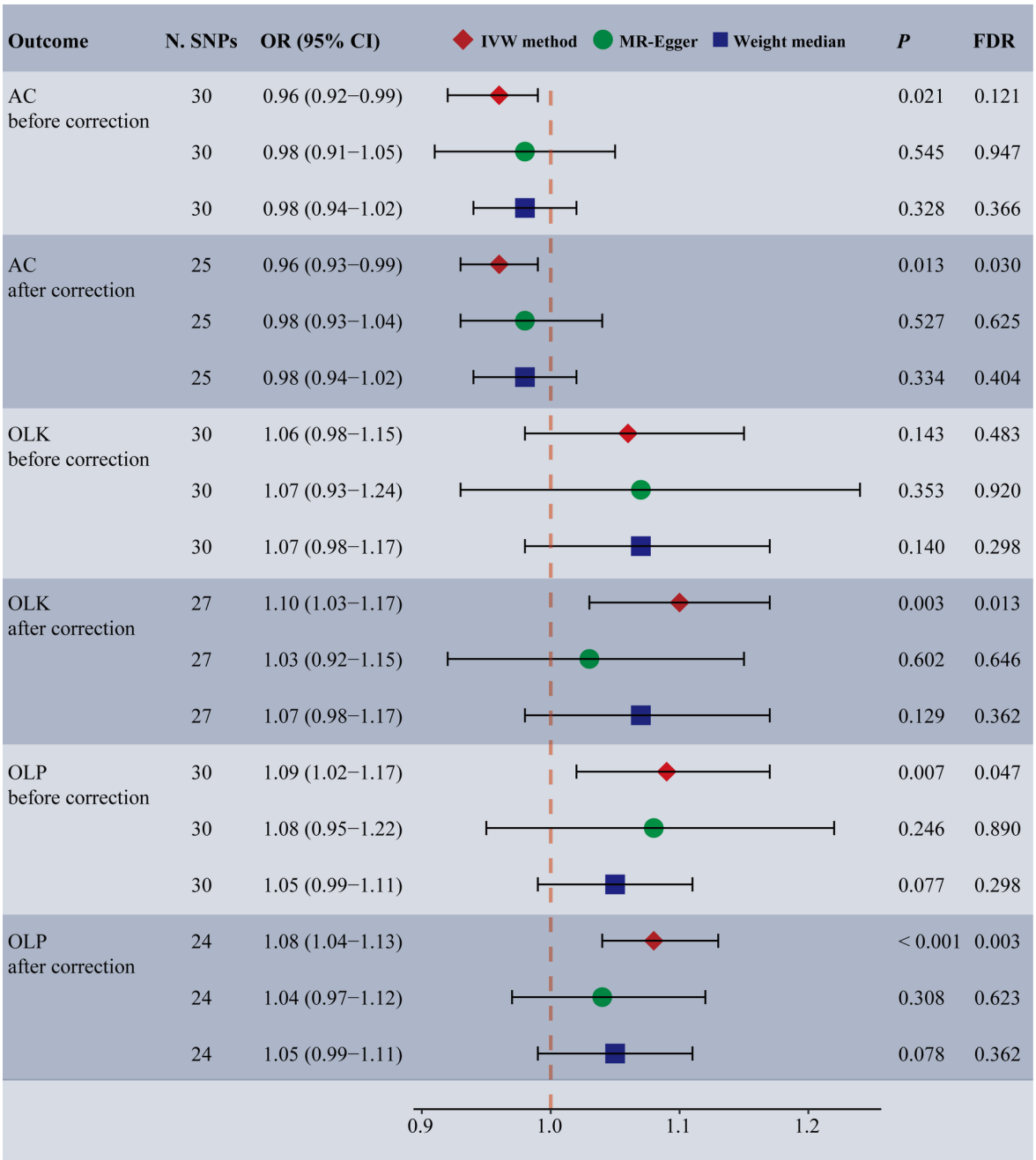


Fig. 3 Forest plot depicting MR results for the association of genetically proxied type 1 diabetes with oral potentially malignant disorders. The association between genetically proxied type 1 diabetes and oral potentially malignant disorders were assessed before and after removing outliers (detected by Radial MR). Odds ratios (ORs) with 95% CIs were calculated for the categorical outcomes. Inverse variance weighted analyses showed that genetically predicted type 1 diabetes is significantly associated with a reduced risk of actinic cheilitis and an increased risk of oral lichen planus, with consistent directions detected by MR–Egger and weighted median approaches. *N. SNPs* number of SNPs used in MR, *OR* odds ratio, *CI* confidence intervals, *IVW* inverse variance weighted, *AC* actinic cheilitis, *OLK* oral leukoplakia, *OLP* oral lichen planus, *FDR* false discovery rate

Multivariable IVW analyses highlighted a significant direct association of T1D with OLP (OR = 1.13, 95% CI 1.03–1.24, $P = 0.011$) and AC (OR = 0.95, 95% CI 0.90–1.00, $P = 0.046$), even after adjusting for FI, FG, and HbA1c levels (Fig. 4; Supplementary Table 6). While similar trends were observed in the MVMR–Egger and MV-median analyses, these findings did not reach statistical significance. No significant effect of T2D on AC

Table 2 Sensitivity analysis of the associations between diabetes-related traits and oral potentially malignant disorders

Analysis	Exposure	Outcome	Heterogeneity statistics			Horizontal pleiotropy	
			Cochran's Q	I^2	*P*	Egger intercept	*P*
Before correction	T1D	AC	47.057	0.384	0.018	− 0.005	0.440
		OLK	49.023	0.408	0.011	− 0.003	0.860
		OLP	84.212	0.656	0.000	0.004	0.745
	T2D	AC	152.565	0.364	0.000	− 0.010	0.093
		OLK	111.670	0.131	0.146	− 0.012	0.250
		OLP	231.559	0.581	0.000	− 0.001	0.886
	HbA1c	AC	119.897	0.491	0.000	− 0.003	0.605
		OLK	84.885	0.281	0.023	− 0.005	0.599
		OLP	104.569	0.417	0.000	− 0.001	0.842
	FG	AC	77.627	0.291	0.024	− 0.003	0.501
		OLK	66.458	0.172	0.138	− 0.002	0.819
		OLP	63.997	0.141	0.190	0.012	0.040
	FI	AC	25.739	0.088	0.587	− 0.002	0.813
		OLK	32.819	0.147	0.242	0.030	0.144
		OLP	42.636	0.343	0.038	− 0.028	0.053
After correction	T1D	AC	21.682	0.107	0.598	− 0.005	0.355
		OLK	19.860	0.309	0.798	0.015	0.186
		OLP	25.652	0.103	0.318	0.010	0.212
	T2D	AC	76.829	0.132	0.774	− 0.007	0.140
		OLK	76.005	0.184	0.854	− 0.003	0.790
		OLP	86.211	0.021	0.534	− 0.008	0.209
	HbA1c	AC	46.329	0.122	0.696	− 0.008	0.066
		OLK	36.167	0.465	0.963	0.001	0.877
		OLP	55.676	0.030	0.412	0.006	0.308
	FG	AC	38.215	0.361	0.923	0.000	0.977
		OLK	45.194	0.128	0.702	− 0.007	0.411
		OLP	51.241	0.034	0.543	0.013	0.023
	FI	AC	17.110	0.520	0.906	0.003	0.765
		OLK	24.148	0.118	0.622	0.022	0.260
		OLP	23.264	0.032	0.504	− 0.018	0.170

T1D type 1 diabetes, *T2D* type 2 diabetes, *FG* fasting glucose, *FI* fasting insulin, *HbA1c* glycated hemoglobin levels, *AC* actinic cheilitis, *OLP* oral lichen planus, *OLK* oral leukoplakia

was observed when accounting for these glycemic traits (MV–IVW: OR = 0.93, 95% CI 0.86–1.01, $P = 0.092$). Instrumental validity tests indicated no weak instrument bias (F-statistic ≥ 19.4). Cochran's *Q* test suggested consistent heterogeneity among all instrumental variables, and multivariable MR–Egger intercept tests showed minimal evidence of pleiotropy (Supplementary Table 6).

To investigate the potential causal relationship between T2D and OPMDs across genders and to strengthen the credibility of our findings, we conducted two-sample MR analyses separately for males and females. Notably, in the female cohort with T2D, there were no significant associations with AC (IVW OR = 0.97, 95% CI 0.92–1.03, $P = 0.303$), OLP (IVW OR = 1.06, 95% CI 0.93–1.21, $P = 0.389$) and OLK (IVW OR = 1.01, 95% CI 0.91–1.11, $P = 0.914$). In contrast, the main IVW analyses for the male group indicated a significant causal relationship between T2D and a reduced risk of AC (OR = 0.94, 95% CI 0.90–0.99, $P = 0.013$), which was consistently supported by other MR methods (Supplementary Table 7).

Causal effects of OPMDs on diabetes-related traits

In the reverse MR analyses, the primary IVW analysis revealed a significant causal effect of OLP on increasing FI (Beta = 0.01, 95% CI 0.00–0.02, $P = 0.006$, FDR $q = 0.042$). In addition, there was a suggestive causal relationship between OLP and an increased risk of T2D (OR = 1.07, 95% CI 1.01–1.13, $P = 0.021$, FDR

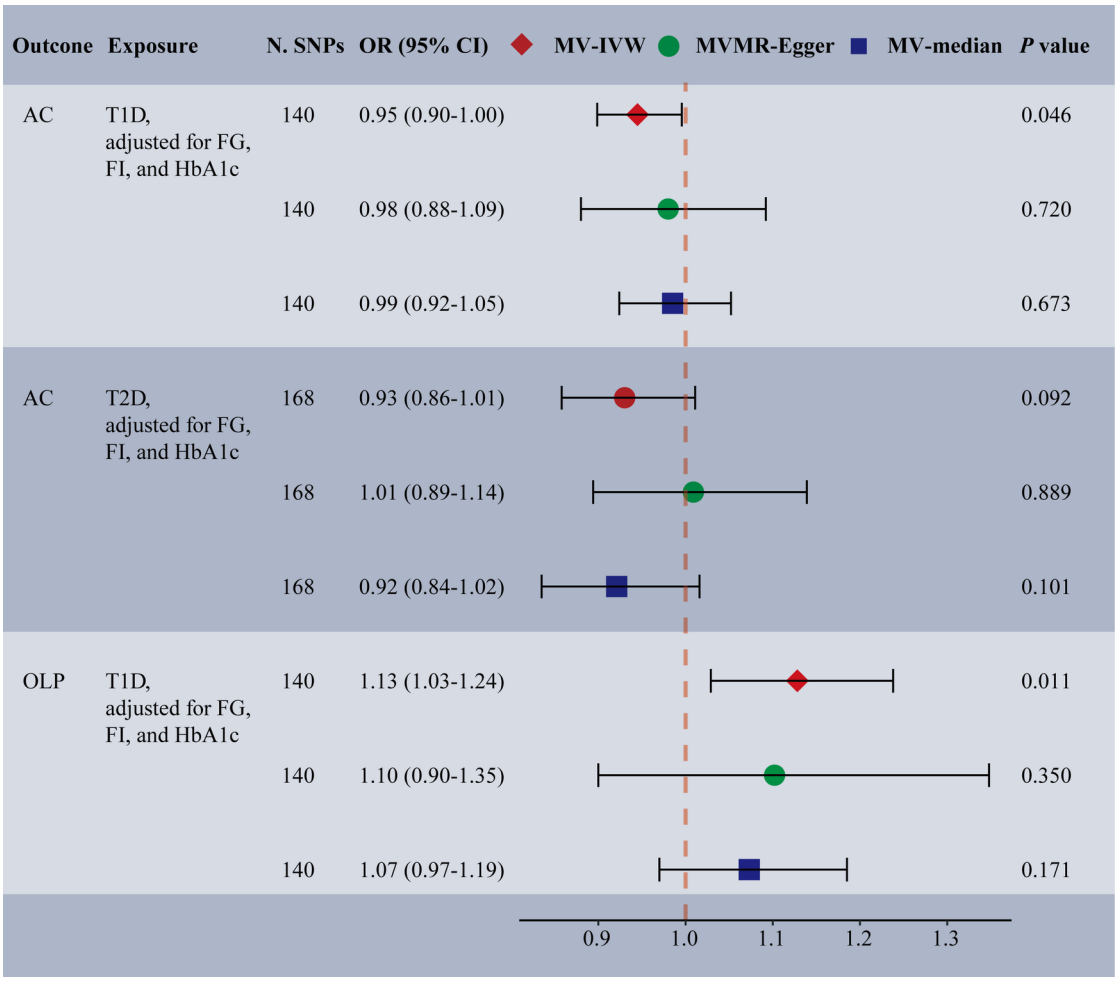


Fig. 4 Multivariable MR estimating the association of diabetes and oral potentially malignant disorders with adjustment for glycemic traits. The independent effects of diabetes on oral potentially malignant disorders were assessed after accounting for several glycemic traits (i.e., fasting glucose, fasting insulin, and glycated hemoglobin). Odds ratios (ORs) with 95% CIs were calculated for the categorical outcomes. Multivariable inverse variance weighted analyses showed that genetically predicted type 1 diabetes remain significantly associated with a reduced risk of actinic cheilitis and an increased risk of oral lichen planus, with consistent directions detected by multivariable MR Egger and multivariable median approaches. *N. SNPs* number of SNPs used in MR, *OR* odds ratio, *CI* confidence intervals, *MV-IVW* multivariable inverse variance weighted, *MVMR–Egger* multivariable MR Egger, *MV-median* multivariable median, *AC* actinic cheilitis, *OLP* oral lichen planus, *T1D* type 1 diabetes, *T2D* type 2 diabetes, *FG* fasting glucose, *FI* fasting insulin, *HbA1c* glycated hemoglobin levels

$q = 0.077$), supported by both the ME–Egger and WM methods (Supplementary Tables 8, 9).

Radial MR analyses identified outlying genetic variants. No outliers were detected for the effect of OLP on FI (Supplementary Table 9). However, following the removal of the specific outlier (rs9459853), the association between OLP and T2D was no longer significant (IVW OR = 1.07, 95% CI 1.01–1.13, $P = 0.104$, FDR $q = 0.320$). Moreover, no evidence of heterogeneity or pleiotropy was detected post-adjustments (all $P > 0.05$) (Supplementary Table 9).

Discussion

This study represents an observation into the causal relationships between diabetes-related traits and OPMDs using bidirectional MR approaches. The findings demonstrate that the genetically predicted T1D increases the risk of OLP while decreasing the likelihood of AC, even after accounting for FI, FG, and HbA1c (Fig. 5). In contrast, genetic predisposition to T2D is significantly associated with a lower risk of AC, a relationship influenced by comprehensive glycemic traits. Other diabetes-related traits showed minimal

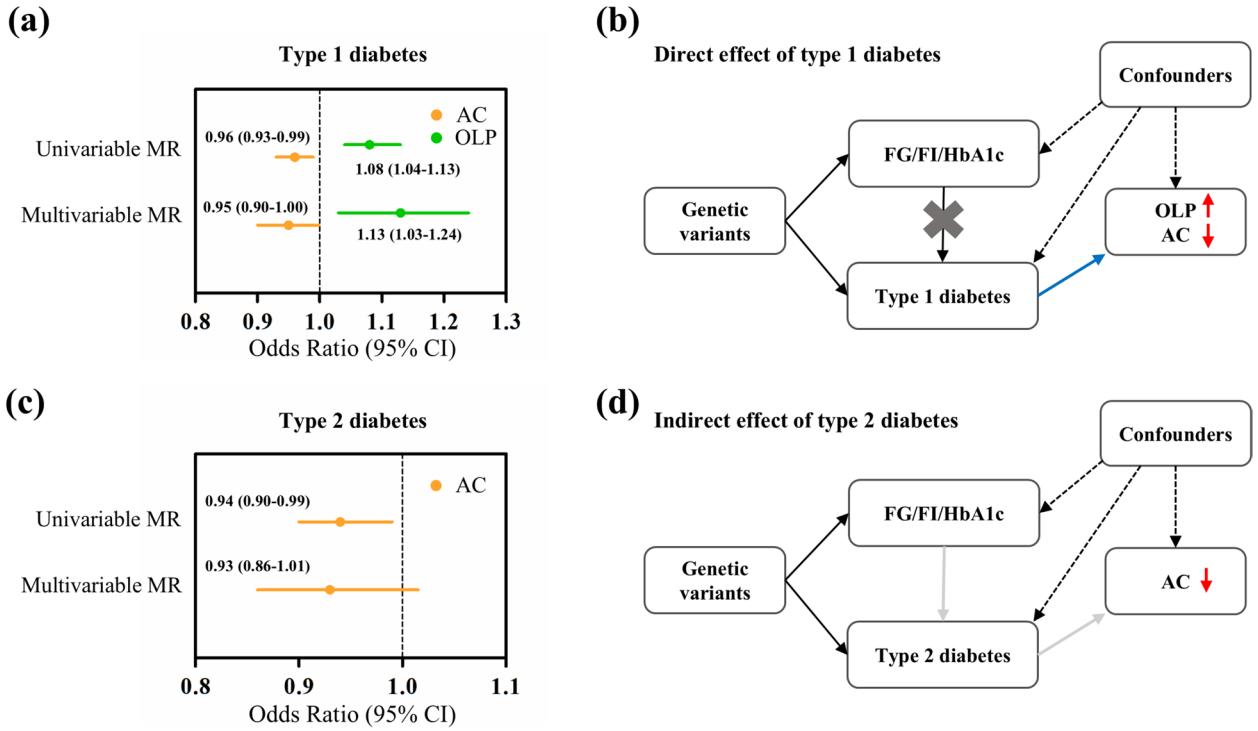


Fig. 5 Key findings of the present MR study. **a** Forest plot illustrating the overall and independent effects of type 1 diabetes on actinic cheilitis (AC) and oral lichen planus (OLP), even accounting for the influence of glycemic traits (fasting glucose, FG; fasting insulin, FI; glycated hemoglobin levels, HbA1c) in multivariable MR. **b** Corresponding schematic diagram for the direct effects of type 1 diabetes. **c** Forest plot illustrating the overall and indirect effects of type 2 diabetes on AC, accounting for the influence of glycemic traits in multivariable MR. **d** Corresponding schematic diagram for the indirect effects of type 2 diabetes. The colored arrows in blue and grey on these graphs illustrate the causal effect of specific diabetes on the outcome being estimated in multivariable MR analyses

evidence of a causal relationship with AC, OLP, or OLK.

The association between OLP and diabetes has been investigated for over six decades [27]. The prevailing hypothesis suggests that hyperglycemia-induced inflammatory responses and disruptions in cellular homeostasis may contribute to OLP development [28]. A substantial body of evidence from case–control, cross-sectional, cohort, and in vivo studies highlight a robust association between diabetes and OLP, with diabetic patients facing a significantly elevated risk of developing OLP (OR = 1.87, 95% CI 1.37–2.57, $p < 0.001$) [29]. Moreover, a 4-year cohort study supported these findings [30]. However, the role of specific diabetes types remains debated. Proponents of a T1D–OLP link argue that both are immune-related conditions with shared pathogenic genes [27]. Yet, a recent meta-analysis found the association between T1D and OLP to be non-significant, while a strong link was established between T2D and OLP [31]. Our MR study confirms a causal relationship between T1D and OLP, with no similar effect observed for T2D. Epidemiological data suggest that over 40% of individuals over 30 years with T1D may be misdiagnosed with T2D, indicating a higher proportion of T1D cases in studies involving diabetic populations [32]. In addition, our reverse MR analysis suggests that OLP might have a causal effect on increased FI and T2D risk, potentially explaining the strong correlations observed in prior studies. From a theoretical perspective, individuals with T1D showed reduced stimulated parotid gland flow rates, leading to lower buffering capacity and elevated levels of cariogenic bacteria, such as *Streptococcus mutans* and *Lactobacillus* [33]. Recent MR studies have identified a causal link between T1D and dental caries, even after adjusting for T2D [16]. Prolonged mechanical irritation from carious teeth could predispose individuals to potentially malignant oral lesions, including OLP, OLK, and oral submucosal fibrosis [34]. Our findings suggest that T1D may contribute to OLP development through non-glycemic mechanisms. The previous MR work and experimental research have highlighted the pivotal role of IL-10, a key inflammatory mediator, in linking T1D to OLP [19, 35]. For example, peripheral blood mononuclear cells from patients with T1D and diabetic retinopathy produced elevated levels of IL-10 and IL-6 when stimulated with lipopolysaccharide or glucose

analogs [36]. Moreover, polymorphisms in the IL-10 gene (-1082G/A, -819C/T and -592C/A) have been associated with OLP, with higher serum IL-10 levels observed in affected patients [37, 38]. Mast cells release chymase and tryptase, which activate matrix metalloproteinases (MMPs) and disrupt the basement membrane of the oral mucosa, facilitating CD8 + T cell infiltration [7]. These infiltrating T cells induce keratinocyte apoptosis, further exacerbating mucosal damage. Although IL-10 exhibits anti-inflammatory properties, it could paradoxically enhance immune activity by increasing CD8 + T cell cytotoxicity. Prolonged IL-10 stimulation can also amplify mast cell degranulation and apoptosis, collectively contributing to OLP development [39].

Clinical trials have also demonstrated that OLP may increase insulin levels, thereby raising the risk of T2D [40]. This study supports this perspective from a genetic standpoint. Glucocorticoids, the primary treatment for erosive OLP, promote hyperglycemia by increasing hepatic glucose production, inducing insulin resistance in muscles, and impairing insulin secretion from β-cells [14, 41]. In addition, the chronic discomfort from erosive OLP may lead to high-fat diets, contributing to obesity, a known T2D risk factor [42].

AC is characterized by the intraepithelial proliferation of atypical keratinocytes, presenting as rough, scaly patches or papules, primarily on sun-exposed areas like the lower lip's vermilion border [1]. Research into the link between AC and diabetes remains limited [5]. Two case–control studies have produced conflicting outcomes: one found no association between diabetes and AC [43], while the other suggested that T2D could be a risk factor [6]. These studies were constrained by small sample sizes (30 and 257 participants, respectively), ambiguous definitions of diabetes, and varying sun exposure levels, reducing their reliability [6, 43]. A large-scale Korean study, monitoring 2,056,580 T2D patients over 7 years, reported 6,404 AC cases, yielding an incidence rate of 0.3% [44]. However, the general Korean population's AC incidence is about 0.5% [45], and in Australia, it reaches around 9% [46], both higher than in the T2D population. These findings suggest that diabetes may be a protective factor against AC. Our genetic analysis indicates that both T1D and T2D have causal effects in reducing the incidence of AC, with T2D's protective role largely dependent on glucose metabolism factors. In hyperglycemia, oxidative stress, reduced antioxidant capacity, and mitochondrial dysfunction are linked to keratinocyte apoptosis and inflammation via the ERK1/2-PI3K/Akt–IRF3 pathway [13]. Moreover, keratinocytes express insulin receptors, and insulin stimulation promotes keratinocyte proliferation through protein kinase C isoforms δ and Na^+/K^+ pump activation [47]. Therefore, lower insulin levels in advanced T2D and T1D hinder keratinocyte proliferation. T1D may influence AC occurrence through non-glycemic pathways, though the precise mechanisms remain unclear.

However, the significant causal relationship between T2D and AC was observed only in men, but not in women, suggesting a sex difference in the association between T2D and OPMDs. This finding aligns with a recent meta-analysis, addressing that AC was more frequent in men than in women, with a statistically significant association ($P < 0.01$) [48]. This lower prevalence of AC in women could be explained by a higher frequency of using sunscreen lipsticks and other protective measures, such as a lower percentage of outdoor workers or a younger retirement age [49]. In the case of men, several reasons justify this higher predisposition to AC: greater exposure to solar radiation derived from professional outdoor activities (farmers, sailors, construction workers, etc.), the lack of solar protective measure. In addition, more frequent smoking in men could enhance the lip changes induced by chronic exposure to solar radiation and increase the probability of malignant degeneration [49].

Dikshit et al. reported that individuals with diabetes have twice the risk of developing OLP compared to the general population [50]. Other studies have shown a 6–6.2% prevalence of OLK among diabetics, with higher rates noted in smokers [51, 52]. However, after adjusting for smoking, one study found no significant difference in OLK prevalence between T2D patients and controls [6]. This study, which accounted for confounding factors, such as smoking, alcohol consumption, psychological state, and cancer susceptibility, found no significant causal relationship between T1D, T2D, and OLK occurrence. While research on the link between diabetes and OPMDs has been ongoing for decades, the results remain inconsistent. However, it has been consistently shown that single glycemic markers, including HbA1c, FG, and random glucose, are insufficient predictors of OPMDs occurrence [1, 5]. Our genetic analysis also confirmed no causal relationship between glycemic traits and conditions, such as AC, OLP, and OLK. This can be explained by several biological factors. First, the data sets for FI, FG, and HbA1c included data from multiple cohorts, with values typically within normal ranges [22]. However, in cases of T1D and T2D, glycemic levels often fall outside these ranges. Second, diabetes is a complex chronic inflammatory and immune disease, and single glycemic markers do not fully reflect the diabetic state. Third, elevated blood glucose levels are not exclusive to diabetes; conditions such as pancreatitis, stroke, and cardiovascular diseases can also exhibit abnormal glucose levels, but they show limited associations with OPMDs [16].

Notably, the diabetic individuals in the present GWAS were not excluded from those with other co-existing morbidities, posing a challenge to fully understanding the independent effects of diabetes on OPMDs.

Managing both diabetes and OPMDs requires a multidisciplinary approach. Our research provides valuable insights into the prevention and treatment of OLP, particularly by identifying individuals with T1D as a high-risk population. Regular dental check-ups and early intervention strategies are essential to prevent the progression of OLP, thereby improving patient quality of life and reducing complications. However, a comprehensive evaluation of oral health knowledge and habits among individuals with diabetes, particularly those with T1D, revealed concerning trends [53]. Among 307 diabetics from 60 countries, 22.8% were smokers, and 26.4% reported a fear of dental treatment [53]. Thus underscores the need for periodic reinforcement of oral hygiene instructions, especially for adolescents and teenagers with T1D, as part of their routine care and early multidisciplinary intervention. Furthermore, during the diagnosis and treatment of OLP patients, especially when glucocorticoids are used, oral healthcare providers should closely monitor insulin and blood glucose levels, along with lifestyle habits, to prevent the onset or worsening of diabetes. Conversely, our findings suggest that genetically regulated glucose homeostasis pathways may contribute to reduced AC susceptibility. Chronic metabolic states in diabetes—such as sustained hyperglycemia or altered insulin signaling—could modulate cutaneous responses to UV radiation, although the precise biological mechanisms require validation through experimental models. While conventional photoprotection (e.g., sunscreen use) remains essential for AC prevention, our results underscore the need to explore whether diabetes-associated metabolic dysregulation engages previously unrecognized molecular pathways affecting UV-induced lip damage. Keratinocytes likely play a central role in linking diabetes to oral lesions, particularly OLP and AC. Notably, OLP is characterized by keratinocyte apoptosis, whereas AC involves keratinocyte proliferation [7, 54]. We hypothesize that the dual roles of diabetes on these conditions may be attributed to its inhibitory influence on keratinocyte function. Understanding these interactions is critical for advancing targeted prevention and treatment strategies. Collaborative efforts among dentists, endocrinologists, and other healthcare professionals are crucial to delivering holistic care and addressing the complex interactions between diabetes and OPMDs.

However, several limitations must be considered when interpreting our findings. First, the generalizability of our results may be restricted by ethnic differences in genetic susceptibility and lifestyle factors. For example, OLP is more prevalent in European populations (1.43% vs 1.01% globally), while T1D shows a higher prevalence in the Americas [27, 55]. These regional differences may influence the strength and direction of our observed associations, limiting the applicability of findings to other populations, particularly those with different genetic backgrounds or environmental exposures. Second, the unavailability of gender-stratified T1D GWAS data limits our ability to evaluate potential sex-specific associations between T1D and OPMDs. Clinical evidence suggests that gender differences exist in the incidence and progression of diabetes and OPMDs, with postmenopausal women experiencing a higher prevalence of OLP likely due to hormonal changes, while men are more prone to lifestyle factors, such as smoking, which exacerbate the risk of AC [56]. Without gender-specific genetic data, it is challenging to discern whether these clinical differences are reflected at the genetic level, potentially introducing bias when applying the results to specific patient subgroups. Third, studies have shown that poor socioeconomic conditions could negatively impact quality of life, self-care, oral health knowledge, and behaviors, such as smoking and alcohol consumption. For example. Individuals with lower income and education levels are more likely to have AC, potentially due to limited awareness of oral potentially malignant lesions, infrequent dental visits, and a higher risk of malignant transformation, especially in the presence of smoking and alcohol use [57]. While the SNPs used in the MR analysis were adjusted for smoking behavior, alcohol consumption, psychosocial conditions and carcinoma, other potential confounders (e.g., socio-economic factors and metformin use) may not have been fully considered, which could introduce bias and affect the robustness of our findings. Immune dysregulation profoundly impacts disease susceptibility, ranging from infections and autoimmune disorders to malignancies. Metformin, the first-line therapy for T2D, exerts immunomodulatory effects through enhancing mitochondrial oxidative phosphorylation and promoting autophagy in immune cells [58]. Notably, the observed inverse association between genetically predicted T2D and AC risk may, at least in part, be influenced by metformin use, given its potential role in UV-induced DNA damage repair [59]. Fourth, the GWAS data for FI, FG, and HbA1c were sourced from healthy populations [22]. Although no causal effect of glycemic traits on OPMDs was identified, we cannot entirely rule out the influence of abnormal glucose levels on the development or malignant transformation of OPMDs. Fifth, available GWAS data globally grouped OLP, OLK, and AC together, leaving the specific causal effect of diabetes and glycemic traits on these OPMDs subgroups unknown. Finally, the conclusion of the dual role of diabetes on OPMDs may

be attractive but challenging due to the shortcomings of the selected GWAS data itself, such as selection bias and potential confounding factors. While the MR approach is highly effective for estimating causality, further research is required to validate the effects of diabetes on OPMDs and to elucidate the underlying mechanisms.

Conclusions

This study suggests that T1D may have a causal role in the development of OLP through non-glycemic mechanisms, highlighting the importance of regular oral health assessments for T1D patients. Interestingly, genetically predicted T1D and T2D are significantly associated with a reduced risk of AC, offering fresh perspectives that challenge previous research on this complex relationship. Further extensive investigations are required to address the limitations of this study and to clarify these associations.

Abbreviations

OPMDs	Oral potentially malignant disorders
OLK	Oral leukoplakia
OLP	Oral lichen planus
AC	Actinic cheilitis
T1D	Type 1 diabetes
MR	Mendelian randomization
GWAS	Genome-wide association study
T2D	Type 2 diabetes
FG	Fasting glucose
FI	Fasting insulin
HbA1c	Glycated hemoglobin
SNPs	Single nucleotide polymorphisms
IVW	Inverse-variance weighted
MR-PRESSO	Mendelian randomized polymorphism RESidual Sum and Outlier
FDR	False discovery rate
MV-IVW	Multivariable IVW

Supplementary Information

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Supplementary material 1.

Supplementary material 2.

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Availability of data and materials
All data generated or analyzed during this study are included in supplementary material or in the data repositories listed in the methods.

Declarations

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The present MR study was based on the previously collected and published data, No ethics approval was required.

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Not applicable.

Competing interests
The authors declare no competing interests.

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