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ORIGINAL RESEARCH

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A causal association between asthma and dental caries: a two-sample bidirectional Mendelian randomization study

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Abstract

Background: Dental caries and asthma are two of the most prevalent chronic illnesses among children. Previous research has indicated a correlation between the two, but confounding factors and inverted causality may influence this correlation. We conducted a two-sample bidirectional Mendelian randomization analysis to investigate the causal relationship between asthma and dental caries at the genetic level. **Methods**: We obtained Genome-wide association study (GWAS) summary statistics for asthma from the UK Biobank database, which involved 56,167 cases and 352,255 controls. GWAS datasets of dental caries were obtained from the FinnGen consortium which included 4170 cases and 195,395 controls. We performed a bidirectional Mendelian randomization analysis using the inverse variance weighted (IVW) approach as the primary method. The reliability of the results was verified by heterogeneity, pleiotropy and sensitivity analysis. **Results**: The results showed that asthma increased the likelihood of developing dental caries (IVW odds ratio (OR) = 1.13, 95% confidence intervals (CI) = 1.03–1.24, $p = 0.010$), but there was no evidence to suggest that dental caries increased the incidence of asthma (IVW OR = 1.02, 95% CI = 0.97–1.08, $p = 0.400$). The sensitivity analysis confirmed the validity of these MR results. **Conclusions**: This study found that asthma increases the likelihood of developing dental caries, but there is no evidence that dental caries is linked to an increased risk of asthma. These findings suggest that more investigations are required to explore possible mediating pathways between the two conditions and that screening and prevention of dental caries in asthmatics should be strengthened in clinical practice.

Keywords

Mendelian randomization analysis; Dental caries; Asthma

1. Introduction

Dental caries is a chronic infectious disease that affects the hard tissues of teeth. It is caused by various factors, primarily bacterial [1]. The process starts when microorganisms on the tooth surface convert free sugars into acids, which results in inorganic demineralization and organic decomposition, ultimately leading to dental caries. The Global Burden of Disease Study published in 2019 highlighted untreated caries in permanent teeth as the most common hygiene problem [2]. According to the Global Oral Health Status Report 2022, the global average prevalence of caries in primary teeth was 43%, and in permanent teeth was 29%, which meant that 514 million children had dental caries in primary teeth and 2 billion people had dental caries in permanent teeth. Additionally, the report also showed that more than one-third of the world's population had untreated caries [3]. Asthma is a chronic inflammatory disease caused by a combination of genetic and environmental factors [4]. It is characterized by airway obstruction and recurrent bronchospasm, resulting in symptoms such as panting, coughing, a choking sensation in the chest, and shortness of breath. Asthma can occur in people of all ages, with the onset peak in childhood. Over the past few decades, there has been a slight increase in the incidence of asthma [5], especially in children under 5 years of age [6], making it the second most common chronic disease among children.

As two of the most common chronic illnesses among children, the association between dental caries and asthma has been the focus of scholars in interdisciplinary fields. Related studies have been widely carried out, but the conclusions on the link between dental caries and asthma are still inconsistent. For instance, a recent cross-sectional study found that individuals with asthma had worse oral health and a higher decayed missing filled teeth/decayed extracted filled teeth index (DMFT/deft index) compared to healthy individuals [7]. In a case-control study, Kumar *et al*. [8] found that bronchial

asthma had an adverse impact on the prevalence and severity of dental caries, plaque and gingivitis in both primary and permanent teeth. A retrospective cohort study from Taiwan noted that the prevalence of dental caries in children with asthma was significantly higher than in those without asthma [9]. However, other scholars have suggested that there is no clear link between dental caries and asthma. Flexeder *et al.* [10] concluded in a cohort study that asthma did not cause dental caries in adolescents. Rezende *et al.* [11] found no clear association between asthma and the prevalence of dental caries in Brazilian children aged 6 to 12 years in a cross-sectional study. A Taiwanese study found no link between asthma, allergic rhinitis, and five common oral diseases (dental caries, periodontitis, pulpitis, gingivitis and stomatitis/aphthous ulcers) in adults [12]. The inconsistency in these findings may arise from the fact that almost all current research on the connection between dental caries and asthma comes from observational epidemiological research. Traditional observational studies are vulnerable to confounding factors and reverse causal associations [13], which may bias the interpretation of the results. Therefore, more investigations are required to ascertain whether dental caries and asthma are causally related. Mendelian randomization (MR) analysis, a new approach to epidemiological research, may be an effective way to explore this problem.

The purpose of Mendelian randomization (MR) is to examine the causal relationship between the exposure and the outcome using genetic variations (GVs) as instrumental variables (IVs) [14, 15]. The core idea of this approach stems from the Mendelian inheritance law, which states that during the creation of gametes, alleles are randomly distributed to the offspring's gametes, leading to the generation of distinct intermediate phenotypes through distinct genotypes. Consequently, the utilization of the "genotype-disease (outcome)" model affords the simulation of the "intermediate phenotype (exposure)-disease" model in causal association studies, eliminating the impact of environmental factors and ensuring a clear causal timeline [16–18]. Mendelian randomization (MR) can cleverly compensate for the shortcomings of traditional epidemiological research which is susceptible to confounders and unclear causal timelines when demonstrating etiological hypotheses. Thus, using large-sample genome-wide association study (GWAS) datasets of dental caries and asthma, we applied a bidirectional MR study on two samples in this research to investigate the causal connection between asthma and dental caries.

2. Materials and methods

We evaluated the causal relationship between asthma and dental caries utilizing a two-sample bidirectional MR study while adhering to the Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian randomization (STROBE-MR) guidelines for scientific integrity and adherence to standards [19].

Our study utilized GWAS data from public databases, which were available for other researchers to utilize. Since genetic variations are randomly allocated in meiosis and fixed upon fertilization, they are not subject to interference by acquired confounders and reverse causation. The MR analysis is exactly built on the above-mentioned concept to achieve reliable inference of causation [20]. In MR analysis, the choice of instrumental variables should follow three fundamental assumptions: (1) Instrumental variables should exhibit a powerful correlation with the exposure but not directly with the outcome. (2) Instrumental variables should remain independent of confounding factors. (3) Instrumental variables should impact the outcome exclusively through the exposure and not alternative pathways [21]. Single nucleotide polymorphisms (SNPs) are typically used as instrumental variables in MR studies. A visual overview of our MR study is provided in Fig. 1.

2.1 Data sources

The asthma GWAS data used in this study was derived from the UK Biobank database. This dataset consisted of 56,167 cases and 352,255 controls from European populations, and it included a total of 34,551,291 SNPs. The positive cases were identified through hospital records (ICD-9 or ICD-10 codes), primary care medical records, and self-reports related to asthma. To prevent demographic stratification, we only considered dental caries data from European populations. To minimize sample overlap and mitigate bias, we selected the GWAS data of dental caries from the FinnGen Biobank database for our analysis. This dataset included 4170 dental caries cases (K02) recorded with the ICD-10 code, 195,395 controls and 16,380,411 SNPs (Table 1).

2.2 Selection and validation of SNPs

To prove the first MR assumption, we selected SNPs that were associated with exposures at a significant threshold of $p < 5 \times 10^{-8}$ and performed linkage disequilibrium (LD) clumping by setting $r^2 < 0.001$ and clump distance >10,000 kb to ensure the SNPs were independent [22]. We used F-statistics to evaluate the strength of these SNPs as instrumental variables [23]. Next, to satisfy the second MR assumption for SNPs, we removed SNPs correlated with confounding factors by reviewing past literature and searching SNPs successively in the PhenoScanner database. We then extracted the chosen SNPs from the outcome GWAS dataset. If certain SNPs were not present in the outcome GWAS dataset, we used a proxy SNP as a substitute. If the proxy SNP could not be found, the SNP was discarded. Finally, we harmonized effect alleles for the exposure and the outcome by eliminating SNPs that had incompatible alleles or were palindromic with intermediate allele frequencies. This allowed us to obtain the SNPs that were ultimately included in our analysis.

2.3 MR analysis

To determine the link between dental caries and asthma, we employed a bidirectional MR analysis using the "TwoSampleMR version 0.5.7" package in the RStudio application of R version 4.3.0. We conducted a positive MR analysis, in which asthma-associated SNPs were used as instrumental variables, and dental caries were the outcome. We also performed a reverse MR analysis, in which caries-associated SNPs were used as instrumental variables, and asthma was the outcome. To

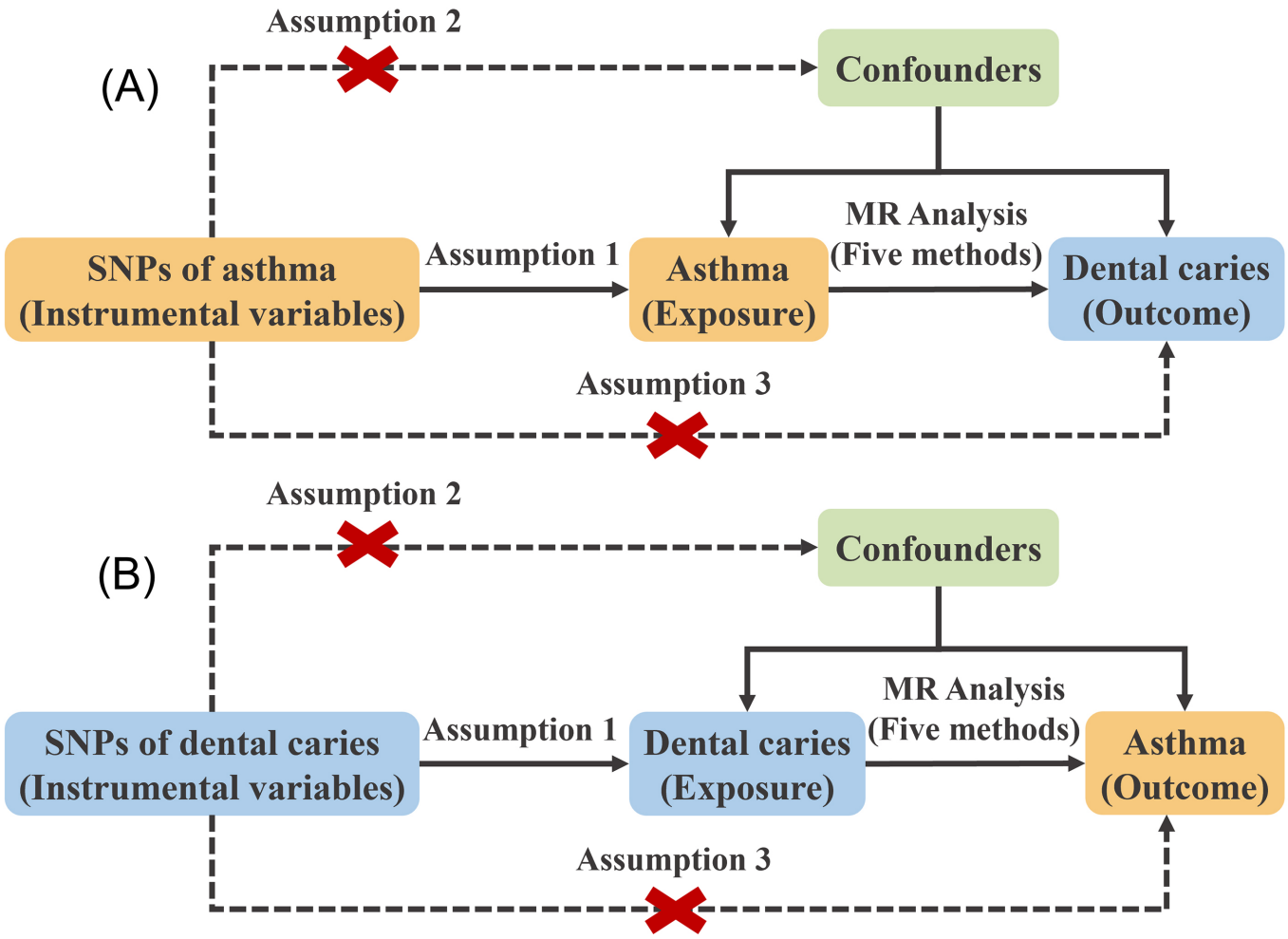

FIGURE 1. Overview of the two-sample bidirectional Mendelian randomization in our study. (A) The design of the positive Mendelian randomization analysis. Asthma-associated SNPs were used as instrumental variables to examine causal associations between asthma and risk of dental caries. (B) The design of the reverse Mendelian randomization analysis. Caries-associated SNPs were used as instrumental variables to examine causal associations between dental caries and the risk of asthma. Instrumental variables (IVs) used in Mendelian randomization analysis should satisfy three core assumptions. Assumption 1, IVs should exhibit a powerful correlation with the exposure but not directly with the outcome; Assumption 2, IVs should remain independent of confounding factors; Assumption 3, IVs should exclusively impact the outcome through the exposure and not through alternative pathways. MR: Mendelian randomization; SNPs: single nucleotide polymorphisms.

TABLE 1. Detailed information on the GWAS datasets applied in this study.

Phenotype	Consortium	Sample size	Number of SNPs	Ethnicity
Asthma	UK Biobank	408,422	34,551,291	European
Dental caries	FinnGen Biobank	199,565	16,380,411	European

GWAS: genome-wide association study; SNPs: single nucleotide polymorphisms.

estimate causal effects, we used the inverse variance weighted (IVW) approach, which is a commonly used MR method. The IVW method assumes that all genetic variations are valid instrumental variables and can robustly detect causal relationships. However, the IVW method requires that genetic variations can only influence the outcome through exposure. Although we excluded SNPs associated with known confounding factors, potential unknown confounders might bias the results. Therefore, we applied four additional methods as supplementary approaches, including Weighted Median (WM), MR Egger, Simple Mode and Weighted Mode. When discrepancies occurred among results from various MR methods, we considered the finding of the IVW method as definitive. We used odds ratio (OR) and 95% confidence intervals (CI) to show the causal impact of exposures on outcomes, and the threshold for statistical significance was set at $p < 0.05$.

2.4 Sensitivity, heterogeneity and pleiotropy assessments

After completing the initial MR analysis, we wanted to check if the results were reliable. To do this, we performed heterogeneity, pleiotropy, and sensitivity analyses. To begin

with, Cochran's Q test was utilized to detect heterogeneity in our study. The greater the difference among the IVs, the stronger the heterogeneity. If the *p*-value is greater than 0.05, it suggests that there is no significant heterogeneity among the IVs. To detect horizontal pleiotropy, we used two methods. The first one was MR Egger intercept method, which examined the horizontal pleiotropy by calculating the intercept term. If the *p*-value is less than 0.05, it indicates that there might be horizontal pleiotropy among the IVs [24]. The second method was the MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO) test, a commonly used method to verify horizontal pleiotropy. We used the "mr_presso" function available in the "MRPRESSO" R package to conduct this test. The MR-PRESSO test consisted of three parts. The first part was to identify the existence of horizontal pleiotropy. The second part was to detect the presence of outliers and provide outlier-adjusted results by removing the outliers. The third part was to compare the results obtained after removing the outliers with the results obtained before removing the outliers [25]. Finally, we performed a leave-one-out test to determine the sensitivity analysis. This test was used to find out if a single SNP would bias the causal effect by removing individual SNPs one by one and then calculating the combined effect from the remaining SNPs [26].

3. Results

In the positive MR analysis, a total of 80 SNPs were found to be strongly correlated with asthma. Among these SNPs, eight SNPs were absent from the outcome database. Proxy SNPs with a strong linkage disequilibrium ($r^2 > 0.8$) to target SNPs were used for five SNPs (rs9273386, rs2800040, rs113981909, rs35225972, rs174557). Three missing SNPs (rs112119265, rs33978241, rs11402155) were excluded as no suitable proxy was identified. One SNP (rs1689510) linked to confounders was manually removed by searching the PhenoScanner database. While harmonizing effect alleles for the exposure and the outcome, we removed rs35320232 owing to incompatible alleles. We also eliminated a palindromic SNP with intermediate allele frequencies such as rs13099273. Ultimately, we included 75 eligible SNPs in our positive direction MR analysis.

In the reversed MR analysis, we adjusted the genome-wide significance level to 5×10^{-6} as the relative sample size was small. We identified ten SNPs highly linked to dental caries, none of which were linked to any relevant confounders. These ten SNPs were extracted from the asthma GWAS dataset and were finally included in the reversed MR analysis after harmonization.

The *F*-values of the IVs included in our analysis were all over 10, which suggested that there was no bias due to weak instrumental variables. Specific information on all SNPs utilized in our analysis was available in **Supplementary Tables 1,2**.

3.1 Causal effects of asthma on dental caries

Table 2 and Fig. 2 present the results of this positive direction MR analysis. According to the result obtained from the IVW method, asthma increases the likelihood of developing dental caries (OR = 1.13, 95% CI = 1.03–1.24, $p = 0.010$). Other MR methods, such as the Weighted median method (OR = 1.17, 95% CI = 1.01–1.34, $p = 0.035$), the MR Egger method (OR = 1.30, 95% CI = 1.03–1.65, $p = 0.032$) and the Weighted mode method (OR = 1.35, 95% CI = 1.04–1.76, $p = 0.029$), also obtained similar results, indicating a significant causal impact of asthma on dental caries. The scatter plot (Fig. 3A) shows regression straight lines obtained from different methods, suggesting that there exists a positive causal relationship between asthma and dental caries. The forest plot (Fig. 3B) also reveals a promoting effect of asthma on dental caries.

When heterogeneity was estimated using Cochran's Q test, neither the IVW method ($p = 0.337$, Cochran's Q = 78.551) nor the MR Egger method ($p = 0.356$, Cochran's Q = 76.850) detected heterogeneity (Table 3). The funnel plot shows that the SNPs are symmetrically distributed on both sides of the IVW line (Fig. 4A). We tested the IVs for horizontal pleiotropy using the intercept of MR Egger regression and the *p*-value of the MR-PRESSO global test. The intercept of MR Egger regression was found to be −0.010 ($p = 0.208$), indicating that there was no horizontal pleiotropy in this MR analysis. Also, the MR-PRESSO analysis gained a similar conclusion ($p = 0.327$). Moreover, the MR-PRESSO method did not detect abnormal outliers. In addition, the leave-one-out method indicated that no single SNP significantly affected the overall effect (Fig. 4B).

3.2 Causal effects of dental caries on asthma

We performed a reverse MR analysis with dental caries as an exposure and asthma as an outcome. The finding of the IVW method shows that having dental caries does not increase the risk of developing asthma (OR = 1.023, 95% CI = 0.970–1.079, $p = 0.400$). All other MR methods reached similar conclusions (Table 2, Fig. 2). The scatter plot reveals that most of the regression straight lines tend to be horizontal in direction (Fig. 5A). The forest plot offers a more intuitive view of the fact that dental caries had no positive promoting effect on asthma (Fig. 5B).

However, our assessment of heterogeneity using a funnel plot indicated that there might be heterogeneity among the SNPs (Fig. 6A). This was supported by both the IVW method ($p = 0.041$, Cochran's Q = 17.562) and the MR Egger method ($p = 0.028$, Cochran's Q = 17.233), as shown in Table 3. Despite this, our study used the IVW method with random effects to estimate causal effects, as it is effective in overcoming the impact of heterogeneity. As the Weighted median method can provide a more accurate causal estimation when only 50% of the IVs are valid or when heterogeneity exists, we also applied the WM method as a supplement to estimate causal effects. The WM method also showed no causal association between dental caries and asthma risk (OR = 1.008, 95% CI = 0.957–1.062, $p = 0.770$). Our study did not detect the presence of

TABLE 2. MR analysis results of the association between dental caries and asthma.

Exposure	Method	n.SNP	β	SE	OR (95% CI)	*p*-value
Asthma						
	MR Egger	75	0.263	0.120	1.30 (1.03–1.65)	0.032
	Weighted median	75	0.153	0.073	1.17 (1.01–1.34)	0.035
	Inverse variance weighted	75	0.123	0.048	1.13 (1.03–1.24)	0.010
	Simple mode	75	0.158	0.168	1.17 (0.84–1.63)	0.348
	Weighted mode	75	0.299	0.135	1.35 (1.04–1.76)	0.029
Dental caries						
	MR Egger	10	0.049	0.072	1.05 (0.91–1.21)	0.519
	Weighted median	10	0.008	0.027	1.01 (0.96–1.06)	0.770
	Inverse variance weighted	10	0.023	0.027	1.02 (0.97–1.08)	0.400
	Simple mode	10	0.009	0.037	1.01 (0.94–1.08)	0.819
	Weighted mode	10	0.007	0.036	1.01 (0.94–1.08)	0.852

MR: Mendelian randomization; n.SNP: number of single nucleotide polymorphism used in MR; OR: odds ratio; CI: confidence interval; SE: standard error.

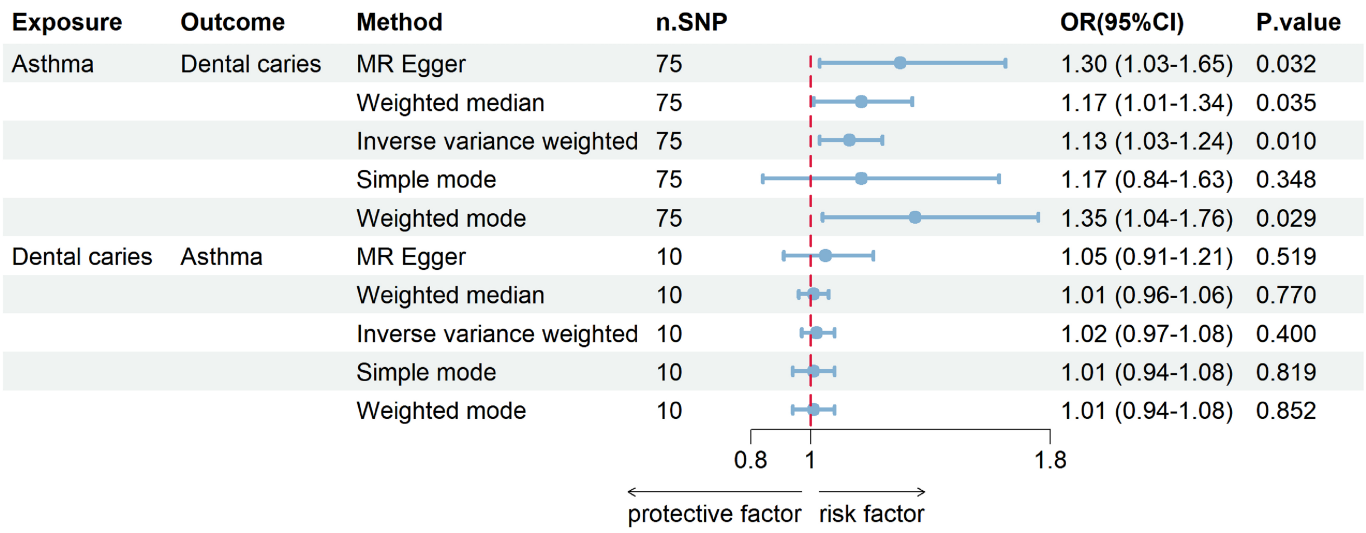

FIGURE 2. Forest plot of causal correlation between asthma and dental caries. Causal estimates results of five MR methods for the forward MR analysis with asthma as an exposure and the reverse MR analysis with dental caries as an exposure. MR: Mendelian randomization; n.SNP: number of single nucleotide polymorphism used in the Mendelian randomization study; OR: odds ratio; CI: confidence interval.

horizontal multiplicity (Table 3), as shown by the MR Egger method (Egger intercept = −0.005, p = 0.706) and the MR-PRESSO method (p = 0.059). Moreover, the MR-PRESSO method did not detect abnormal outliers. According to the leave-one-out test, no single SNP significantly affected the overall effect (Fig. 6B).

4. Discussion

To our knowledge, this is the first MR study to explore the bidirectional causal relationship between asthma and dental caries. Our research indicates a causal correlation between asthma and the risk of dental caries. However, there is no conclusive genetic evidence linking dental caries to an increased risk of asthma.

In this study, all the SNPs used were extracted through strict screening criteria and were strong instrumental variables (F-values > 10), which circumvented any potential bias due to weak instrumental variables. We employed the IVW approach with random effects as the primary method, which was valid in overcoming the effects of heterogeneity. Furthermore, we supplemented this with a variety of MR methods including Weighted Median (WM), MR Egger, Simple Mode, and Weighted Mode to rigorously estimate causal effects. In our study, we utilized both the MR Egger intercept method and the MR-PRESSO test to detect horizontal pleiotropy, both methods revealed no horizontal pleiotropy in either forward MR analysis or reverse MR analysis, indicating that our results were reliable. Additionally, we conducted a leave-one-out test, which demonstrated that none of the SNPs had a significant impact on the results, suggesting that our findings were credible.

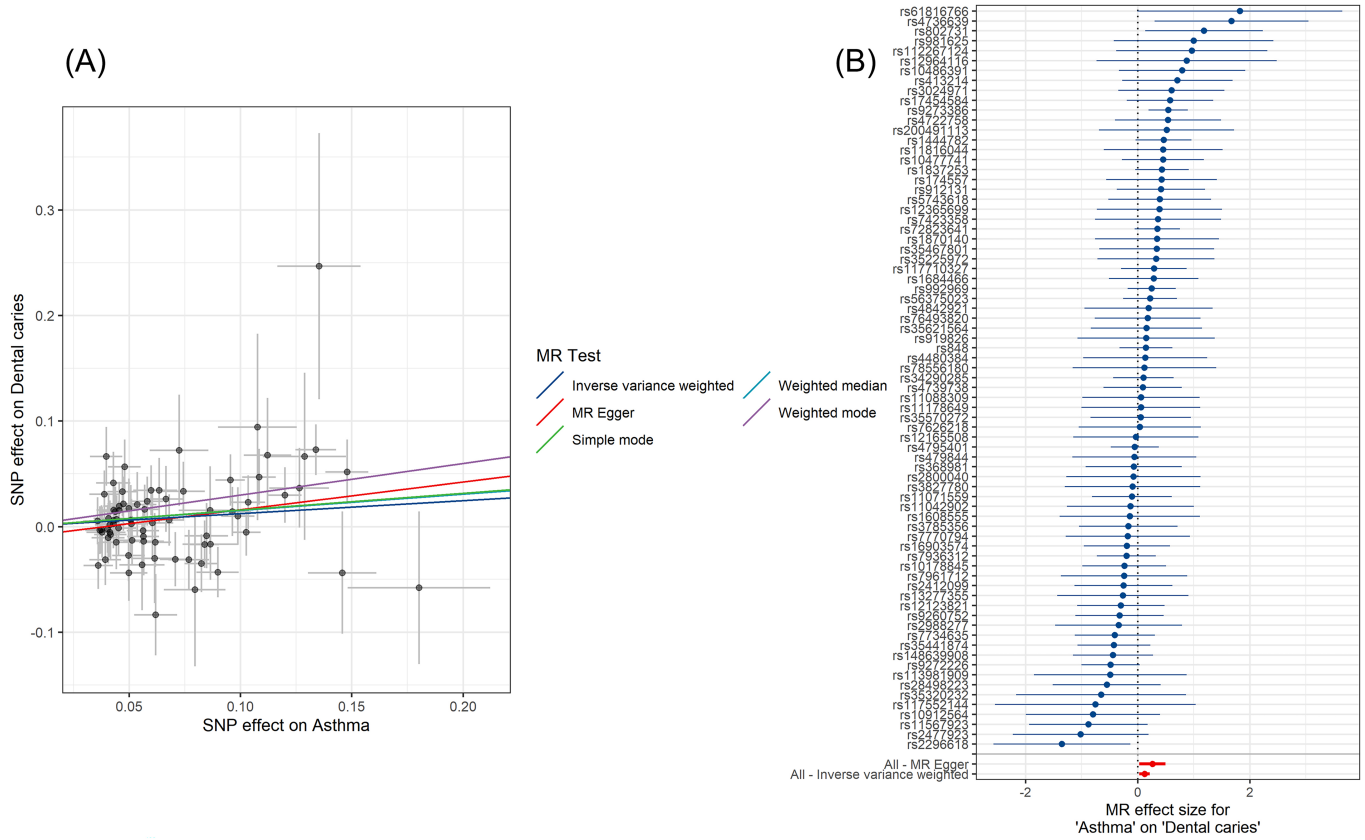

FIGURE 3. Scatter plot and forest plot of causal estimates for asthma on dental caries. (A) Scatter plot of causal estimates for asthma on dental caries performing five MR methods. In the scatter plot, each black dot represents a SNP. The horizontal coordinate is the SNP effect on exposure and the vertical coordinate is the SNP effect on outcome. The black crosshairs around each black dot represent 95% CI of the effect value. The colored horizontal lines represent the fitting results of different MR methods, and the trend of the horizontal lines indicates the causal trend of exposure and outcome. From the figure, it can be inferred that the risk of dental caries increases with elevated asthma. However, this figure cannot determine whether the results are statistically significant. (B) Forest plot of causal estimates for asthma on dental caries. In the forest plot, each horizontal line represents the causal estimate of a single SNP by calculating the Wald ratio. The bottom red horizontal line shows the aggregated result for all SNPs. The bottom red line in the figure shows that asthma increases the risk of dental caries. MR: Mendelian randomization; SNP: single nucleotide polymorphism; CI: confidence interval.

TABLE 3. Heterogeneity and pleiotropy assessments of individual SNPs.

Exposure	n.SNP	Heterogeneity				Pleiotropy		
		MR Egger		IVW				
		Cochran's Q	*p*-value	Cochran's Q	*p*-value	Egger intercept	Egger *p*-value	*p*-value of MR-PRESSO global test
Asthma	75	76.850	0.356	78.551	0.337	−0.010	0.208	0.327
Dental caries	10	17.233	0.028	17.562	0.041	−0.005	0.706	0.059

SNPs: single nucleotide polymorphisms; n.SNP: number of single nucleotide polymorphism used in MR; MR: Mendelian randomization; IVW: inverse variance weighted; MR-PRESSO: MR Pleiotropy RESidual Sum and Outlier.

Our findings show that individuals with asthma may be more susceptible to developing dental caries, which is consistent with most previous observational studies. A meta-analysis of whether asthma increases the risk of developing dental caries found that individuals with asthma had approximately 1.5 times increased risk of developing dental caries in both primary dentition and permanent dentition compared to healthy patients [27]. Meanwhile, another cross-sectional study based on U.S. adults showed that adults with asthma were more likely to develop dental caries than those without asthma, and they were more likely to have more untreated tooth decay [28]. Another recent meta-analysis comprising 16 studies showed that children/adolescents with asthma were more likely to develop dental caries than those without asthma [29]. Although it remains unclear how exactly asthma causes dental caries, it may be related to changes in the properties of saliva, changes in

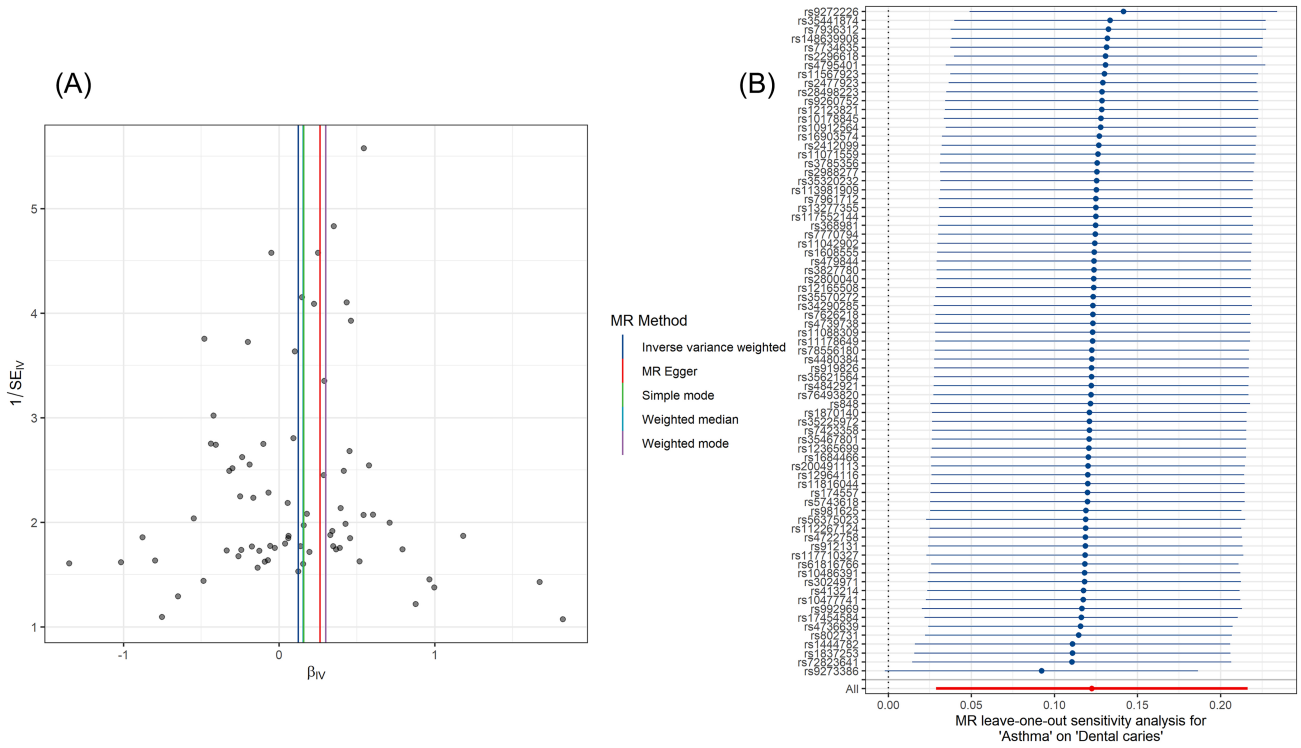

FIGURE 4. Funnel plot and leave-one-out plot of causal estimates for asthma on dental caries. (A) Funnel plot of causal estimates for asthma on dental caries. In the funnel plot, each black dot represents a SNP and colored vertical lines represents different MR methods. As can be seen in the figure, the SNPs are symmetrically distributed on both sides of the IVW line. (B) Leave-one-out plot of causal estimates for asthma on dental caries. Each dot in the figure represents the overall effect of all remaining SNPs after removing one SNP, and the horizontal line indicates a 95% CI of the effect value. In the leave-one-out plot, all dots are on one side of the zero scale line, indicating that removing any SNP would not have a significant impact on the overall effect. SNP: single nucleotide polymorphism; MR: Mendelian randomization; IVW: inverse variance weighted; CI: confidence interval; SE: standard error.

oral flora, and the use of anti-asthmatic drugs in patients with asthma.

Some studies have found that patients with asthma have lower salivary flow, salivary pH, and salivary buffering capacity than the normal control group [30–32]. Aquaporin5 (AQP5) is one of the important aquaporins (AQPs) in the process of salivary gland secretion, which plays an important role in saliva secretion. A recent study showed that the expression of Aquaporin5 (AQP5) in patients with asthma was decreased [33], suggesting that the decrease in saliva secretion among asthmatic patients might be related to this [34]. Reduced salivary flow and buffering capacity can lead to a decrease in oral defense capability. When food particles and microorganisms attach to the tooth surface, they cannot be washed out in time. The acid produced by bacteria cannot be neutralized in time, which greatly increases the incidence of dental caries. Furthermore, other studies have found that the level of secretory immunoglobulin A (SIgA) in saliva, which is significantly reduced among asthmatic children, is noticeably negatively correlated with deft and DMFT [35]. SIgA is the most abundant immunoglobulin in saliva, and it is also an important component of the mucosal immunity system. The reduction of SIgA levels weakens the resistance of the oral cavity to bacteria, thereby increasing the risk of dental caries in asthmatic patients.

Reduced salivary flow caused by asthma results in a decrease in the antimicrobial component of saliva and disrupts salivary defenses [31]. This makes it easier for bacteria to colonize dental surfaces, with an increase in plaque formation and caries-associated causative organisms' abundance in the oral cavity, leading to a higher risk of dental caries prevalence among asthmatic patients. One study revealed that *spaP*, *gtfB*, *gbpB*, *ldh*, *brpA* and *luxS* genes associated with dental plaque biofilm formation was upregulated in patients with asthma and positively associated with dental plaque formation [36]. The upregulation of these genes, which are associated with bacterial adhesion, biofilm formation, extracellular polysaccharide formation, sugar uptake and glycometabolism, acid formation and acid-resistivity, may be responsible for the increased plaque formation in asthmatics. Also, the use of anti-asthma medications may promote the increase of plaque formation among asthmatics [8]. It has been shown that children with asthma who receive long-term inhaler therapy have higher concentrations of *Streptococcus mutans* in their mouths than healthy children [37]. *Streptococcus mutans* is the main pathogenic microorganism associated with dental caries, and its cariogenicity is mainly derived from its strong acid-producing ability and acid-tolerant nature. *Streptococcus mutans* surviving in the plaque can cause the local pH within the plaque to fall below 5.5 and can maintain it for

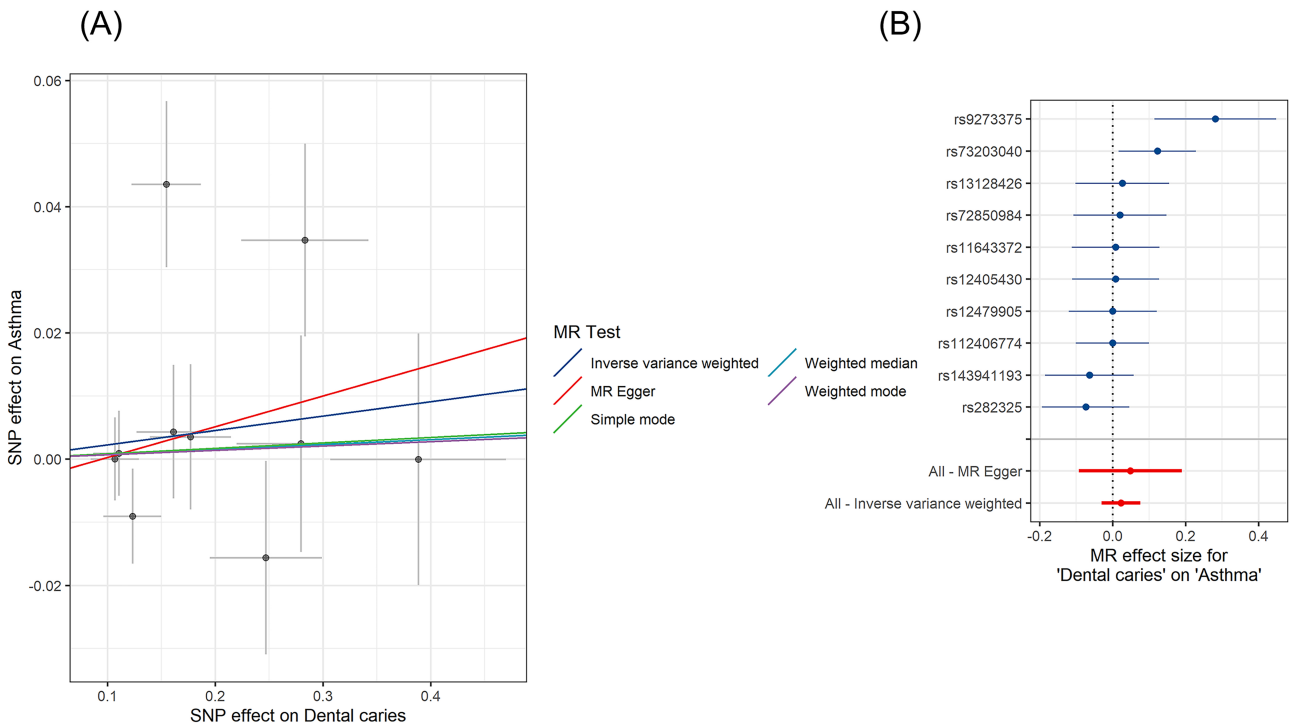

FIGURE 5. Scatter plot and forest plot of causal estimates for dental caries on asthma. (A) Scatter plot of causal estimates for dental caries on asthma performing five MR methods. The meaning of the black dots and lines in this figure is the same as depicted in Fig. 3. In the scatter plot, the regression lines' trend lacks consistency, with most of them being horizontally directed. (B) Forest plot of causal estimates for dental caries on asthma. The meaning of the horizontal lines in this figure is the same as depicted in Fig. 3. In the forest plot, the bottom red line indicates that dental caries does not have a positive promoting effect on asthma. MR: Mendelian randomization; SNP: single nucleotide polymorphism.

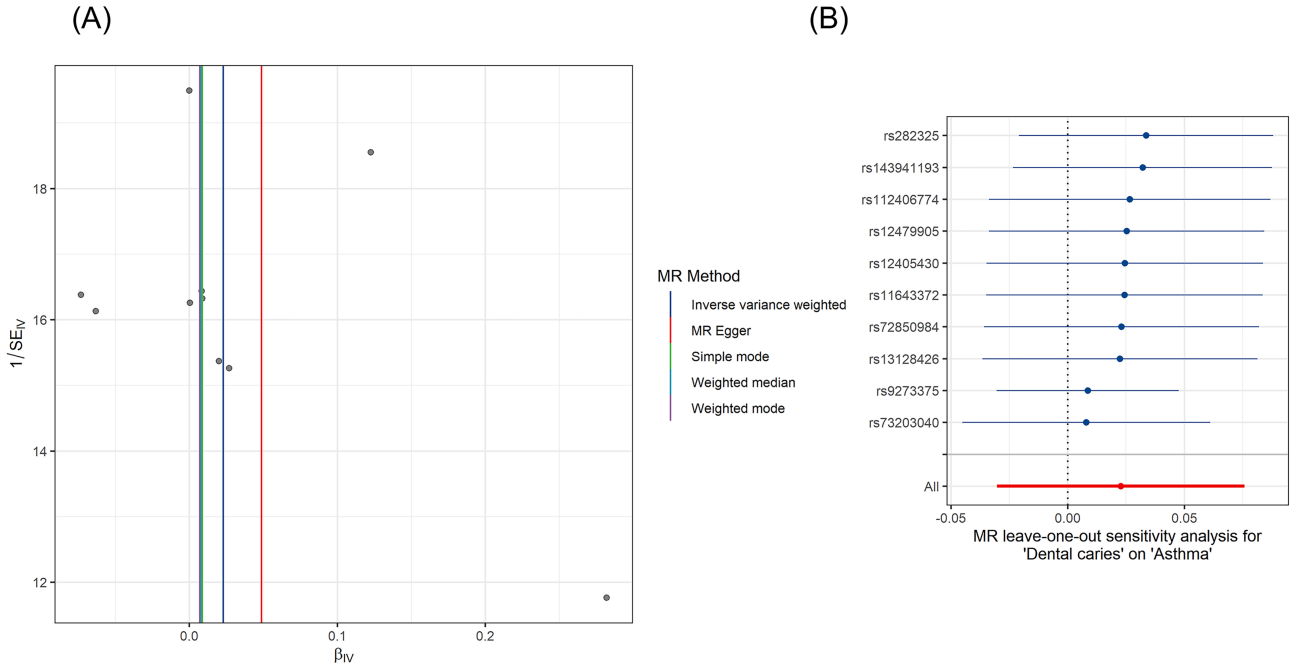

FIGURE 6. Funnel plot and leave-one-out plot of causal estimates for dental caries on asthma. (A) Funnel plot of causal estimates for dental caries on asthma. The meaning of the black dots and lines in this figure is the same as depicted in Fig. 4. The funnel plot does not present as a typical inverted funnel pattern. (B) Leave-one-out plot of causal estimates for dental caries on asthma. The meaning of the dots and lines in this figure is the same as depicted in Fig. 4. In the leave-one-out plot, all dots are on one side of the zero scale line, indicating that removing any SNP would not have a significant impact on the overall effect. SNP: single nucleotide polymorphism; MR: Mendelian randomization; SE: standard error.

a considerable time, thus causing local demineralization and eventually leading to dental caries by avoiding the buffering effect of saliva. In addition, opportunistic pathogenic bacteria such as *Neisseria*, *Prevotella* and *Haemophilus* are present at high abundance among asthmatic children [38]. These bacteria are recognized not only as respiratory pathogens but also as caries-associated pathogens which may be associated with the pathogenesis of both asthma and dental caries.

Previous studies have shown that patients taking anti-asthma medications have a higher risk of suffering dental caries [39]. Common medications used to treat asthma include long-acting beta-agonists (LABA), inhaled corticosteroids (ICS), long-acting muscarinic antagonists (LAMA), and antihistamines. LABA and ICS can reduce the saliva flow rate and total SIgA content, which are closely related to high caries susceptibility in asthma patients [35]. The secretion of saliva is innervated by the sympathetic and parasympathetic nerves. When the sympathetic nerve is activated, the amount of saliva secretion is small and viscous, and the protein content in saliva is high. When the parasympathetic nerve is activated, the saliva secretion is large and thin, with less protein and higher water content [40]. Therefore, using LABA to stimulate the sympathetic nerves or using LAMA to block the parasympathetic nerves can cause a decrease in oral saliva secretion and salivary flow, which can lead to increased caries susceptibility in asthmatics. In addition, there are usually sugar additives in asthma drug inhalers [41], which might potentially raise the chance of dental caries among individuals who have asthma.

In the reverse MR analysis, we did not find any link between dental decay and asthma risk. Cherkasov *et al.* [38] have proposed that certain highly pathogenic opportunistic bacteria such as *Streptococcus*, *Neisseria*, *Veillonella*, *Prevotella*, *Haemophilus*, *Kingella* and *Porphyromonas* were found in the teeth of asthmatic children, which might correlate with the onset of dental caries and asthma. By activating underlying antigen-presenting cells and inducing an immunological response, these bacteria may cause an influx of neutrophils or eosinophils into the airway and finally lead to asthma [42]. However, our study did not provide similar results, possibly due to the limited quantity of eligible SNPs. Although our study does not provide a causative relationship between dental caries and asthma risk, it is important to note the significant role that the oral microbiota plays in the development of asthma.

Meanwhile, the finding also provides some suggestions for the self-management of asthmatics in dental practice. Firstly, asthma patients should be aware of the impact of asthma on oral health. In addition to regular oral health checks, they should also consciously develop good oral hygiene habits, such as brushing their teeth or rinsing their mouth after using an inhaler [43] and chewing sugar-free gum to stimulate salivary secretion thereby alleviating the symptoms of dry mouth [44]. Secondly, dentists should pay more attention to the oral health of people with asthma and educate them on proper oral health care, as well as healthy eating habits. In the face of high caries-risk groups, dentists can also use topical fluoride regularly to prevent the development of dental caries while controlling the risk of caries.

This research project provides the first MR analysis investigating the bidirectional causal relationship between dental caries and asthma, which expands the horizons of traditional observational research. In addition, the study uses GWAS datasets that are appropriate and have large sample sizes, minimizing the influence of confounders and inverted causality. To avoid bias from demographic heterogeneity, this study focuses on European ancestries, and uses pooled data from different databases, reducing the likelihood of sample overlap.

Meanwhile, this research has several limitations. Firstly, the research only applies to people of European descent and may not be generalizable to other ethnic groups. Secondly, all data utilized comes from publicly available databases, and only aggregated-level data is accessible, which limits subgroup analyses based on the type of dental caries and asthma, age of onset and sex. Thirdly, our study only excludes known confounders, and it may not avoid the possible impact of unknown confounders on this study. Finally, the definition of asthma data adopted in this study is relatively broad, including medical records and patients' self-reports, which may affect the persuasiveness of the conclusion. Nonetheless, this finding is still valuable in providing evidence of a causal link between asthma and dental caries.

5. Conclusions

In this bidirectional MR study, we found that asthma increases the risk of dental caries while there is no evidence indicating that dental caries increases the risk of asthma. In addition, this MR analysis did not explain the underlying biological mechanisms that account for causative connections between dental caries and asthma. Consequently, further investigations are necessary to explore possible mediating pathways between the two in the future along with strengthening the screening and prevention of dental caries in asthmatics in clinic.

ABBREVIATIONS

MR, Mendelian randomization; GVs, genetic variations; IVs, instrumental variables; GWAS, genome-wide association study; STROBE-MR, the Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian randomization; SNPs, single nucleotide polymorphisms; ICD, the International Classification of Diseases; LD, linkage disequilibrium; IVW, inverse variance weighted; WM, Weighted Median; OR, odds ratio; CI, confidence intervals; MR-PRESSO, MR Pleiotropy RESidual Sum and Outlier; AQP5, Aquaporin5; AQPs, aquaporins; SIgA, secretory immunoglobulin A; LABA, long-acting beta-agonists; ICS, inhaled corticosteroids; LAMA, long-acting muscarinic antagonist; DMFT/deft index, decayed missing filled teeth/decayed extracted filled teeth index.

AVAILABILITY OF DATA AND MATERIALS

The data utilized in this study are openly available from the UK Biobank database and the FinnGen Consortium. The relevant data can be accessed and downloaded free of charge for research at https://gwas.mrcieu.ac.uk/, accession

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AUTHOR CONTRIBUTIONS

DLS and JJY—designed the research study. WBOY and SOY—collected the data. CKL and XXX—analyzed the data. JJY and HQW—prepared figures and tables. JJY—wrote the manuscript. DLS—revised and refined the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The data of genome-wide association studies involved in this study were derived from aggregate data published by public databases. Ethics approval and informed consent of participants involved in original studies of public databases have been obtained. Our research is based on these publicly available data, thus there are no ethical issues or other conflicts of interest.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.jocpd.com/files/article/1896439731788365824/attachment/Supplementary%20material.docx.

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