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Genetically predicted causal associations between periodontitis and psychiatric disorders

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ABSTRACT

Background Psychiatric disorders have serious harm to individuals' lives with high disease burden. Observational studies reported inconsistent associations between periodontitis and some psychiatric disorders, and the causal correlations between them remain unknown.

Objective This study aims to explore the causal associations between periodontitis and psychiatric disorders.

Methods A series of two-sample Mendelian randomisation (MR) analyses were employed using genome-wide association study summary statistics for periodontitis in adults from Gene-Lifestyle Interactions in Dental Endpoints Consortium and 10 psychiatric disorders from Psychiatric Genomics Consortium. Causal effects were primarily estimated using the inverse-variance weighted (IVW) method. Various sensitivity analyses were also conducted to assess the robustness of our results.

Findings The MR analysis suggested that genetically determined periodontitis was not causally associated with 10 psychiatric disorders (IVW, all p>0.089). Furthermore, the reverse MR analysis revealed that 10 psychiatric disorders had no causal effect on periodontitis (IVW, all p>0.068). We discovered that all the results were consistent in the four MR analytical methods, including the IVW, MR-Egger, weighted median and weighted mode. Besides, we did not identify any heterogeneity or horizontal pleiotropy in the sensitivity analysis.

Conclusions These results do not support bidirectional causal associations between genetically predicted periodontitis and 10 common psychiatric disorders. Potential confounders might contribute to the previously observed associations.

Clinical implications Our findings might alleviate the concerns of patients with periodontitis or psychiatric disorders. However, further research was warranted to delve into the intricate relationship between dental health and mental illnesses.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Psychiatric disorders have serious harm to individuals' lives with high disease burden. Growing observational studies have reported inconsistent associations between periodontitis and some psychiatric disorders. However, the causal correlations between them remain unknown.

WHAT THIS STUDY ADDS

⇒ This is the first research which comprehensively examines the bidirectional causal associations of periodontitis with common psychiatric disorders by using the most updated or largest scale data. Contrary to most previous observational findings, our research demonstrates that genetically predicted periodontitis is not causally associated with psychiatric disorders and vice versa.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study provides new insights into the causal associations between periodontitis and psychiatric disorders. The finding could alleviate the concerns of patients suffering from periodontitis or psychiatric disorders to a certain extent and encourage researchers to further delve into the intricate relationship between dental health and mental illnesses.

INTRODUCTION

Psychiatric disorders are complicated psychological problems with diagnostic significance primarily characterised by changes in cognition, emotion and behaviour.[1] According to the Global Burden of Disease 2019, psychiatric diseases, the seventh leading cause of disability-adjusted life-years in 2019, contributed significantly to the global disease burden.[2] The significant burden highlights the need to explore other specific diseases in the aetiology of mental disorders to develop novel prevention and treatment strategies and eventually lighten the disease burden.

Recent studies have shed light on the interactions between the oral cavity and the brain and indicated the important role of the oral microbiome in inflammation and immune dysfunction, which may contribute to mental disorders.[3 4] Periodontitis, a chronic inflammatory disorder initiated by infection of periodontal microflora, has high prevalence and affects approximately 20–50% of the global population.[5] It can result in tooth loss and negatively impact chewing function, aesthetics and quality of life.[5] Concerns have been raised about the concomitance of periodontitis and psychiatric disorders. Several observational studies have indicated associations between periodontitis and increased risk of multiple psychiatric disorders.

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Specifically, a meta-analysis revealed a significant association of periodontitis with anxiety disorders (AD, OR=1.36, 95% CI 1.11–1.66) and depression (OR=1.70, 95% CI 1.01–2.83).[6] Furthermore, a Taiwan cohort study, involving nearly 180 000 subjects, found a significant association between periodontitis and bipolar disorder (BD, adjusted HR=1.46, 95% CI 1.17–1.81).[7] Also, a small cross-sectional study highlighted a potential relationship of periodontitis with schizophrenia (SCZ).[8] In contrast, several cohort studies revealed that anxiety and depression were not significantly correlated with periodontitis.[9 10] For example, in a prospective birth cohort study of 539 individuals, major depressive episode was not associated with periodontitis (risk ratio=0.95, 95% CI 0.80–1.18).[10]

Current associations from the observational studies have difficulty in demonstrating a causal relationship due to confounding factors, small sample size or reverse causation. An alternative unbiased approach is Mendelian randomisation (MR) analysis, which uses genetic variants as instrumental variables (IVs) to examine the causality between an exposure and an outcome. The MR method is analogous to the randomised controlled trial (RCT) study in concept, because genetic variants are assigned to individuals randomly during meiosis according to the Mendel's second law. Additionally, the genetic variants are non-modifiable, and they can ensure lifelong exposure as well as be independent of potential confounding factors and reverse causation.[11 12] Hence, we used a two-sample bidirectional MR design to comprehensively assess the causal correlations between genetically predicted periodontitis and 10 common psychiatric disorders.

MATERIAL AND METHODS

Data sources

A summary statistic dataset of periodontitis, including 17 353 periodontitis cases and 28 210 controls, was taken from the adult samples of Gene-Lifestyle Interactions in Dental Endpoints Consortium. Periodontitis cases were defined using the Community Periodontal Index, the Centers for Disease Control and Prevention/American Academy of Periodontology criteria or self-reports of the periodontitis diagnosis.[13] Publicly available summary-level data for psychiatric disorders were primarily obtained from the Psychiatric Genomics Consortium (PGC), including AD (7016 cases and 14 745 controls), panic disorder (PD, 2147 cases and 7760 controls), major depressive disorder (MDD, 170 756 cases and 329 443 controls), SCZ (53 386 cases and 77 258 controls), BD (41 917 cases and 371 549 controls), anorexia nervosa (AN, 16 992 cases and 55 525 controls), post-traumatic stress disorder (PTSD, 23 212 cases and 151 447 controls), autism spectrum disorder (ASD, 18 381 cases and 27 969 controls), attention-deficit/hyperactivity disorder (ADHD, 19 099 cases and 34 194 controls) and obsessive-compulsive disorder (OCD, 2688 cases and 7037 controls). Ten cases of psychiatry disorders from the above genome-wide association studies (GWAS) were diagnosed mainly based on the Diagnostic and Statistical Manual of Mental Disorders-Version IV or International Classification of Diseases, 10th Revision.

Another one or two datasets were identified as complements to validate the accuracy of the results. Most of the participants included in the datasets were of European ancestry. A detailed description of the GWAS datasets is presented in table 1.

IV selection

IVs, including single nucleotide polymorphisms (SNPs), were only considered valid if they met the following three assumptions: (1) SNPs are significantly associated with the exposure; (2) SNPs are unrelated to confounders of the exposure–outcome association; and (3) SNPs cannot affect the outcomes unless via the association with exposure.[11] SNPs that revealed correlation at $p<5\times10^{-8}$ were extracted as IVs. Datasets of periodontitis and some psychiatric disorders had less than three genome-wide significant SNPs after filtering and clumping, so the significance threshold was relaxed to $p<5\times10^{-6}$ for those datasets. Next, independent SNPs were retained as IVs via a strict clumping procedure (criteria: $r^2>0.001$, kb>10 000) based on the European 1000G panel. After the clumping process, two stringent criteria were applied to filter thelinkage disequilibrium (LD) independent SNPs for the exposure: first, the specific SNPs must be present in the outcome GWAS; and second, no ambiguous SNPs may exist. After satisfying all criteria, the final SNPs selected as IVs for exposures were derived.

F-statistics were calculated for each SNP using the formula to test weak IVs: $F=\beta^2/se^2$ (β: beta for the correlation of SNP–exposure, se: standard error).[14] Additionally, R^2 was calculated to reflect the proportion of exposure variance explained by IVs.

Statistical analysis

A series of two-sample MR analyses were performed to determine whether there were causal correlations between periodontitis on 10 psychiatric disorders using four approaches (figure 1). The inverse-variance weighted (IVW) test was applied as the main MR analysis to estimate the causal effect of periodontitis on 10 psychiatric disorders, and the other approaches, including MR-Egger, weighted median and weighted mode, were used to provide additional verification of the results.[12] IVW method assumes balanced horizontal pleiotropy and is optimally efficient when all IVs are valid.[15] MR-Egger allows for all IVs to be invalid which is less biased but less efficient than IVW.[15] The weighted median method, which presumes that over 50% of the IVs are valid, exhibits less bias than the IVW method, while it has relatively higher type 1 error rate.[16] Under the assumption that the majority of IVs are valid, weighted mode method has relatively lower type 1 error rate inflation but limited power to evaluate the causal effect.[16] A p value after false discovery rate (FDR) correction (<0.05) was considered significant for evaluation. The causal estimates of periodontitis with 10 psychiatric disorders were examined using the ORs and 95% CIs. Printed scatter plots were used to present these causal estimates. MR-Egger intercept test and the MR pleiotropy residual sum and outlier (MR-PRESSO) global test were used to determine the existence of horizontal pleiotropy.[17] The IVW results were reliable only if the horizontal pleiotropy was absent. Furthermore, the heterogeneity for MR-Egger regression and the IVW method was evaluated via Cochran's Q test and printed forest plots, leave-one-out plots and funnel plots for sensitivity analysis. A reverse MR analysis was performed to explore the causal effect of 10 psychiatric disorders on periodontitis (figure 1). When one IV of psychiatric disorders was identified, the Wald ratio measured the relationship between psychiatric disorders and periodontitis.[18] MR estimates were computed using the IVW test for two SNPs that remained as IVs. Four MR approaches were used, including IVW, MR-Egger, weighted median and weighted mode, for the remaining three or more SNPs. Other analytical procedures were the same as the above MR analyses.

The MR analyses were performed using R software (V.4.2.1) with 'TwoSampleMR' and 'MR-PRESSO' packages.[17 19] The statistical power (at $\alpha=0.05$) for each MR analysis was calculated using an online MR power calculation tool (https://shiny.

Table 1 Overview of the GWAS summary statistics of the periodontitis and psychiatric disorders

Diseases	Cases	Controls	Sample size	Populations	PubMed ID	Source
Periodontitis						
Periodontitis*	17353	28210	45563	European and Hispanic/Latino ancestry	31235808	GLIDE
Periodontitis	950	455398	456348	Europeans	34737426	UK Biobank
Psychiatric disorders						
AD*	7016	14745	17310	Europeans	26754954	PGC
AD	3228	278818	282046	Europeans	36653562	FinnGen
PD*	2147	7760	9907	Europeans	31712720	PGC
PD	3614	278818	282432	Europeans	36653562	FinnGen
MDD*	170756	329443	500199	Europeans	30718901	PGC
MDD	7264	49373	56637	Europeans	33893285	GERA
MDD	33812	271380	305192	Europeans	36653562	FinnGen
SCZ*	53386	77258	130644	Europeans	35396580	PGC
SCZ	6050	297496	303546	Europeans	36653562	FinnGen
BD*	41917	371549	413466	Europeans	34002096	PGC
BD	5763	271380	277143	Europeans	36653562	FinnGen
AN*	16992	55525	72517	Europeans	31308545	PGC
AN	1489	301716	303205	Europeans	36653562	FinnGen
PTSD*	23212	151447	174659	Europeans	31594949	PGC
PTSD	1639	278818	280457	Europeans	36653562	FinnGen
ASD*	18381	27969	46350	Europeans	30804558	PGC
ASD	22916	32504	55420	Europeans	32747698	SPARK
ADHD*	19099	34194	53293	Europeans	30478444	PGC
ADHD	1357	304758	306115	Europeans	36653562	FinnGen
OCD*	2688	7037	9725	Europeans	28761083	PGC
OCD	1466	278818	280284	Europeans	36653562	FinnGen

*Primary datasets for Mendelian randomisation analyses.
AD, anxiety disorder; ADHD, attention-deficit/hyperactivity disorder; AN, anorexia nervosa; ASD, autism spectrum disorder; BD, bipolar disorder; GERA, Genetic Epidemiology Research on Adult Health and Aging cohort; GLIDE, Gene-Lifestyle Interactions in Dental Endpoints Consortium; GWAS, genome-wide association studies; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; PD, panic disorder; PGC, Psychiatric Genomics Consortium; PTSD, post-traumatic stress disorder; SCZ, schizophrenia; SPARK, Simons Foundation Powering Autism Research for Knowledge.

cnsgenomics.com/mRnd/) based on IVW-MR estimates. To reinforce the statistical power, we conducted a meta-analysis under the fixed-effects model using STATA V.17.0 (STATA, College Station, Texas), merging risk estimates from the PGC and FinnGen psychiatric disorder datasets.

RESULTS

IV selection

A cut-off of $p<5\times10^{-6}$ was used for the primary dataset of periodontitis (figure 2). For primary datasets of psychiatric disorders, a cut-off of $p<5\times10^{-8}$ was used for MDD, SCZ, BD, AN and ADHD, and $p<5\times10^{-6}$ for the rest of primary datasets, including AD, PD, PTSD, ASD and OCD (figure 3). Online supplemental table 1 lists the final SNPs selected as IVs for periodontitis. Online supplemental tables 2 and 3 list additional groups of SNPs used as IVs in reverse MR analyses for 10 mental illnesses. The F-statistics for each SNP were all larger than 10, ranging from 20.76 to 175.28, suggesting that our study did not consider the possibility of a weak IV bias (online supplemental tables 1–3).

The causal associations of periodontitis with AD, PD and MDD

We explored the causal effects of periodontitis on AD, PD and MDD and discovered no causal associations of periodontitis with AD (IVW, OR=0.956, 95% CI 0.658–1.388, p=0.813), PD (IVW, OR=1.105, 95% CI 0.904–1.352, p=0.329) and MDD (IVW, OR=1.006, 95% CI 0.975–1.038, p=0.709). The estimated power of IVW-MR could be found in online supplemental table 4. Causal effect estimates for periodontitis on AD, PD and MDD in four analytical methods, including IVW, MR-Egger, weighted median and weighted mode, indicated consistent null associations (figure 2). In the meta-analysis of PGC and FinnGen datasets, we also observed no causal associations between genetically predicted periodontitis and PD (OR=1.038, 95% CI 0.945–1.140, p=0.437) or MDD (OR=1.011, 95% CI 0.985–1.038, p=0.397). A potential causal effect of genetic liability to periodontitis on AD was detected (OR=1.135, 95% CI 1.013–1.271, p=0.029). However, after adjusting for FDR, the p value increased to 0.290, indicating that the result might be a false positive and the causal associations between periodontitis on AD could not be established (online supplemental figure 1, online supplemental table 4).

Regarding sensitivity analyses, Cochran's Q test revealed no significant heterogeneity in the analyses of AD (IVW, Q=5.198, p=0.268), PD (IVW, Q=3.847, p=0.797) and MDD (IVW, Q=3.730, p=0.589). Moreover, no horizontal pleiotropy of the results was identified based on the MR-PRESSO global test and MR-Egger intercept test (figure 2, online supplemental table 4). According to plots of leave-one-out, all results were stable and could not be significantly altered by any of the SNPs acted as the IV (online supplemental figures 2–4). Online supplemental table 5 lists the final MR results from supplementary datasets for exposure (periodontitis) and each outcome (AD, PD and MDD) to validate previously presented findings.

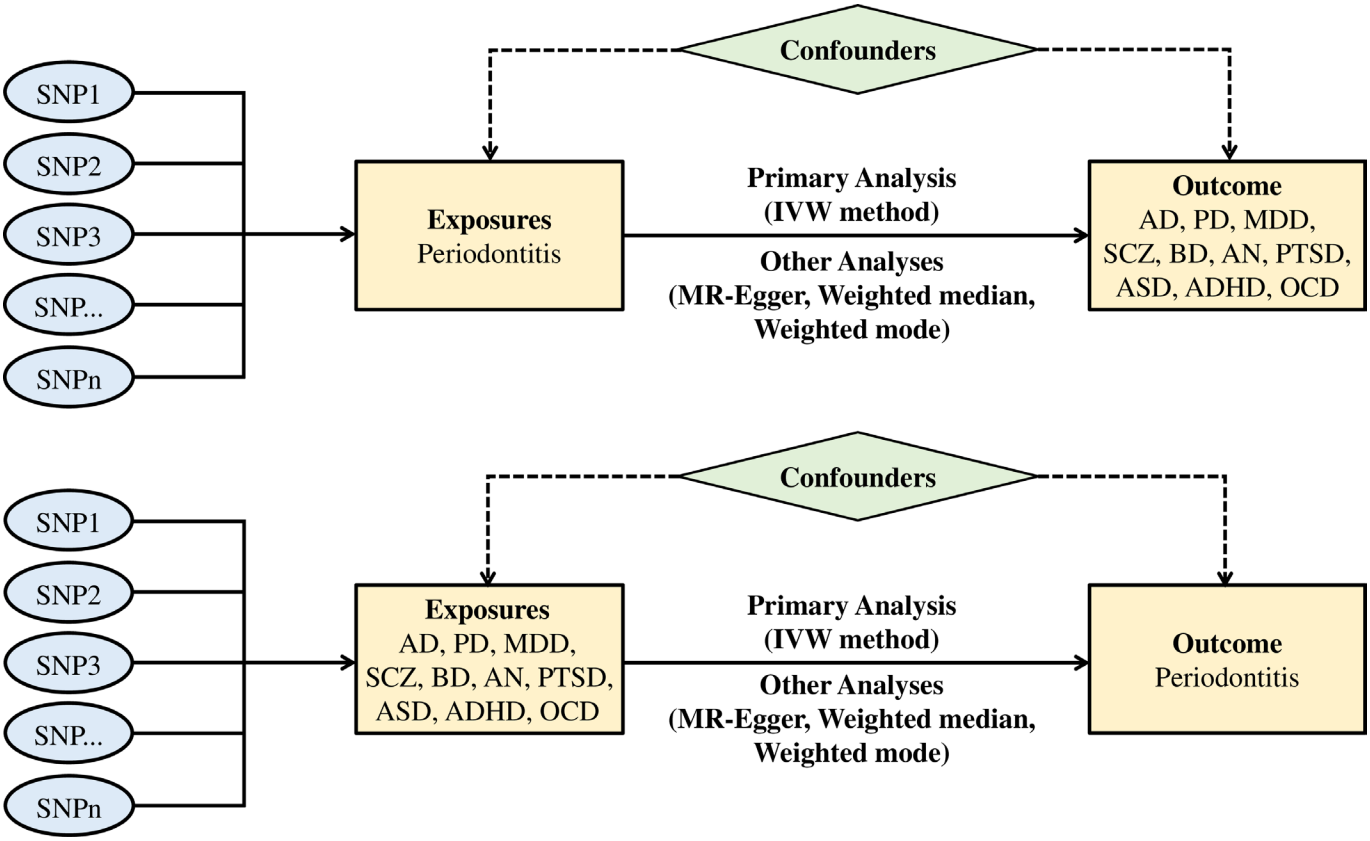

Figure 1 Bidirectional Mendelian randomisation (MR) study workflow. AD, anxiety disorder; ADHD, attention-deficit/hyperactivity disorder; AN, anorexia nervosa; ASD, autism spectrum disorder; BD, bipolar disorder; IVW, inverse-variance weighted; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; PD, panic disorder; PTSD, post-traumatic stress disorder; SCZ, schizophrenia; SNP, single nucleotide polymorphism.

The causal associations of periodontitis with SCZ and BD

Next, we evaluated the causal effects of periodontitis on SCZ and BD (figure 2, online supplemental table 4) and found a lack of evidence for a causal link between periodontitis and SCZ (IVW, OR=1.003, 95% CI 0.935–1.076, p=0.932). Similarly, our results discovered that periodontitis had no causality with BD (IVW, OR=1.081, 95% CI 0.988–1.182, p=0.089). Online supplemental table 4 lists the MR power of risk estimates obtained from IVW and reveals that the above MR effect estimates are consistent compared with the other three MR analytical methods. The subsequent meta-analysis of the PGC and FinnGen datasets of SCZ and BD still could not identify the causality of periodontitis on SCZ (OR=1.018, 95% CI 0.957–1.082, p=0.576) and BD (OR=1.064, 95% CI 0.991–1.142, p=0.089), as presented in online supplemental figure 1.

In the sensitivity analyses, we could not detect any confounding heterogeneity by Cochran's Q test or any potential horizontal pleiotropy by MR-PRESSO global test and MR-Egger intercept test (online supplemental table 4). The forest plots, leave-one-out plots, scatter plots and funnel plots showing the MR results between periodontitis and SCZ as well as BD are presented in online supplemental figures 5 and 6. Extra datasets applied for validation also generated the same results (online supplemental table 5).

The causal associations of periodontitis with AN, PTSD, ASD, ADHD and OCD

There was no statistically significant evidence to support the causal associations of periodontitis with AN (IVW, OR=1.037, 95% CI 0.899–1.197, p=0.617), PTSD (IVW, OR=1.061, 95% CI 0.955–1.179, p=0.270), ASD (IVW, OR=0.995, 95% CI 0.913–1.084, p=0.913), ADHD (IVW, OR=1.090, 95% CI 0.936–1.268, p=0.269) and OCD (IVW, OR=1.093, 95% CI 0.833–1.434, p=0.520) using IVW method. The statistical power of these analyses ranged from 5% to 50%. The remaining three methods and the meta-analysis of the PGC and FinnGen datasets were consistent with these results (figure 2, online supplemental table 4, online supplemental figure 1). Besides, heterogeneity and pleiotropy (all p>0.05) were not observed. Online supplemental table 4 lists the complete results of the sensitivity examination. Online supplemental figures 7–11 illustrate the plots of leave-one-out, suggesting the robustness of our results. Likewise, other auxiliary datasets confirmed this MR effect estimates further (online supplemental table 5).

The causal associations between 10 psychiatric disorders and periodontitis

In the reverse MR analysis, the results did not present a strong association between 10 selected psychiatric disorders and periodontitis (figure 3), including AD (IVW, OR=1.014, 95% CI 0.945–1.089, p=0.692), PD (IVW, OR=1.005, 95% CI 0.947–1.066, p=0.867), MDD (IVW, OR=1.032, 95% CI 0.864–1.233, p=0.728), SCZ (IVW, OR=1.017, 95% CI 0.971–1.066, p=0.478), BD (IVW, OR=1.059, 95% CI 0.980–1.143, p=0.146), AN (IVW, OR=1.070, 95% CI 0.910–1.257, p=0.415), PTSD (IVW, OR=0.933, 95% CI 0.841–1.035, p=0.191), ASD (IVW, OR=0.991, 95% CI 0.913–1.074, p=0.819), ADHD (IVW, OR=0.979, 95% CI 0.860–1.115, p=0.749) and OCD (IVW, OR=1.047, 95%

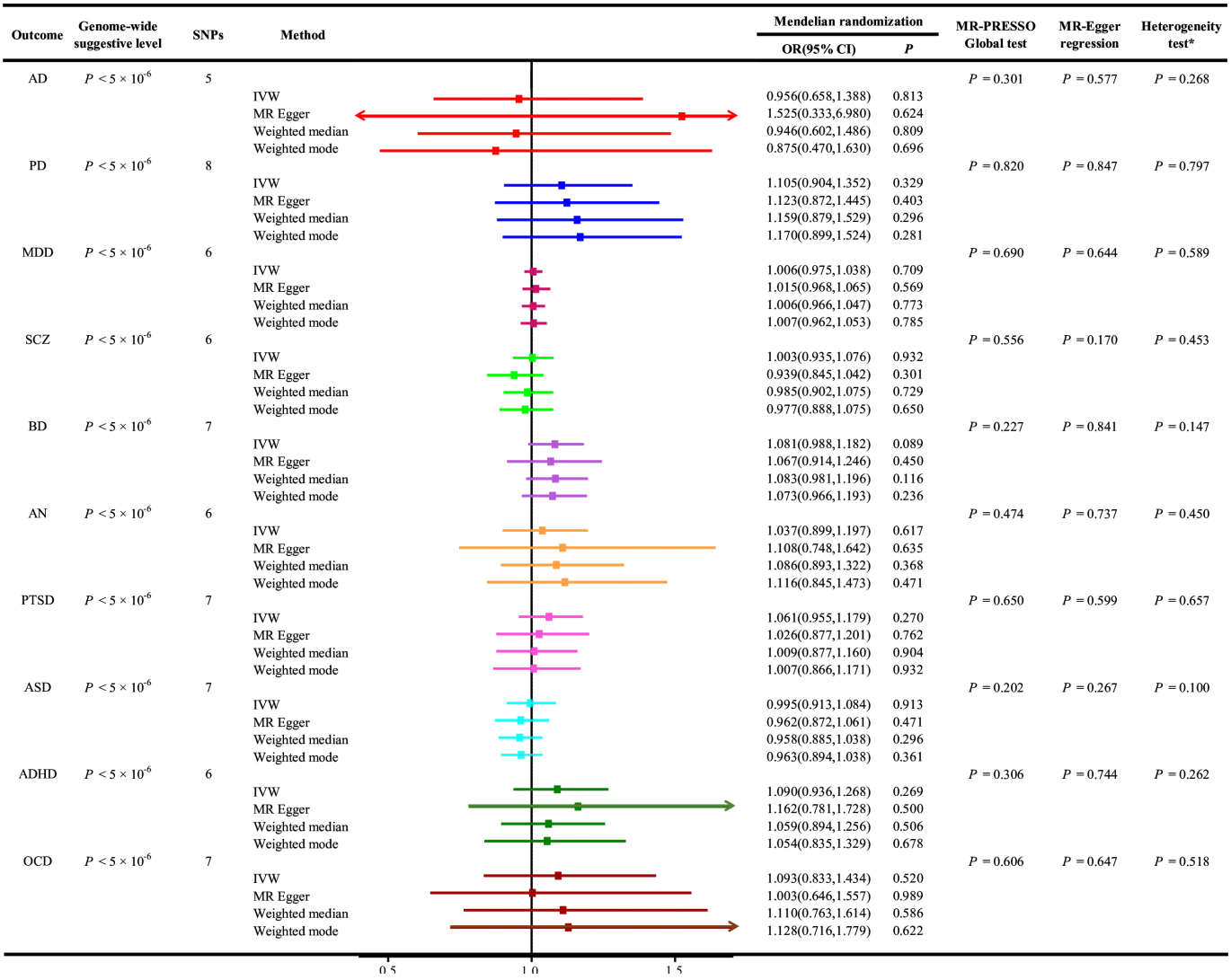

Figure 2 The associations between periodontitis and 10 psychiatric disorders. All datasets of the psychiatric disorders were obtained from Psychiatric Genomics Consortium (PGC) and the dataset of periodontitis was from the Gene-Lifestyle Interactions in Dental Endpoints Consortium (GLIDE). *Heterogeneity test for IVW. AD, anxiety disorder; ADHD, attention-deficit/hyperactivity disorder; AN, anorexia nervosa; ASD, autism spectrum disorder; BD, bipolar disorder; IVW, inverse-variance weighted; MDD, major depressive disorder; MR, Mendelian randomisation; MR-PRESSO, MR pleiotropy residual sum and outlier; OCD, obsessive-compulsive disorder; PD, panic disorder; PTSD, post-traumatic stress disorder; SCZ, schizophrenia; SNP, single nucleotide polymorphism.

CI 0.997–1.099, p=0.068). The estimated MR power was observed from 5% to 43% (online supplemental table 6). Then we performed the comprehensive meta-analyses of the PGC and FinnGen datasets and found no causal links between psychiatric disorders and periodontitis (online supplemental figure 12). Furthermore, causal estimates for 10 psychiatric disorders and periodontitis were broadly concordant in all the MR analysis approaches, whether using the primary datasets (online supplemental table 6) or the secondary datasets (online supplemental table 7).

Moreover, we identified no heterogeneity (all p>0.05) in the results based on Q values of MR-Egger and IVW tests. Concurrently, the MR-PRESSO global test and MR-Egger intercept test failed to identify pleiotropy (figure 3, online supplemental table 6). Online supplemental figures 13–22 exhibit the forest plots, leave-one-out plots, scatter plots and funnel plots of the association between psychiatric disorders and periodontitis.

DISCUSSION

In the present study, we conducted a series of two-sample MR analyses to evaluate correlations between periodontitis and 10 psychiatric diseases. Our research indicated no causal effects of periodontitis on 10 mental disorders (and vice versa) for the first time. In our multiple validation analysis, we detected no substantial indications of heterogeneity or horizontal pleiotropy, implying that our results were robust and consistent.

Increasing evidence from epidemiological investigations revealed a concomitance of periodontitis and psychiatric disorders.[6 20] Numerous controversies surrounded the relationship between periodontitis and the two most prevalent mental disorders, including AD[21 22] and MDD.[23 24] A recent meta-analysis encompassing 12 cross-sectional studies found a significant association between periodontitis and anxiety.[6] Similarly, the meta-analysis of eight case–control studies revealed a notable link between periodontitis and depression.[6] In contrast, an earlier meta-analysis, which included a smaller number of studies, did

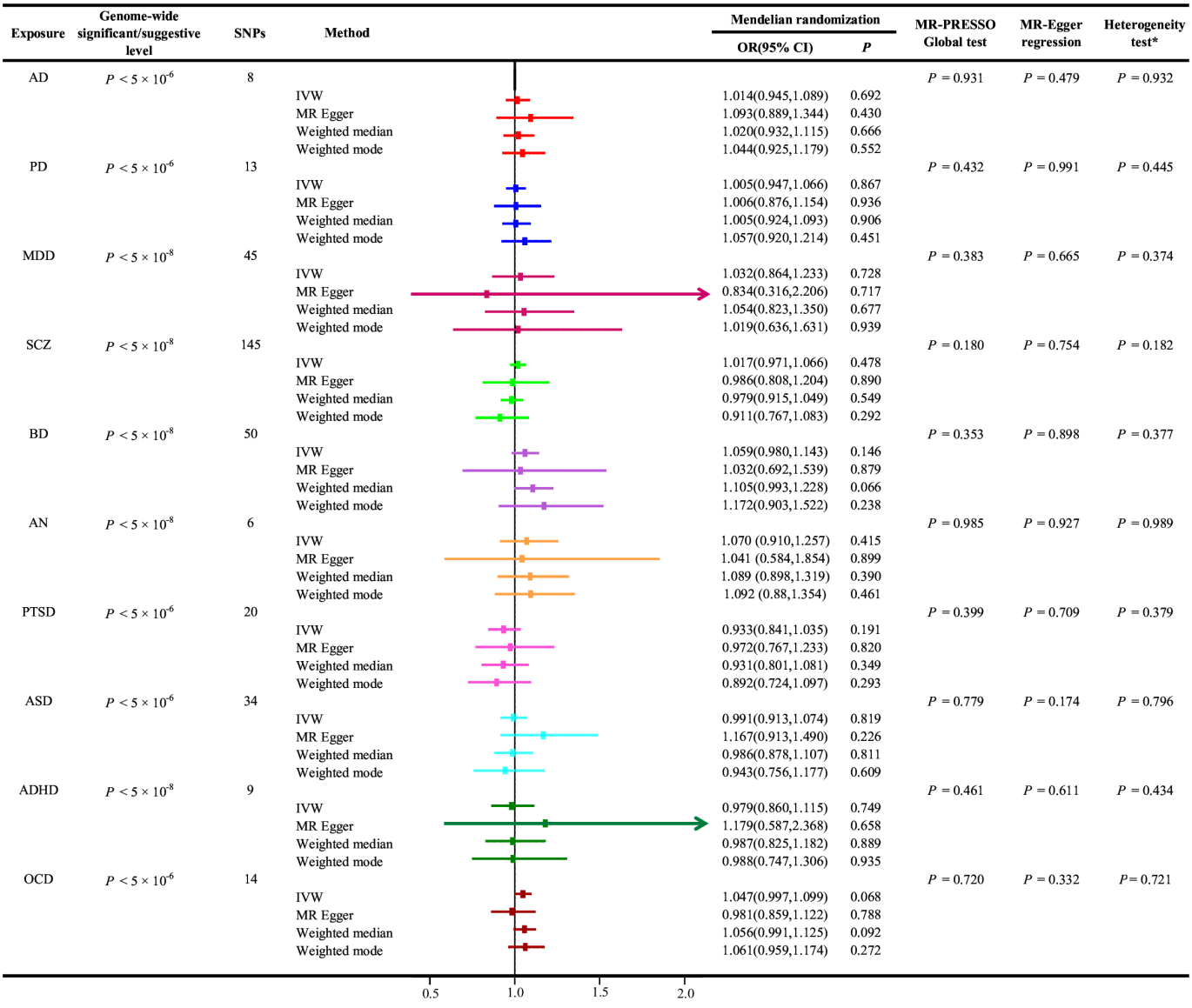

Figure 3 The associations between 10 psychiatric disorders and periodontitis. All datasets of the psychiatric disorders were obtained from Psychiatric Genomics Consortium (PGC) and the dataset of periodontitis was from the Gene-Lifestyle Interactions in Dental Endpoints Consortium (GLIDE). *Heterogeneity test for IVW. AD, anxiety disorder; ADHD, attention-deficit/hyperactivity disorder; AN, anorexia nervosa; ASD, autism spectrum disorder; BD, bipolar disorder; IVW, inverse-variance weighted; MDD, major depressive disorder; MR, Mendelian randomisation; MR-PRESSO, MR pleiotropy residual sum and outlier; OCD, obsessive-compulsive disorder; PD, panic disorder; PTSD, post-traumatic stress disorder; SCZ, schizophrenia; SNP, single nucleotide polymorphism.

not find associations between them, with the exception of PD, a subtype of AD.[24] Our study found no evidence that genetically predicted periodontitis has a causal effect on anxiety and depression, which was corroborated with the finding from an MR study of single phenotypic pairings indicating no causal relationship between periodontitis and depression.[25] Additionally, periodontitis has been linked to severe mental disorders (SMD), including SCZ and BD.[26 27] A recent cohort study followed 123 216 controls and 61 608 periodontitis cases for 7.36 and 7.45 years, respectively, and discovered that the morbidity of BD was 46% higher in the periodontitis cohort.[7] A review also reported that periodontal disease would reinforce the role of inflammation in the pathophysiology of SCZ.[28] The results of our research did not identify any causal relationships between periodontitis and 10 mental disorders, contrasting with some previous observational studies. The lack of evidence supporting associations between periodontitis and AN, PTSD, ASD and ADHD may help us understand our results.

Our MR research and some observational studies have disparities. It seems plausible that confounding factors rather than direct causality have contributed to the false observed connections. Interleukin (IL)-6 was involved in the pathogenesis and risk of periodontitis,[29] meanwhile, genetically predicted IL-6 might have a potentially causal role in depression and SCZ, as reported in the updated MR study.[30] Although the correlations between periodontitis and psychiatric disorders have been observed in traditional studies, many traditional studies have been confined to cross-sectional designs with high statistical heterogeneity or involved in small to medium samples which might produce false-positive results. Our MR analysis has more sufficient power to make a causal estimate by leveraging large-scale GWAS data and excluding the impact of confounders. It is highly recognised that

MR analysis is a favoured technique for causal inference, particularly when RCT is not practical.[11]

Excess mortality in SMD, including SCZ, BD, severe depression and severe anxiety, is a major public health challenge and warrants attention. A vast majority of deaths in these conditions can be attributed to preventable health issues, including infections.[26] Periodontitis is an infectious disease that may need lifelong periodontal self-care to prevent disease progression.[31] Despite the mounting evidence suggesting a connection between periodontitis and psychiatric disorders,[32] a comprehensive MR analysis assessing the causality between periodontitis and the risk of psychiatric disorders has not been conducted. Inadequate recognition of the connection is likely to overlook the impact of teeth-related phenotypes on mental disorders and underestimate the burden of mental disorders.[33] Our research found no causal associations between periodontitis and psychiatric disorders, which might mitigate unnecessary concerns for patients diagnosed with either condition to an extent. Nonetheless, the relationship between dental health and psychological stress is still largely unexplored. Davis *et al* recently proposed that teeth might serve as indicators for future psychological health risk, potentially aiding in identification of youths at higher risk of mental disorders, which encourages researchers to further delve into the intricate relationship between dental health and mental illnesses.[34]

This study has some noteworthy strengths. According to our knowledge, this is the first study to examine the bidirectional causal associations between periodontitis and 10 common psychiatric disorders. We used the two-sample MR design, a powerful tool for detecting the causal effect that could limit confounding factors and reverse causation bias. Besides, we adopted the most updated or largest scale GWAS data of periodontitis and psychiatric disorders. What's more, we performed multiple validations to prove three key assumptions of the MR analysis. The selected SNPs satisfied the first assumption as they were associated with the exposure at genome-wide significance and all F-statistics of the SNPs were larger than 10. The second and third assumptions are often violated by horizontal pleiotropy. We applied the MR-PRESSO test and the MR-Egger regression test and found no potential horizontal pleiotropy effect. Therefore, all assumptions were well satisfied, indicating that the result of our study is valid and robust. Nonetheless, the study also has some limitations. First, our study primarily focused on individuals of European ancestry; therefore, it remains to be determined whether the results apply to other ethnicities. Second, given the inherent limitations of the GWAS summary statistics, we were unable to conduct a deeper subgroup analysis due to the absence of stratification data, including sex, age at onset and disease severity. Third, our initial analysis showed relatively low statistical power; however, we conducted a series of fixed-effects meta-analyses to bolster the statistical power. Furthermore, the utilisation of larger scale datasets, extensive validation datasets, multiple sensitivity analyses and stringent FDR correction strengthens the robustness of our results and enhances the overall credibility.

CONCLUSION

In summary, our research does not demonstrate causal associations between periodontitis and 10 common psychiatric disorders (and vice versa) based on bidirectional MR analysis. Further research, such as well-designed prospective studies or updated MR analysis with larger high-quality scale GWAS summary data in this field, would be warranted to clarify the causal relationships between periodontitis and psychiatric disorders. Our study could alleviate the concerns of patients suffering from periodontitis or psychiatric disorders.

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Contributors Conceptualisation and design: FWL, WS, HC. Collection and assembly of data: ST, YL, WH. Data analysis and interpretation: ST, YL. Manuscript writing—original draft: ST, YL. Manuscript writing—review and editing: ST, YL, RZ, RJ, WH, FWL, WS, HC. HC was responsible for the overall content as guarantor. All authors reviewed and approved the final manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Data availability statement Data are available in a public, open access repository. Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information. Datasets of psychiatric disorders are downloaded at https://pgc.unc.edu/for-researchers/download-results/, https://www.ebi.ac.uk/gwas/ and https://www.finngen.fi/en/access_results, and datasets of periodontitis are downloaded at https://data.bris.ac.uk/data/dataset/2j2rqgzedxlq02oqbb4vmycnc2 and https://www.ebi.ac.uk/gwas/. GWAS summary statistics are available from published studies (table 1). The analysis code used in this study is available from the corresponding author upon reasonable request.

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