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Cannabis use and the risk of periodontitis: A two-sample Mendelian randomization study

Sebastian-Edgar Baumeister[1] | Zoheir Alayash[1] | Hansjörg Baurecht[2] | Stefan Lars Reckelkamm[1] | Thomas Kocher[3] | Birte Holtfreter[3] | Benjamin Ehmke[4] | Michael Nolde[1]

[1]Institute of Health Services Research in Dentistry, University of Münster, Münster, Germany

[2]Department of Epidemiology and Preventive Medicine, University of Regensburg, Regensburg, Germany

[3]Department of Restorative Dentistry, Periodontology, Endodontology, and Preventive and Pediatric Dentistry, University Medicine Greifswald, Greifswald, Germany

[4]Clinic for Periodontology and Conservative Dentistry, University of Münster, Münster, Germany

Correspondence
Sebastian-Edgar Baumeister, Institute of Health Services Research in Dentistry, University of Münster, Albert-Schweitzer-Campus 1, 48149 Münster, Germany.
Email: sebastian.baumeister@uni-muenster.de

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Abstract

Aim: This study aimed to leverage human genetic data to investigate whether cannabis use causally affects periodontitis.

Materials and Methods: Data were obtained from summary statistics of genome-wide association studies of lifetime cannabis use ($N = 184{,}765$), cannabis use disorder (17,068 cases; 357,219 controls), and periodontitis (17,353 cases; 28,210 controls). We performed two-sample Mendelian randomization (MR) analysis using 6 genetic variants as instrumental variables for lifetime cannabis use and 11 variants as instruments for cannabis use disorder to estimate associations with periodontitis.

Results: There was no evidence for an association between genetic liability for lifetime cannabis use or cannabis use disorder with periodontitis. The estimates from the primary analyses were supported in multivariable MR analysis, which considered potential pleiotropic pathways and in weak instrument analyses.

Conclusions: This study provides little evidence to support a detrimental effect of genetic liability for cannabis use on periodontal health.

KEYWORDS
cannabis, confounding, Mendelian randomization, periodontitis, risk factors

Clinical Relevance

Scientific rationale for study: Observational studies have suggested that cannabis use might be positively associated with periodontitis. However, its role independent of tobacco smoking and whether the association reflects causality remain debatable.

Principal findings: Mendelian randomization analysis provided no evidence for an effect of cannabis use on periodontitis.

Practical implications: The results do not support a role of cannabis in the aetiology of periodontitis.

1 | INTRODUCTION

Periodontitis is a microbially associated inflammatory disease of the tooth-supporting tissue that affects approximately 50% of the adult population, with 10% suffering from severe periodontitis (Papapanou et al., 2018; Bernabe et al., 2020). It is a major cause of tooth loss (Papapanou et al., 2018). Subgingival bacterial dysbiosis, diabetes mellitus, and tobacco smoking are well-recognized risk factors for periodontitis (Chapple et al., 2017; Lalla & Papapanou, 2022; Papapanou & Demmer, 2022). Cannabis is the most widely smoked substance after tobacco, and its prevalence is increasing as more legal markets emerge (Manthey et al., 2021). There is strong evidence from prospective observational studies, Mendelian randomization (MR) studies, and laboratory-based studies that tobacco smoking increases the risk of periodontitis (Baumeister et al., 2021; Chaffee et al., 2021). Cannabis smoke shares many of the chemical constituents of tobacco, except for cannabinoids and nicotine (Tashkin & Roth, 2019). The well-established effect of tobacco smoke on the periodontium and the oral mucosa and the similarities in the toxicological profiles of tobacco and cannabis smoke suggest that cannabis may also be a candidate in the aetiology of periodontal disease.

Observational studies have indicated that cannabis use may increase the risk of periodontitis. Three systematic reviews examined the available evidence from cross-sectional and prospective observational studies (Baghaie et al., 2017; Chisini et al., 2019; Mayol et al., 2021). The latest review included 14 articles from 11 studies and supported a possible deterioration of periodontal health in cannabis smokers (Mayol et al., 2021). However, only one of the included studies was prospective (Meier et al., 2016). Another review meta-analysed three cross-sectional studies and one prospective study and reported a pooled prevalence ratio of 1.12 (95% confidence interval [CI]: 1.06–1.19) comparing cannabis use and non-use (Chisini et al., 2019). The longitudinal Dunedin Multidisciplinary Health and Development Study cohort study followed young adults up to age 38 years and concluded that cannabis use may increase the risk of early onset periodontitis (Meier et al., 2016). A cross-sectional analysis of middle-aged participants of the US National Health and Nutrition Examination Survey reported a dose–response association concerning cannabis use frequency and periodontitis (Shariff et al., 2017). The reasons that may underpin this potential relationship are yet to be elucidated but several mechanisms may explain the relationship. Cannabis use has been associated with increased sensations of lethargy and sleepiness (Kaul et al., 2021) and a preference for sweet foods (Gelfand & Tangney, 2021), which may lead to individuals being less likely to engage in beneficial health behaviours, including a healthy diet, oral hygiene, and regular dental visits, thereby contributing to worsening periodontal health (Joshi & Ashley, 2016; Rossow, 2021). The proposed biological mechanisms include a diminished salivary flow, an altered oral microbiome, impaired immune response, and increased production of destructive cytokines and enzymes (Rossow, 2021; Scott et al., 2021).

Although observational and mechanistic evidence supports a role of cannabis use in the development of periodontitis, attributing the association to cannabis use is challenging when relying on observational epidemiological study designs because cannabis is frequently consumed in combination with tobacco (Agrawal et al., 2012). Because of the combination of cannabis and tobacco use, it is difficult to separate the effect of cannabis from that of tobacco when relying on conventional observational designs (Westreich & Cole, 2010; Mofidi et al., 2019). An emerging epidemiological approach to strengthen the inference in the presence of observational confounding is MR. MR leverages genetic information as a random source of variation of the exposure such that the source of variation is unrelated to confounding factors (Davies et al., 2018; Smith et al., 2020). It makes use of the natural randomization that occurs in the generation of an individual's genetic make-up in a way that is analogous to the design of a randomized controlled trial and uses genetic variants in instrumental variable analysis to infer an effect of a modifiable exposure on an outcome. We performed a two-sample MR analysis using summary statistics from genome-wide association studies (GWAS) to investigate the association of genetically proxied lifetime cannabis use and cannabis use disorder with periodontitis.

2 | MATERIALS AND METHODS

2.1 | Overall study design

MR uses genetic variants associated with an exposure to strengthen inference regarding their potential causal influence on an outcome. The approach draws on Mendel's laws of segregation and independent assortment, whereby genetic variants are allocated independently of environmental and other genetic factors (except those in close proximity through linkage disequilibrium [LD]; Smith et al., 2020; Richmond & Smith, 2022). By design, genetic associations should therefore be free from confounding, and differences in outcomes can be attributed to exposures. Thus, the association between an outcome and a genetic variant proxying a risk factor mimics the relationship between the risk factor and the outcome and can be used to estimate this association with less confounding and bias than conventional epidemiological approaches. Certain qualities make genetic variants useful in causal inference: they can be robustly associated with the risk factor, are fixed at conception, are not affected by disease processes (less susceptible to reverse causation), are commonly not subject to measurement error, and typically have long-term effects on the exposure (Smith et al., 2020; Richmond & Smith, 2022). This study is reported based on recommendations by STROBE-MR and "Guidelines for performing Mendelian randomization investigations" (Burgess et al., 2020; Skrivankova et al., 2021). The study protocol and details were not pre-registered.

2.2 | Data sources

Genetic association estimates of single nucleotide polymorphisms (SNPs) with periodontitis were considered as outcomes obtained from

TABLE 1 Genome-wide association studies used to obtain summary statistic for lifetime cannabis use, cannabis use disorder and periodontitis

Phenotype	Sample size	Cases	Controls	Percentage of female	First author (year, PMID)
Lifetime cannabis use	184,765			55	Pasman et al. (2018, 30150663)
Cannabis use disorder		17,068	357,219	45	Johnson et al. (2020, 33096046)
Periodontitis		17,353	28,210	54	Shungin et al. (2019, 31235808)

Abbreviation: PMID, PubMed identifier.

a European GWAS contributing to the GeneLifestyle Interactions in Dental Endpoints consortium, totaling 17,353 clinical periodontitis cases and 28,210 controls (Shungin et al., 2019) (Table 1, Table S1). Periodontitis cases were classified by either the Centers for Disease and Control and Prevention/American Academy of Periodontology or the Community Periodontal Index case definition, or through study participant reports of diagnosis of periodontitis (Shungin et al., 2019). Genotyping was performed on commercially available arrays (including the Affymetrix Genome-Wide Human SNP array, Illumina Human610 Quadv1_B, and Affymetrix UK BiLEVE Axiom array), and standard quality control checks were performed before imputation. GWAS for the periodontitis trait was performed using a mixed logistic model accounting for age, sex, and genetic principal components. SNP associations for the lifetime cannabis use exposure were derived from GWAS of 184,765 individuals of European descent (Pasman et al., 2018). Lifetime cannabis use was defined as any use during a lifetime. The data consisted of three sources and included the International Cannabis Consortium, 23andMe, and UK Biobank. Genotyping was performed on various genotyping platforms, and standard quality control checks were performed before imputation. The GWAS model for lifetime use had been adjusted for age, sex, ancestry, and genotype batch. Summary statistics for the cannabis use disorder exposure came from a GWAS of 17,068 European ancestry cases and 357,219 controls using 18 samples from the Psychiatric Genomics Consortium Substance Use Disorders working group, Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH), and deCODE (Johnson et al., 2020). Psychiatric Genomics Consortium cases met criteria for a lifetime diagnosis of DSM-IV (or DSM-III-R) cannabis abuse or dependence derived from clinician ratings or semi-structured interviews. Cases from iPSYCH had ICD-10 codes of F12.1 (cannabis abuse) or F12.2 (cannabis dependence). Cases in deCODE were defined as lifetime DSM-III-R or DSM-IV cannabis abuse or dependence or DSM-V cannabis use disorder. Association analyses were conducted using logistic models and further included sex and principal components as covariates.

We also assessed the consistency of evidence in multivariable MR analyses adjusting for genetically proxied body mass index (BMI), cigarette smoking, and educational attainment. Genetic association estimates for BMI were obtained from GWAS of 806,834 European ancestry individuals (Pulit et al., 2019). The GWAS of the number of cigarettes per day included 337,334 individuals (Liu et al., 2019). Cigarettes per day was defined as the average number of cigarettes smoked per day, either as a current smoker or former smoker. Genetic association estimates for educational attainment were obtained from GWAS meta-analysis of 1.13 Mio. individuals of European descent (Lee et al., 2018). Educational attainment was defined as the number of years of education and was unified across the included studies according to the International Standard Classification of Education. More details on the population characteristics are provided in Table S1. Specific trait definitions relating to all these summary genetic association estimates are available in their original publications.

2.3 | Selection of genetic variants as instrumental variables

Six SNPs were identified as instruments associated with lifetime cannabis use at a genome-wide significance level with a p-value $< 5 \times 10^{-8}$, following clumping for LD at $r^2 < 0.01$ (Table S2). We selected 11 LD-independent SNPs at a genome-wide p-value $< 5 \times 10^{-8}$ as instruments for cannabis use disorder (Table S2). In addition, we adopted a liberal instrument selection approach (p-value $< 5 \times 10^{-5}$, $r^2 < 0.1$) to strengthen the instrument and achieve higher statistical power (Burgess et al., 2020). The liberal approach provided 267 SNPs for lifetime cannabis use and 154 SNPs for cannabis use disorder.

2.4 | Statistical power to detect effect sizes

A priori statistical power was calculated (Deng et al., 2020). Given $\alpha = 2.5\%$, we had ≥80% power for the primary analysis when the expected odds ratios (ORs) for periodontitis were ≥1.51 and ≥1.42 for lifetime cannabis use and cannabis use disorder, respectively. In the secondary analysis, employing a liberal instrument selection approach, detectable ORs for periodontitis were ≥1.09 for lifetime cannabis use and ≥1.13 for cannabis use disorder at $\alpha = 2.5\%$ and power of ≥80%.

2.5 | Statistical analysis

Two-sample MR analysis was implemented using instrumental variable estimation. A genetic variant qualifies as a valid instrument if it is robustly associated with the exposure ("relevance"), if it does not share common causes with the outcome ("exchangeability"), and if it

affects the outcome exclusively through the exposure ("exclusion restriction") (Hemani et al., 2018; Labrecque & Swanson, 2018). SNPs that pass a genome-wide significance threshold (p-value < 5×10^{-8}) are commonly selected as instruments to meet the relevance assumption. The strength of the instrument is further tested by means of the proportion of variance explained and the F-statistic (Burgess & Thompson, 2011). Violations of the exchangeability and exclusion restriction assumption can occur through horizontal pleiotropy when the genetic variant affects the exposure and outcome but through different pathways (Hemani et al., 2018; Richmond & Smith, 2022). This can produce biased instrumental variable estimates if the genetic variant influences the outcome via a mechanism other than through the exposure of interest. Although it is not possible to prove that the exchangeability and exclusion restriction assumptions hold in an MR study, sensitivity analysis can be used to uncover possible violations of these assumptions. One way is to search for previous reports of associations of the genetic instruments with traits potentially confounding the exposure–outcome association or the SNP–outcome association (e.g., using PhenoScanner) (Hemani et al., 2018; Kamat et al., 2019). If this search reveals potential horizontal pleiotropic pathways, multivariable MR can then be used to adjust for pleiotropy (Sanderson et al., 2019). Additional approaches include the assessment of potential violation of the exclusion restriction assumption through evaluation of the heterogeneity of the individual SNP estimates and through pleiotropy-robust approaches, which can provide unbiased estimates in the presence of pleiotropic instruments (Hemani et al., 2018; Slob & Burgess, 2020).

We derived Wald ratios for each SNP by dividing the effect estimate for the SNP–outcome association by the coefficient of the SNP–exposure association, with standard errors of the Wald ratio approximated by the delta method (Burgess et al., 2017). The Wald ratios were combined using the multiplicate random-effects inverse variance weighted (IVW) method (Burgess et al., 2017). The pooled OR estimates for periodontitis were scaled to a doubling in genetically predicted lifetime cannabis use or cannabis use disorder (Burgess & Labrecque, 2018). PhenoScanner was searched for previous reports with potential confounders. We performed multivariable multiplicative random-effects IVW analysis to adjust for measured correlated pleiotropy (Sanderson et al., 2019). The instrument strength in the multivariable IVW analyses was quantified using the conditional F-statistic (Sanderson et al., 2021). For the multivariable MR analysis, only variants for which genetic summary statistics were available for all the traits being examined in each multivariable analysis were considered. Thus, to maintain consistency in variants used as instrumental variables across different analyses, proxies were not used.

We assessed heterogeneity using Cochran Q, I_{GX}^2, and performed the outlier test using the MR pleiotropy residual sum and outlier (MR-PRESSO) (Hemani et al., 2018; Verbanck et al., 2018). Random-effects IVW estimates are unbiased when the pleiotropy is "balanced" or "undirectional" (i.e., when the random effects have zero weighted mean). The MR Egger intercept test was used to test for directional pleiotropy (Hemani et al., 2018). We conducted leave-one-out analysis to assess whether the IVW estimate was driven by a single SNP, and examined funnels plots of single SNP Wald ratio estimates and scatter plots of SNP–outcome associations versus SNP–exposure associations to identify any leverage points with high influence. Pleiotropy-robust approaches included the penalized weighted median, the IVW radial regression, and MR-PRESSO (Bowden et al., 2018; Hemani et al., 2018; Slob & Burgess, 2020). Because there were only six SNPs used for the analysis on lifetime cannabis use and periodontitis, we reported the penalized weighted median but not the IVW radial regression and the MR-PRESSO (Slob & Burgess, 2020).

After applying the liberal instrument selection strategy, we carried out the weak instruments multiplicative random-effects IVW and pleiotropy-robust methods in secondary analyses on sets of weak instruments (Burgess et al., 2017, 2020). The Causal Analysis Using Summary Effect Estimates (CAUSE) MR method (Morrison et al., 2020) was applied as an additional technique to improve statistical power and lower the risk of weak instrument bias. CAUSE leverages on genome-wide data for the exposure trait, and calculates posterior probabilities of the causal effect and a shared (non-causal) effect, where the causal effect reflects the effects of the variants on the outcome through the exposure and the shared effect reflects correlated horizontal pleiotropy. We performed the analysis using R version 4.1.2 (R Foundation for Statistical Computing) using the cause (1.2.0.335), MendelianRandomization (0.5.1), MVMR (0.3), MR-PRESSO (1.0), and TwoSampleMR (0.5.6) packages.

3 | RESULTS

The six SNPs for lifetime cannabis use explained 0.5% of the variance in lifetime cannabis use, corresponding to an F-statistic of 30.7. The 11 SNPs for cannabis use disorder explained 0.8% of the phenotypic variance and had an F-statistic of 26.5. We did not find evidence supporting an effect of genetically predicted lifetime cannabis use on the risk of periodontitis (IVW OR per doubling in exposure = 1.05; 95% CI: 0.93–1.19; $p = .411$) (Figure 1). The IVW analysis for genetically predicted cannabis use disorder and risk of periodontitis did not support an association (OR per doubling in exposure = 0.97; 95% CI: 0.92–1.02; $p = .244$).

The PhenoScanner search yielded associations of SNPs instrumenting lifetime cannabis use with obesity-related phenotypes, which might have opened a horizontal pleiotropy pathway (Table S3). The SNPs for cannabis use disorder were found to associate with educational attainment (Table S3). We, therefore, performed multivariable IVW adjusting for these genetically proxied phenotypes. Although the PhenoScanner search did not pick up pleiotropy via cigarette smoking, we additionally adjusted the multivariable analyses for tobacco smoking to account for potential unaccounted pleiotropy. The multivariable analysis did not indicate that the modelled phenotypic traits introduced pleiotropy in the univariable MR estimates (Table 2). The conditional F-statistics were 20.4 and 23.9 for lifetime cannabis use and cannabis use disorder, respectively.

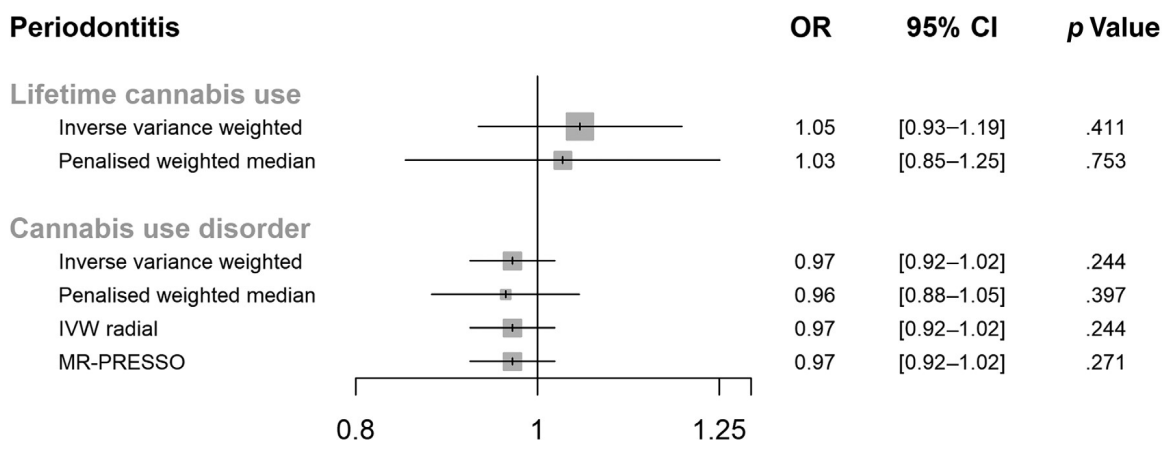

FIGURE 1 Mendelian randomization (MR) estimates for the effect of lifetime cannabis use and cannabis use disorder on periodontitis. IVW, inverse variance weighted; MR-PRESSO, MR pleiotropy residual sum and outlier.

Exposure	Adjustment	OR	95% CI	*p*-Value
Lifetime cannabis use	Body mass index, cigarettes per day	0.98	0.87–1.11	.769
Cannabis use disorder	Education, cigarettes per day	1.02	0.96–1.07	.515

Abbreviations: CI, confidence interval; OR, odds ratio.

TABLE 2 Multivariable inverse variance weighted estimates for adjusted effect of lifetime cannabis use and cannabis use disorder on periodontitis

There was no heterogeneity in the IVW analyses (Table S4). The intercepts from the MR Egger regression were centred around zero and provided no evidence for unbalanced pleiotropy (Table S4). Using the MR-PRESSO global outlier test, we found no evidence for outliers (*p*-value for lifetime cannabis use = .595; *p*-value for lifetime cannabis use = .83). The IVW leave-one-out analyses, funnel plots of single SNP estimates, and scatter plots of SNP–outcome associations versus SNP–exposure associations did not identify any leverage points with high influence (Table S5, Figures S1–S4). Evaluation of the MR estimate under other pleiotropy-robust models showed consistency with the original IVW estimate (Figure 1). In analyses adopting a liberal instrument selection criterion, the 267 SNPs for lifetime cannabis use explained 12.1% of the variance and had an *F*-statistic of 16.4. The 154 SNPs for cannabis use disorder explained 6.9% of the variance and had an *F*-statistic of 16.5. Estimates of secondary analyses, adopting a liberal threshold for SNP selection and applying weak instrument IVW, robust MR, and CAUSE analyses, did not support any associations between lifetime cannabis use or cannabis use disorder with risk of periodontitis (Table S6).

4 | DISCUSSION

In this two-sample MR analysis among people of European descent, we found little evidence for effects of genetic liability for lifetime cannabis use and cannabis use disorder on the risk of periodontitis. However, the upper CI limit for lifetime cannabis use was 1.19, pointing to the possibility that larger MR studies could show a positive association between cannabis use and periodontitis risk. The estimates were consistent using different MR methods. The sensitivity analyses and multivariable MR models did not indicate biasing influences of horizontal pleiotropic or weak instrument bias.

Although available observational studies suggest that cannabis use is positively associated with periodontitis (Chisini et al., 2019; Mayol et al., 2021), the majority of these studies are cross-sectional, reducing the potential to infer cause–effect relations because the design does not ensure that the exposure precedes the outcome (VanderWeele, 2015). With cross-sectional data, it is difficult to rule out feedback and reverse causation; for example, cannabis might be used to provide relief from gum soreness related to periodontal disease (Lowe et al., 2021). Thus, with cross-sectional data in which temporal ordering is not clear and in which causality may occur in both directions, we cannot reliably draw conclusions. Furthermore, the published studies attempt to adjust for tobacco smoking using multivariable regression analysis. However, in many of the previous observational studies cannabis smokers were also tobacco smokers, which hampers confounding adjustment due to (near) positivity violations (Westreich & Cole, 2010; Hernán & Robins, 2020). The assumption of positivity or experimental treatment assignment requires that observed exposure levels vary within confounder strata. It is violated when there are no or few cannabis users refraining from tobacco smoking in a given study. In addition, additional potential confounders were not considered in the existing studies, including oral hygiene and diabetes (Mofidi et al., 2019). Quantitative sensitivity analysis can be leveraged to quantify the extent of unobserved confounding needed to explain away the observed associations derived from meta-analysis of observational studies to characterize evidence strength (Mathur & VanderWeele, 2021). As such, the *E*-value can be calculated, which represents the confounder strength (on a relative risk scale) required to shift the pooled estimate and the lower CI to the null (Mathur &

VanderWeele, 2021). Computing the *E*-value for the meta-analysis of Chisini et al. (2019) (pooled prevalence ratio = 1.12; 95% CI: 1.06–1.19) indicated that unmeasured confounder(s) associated with an average relative risk of 1.48-fold potentially could shift the pooled estimate to the null, and average confounding associations of 1.31-fold could shift the lower CI limit to the null. However, for example, the associations of smoking and diabetes with periodontitis derived from meta-analyses are stronger than these *E*-values (Leite et al., 2018; Nascimento et al., 2018).

The study has several limitations. First, the periodontitis GWAS used a broadly defined phenotype, including clinical criteria and self-reported diagnosis, which might have introduced outcome misclassification. However, classical measurement error is not expected to affect asymptotic estimates from instrumental variable analysis (Pierce & VanderWeele, 2012). Second, since cannabis exposure is uncommon because of its legal status, the effect of the exposure can often not be attributed to the exposure itself. Participants in the periodontitis GWAS may carry the risk allele but may have never been exposed to cannabis. In such situations, the causal effect estimate should be interpreted as the effect of genetic liability for cannabis (Smith & Munafò, 2019; Howe et al., 2021). Third, a more detailed dose assessment of lifetime cannabis exposure with genetic variants instrumenting cannabis use at different life stages or SNPs for a biomarker of direct cannabis exposure was unavailable. Fourth, there were no overlapping samples in the univariable MR analysis, but there was overlap in the samples used to select instruments for multivariable MR. Given that all instrumental variables in the analysis were strong (conditional *F*-statistics > 10), any bias should be minimal (Minelli et al., 2021). Fifth, the genetic variants explained only a small portion of the cannabis traits. We performed additional weak instrument analyses, which yielded estimates that were consisted with the primary analysis. Nevertheless, we cannot rule out the possibility that weak instrument biased the two-sample MR estimates towards the null. Last, in the present study, the cannabis and periodontitis SNP effect estimates were obtained from European (ancestry) studies, thus minimizing the possibility of population stratification bias and increasing the plausibility of the two-sample MR assumption that summary associations derived from comparable populations. Nevertheless, caution is warranted before generalizing findings to other populations.

In conclusion, the present MR analysis found little evidence that genetic liability for cannabis use influences periodontitis. In future, replication of these findings using larger and GWAS with a more precisely phenotyped cannabis exposure are required.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Sebastian-Edgar Baumeister, Zoheir Alayash, Benjamin Ehmke, and Michael Nolde. *Development of methodology*: Sebastian-Edgar Baumeister, Zoheir Alayash, Michael Nolde, Hansjörg Baurecht, and Birte Holtfreter. *Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.)*: Sebastian-Edgar Baumeister, Thomas Kocher, and Birte Holtfreter. *Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis)*: Sebastian-Edgar Baumeister, Zoheir Alayash, Hansjörg Baurecht, Stefan Lars Reckelkamm, and Michael Nolde. *Writing, review, and/or revision of the manuscript*: Sebastian E. Baumeister, Zoheir Alayash, Michael Nolde, Hansjörg Baurecht, Stefan Lars Reckelkamm, Birte Holtfreter, Thomas Kocher, and Benjamin Ehmke. *Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases)*: Sebastian-Edgar Baumeister, Zoheir Alayash, Birte Holtfreter, and Michael Nolde.

DATA AVAILABILITY STATEMENT

The periodontitis summary data are available at https://data.bris.ac.uk/data/dataset/2j2rqgzedxlq02oqbb4vmycnc2. The lifetime cannabis use and cannabis use disorder summary statistics are available at https://www.ru.nl/bsi/research/group-pages/substance-use-addiction-food-saf/vm-saf/genetics/international-cannabis-consortium-icc/ and https://www.med.unc.edu/pgc/download-results/. Summary genetic data for educational attainment are available from the Social Science Genetic Association Consortium portal (https://www.thessgac.org/data). The summary statistics for the smoking GWAS are available at https://genome.psych.umn.edu/index.php/. The body mass index summary can be accessed at https://github.com/lindgrengroup/fatdistnGWAS.

ETHICS STATEMENT

The individual studies had previously obtained relevant ethical approval and participant consent. This study complied with all relevant ethical regulations, including the Declaration of Helsinki, and ethical approval for data collection and analysis was obtained by each study from local boards as described in the included GWAS.

ORCID

Sebastian-Edgar Baumeister https://orcid.org/0000-0002-9391-6602
Zoheir Alayash https://orcid.org/0000-0002-6850-5668
Hansjörg Baurecht https://orcid.org/0000-0002-9265-5594
Stefan Lars Reckelkamm https://orcid.org/0000-0002-5273-7288
Birte Holtfreter https://orcid.org/0000-0002-6541-3127
Benjamin Ehmke https://orcid.org/0000-0002-2418-6765
Michael Nolde https://orcid.org/0000-0001-6893-7367

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