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Angaben zur Veröffentlichung / Publication details:

Baumeister, Sebastian Edgar, Dennis Freuer, Hansjörg Baurecht, Stefan Lars Reckelkamm, Benjamin Ehmke, Birte Holtfreter, and Michael Nolde. 2022. "Understanding the consequences of educational inequalities on periodontitis: a Mendelian randomization study." *Journal of Clinical Periodontology* 49 (3): 200–209.
<https://doi.org/10.1111/jcpe.13581>.

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ORIGINAL ARTICLE

Understanding the consequences of educational inequalities on periodontitis: A Mendelian randomization study

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Funding information

The authors did not receive funding for this study.

Abstract

Aim: Higher educational attainment is associated with a lower risk of periodontitis, but the extent to which this association is causal and mediated by intermediate factors is unclear.

Materials and Methods: Using summary data from genetic association studies from up to 1.1 million participants of European descent, univariable and multivariable Mendelian randomization analyses were performed to infer the total effect of educational attainment on periodontitis and to estimate the degree to which income, smoking, alcohol consumption, and body mass index mediate the association.

Results: The odds ratio of periodontitis per 1 standard deviation increment in genetically predicted education was 0.78 (95% CI: 0.68–0.89). The proportions mediated of the total effect of genetically predicted education on periodontitis were 64%, 35%, 15%, and 46% for income, smoking, alcohol consumption, and body mass index, respectively.

Conclusions: Using a genetic instrumental variable approach, this study triangulated evidence from existing observational epidemiological studies and suggested that higher educational attainment lowers periodontitis risk. Measures to reduce the burden of educational disparities in periodontitis risk may tackle downstream risk factors, particularly income, smoking, and obesity.

KEYWORDS

educational attainment, Mendelian randomization, periodontitis, risk factors

Clinical Relevance

Scientific rationale for study: Lower levels of education are related to a higher risk of periodontitis, but it is unclear whether this association is causal and the connecting pathways are unknown.

Birte Holtfreter and Michael Nolde contributed equally to this study.

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Principle findings: Higher education lowers periodontitis risk. Income, smoking, and body weight mediate the effect of education.

Practical implications: Periodontitis attributable to lower levels of education can be reduced by intervening on these risk factors.

1 | INTRODUCTION

Oral conditions disproportionally affect socially disadvantaged members of society. A strong and consistent social gradient exists between socio-economic position and the prevalence and severity of oral diseases (Peres et al., 2019). Socio-economic position refers to the socially derived economic factors that influence what positions individuals or groups hold within the structure of a society and is typically characterized along the dimensions of education, income, and occupational position or prestige (Berkman et al., 2014; Siegrist & Marmot, 2006). Major oral health inequalities prevail along all three dimensions (Borrell & Crawford, 2012; Schwendicke et al., 2015; Singh et al., 2018, 2019). Even in high-income countries where absolute poverty is rare, there is a fine and graduated pattern of disparity in health across the full socio-economic spectrum, suggesting that there is not a threshold of absolute deprivation but rather a linear relation between socio-economic position and health outcomes (Heckman, 2012). Observational research has consistently shown that individuals with lower educational attainment are at increased risk to develop periodontitis and suffer from more rapid progression (Borrell & Crawford, 2012; Schuch et al., 2017; Singh et al., 2019). While there is little controversy that poorly controlled diabetes or smoking causally increase the risk of periodontitis (Chapple et al., 2017), although there is a substantial indication from observational studies, few studies have provided a strong foundation for the causal effect of educational attainment on periodontal disease.

The socio-economic inequalities in oral diseases have been extensively described and are consistent across countries; however, few studies have examined whether socio-economic factors are a cause (rather than merely a correlate) of oral health. Despite recognition of the long-standing history of epidemiological studies, plausible causal inference approaches in this area of research are elusive, and in perennial contention with selection bias, reverse causation, and confounding by unobservables (McMartin & Conley, 2020). Researchers have been able to overcome some of the challenges by taking advantage of natural experiments, such as changes in compulsory schooling laws, desegregation policies, and seasonal breaks in school attendance or natural disasters, to estimate the effects of educational achievements on downstream health outcomes (Galama et al., 2018). One notable exemplar in dental research is a study leveraging the Japanese earthquake and tsunami of 2011 as an instrumental variable (IV) to study the causal effect of socio-economic circumstances on tooth loss (Matsuyama et al., 2017). More recently, studies have attempted to estimate the effect of education on health outcomes using Mendelian randomization (MR; Anderson et al., 2020; Carter et al., 2019; McMartin & Conley, 2020). MR is a form of IV analysis, in which

genetic variants are used as proxies for environmental exposures (Burgess et al., 2019). Because of the random allocation at conception, genetic variants associate with a particular risk factor largely independent of potential confounders that might otherwise bias the association of interest when using observational study data. Genetic variants also cannot be modified by subsequent disease, thereby minimizing potential bias by reverse causation. MR is not used to identify the presence of a genetic effect on a trait but, rather, uses genetic variation as a natural experiment to investigate the causal relationship between phenotypic traits (Davies et al., 2018).

An understanding of the mechanisms underlying the association between educational position and periodontal health is likely to be helpful to address social disparities in periodontitis. Mediation analysis can help identify factors that facilitate the association between education and periodontitis, enabling intervention on modifiable mediators to reduce the effects of lower educational position (T. VanderWeele, 2015). Traditional observational mediation methods use snapshots of risk factors, which could incompletely capture a person's cumulative lifetime exposure (Carter et al., 2019). Multivariable MR for mediation analysis (Burgess, Thompson, et al., 2017) can help uncover the link between educational position and periodontal health that is typically thought to be due to environmental factors, including access to resources, exposure to harmful or stressful environments, and adverse health behaviours, such as smoking, poor diet, and excessive alcohol consumption (Phelan et al., 2010; Watt & Sheiham, 2012; Schuch et al., 2017; Singh et al., 2019). We are interested in the mechanisms or pathways through which educational attainment acts to affect periodontitis. We use MR mediation analysis in an attempt to unpick the total effect of educational attainment on periodontitis risk and determine the connecting pathways. Understanding the structure of this relationship is particularly important because modifying the educational attainment is difficult once adulthood is reached. Mediation analysis can thus help identify modifiable intermediate targets that can enable intervention to mitigate the adverse effects of lower educational attainment.

2 | MATERIALS AND METHODS

The study was conducted using publicly available genome-wide association studies (GWAS) summary data. The study was 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.

2.1 | Data sources

Genetic association estimates for educational attainment were obtained from a Social Science Genetics Association Consortium GWAS meta-analysis of 1,131,881 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. Genetic association estimates for income were obtained from a GWAS of 332,050 European-ancestry individuals in the UK Biobank (Hill et al., 2019). Self-reported household income was collected using a 5-point scale corresponding to the total household income before tax, 1 being less than £18,000, 2 being £18,000–£29,999, 3 being £30,000–£51,999, 4 being £52,000–£100,000, and 5 being greater than £100,000. The GWAS of the number of cigarettes per day included 337,334 individuals from the Sequencing Consortium of Alcohol and Nicotine use (GSCAN), UK Biobank, and 23andMe. Cigarettes per day (referred to hereon as smoking) was defined as the average number of cigarettes smoked per day, either as a current smoker or former smoker (Liu et al., 2019). The GWAS of alcohol consumption was based on the number of drinks consumed per week in 941,280 individuals from several cohorts including 23andMe, UK Biobank, and deCODE. Drinks per week was defined as the number of drinks a study participant reported drinking each week, aggregated across types of alcohol (Liu et al., 2019). Genetic association estimates for body mass index were obtained from the GIANT Consortium GWAS meta-analysis of 806,834 European-ancestry individuals (Pulit et al., 2019). We extracted estimates of the effects of exposure- and mediator-associated variants on periodontitis from a GWAS of European studies contributing to the GeneLifestyle Interactions in Dental Endpoints (GLIDE) consortium, totaling 17,353 clinical periodontitis cases and 28,210 controls (Shungin et al., 2015; Shungin et al., 2019). Periodontitis cases were classified by either the Centers for Disease and Control and Prevention/American Academy of Periodontology (Page & Eke, 2007) or the Community Periodontal Index (CPI; World Health Organization, 2013) case definition (Shungin et al., 2015). More details on the population characteristics and specific trait definitions relating to all these summary genetic association estimates are available in their original publications.

2.2 | Selection of genetic instrumental variables

Single-nucleotide polymorphisms (SNPs) serving as IV in the MR analysis to estimate the total effect of education on periodontitis were selected at genome-wide significance (p -value $< 5 \times 10^{-8}$) and were in pairwise linkage disequilibrium (LD) $r^2 < .001$. To select instruments for mediation analysis, all non-overlapping SNPs for educational attainment or mediators at genome-wide significance were pooled and clumped to pairwise LD $r^2 < .001$. For the analyses performed in this current work, genetic variants from different studies were harmonized by their effects, and exclusions were made for palindromic variants. Only variants for which genetic summary statistics were

available for all the traits being examined in a given analysis were considered. Thus, to maintain consistency in variants used as instrumental variables across different analyses, proxies were not used. The SNP-educational attainment and SNP-periodontitis estimates are provided in Table S1.

2.3 | Statistical analysis

MR applies IV estimation by leveraging genetic information as an effective random source of variation in the exposure such that the source of variation is unrelated to the counterfactual value of the outcome under any particular value of the exposure (Didelez & Sheehan, 2007). The IV approach was developed a century ago and is widely applied in economics (Wooldridge, 2010) and epidemiology (Greenland, 2000; Hernán & Robins, 2006). MR can be used to evaluate a causal effect of an exposure X on an outcome Y even when there is unmeasured confounding or selection bias of the exposure–outcome relationship in non-experimental data. The genetic variants are randomized at conception and therefore largely inherited independently from other variants affecting confounding factors. These variants are also unchanged throughout the lifetime and so are unlikely to be affected by Y , therefore reducing bias from reverse causation. IV estimation can be used to falsify the sharp null hypothesis that there is no effect of the exposure on the outcome for any individual in the study and to quantify the magnitude of the exposure–outcome relationship (Swanson et al., 2018). Three conditions are required for the genetic variant to qualify as a valid IV: (1) the IV G is robustly associated with X (“relevance”); (2) no back-door paths are linking G and Y , for example, no shared causes of G and Y (“exchangeability”); and (3) there are no paths via which G influences Y that do not pass through X (“exclusion restriction”; Labrecque & Swanson, 2018). The IV assumptions can be formalized with directed acyclic graphs (DAGs), following the rules of causal DAGs (Pearl, 2009; Labrecque & Swanson, 2018).

In the causal DAG in Figure 1, G fulfils the IV conditions above with respect to X and Y . These assumptions are all that is needed to evaluate the sharp null hypothesis of no effect in any individual. The sharp null implies that G is d-separated from, and therefore independent of, Y . This sharp null can be assessed even if X is unmeasured since it only requires information on G and Y (Didelez & Sheehan, 2007; T. J. VanderWeele et al., 2014). The standard (univariable) MR analysis can be conducted with either individual-level or summary

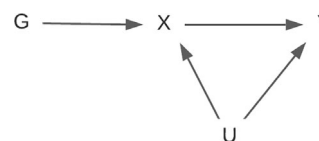


FIGURE 1 Directed acyclic graph showing causal assumptions under which G is a valid instrument for the effect of exposure X on outcome Y , despite the presence of shared common causes U (i.e., unmeasured confounders) of the X – Y association

data from GWAS, which provides the estimated effect of each SNP on X and Y . When genetic, exposure, and binary outcome data are available on the individual level, a two-stage residual inclusion or a logistic structural mean model can be used for IV analysis (Burgess, Small, & Thompson, 2017). In the present two-sample, summary data MR analysis, the total effect of educational attainment on periodontitis was investigated using the Wald ratio method (SNP–outcome estimate divided by the SNP–exposure estimate) with standard errors estimated using the delta method (Burgess, Small, & Thompson, 2017). We used multiplicative random-effects inverse-variance weighted (IVW) meta-analysis to pool the individual SNP effects for estimating the total association of genetically predicted educational attainment on periodontitis risk (Burgess et al., 2019). IVW estimates are presented as odds ratios (OR) per 1 standard deviation (SD) increment in educational attainment (corresponding to a 4.2 year increase in years of education). Following the advice by Burgess et al. (Burgess et al., 2021), we separate the description of MR analysis results from the inference that is made. We, therefore, report on associations of genetically predicted exposure values with an outcome.

For the univariable MR analysis to provide a valid estimate of the exposure on the outcome, the three IV assumptions, outlined above, must be satisfied. To satisfy the first MR assumption, we chose SNPs that were associated with educational attainment at a level of genome-wide significance. To further verify the assumption, we computed the F -statistic and the percentage of variance in educational attainment explained by the variants (Burgess & Thompson, 2011). To verify the second and third MR condition, we examined potential pleiotropy by testing for heterogeneity of the individual SNP effects using the Cochran Q and I_{GX}^2 -statistics, applied the MR Egger intercept test of directional pleiotropy, the global outlier test using the MR Pleiotropy Residual Sum and Outlier (MR-PRESSO), and performed leave-one-out analysis to assess whether the IVW estimate was driven by a single SNP (Hemani et al., 2018; Verbanck et al., 2018). The penalized weighted median, IVW radial regression, and MR-PRESSO were used in sensitivity analyses to explore the robustness of the estimates to potential horizontal pleiotropic effects, which may result from violations of the IV assumptions 2 or 3 (Bowden et al., 2018; Hemani et al., 2018; Verbanck et al., 2018; Slob & Burgess, 2020). The penalized weighted median method gives consistent effect estimates under the assumption that no more than 50% of the weight of the MR effect estimate comes from pleiotropic SNPs, where weight is determined by the strength of their association with the exposure. The contribution of heterogeneous SNP-specific estimates to the overall estimate is further minimized by a penalization parameter. Radial regression uses modified second-order weights to detect and remove outlying SNPs. In MR-PRESSO, the IVW method is implemented by regression, and the residual sum of squares (RSS) is calculated as a heterogeneity measure. If the RSS is decreased compared to a simulated expected distribution, then the SNP is removed from the analysis.

Univariable MR analysis estimates the total effect of X on Y . We additionally performed multivariable MR, an extension of the standard MR approach, to investigate potential intermediate factors that are on the causal pathway from educational attainment to periodontitis.

Mediation analysis can help improve the aetiological understanding and identify variables as potential intervention targets when intervening on an exposure (such as educational attainment in mid-adulthood) is not easily feasible. It allows for the decomposition of a total effect into the direct and indirect effects (T. VanderWeele, 2015). Three parameters are estimated in traditional (observational) mediation analysis: (1) the total effect of X on Y through all pathways; (2) the direct effect, either controlled or natural (the effect of X on Y remaining and acting through other pathways after conditioning on a mediator M); and (3) the indirect effect (the path from X to Y that acts through M). A common approach to estimate the indirect effect in a non-IV observational regression-based mediation analysis is the “difference method” (T. VanderWeele, 2015). The approach first regresses Y on X , adjusting for observed confounders C . The estimated parameter for X from this regression gives the total effect of X on Y . A second model refits the regression after additionally including one or more prespecified mediators as covariates. The estimated parameter for X gives the direct effect of X on Y that does not act through M .

An estimate of the proportion of the total effect that is mediated by the mediators is computed by subtracting the regression coefficient of the second from the coefficient of the first model. Figure 2 provides DAGs of the classical difference-in-coefficients method of mediation analysis for non-experimental data.

We performed MR for mediation analysis to estimate the direct effect of genetically predicted educational attainment on periodontitis that was not mediated by the investigated intermediate factors (Burgess, Thompson, et al., 2017; Carter et al., 2021; Sanderson, 2021). Multivariable MR estimates the direct effect of an exposure, conditioning for one or more mediating traits. The natural direct and

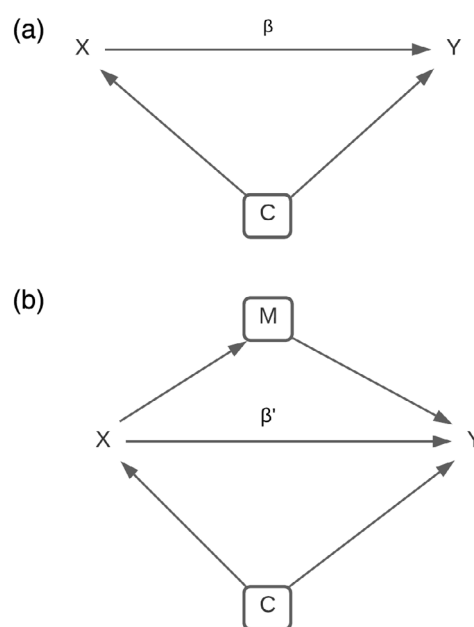


FIGURE 2 Decomposed effects in a non-IV regression-based mediation analysis where β represents the total effect, β' represents the direct effect and the indirect effect can be estimated by subtracting β' from β (difference method)

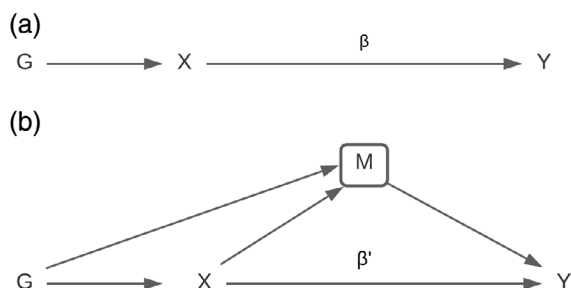


FIGURE 3 (a) Univariable Mendelian randomization for estimating the total effect β . (b) Multivariable Mendelian randomization for estimating the direct effect β'

TABLE 1 Univariable MR analysis for the association of genetically predicted educational attainment on periodontitis

Method	OR	(95% CI)	p-Value
Inverse variance weighted	0.78	(0.68–0.89)	.0004
Penalized weighted median	0.75	(0.59–0.96)	.0242
Radial regression	0.78	(0.68–0.89)	.0004
MR-PRESSO	0.78	(0.68–0.89)	.0004

Note: OR (odds ratio) per 1 standard deviation increase in years of education.

Abbreviations: CI, confidence interval; MR-PRESSO, MR Pleiotropy RESidual Sum and Outlier.

indirect effects when M takes its natural level given X are estimated in multivariable MR (T. VanderWeele, 2015; Carter et al., 2021). It conditions the SNP–exposure effects on their corresponding effects on other putative risk factor traits that are on indirect pathways by regressing the summary genetic associations with the outcomes on the genetic associations with the exposure and mediator(s) using a weighted regression model (Burgess, Thompson, et al., 2017). The genetic variants for X and M are included as IV.

Univariable MR estimates the total effect of X on Y , and multivariable MR estimates the direct effect of X on Y conditional on the mediators. The difference between these estimates gives the

indirect effect of X on Y via the mediators (Figure 3; Sanderson, 2021). When using multivariable MR for mediation, genetic variants included as IV for X and M should be independent (Carter et al., 2021). In contrast, when multivariable MR is used to adjust for horizontal pleiotropic pathways, variants associated with X and the confounder of the X – Y relationship should be included (Sanderson et al., 2019). As with univariable MR, the three IV assumptions are to be satisfied.

The SNP–outcome association estimates were regressed on the SNP–exposure and SNP–mediator estimates, with the intercept fixed at zero, to adjust for genetically predicted income, smoking, alcohol, and body mass index. Figure S1 shows a causal DAG of the mediating pathways. The available empirical evidence for each of the education–mediator and mediator–periodontitis arrows is provided in Table S2. We reported log OR per 1 SD increment in educational attainment after adjustment for mediators separately and together in the same multivariable MR model. We presented log OR as measures for the direct effects because of the non-collapsibility of ORs, meaning that the association between the exposure and outcome would not be constant on the OR scale by strata of covariates (Greenland et al., 1999). Multivariable MR analysis was performed to estimate the proportion of the total effect of education on periodontitis that was mediated through each of the considered mediators, and all mediators combined. In particular, the indirect effect of genetically predicted education on periodontitis was divided by the total effect (Burgess, Thompson, et al., 2017; Carter et al., 2021). The proportions mediated of separate multivariable MR analyses do not necessarily add to 100% owing to possible vertical pleiotropy, where the genetic instrument affects a cascade of mediators along a pathway. We performed the analysis using R version 4.0.5 (R Foundation for Statistical Computing) using the TwoSampleMR (0.5.6), MRPRESSO (1.0), and MendelianRandomization (0.5.1) packages.

3 | RESULTS

Phenotypal descriptive statistics of studies included in the exposure, mediator, and outcome GWAS are provided in Table S3. The sample

TABLE 2 Direct effect of genetically predicted educational attainment on periodontitis, after adjustment for mediators separately and together in the same multivariable MR model

	Log OR	(95% CI)	p-Value	Proportion mediated
Total effect from univariable MR	−0.25	(−0.38 to −0.11)	.0004	–
Direct effect after adjustment for mediator				
Income	−0.09	(−0.26 to 0.08)	.2973	63.6
Cigarettes per day	−0.16	(−0.30 to −0.02)	.0206	35.1
Drinks per week	−0.21	(−0.34 to −0.08)	.0018	14.6
Body mass index	−0.13	(−0.32 to 0.05)	.1594	45.9
All mediators	−0.02	(−0.24 to 0.20)	.8322	90.4

Note: Log odds ratio (OR) per 1 standard deviation increase in years of education. Proportion mediated (as a percentage) computed as indirect effect (log OR total effect – log OR direct effect)/total effect (log OR).

Abbreviation: CI, confidence interval.

size-weighted mean of education was 16.8 years of schooling with an SD of 4.2 years.

The main univariable MR analysis for the total effect showed that higher genetically predicted educational attainment was associated with a reduced periodontitis risk [IVW OR per SD = 0.78; 95% confidence interval (CI): 0.68–0.89; p -value = .0004; Table 1]. The 332 SNPs selected as IVs for educational attainment explained 5.2% of the variance (Table S1). The minimum F -statistic was 29.6. There was no evidence of heterogeneity between Wald ratios in the main IVW analysis for the total effect (Table S4). The intercept estimated from the MR Egger regression was centred around zero and provided no support for unbalanced pleiotropy (Table S4). Using MR-PRESSO, we found no evidence for pleiotropy (p -value global test = .999). IVW leave-one-out analysis did not identify any leverage points with high influence. There was consistent evidence across estimates from IVW, penalized weighted median, radial regression, and MR-PRESSO (Table 1).

There was attenuation in the association between genetically predicted education and periodontitis after adjustment for genetically predicted income, smoking, alcohol consumption, and body mass index (Table 2). The log OR of -0.25 (95% CI: -0.38 to -0.11) for the total effect on periodontitis associated with a 1 SD increment in educational attainment attenuated to -0.09 (95% CI: -0.26 to 0.08) after adjusting for income, to -0.16 (95% CI: -0.30 to -0.02) after adjusting for smoking, to -0.21 (95% CI: -0.34 to -0.08) after adjusting for alcohol, and to -0.13 (95% CI: -0.32 to 0.05) after adjusting for body mass index. Adjusting for all mediators together in the same model, the OR attenuated to -0.02 (95% CI: -0.24 to 0.20). The percentage attenuation in the total effect of genetically predicted educational attainment was 64%, 35%, 15%, and 46%, for income, smoking, alcohol, and body mass index (Table 2). All mediators together accounted for 90% of the total effect of genetically predicted educational attainment on periodontitis risk.

4 | DISCUSSION

Using large-scale genetic association data within an MR framework, we found support for a robust inverse association of higher educational attainment with lower periodontitis risk. The results suggest that most of the total effect of educational attainment on periodontitis is mediated through risk factors. The study supports mechanisms whereby education may be reducing periodontitis risk by facilitating higher income, minimizing exposure to tobacco smoking and alcohol, and reducing excess body weight.

The findings of previous systematic reviews of observational studies suggested that lower socio-economic position increases the risk and progression of periodontitis, regardless of which indicator of socio-economic position is used (Boillot et al., 2011; Borrell & Crawford, 2012; Schuch et al., 2017). Boillot and colleagues pooled confounder-adjusted regression model estimates from two cross-sectional and two longitudinal studies published before 2011 and

reported a summary OR of 0.65 (95% CI: 0.54–0.77) for periodontitis associated with higher compared to lower educational attainment (Boillot et al., 2011). Previous work further suggested pathways connecting educational position and periodontal disease through income, access to dental care, health behaviours, body fat, glycaemic traits, and stress-induced inflammation (Boillot et al., 2011; Schuch et al., 2017; Singh et al., 2019). The level of education attained by an individual captures the aspects of social opportunities for education, and parent's choices and constraints over how they can influence their children's socio-economic circumstances, as education will be a strong determinant of the individual's future employment and income (Klinge & Norlund, 2005; Siegrist & Marmot, 2006; Berkman et al., 2014; Gunderson & Oreopolous, 2020). Income influences health through enabling access to material resources, health insurance, and health services (Pourat et al., 2015; Singh et al., 2019). Income is also assumed to modify health outcomes through stress, locus of control, and health literacy and behaviours (Hill et al., 2019). Systemic reviews concluded that a lower income is associated with a higher risk of periodontal disease (Borrell & Crawford, 2012; Schuch et al., 2017; Singh et al., 2019).

The existing observational literature also clearly demonstrates socio-economic gradients in the potential mediators examined in the present study. Smoking is socio-economically patterned and a well-established risk factor for periodontitis (Hiscock et al., 2012; Leite et al., 2018; Baumeister et al., 2021). Those in higher socio-economic strata are more likely to drink alcohol and tend to drink more excessively (Gilmore et al., 2016). Alcohol consumption is positively associated with periodontitis risk (Pulikkotil et al., 2020; Baumeister et al., 2021). Lower educational attainment has been consistently related to higher obesity risk in developed countries, and there is moderate certainty evidence from observational and MR studies that overweight or obesity is linked to a higher risk of periodontitis (Shungin et al., 2015; Shungin et al., 2019; Jepsen et al., 2020). Health behaviours are an expression of the social circumstances that condition and constrain people's behaviours. People respond to psychological stress and adverse circumstances by smoking, excessive alcohol consumption, risk-taking, and comfort eating (Phelan et al., 2010; Watt & Sheiham, 2012; Deary et al., 2021). The clustering of health behaviours can be viewed as a way in which social groups translate their socio-economic situation into patterns of behaviour, indicating that these behaviours are formed by the social environments and social conditions in which people live. Better social conditions affect access to social networks, social capital, occupations, and living environments that are less stressful and lead to benefits that translate into better oral health by enabling them to act on health-related knowledge about risk and protective factors. People with less optimal social conditions have increased exposure to occupational, environmental, and behavioural health hazards, less sense of control, and chronic stress. Those in lower socio-economic groups are in less favourable material circumstances than higher socio-economic groups and more often tend to engage in damaging health behaviours. The unequal

distribution of these mediating factors is associated with differences that generate oral health inequities (Singh et al., 2019).

Several potential limitations need to be considered. First, our analysis assumes a linear relationship between the risk factors and the outcome. Quantitative estimates may be misleading if the true relationship is non-linear; although estimates are still reflective of the presence and direction of the population-averaged causal effect (Burgess et al., 2020). Second, the genetic associations were drawn from European populations and should be interpreted with caution when extrapolating to other ethnic groups. Third, in the presence of weak instruments, sample overlap in two-sample MR can bias estimates towards the observational estimate. There were no overlapping samples in the univariable MR analysis of educational attainment and periodontitis risk, but there was overlap in the samples used to select IVs for multivariable MR. Given that all IVs in the analysis were strong (associated with the risk factors at p -value $< 5 \times 10^{-8}$; F -statistic > 20), any bias should be minimal (Minelli et al., 2021). Fourth, a theoretical weakness that potentially threatens the validity of all MR studies is bias from undiscovered horizontal (biological) pleiotropy of the genetic variants used as IVs for the phenotypes under study, whereby they may directly affect the outcome through pathways independent of the exposure or mediators being examined. Although horizontal pleiotropy cannot be excluded entirely, it is reassuring that our sensitivity analysis did not indicate pleiotropy, and estimates from pleiotropy-robust and standard IVW analyses were similar. Fifth, there is a potential for dynastic effects, whereby the genotype of the parent, including alleles that are not passed to offspring, influences the phenotype of the offspring ("genetic nurture"; McMartin & Conley, 2020; Deary et al., 2021). This can take the form of parental genetics influencing the environment that a child is raised in and, in turn, affects outcomes, violating the exchangeability assumption. A future MR study on educational attainment and periodontitis conducted within families could avoid issues arising from dynastic effects. Finally, our SNPs instrumented educational attainment assessed using the number of years of schooling at academic institutions. Thus, it is unclear whether the same variants would be associated with skills and values learned outside of formal academic training or other types of formal education (e.g., vocational training).

In conclusion, our MR analyses align with previous observational studies suggesting that educational attainment reduces the risk of periodontitis among individuals of European ancestry. Using the multivariable MR mediation framework, this work further suggests that a majority of the effect of education on periodontitis risk is mediated through income, smoking, and body weight.

ACKNOWLEDGEMENTS

The authors acknowledge and thank the investigators of the original GWAS studies for sharing summary data used in this study.

CONFLICT OF INTEREST

The authors declare no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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

DATA AVAILABILITY STATEMENT

Summary genetic data for educational attainment are available from the Social Science Genetic Association Consortium portal (<https://www.thessgac.org/data>). The periodontitis summary data are available at <https://data.bris.ac.uk/data/dataset/2j2rqgzexlq02oqbb4vmcnc2>. The income summary data can be accessed at <https://www.lothianbirthcohort.ed.ac.uk/content/summary-data-and-other-resources>. The summary statistics for the smoking and alcohol GWAS are available at <https://genome.psych.umn.edu/index.php/>. The body mass index summary can be assessed at <https://github.com/lindgrensgroup/fatdistnGWAS>.

ETHICS STATEMENT

Each of the more than 80 studies contributing to the GWAS meta-analyses obtained informed consent from the study participants. 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 (Lee et al., 2018; Hill et al., 2019; Liu et al., 2019; Pulit et al., 2019; Shungin et al., 2019).

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How to cite this article: Baumeister, S.-E., Freuer, D., Baurecht, H., Reckelkamm, S. L., Ehmke, B., Holtfreter, B., & Nolde, M. (2022). Understanding the consequences of educational inequalities on periodontitis: A Mendelian randomization study. *Journal of Clinical Periodontology*, 49(3), 200–209. <https://doi.org/10.1111/jcpe.13581>