

Causal Protective Effect of Educational Attainment Against Tooth-loss: A Two Sample Mendelian Randomization Study

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Abstract:

Background: Educational level has been associated with dental health outcomes in multiple studies but evidence of a causal role of education in impacting dental health is scarce owing to the difficulty of controlling adequately for multiple potentially confounding environmental variables that may mediate this association as educational attainment is a complex trait. A deeper understanding of whether education plays a causal role in affecting dental health outcomes can enable the development of interventions to aid improvement in dental health. The present study aimed to leverage genome-wide association study (GWAS) outcome data with Mendelian randomization (MR) analysis to analyze the causality and direction of association between educational attainment and dental health outcomes. **Methods:** A two-sample MR analysis was performed using UK biobank GWAS summary statistics for years of education as an exposure dataset and self-reported denture use as a proxy for self-reported tooth loss as an outcome dataset. MR analysis was implemented using the inverse variance weighted method as a primary method. Heterogeneity and directional pleiotropy were assessed, and a leave-one-out analysis was performed to assess the robustness of results. **Results:** MR results using 211 genetic variants as instrumental variables showed a significant protective effect of educational attainment against self-reported tooth loss as indicated by denture use (Inverse variance weighted method (OR= 0.981, 95% CI=0.983-0.979, $p<0.0001$). No significant heterogeneity or directional pleiotropy was noted. MR Steiger's test of directionality verified the causal direction of the exposure leading to the outcome. Leave-one-out analysis showed no disproportionate effect of any single genetic variants. **Conclusion:** By leveraging population-scale GWAS data, MR analysis presented robust evidence that the genetic liability for educational attainment independently plays a causal protective role against self-reported tooth loss as indicated by denture wear.

Keywords:

Mendelian Randomization, Educational Attainment, Tooth Loss, Dental Epidemiology

1. Introduction

Oral diseases, like other diseases, are equally important for individual quality of life [1]. Impaired or lost chewing function caused by oral diseases and consequent tooth loss compromises dietary and nutritional status, leading to adverse health outcomes. Tooth loss also negatively impacts appearance and can adversely affect the psychological health and interpersonal relationships of an individual. Poor oral health conditions, such as dental caries and periodontal disease, also have negative effects on cognition and physical functioning [2].

Socioeconomic status (SES) correlates with health status and an increase in SES is accompanied by a corresponding increase in health status [3]. The relationship between socioeconomic status and health has been explained as higher socioeconomic status improving access to various resources, enabling individuals to protect themselves from disease and preventable death [4,5]. To reduce disparities in oral health and provide greater dental care services for socially disadvantaged groups, it is necessary to understand the specific characteristics and influence of multiple factors on health-related behaviors and outcomes. Identifying factors associated with the occurrence of oral diseases can help healthcare managers and professionals intervene effectively and equitably [6]. Educational level and income are commonly used indicators to measure current socioeconomic status. Each indicator may reflect the common influence of rank ordering of social class and the specific effects of the indicator [7]. Among these, educational attainment is often the first to be obtained in the life course, representing the acquisition of knowledge, and skills to manage the social system to achieve desired goals, and being closely related to lifestyle and behavior [3]. Furthermore, education provides formal qualifications that promote socioeconomic status through occupations and income [7]. Early life conditions including parents' education or occupational status, may be associated with periodontal health (8). Educational level, as a relatively stable and important indicator of socioeconomic status, is easily measured in self-administered questionnaires. However, whether the effects of education on health outcomes are direct or indirect has been a subject of significant debate [9,10]. The indirect effects of education on health may be mediated by income, occupational, and social status among others [11]. In addition, epidemiological models demonstrating the causal effects of education on health outcomes are subject to several inherent biases despite adjusting for confounders [12].

Mendelian randomization (MR) studies offer a means for causality assessment between a modifiable exposure and a clinical outcome in situations where randomized clinical trials cannot be conducted [13,14]. In brief, MR assesses causality by using genetic variants associated with an exposure of interest as proxies for the exposure which averts the issue of confounding by environmental and other modifiable factors [13,14]. The recent accumulation of large publicly available genome-wide association study (GWAS) datasets provides a large number of robust gene-phenotype associations (15) that can be leveraged for MR studies. Multiple GWAS studies have documented genetic variants associated with educational attainment [16,17,18]. Dental caries and periodontal disease are the major causes of tooth loss in humans and are complex, multifactorial diseases also associated with specific genetic variants [19,20,21]. In the present study, we hypothesized that education as an exposure has a causal effect on tooth loss and aimed to conduct a two-sample MR analysis to address the causal role of education on self-reported tooth loss using publicly available large GWAS datasets.

2. Materials and Methods

2.1. Data Sources

Full GWAS summary datasets for exposure and outcome were sought from the MRC IEU Open GWAS project [22]. For the exposure, educational attainment (years of education) the UK Biobank GWAS dataset ID: ebi-a-GCST90029013 from the Loh consortium with a sample size of 461,457, and 11,972,619 SNPs [23] was utilized. The outcome GWAS summary dataset ID was ukb-b-12930, from the MRC IEU consortium, with a sample size of 461,113 with 77,732 cases of dentures, considered indicative of self-reported edentulousness or tooth loss, and included 9,851,867 SNPs [24].

2.2. Selection of Instrumental Variables and MR Analysis Methods

The MR analysis was conducted using ‘TwoSampleMR’ R package and the ‘MRBase’ Web App [25]. Genetic variants were selected as instrumental variables with a genome-wide significance threshold of $5e-8$ for association with the exposure variable. SNPs significantly associated with educational attainment in the exposure dataset were selected as instrumental variables for extraction from the outcome dataset. A minimum linkage disequilibrium R^2 value of 0.8 was applied for linkage disequilibrium proxies. Allele harmonization with pruning of palindromic SNPs was performed. A minor allele frequency threshold up to 0.3 SNPs was allowed for palindromic SNPs. For allele harmonization, alignment was attempted and palindromic SNPs with minor allele frequencies around 0.5 were removed. Significant MR analysis methods included Inverse variance weighted as the primary method as it has been recommended for use with summarized data [26] and MR Egger, Weighted median, and Weighted mode methods were included as additional methods. Odds ratios (OR) and 95% confidence intervals were determined. Heterogeneity was assessed using Cochrane’s Q test with Inverse variance weighted and MR Egger methods. Directional horizontal pleiotropy was assessed using Egger’s regression test intercept and was considered insignificant if $p > 0.05$ [27]. The MR Steiger test of directionality was applied to test the assumption that exposure causes outcome [28]. To identify SNPs that could impact the causal association between educational attainment and tooth loss, leave-one-out analysis was applied by systematically removing individual SNPs and repeating the analysis.

3. Results

A total of 217 SNPs were identified as instrumental variables in the exposure dataset from which 211 instrumental variables were used for MR analysis after harmonization (Supplementary data). The results of the MR analysis are presented in Table 1. Significantly lower OR of self-reported tooth loss for a unit increase in educational attainment was evident (Inverse variance weighted method OR= 0.981 95% CI=0.983-0.979, $p < 0.0001$) and the results were consistent using all the applied methods. A comparison of the results using different methods is depicted in Figure 1 as a scatter plot showing causal estimates for different methods for the associations of 211 genetic variants with educational attainment (exposure) and self-reported tooth loss/denture (outcome).

Table 1. Results of MR analysis for Educational attainment (years of education) as exposure and self-reported tooth-loss as outcome.

Method	Beta	Standard error of Beta	Odds ratio (OR)	95 % Confidence Interval of OR	P value
Exposure: Educational Attainment (years of education); Outcome: Self-reported tooth loss (dentures); Instrumental variables=211					
Inverse variance weighted	-0.019	0.001	0.981	0.983-0.979	<0.0000001
MR Egger	-0.022	0.005	0.979	0.988-0.969	0.0000125
Weighted median	-0.018	0.001	0.982	0.985-0.979	<0.0000001
Weighted mode	-0.018	0.004	0.982	0.990-0.975	0.0000126

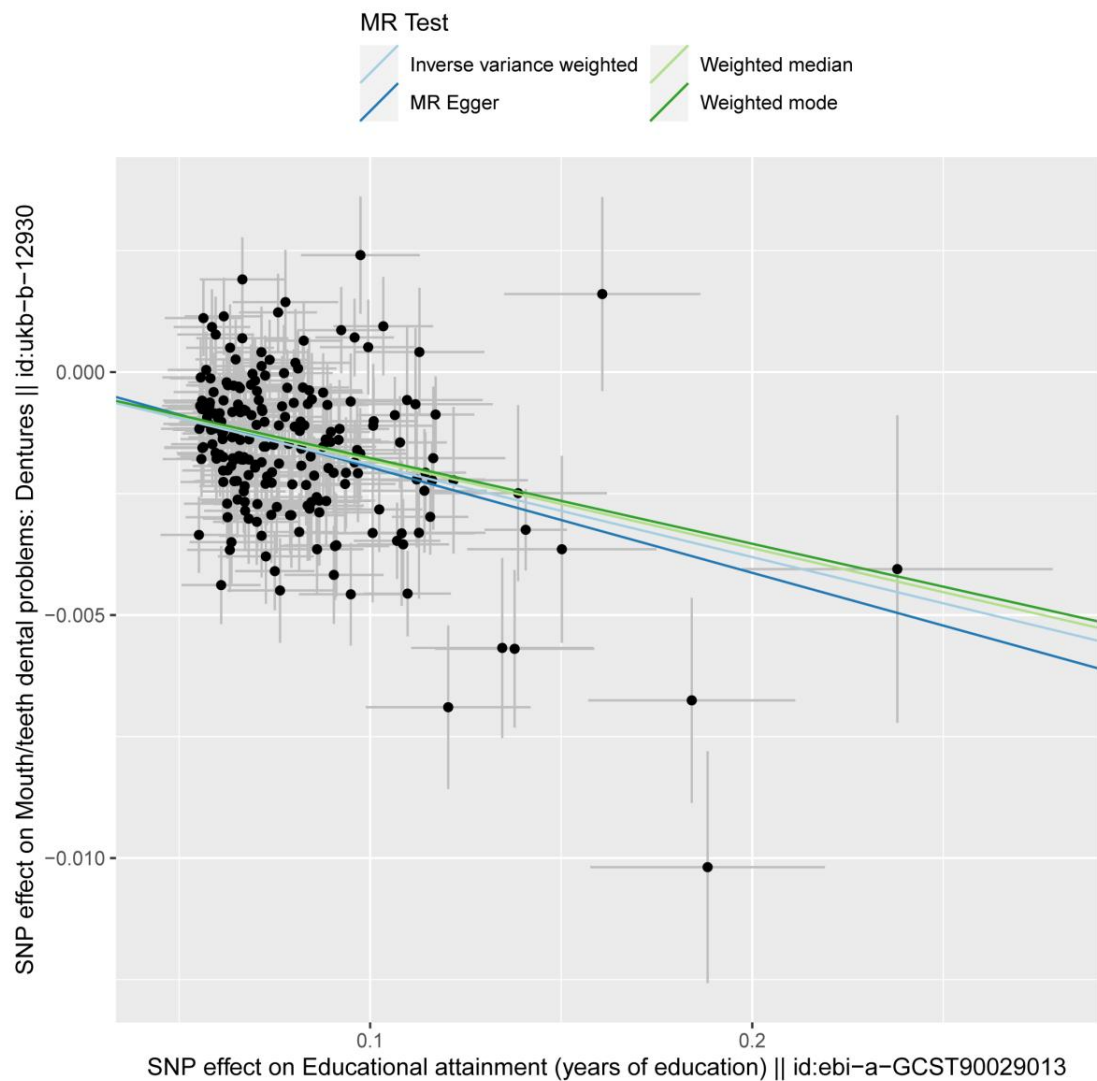


Figure 1. A comparison of MR results using different methods using a scatter plot. Scatterplot of associations of 211 genetic variants selected as instrumental variable with educational attainment (exposure) and self-reported tooth loss/denture (outcome).

Heterogeneity tests showed non-significant results suggesting a lack of significant heterogeneity (MR Egger method: $Q=418.27$, $p<0.000001$; Inverse variance weighted method: $Q=418.9246$, $p<0.000001$). Horizontal pleiotropy was assessed using MR Egger's regression test and showed the absence of significant pleiotropy (Egger's intercept= 0.00021, $SE= 0.00037$, $p=0.57$). A funnel plot depicted in Figure 2 showed a symmetrical pattern consistent with the absence of significant directional pleiotropy and the robustness of the results.

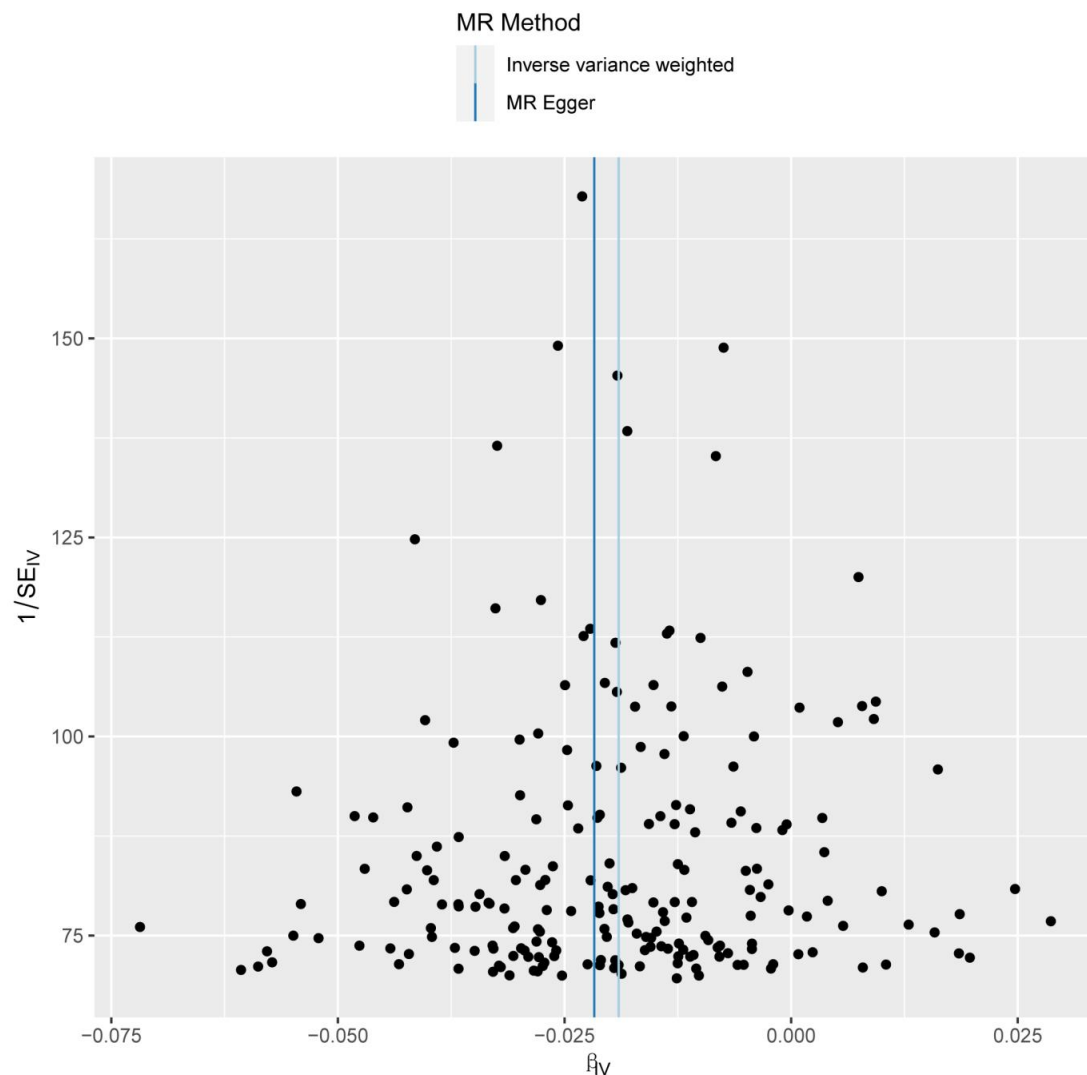


Figure 2. Funnel plot depicts the estimate for each genetic variant instrumental variable against the precision using Inverse variance weighted and MR Egger methods and shows symmetry. *SE:* standard error; *IV:* instrumental variable; β : Estimate.

MR Steiger test results showed causality in the selected direction (R squared for exposure= 0.0211; R squared for outcome=0.0022; p value= <0.000001). The 211 instrumental variable genetic variants accounted for $\sim 2\%$ variance in educational attainment and $\sim 0.2\%$ in the outcome. Leave-one-out sensitivity analysis shown in Figure 3 was employed and showed no marked difference in causality estimates indicative of no single SNPs playing a disproportionate role in mediating the effect.

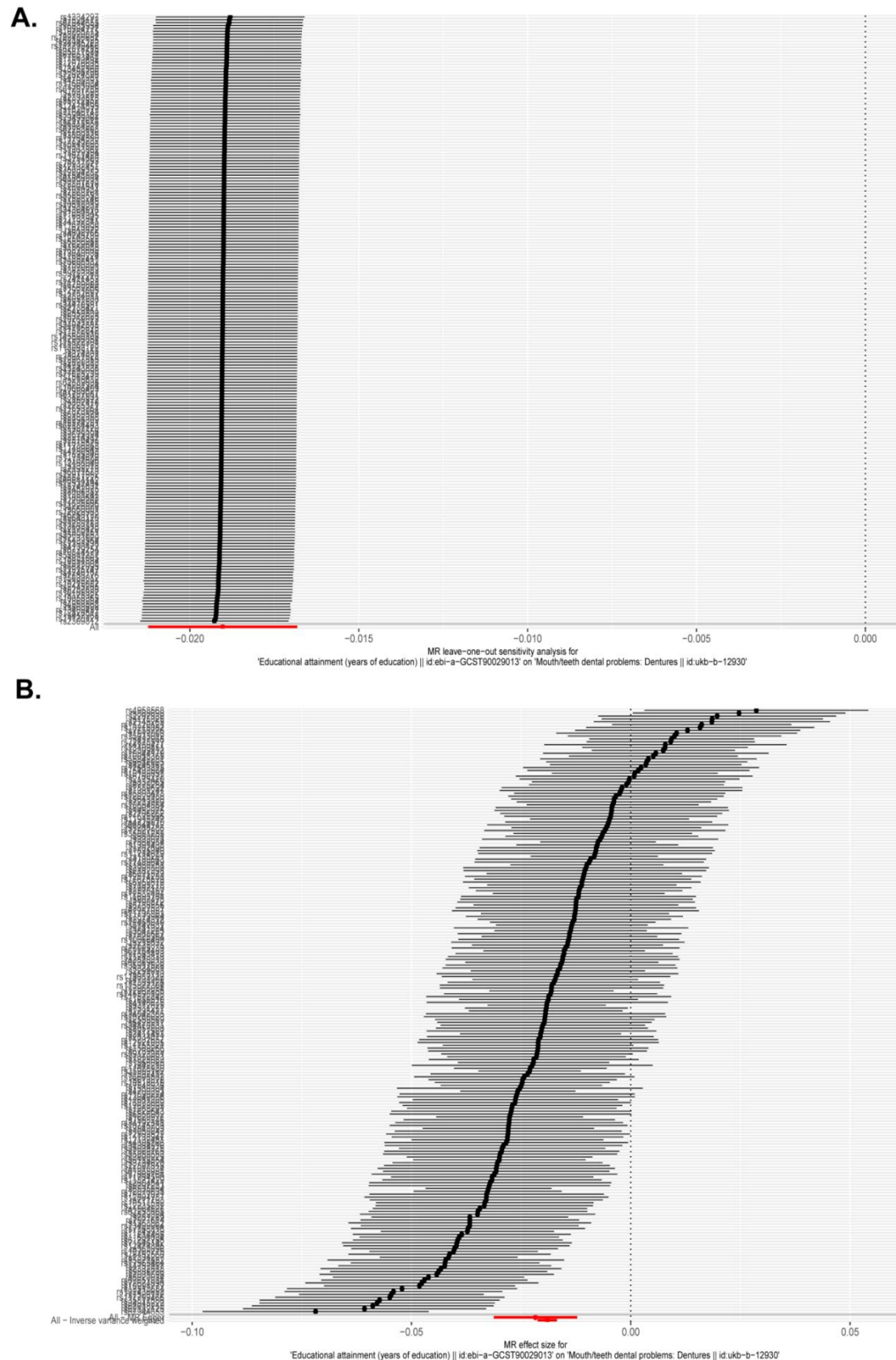


Figure 3. A: Leave-one-out sensitivity analysis. B: Forest plot showing causal estimates using individual SNPs along with that using all the SNPs with MR-Egger and IVW. Error bars show 95% CI.

4. Discussion

In the present study, we identified the causal association of educational attainment with self-reported tooth loss using large population-based cohorts of European ancestry sourced from the UK Biobank and IEU OpenGWAS project. Large GWAS studies have identified several genetic variants associated with educational attainment and owing to allele segregation this association is independent of environmental modifiable influences [29]. Applying two-sample MR analysis we found a protective effect of genetically predicted educational attainment in terms of years of education against self-reported tooth loss as indicated by reported denture use. This study corroborates prior evidence reporting the association of educational status with tooth loss and supports a direct impact of education on protection from tooth loss [30].

Several behavioral factors may account for the causal protective effect of educational attainment against tooth loss. Dental attendance rates have been found positively correlated with educational levels [31], where individuals with lower education levels were found less likely to seek restorative treatments for dental caries [32]. Higher education was also found significantly associated with greater toothbrushing frequency and better oral hygiene habits [33]. Individuals with lower education levels reportedly consume more sugar [34] and have more frequent exposure to active or passive smoking [35]. Additionally, individuals with lower education levels have been found more likely to opt for tooth extraction rather than conservative treatment [36]. This evidence also corroborates broader emerging evidence from MR studies of other health outcomes which demonstrate that genetic liability to educational attainment is causally linked to better health outcomes such as coronary health, certain cancer types, depression, and Type 2 diabetes [37,38,39,40].

At the same time, the analysis is subject to limitations. Previous research has noted that educational attainment is a complex genetic trait subject to large indirect genetic effects and MR analysis from unrelated individuals may be biased owing to this and other effects such as population stratification and geographical variation [41,42]. In addition, while educational attainment as an exposure has been quantified in terms of years of education, the effects of education at different levels are documented as non-uniform [43,44]. For example, tertiary education has shown a greater impact in improving multiple health outcomes [45]. This aspect begets a consideration of functional form in the contextualization of educational attainment as an exposure linked to dental health outcomes. The present MR analysis did not perform multivariable analysis to analyze the influence of factors such as intelligence and cognition which are genetically associated with educational attainment [46,47]. However, the findings of the present study have implications for dental public health policy for dental health promotion by dissecting the role of education as a variable in the genetic and sociodemographic context of tooth loss.

5. Conclusions

In sum, the present study employed MR analysis to show that self-reported tooth loss as indicated by denture use was causally affected by educational attainment or its genetic liability independent of environmental socio-demographic variables, and education has a causal protective effect against tooth loss.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Author Contributions

BL and SL performed the literature search, performed the data analysis, and drafted the manuscript. JD and LJ reviewed and edited the manuscript. SH administered and supervised the whole research project.

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Availability of Data and Materials

The GWAS summary datasets analyzed during the current study are available in the IEU Open GWAS repository at <https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90029013/> and <https://gwas.mrcieu.ac.uk/datasets/ukb-b-12930/>. Data generated during this study are included in the supplementary information files.

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