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Leveraging Mendelian Randomization for Causal Inference in Periodontal Research

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Mini Review

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ABSTRACT

Mendelian Randomization (MR) is an analytical approach assessing the causal inference in putative exposure-outcome pathways by employing genetic variants as proxies for exposures of interest. Due to the randomized allocation of genetic variants, MR is less susceptible to confounding, reverse causation, and measurement error, as compared with conventional epidemiological observational studies. Periodontal disease is a multifactorial inflammatory disorder. The risk factors for periodontal diseases are often identified by epidemiological observational studies, lacking causality. In addition, consistency and sustainability are not established in studies evaluating the effect of periodontal disease on systemic conditions. MR can be therefore leveraged to provide alternative lines of evidence to infer causality in periodontal research. In this review, we will briefly review the recent application of MR in periodontal research. In addition, although we recognize the potential of MR to make a significant impact in periodontal research, we want to stress the importance of triangulation with multiple lines of evidence to draw a conclusion on the cause-effect relationship.

Keywords: Mendelian randomization; Periodontal diseases; Risk factor; Genetic variant

INTRODUCTION

Periodontal diseases, covering gingivitis and periodontitis, are initiated by dysbiotic microbiota. However, it is the host inflammatory response to this microbial challenge that inflicts damage to periodontal tissues. Identifying modifiable risk factors that tip the bone-remodeling balance toward bone resorption is of great importance in the management of periodontitis [1]. On the other hand, periodontal diseases contribute to an increased risk of extra oral diseases [2].

Specifically, well-designed large-scale Randomization Controlled Trials (RCTs) provide evidence of the beneficial effect of periodontal treatment on the reduction of inflammatory biomarkers, improvement of endothelial function, and glycemic control [3,4]. However, consistency and sustainability are not established across RCTs. Alternative lines of evidence are highly warranted to infer causal association in periodontal research, with periodontal disease as either exposure or outcome.

LITERATURE REVIEW

What is mendelian randomization

RCTs are considered the gold standard for testing a causal hypothesis, but they are costly and high risk, and sometimes unethical or unpractical (e.g., it is unethical to randomize the participant into the smoking group to test the causal role of periodontitis). When clinical trials are unavailable, evidence could be obtained from observational epidemiological studies. However, observational findings are prone to confounding and reverse causation, making it difficult to conclude causality. An alternative analytical approach is a Mendelian Randomization (MR). MR assesses the causal inference in putative exposure-outcome pathways by employing genetic variants as proxies for exposures of interest. Since the genetic variants are randomly allocated at conception and fixed throughout life, the major advantages of MR over epidemiological observational studies, are less susceptible to confounding, reverse causation, and measurement error. Indeed, findings from well-performed MR often provide more reliable evidence than traditional epidemiological studies. Moreover, MR can help identify potential risk factors which worth traditionally prioritizing follow-up RCTs [5].

Although MR has many advantages. A valid MR depends on three key assumptions: i) the “relevance” assumption where the genetic variants are robustly associated with the exposure; ii) the “independence” assumption where the genetic variants are not associated with confounding factors; iii) the “exclusion restriction” assumption where the genetic variants do not affect the outcome via some pathways other than the exposure, meaning no horizontal pleiotropy [6,7]. MR estimations are reliable only when these underlying assumptions are adequately satisfied.

With the increasing discovery of Single-Nucleotide Polymorphisms (SNPs) in Genome-Wide Association Studies (GWAS) and the availability of data from global genetic consortia, MR has been widely adopted to examine the causal relationships between modifiable risk factors and disease [8]. Next, we will briefly review the recent application of MR in periodontal research.

DISCUSSION

Application of MR in periodontal research

Obesity: In 2015, a one-sample MR study found no causal association between obesity with periodontitis [9]. However, the wide range of Interval Confidence (CI) suggests the lack of power to detect a small effect. Two-sample MR is superior to one-sample MR in statistical power as it uses two non-overlapping GWAS summary statistics [10]. Within the framework of two-sample MR, our group showed that genetically predicted Body Mass Index (BMI) and Waist Circumference (WC) has a causal effect on periodontitis. Consistently, Li, et al., also found a causal role of BMI and body fat percentage on an increased risk of periodontitis [11,12] . The MR estimates are by observational findings, suggesting that periodontists should raise their awareness when offering treatment to obese individuals.

Glycemic traits: Two-way interaction between periodontitis and Diabetes Mellitus (DM) has been proposed. Hyperglycemia is a major risk factor for the development and progression of the periodontitis, and periodontitis contributes to worsening glycemic control [13]. However, the effect of hyperglycemia on periodontitis is mainly based on observational studies, and inconsistent results were found on whether periodontal treatment favours glycemic control. Our MR estimations reaffirm the causal effect of hyperglycemia on periodontitis, highlighting the importance of glycemic control in the management of periodontal/oral health [14,15]. While on the reverse direction, genetic liability to periodontitis was not causally linked to glycemic traits (fasting glucose, fasting insulin, and HbA1c level) and type 2 diabetes, suggesting the previous observational findings could be biased by confounding factors [16,17].

Cardiovascular disease: The association of periodontal disease with Cardio Vascular Disease (CVD) is evident, however, whether such a relationship is causal is not confirmed. Although many RCTs have shown that periodontal treatment leads to a reduction of inflammatory biomarkers and improvement of surrogate markers for subclinical atherosclerosis, the evidence on the effects of the periodontal intervention on specific CVD events is limited. To date, at least three MR studies have investigated the causal association of periodontitis with CVD [18-21]. However, all of these MR analyses failed to provide robust evidence on the causal impact of periodontitis on CVDs (i.e., stroke and its major subtypes, coronary artery disease, heart failure, and atrial fibrillation) and subclinical atherosclerosis marker (carotid intima-media thickness). Interestingly, one MR study found a causal association of periodontitis with increased blood pressure [22]. Hypertension is a well-known risk factor for CVD. The contribution of periodontitis to hypertension may be so small that a change in CVD risk cannot be detected by current MR approaches.

COVID-19: The coronavirus disease 2019 (COVID-19) pandemic is an infectious disease stemming from the widespread of a novel severe acute respiratory syndrome Corona Virus 2 (SARS-CoV-2). Limited observational studies have identified periodontitis as a potential risk factor for COVID-19. It is infeasible and difficult to conduct a longitudinal study or clinical trial to test whether such an association is causal during the pandemic. We took the advantage of MR and provided robust evidence that periodontitis could account for host susceptibility to COVID-19 and its severity identified by hospitalization and very severe respiratory syndrome. A recent study extended our results by showing the causal inference of gingival cervical fluid Interlukin-1β level on COVID-19 susceptibility [23-26].

Cancer: Observational studies have suggested a positive association between periodontal disease and lung, colorectal, and pancreatic cancers. Additional evidence for a causal association is needed. Corlin, et al., performed an MR study and demonstrated that genetically proxied periodontitis could be associated with colorectal cancer, but not lung and pancreatic cancers. A null association of periodontitis with breast cancer was found in a recent MR study, which contrasts observational findings [27-29].

Social, behavioral and psychological factors: Periodontal disease is an infectious disease initiated by the dysbiotic biofilm, but negative social, behavioral and psychological factors could tip the host-microbial balance toward bone resorption and disease progression. Baumeister and his colleagues have identified higher education attainment could reduce periodontitis risk, which is possibly mediated through downstream factors including income, smoking, and obesity. Furthermore, their group performed a series of MR analyses, suggesting an association of tobacco smoking and alcohol consumption with periodontitis, while no evidence for the detrimental effect of cannabis use. They also found no evidence supporting the bidirectional relationship between periodontitis and depression [31-35].

MR in periodontal research

Several limitations have to be addressed before the interpretation of MR association in periodontal research. First, many MR studies retrieved summary statistics from the meta-analysis GWAS (GeneLifestyle Interactions in Dental Endpoints, GLIDE consortium), in which only one SNP reached genome-wide significance ($P<5 \times 10\text{-}8$) [36]. Accordingly, the genetic instruments used as proxies for periodontitis only explained a very small proportion of the phenotypic variance. As such, the null MR association (when periodontitis was adopted as exposure) does not necessarily mean there is no causal inference of periodontitis on extra-oral diseases. Second, the majority of GWAS are implemented in European ancestry, so the MR estimation may not be generalized to other ethnic groups. Third, the genetic variants represent life-long exposure. Therefore, the MR association is likely to reflect the life-long effect of risk factors on periodontitis, or the life-long effect of periodontitis on systemic disease [37].

CONCLUSION

We are optimistic about the contribution of MR to confirm or contradict the risk factors identified by epidemiological studies, which will offer alternative lines of evidence. MR can also be used to discover novel therapeutic targets on periodontitis that have not been assessed by clinical studies. On the other hand, limited genetic instruments could be an obstacle when assessing the effect of periodontitis on systemic conditions. This is probably due to the heterogenic nature and lack of a unified definition of periodontitis in previous GWAS. Future GWAS with large sample sizes, unified disease definition, and refined phenotype could help identify genetic variants that are strongly associated with periodontitis, boosting the power of MR to detect the effects of periodontitis. Furthermore, it should be emphasized that MR is not a cure-all solution. The most convincing proof of a cause-effect relationship arises when various approaches, each with its drawbacks, all arrive at the same findings. At last, we want to highlight the necessity to conduct intervention trials to confirm the efficacy of prevention strategies based on MR results.

DECLARATIONS

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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