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Periodontitis and Chronic Obstructive Pulmonary Disease: A bidirectional Mendelian randomization study

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Objective: Observational studies have suggested an association between chronic periodontitis (CP) and chronic obstructive pulmonary disease (COPD). This study aimed to determine whether there is a causal relationship between CP and COPD incidence. ***Design***: Two-sample Mendelian Randomization (MR) analysis using summary statistics from two genome-wide association studies (GWASs) of European ancestry. Single nucleotide polymorphisms (SNPs) associated with COPD were obtained from the FinnGen database, which included 16,380,382 SNPs. The diagnosis of COPD was based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD 2023). We also obtained SNPs associated with CP from the FinnGen database, which included 16,380,378 SNPs. ***Results***: Sixteen eligible SNPs were extracted to analyze the causal effect of CP on COPD incidence. There was no causal correlation between CP and COPD using the inverse variance-weighted method (IVW) (OR=0.97, 95%CI= 0.91–1.05; p=0.482). Seven eligible SNPs were extracted to analyze the causal effect of COPD on CP incidence. Again, there was also no causal correlation between using IVW (OR=1.09, 95%CI=0.93–1.28; p=0.279). ***Conclusion***: We did not demonstrate a causal relationship between genetically predicted CP and COPD, or between genetically predicted COPD and CP.

Keywords: *Periodontitis, Chronic obstructive pulmonary disease, Mendelian randomization study*

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the top three causes of death worldwide, behind cardiovascular diseases and neoplasms. COPD is induced by substantial exposure to harmful granules or gas in the environment, allergens, chemical toxins, and cigarette smoke, resulting in airway and/or alveolar abnormalities that trigger progressive respiratory syndrome and incompletely reversible flow limitation (Venkatesan, 2023). Among these factors, cigarette smoke is the most common risk factor. Typically, people with COPD have been exposed to cigarette smoke for several decades and do not experience symptoms of the disease until later in life. Cigarette smoke stimulates inflammatory regurgitation, a driver of COPD pathogenesis (Giordano *et al*., 2022) COPD is often associated with severe comorbidities that affect morbidity and mortality.

Periodontitis is a typical chronic inflammatory disease associated with microorganisms and is among the six most prevalent noncommunicable diseases in the world (CGBD 2017 Oral Disorders Collaborators *et al*., 2020). In chronic periodontitis (CP), ecological dysregulation of the microbiome on the tooth surface triggers inflammation. However, the specific pathogenesis of periodontitis has not yet been fully explained. Smoking is a prominent risk factor for chronic periodontitis through a variety of mechanisms, including inflammation and perturbation of host responses to pathogens, alterations in subgingival microbial communities, and impaired tissue healing potential, all of which can lead to an imbalance of tissue homeostasis (Apatzidou, 2022).

COPD and periodontitis are both inflammatory disorders, with smoking as a common risk factor. Despite epidemiological studies suggesting a link between COPD and CP, such as the research by (Xiong *et al*., 2023) indicating that periodontitis may elevate the risk of developing COPD, a definitive causal relationship between the two has yet to be established. Traditional observational studies are frequently constrained by confounding and bias. Mendelian Randomization (MR), drawing on the principles of genetic inheritance first postulated by Gregor Mendel, harnesses naturally occurring genetic variations to randomly assign individuals to different treatment groups. This random allocation mitigates the influence of confounding factors, thereby enabling more reliable inference of causality (Burgess *et al*., 2023). Consequently, we aimed to determine whether there is a causal relationship between COPD and CP.

Materials and Methods

We performed bidirectional two-Sample MR to infer a causal relationship between COPD and CP incidence. There are 3 fundamental assumptions of MR studies:

1. Relevance: the instrumental variables (IVs) are associated with the exposure of interest;
2. Independence: the IVs are not associated with unmeasured confounders;
3. Exclusion restriction: the IVs influence the outcome only through the risk factor of interest (Burgess *et al.*, 2023).

We used genome-wide association study (GWAS) summary data and extracted single nucleotide polymorphisms

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(SNPs) associated with COPD to investigate the causal effects of CP on COPD incidence. Reverse processes were also conducted to investigate the causal effect of COPD on CP. Multiple MR statistical methods were used to ensure that all the assumptions were met.

We obtained SNPs associated with COPD from the FinnGen database (IEU OpenGWAS project (mrcieu.ac.uk)), which included 16,380,382 SNPs. The diagnosis of COPD was based on the Global Initiative for Chronic Obstructive Lung Disease classification (GOLD, 2023). In addition, we obtained SNPs associated with CP from the FinnGen database, which included 16,380,378 SNPs (Supplementary Table S1 (Available at: https://www.cdhjournal.org/supplementary/a1afa13fd44a277bbc186c0a7c9ae099)).

We selected SNPs that were robustly correlated with exposure as IVs to explore the causal correlation between CP and COPD. There were no SNPs that met the typical significance threshold ($p<5\times10^{-8}$) for CP and few for COPD. We progressively adjusted the threshold of significance to identify more robust instrumental variables, selecting SNPs with a significance threshold of $p<5\times10^{-6}$ for periodontitis and $p<5\times10^{-7}$ for COPD. Our analysis revealed no indications of horizontal pleiotropy. The *F* statistic of each SNP was calculated to confirm the strength of the correlation between the IVs and the exposure. An *F* statistic greater than 10 indicates a robust correlation between the IVs and the exposure (Burgess *et al*., 2011). We clumped selected SNPs to ensure independence among them. The clumping window was set at 10 000 kb, and the threshold of r^2 was set at 0.01 (Burgess *et al*., 2011).

We used the "TwoSampleMR" package in R studio (version 4.3.1) for a two-Sample MR analysis between periodontitis and COPD to detect a causal correlation (Hemani *et al*., 2018). The random-effects inverse variance-weighted method (IVW) was used to assess the causal effect of individual SNPs. MR–Egger, the weighted median, the simple mode, and the weighted mode were used as supplementary analyses methods (Hemani *et al*., 2018). The IVW method allows the presence of heterogeneity among SNPs. Heterogeneity among causal effects of each SNP was evaluated based on Cochran's *Q* test. Heterogeneity was considered as present if $p<0.05$. To adhere to the second and third assumptions, we first used the intercept of MR-Egger regression to evaluate the horizontal pleiotropy of the effect assessment (Xian *et al*., 2023). The weighted median method was also used as it permits unbiased results to be valid for only half the IVs, which allows stronger SNPs to contribute more toward the estimate. To avoid bias caused by a single SNP, we performed leave-one-out analysis by sequentially removing 1 SNP at a time. We applied the mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) test to identify potential outliers (Xian *et al*., 2023).

Results

Seven eligible SNPs with exposure at a significance threshold of p<5×10−7 were extracted to analyze the causal effect of COPD on CP incidence (Supplementary Table S2 (Available at: https://www.cdhjournal.org/supplementary/479341ee227ae150329a5a20ba257c94)). There was also no causal correlation between COPD and CP based on the results of IVW (OR=1.09, 95%CI=0.93–1.28, p=0.279), MR-egger (OR=1.17, 95%CI=0.68–2.01, p=0.598), weighted median (OR=1.10, 95%CI=0.91–1.34, p=0.327), simple mode (OR=1.04, 95%CI=0.78–1.39, p=0.792), weighted mode (OR=1.21, 95%CI=0.96–1.53, p=0.157) (Supplementary Table S3 (Available at: https://www.cdhjournal.org/supplementary/bb37bef5766801bdebcc90a14aa5f45c) and Figure 1). Cochran's Q test did not reveal heterogeneity among these IVs (p=0.93) (Figure S1 and Supplementary Table S4 (Available at: https://www.cdhjournal.org/supplementary/f329091c4688c6a772f58bfc401f5578)). MR-Egger regression did not show horizontal pleiotropy (p=0.805) (Supplementary Table S4 (Available at: https://www.cdhjournal.org/supplementary/2eaf8b58968c572cfc872e551314e3ee)). Leave-one-out analysis showed that the causal estimation of periodontitis was not driven by any single SNP (Figure 2).

Sixteen eligible SNPs were extracted at a significance threshold of $p<5\times10^{-6}$ to analyze the causal effect of CP on COPD (Supplementary Table S2 (Available at: https://www.cdhjournal.org/supplementary/479341ee227ae150329a5a20ba257c94)). There was no causal correlation between the CP and COPD based on the results of IVW (OR=0.97, 95%CI= 0.91–1.05, p=0.482), MR-egger (OR=1.01, 95%CI=0.87–1.19, p=0.859), weighted median (OR=0.98, 95%CI=0.89–1.08, p=0.724), simple mode (OR=0.95, 95%CI=0.8–1.14, p=0.614), weighted mode (OR=0.96, 95%CI=0.81–1.15, p=0.689) (Supplementary Table S3 (Available at: https://www.cdhjournal.org/supplementary/bb37bef5766801bdebcc90a14aa5f45c) and Figure 3). Cochran's Q test did not reveal heterogeneity among these IVs (p=0.89) (Figure S2 and Supplementary Table S4 (Available at: https://www.cdhjournal.org/supplementary/ec35682ae766f9b12dd344fd975b6c69)). MR-Egger regression did not show horizontal pleiotropy (p=0.576) (Supplementary Table S4 (Available at: https://www.cdhjournal.org/supplementary/2eaf8b58968c572cfc872e551314e3ee)). Leave-one-out analysis showed that the causal estimation of periodontitis was not driven by any single SNP (Figure 4).

Discussion

This was the first study to conduct a bidirectional Mendelian randomization study to investigate any causal effect between COPD and chronic periodontitis. This two-sample MR analysis did not reveal COPD to be linked to chronic periodontitis. The reverse MR analysis did not support a causal link between CP and COPD.

These results appear to be at odds with a recent meta-analysis (Molina *et al*., 2023) and a review by Xiong et al. (2023) that concluded that periodontitis is closely associated with COPD. Likewise, a randomized controlled trial found that periodontal treatment improved lung function and reduced the frequency of COPD exacerbations (Zhou *et al*., 2014). A prospective, controlled group trial also reported initial periodontal therapy may reduce the exacerbation frequency in patients with COPD (Kucukcoskun

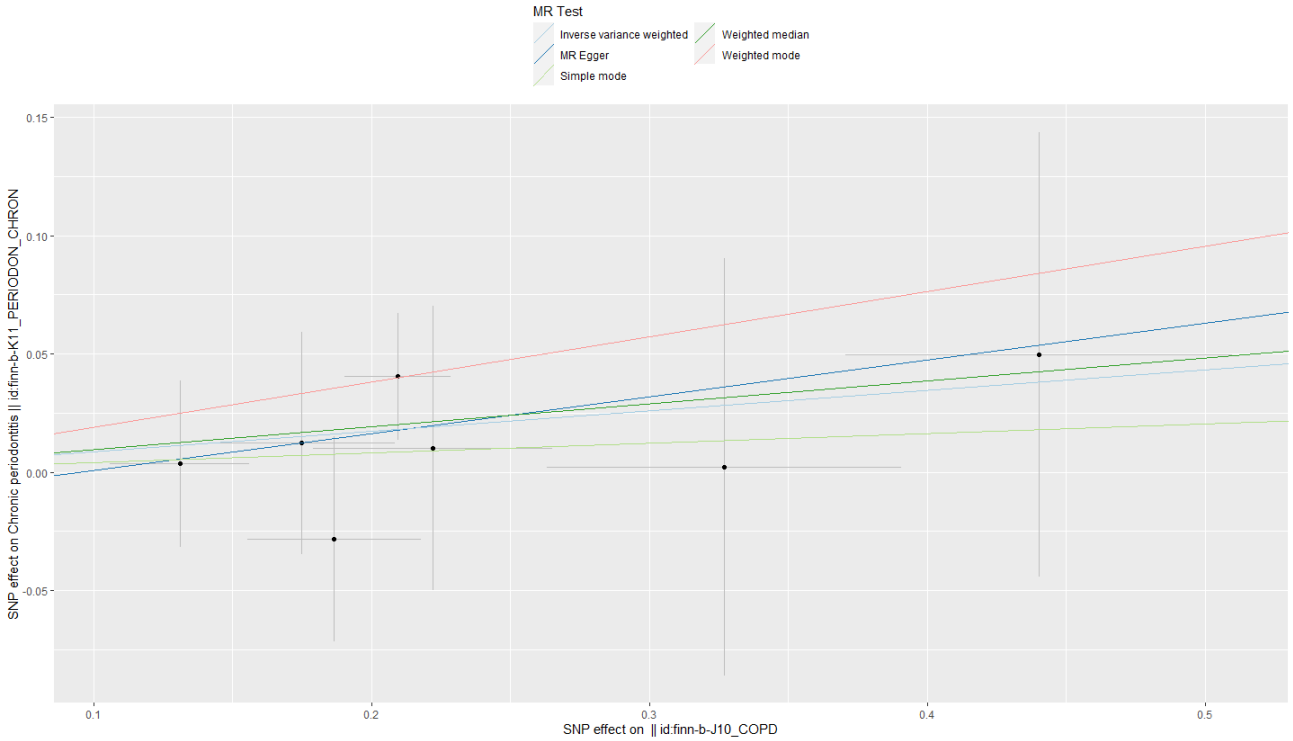

Figure 1. *The results of MR analysis in COPD on CP.*

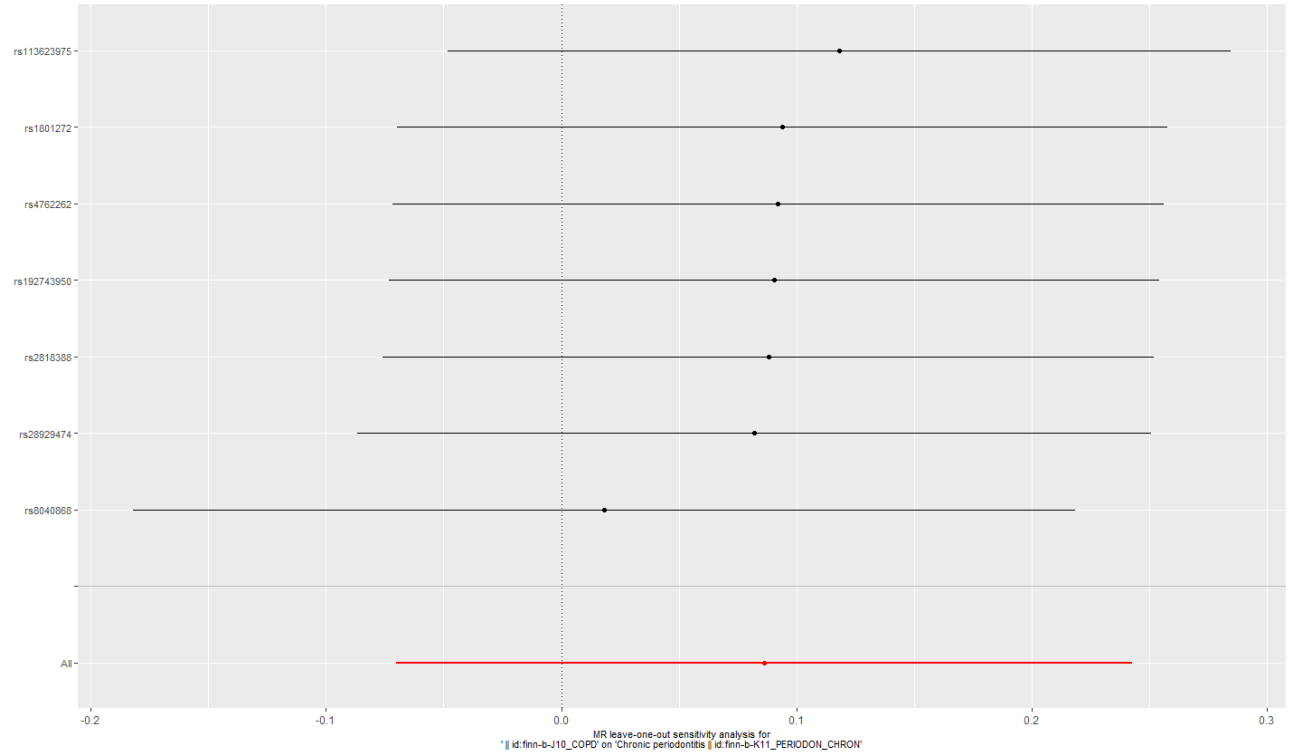

Figure 2. *The results of leave-one-out analysis in COPD on CP.*

et al., 2013). An artificial intelligence-based analysis of NHANES III data indicated that periodontitis might be an important predictor of COPD (Vollmer *et al*., 2022). The risk factors, microbial communication, and pathology, as well as epidemiological and clinical features, are similar between periodontitis and COPD. However, studies with opposite conclusions also exist. A pilot study suggested that periodontal debridement for chronic periodontitis affects quality of life or disease status in patients with COPD (Agado *et al*., 2012). Thus, the relationship between COPD and periodontitis is still controversial.

We did not establish a causal relationship between genetically predicted periodontitis and COPD, nor between genetically predicted COPD and periodontitis. However, previous studies have uncovered a connection between the two from a pathophysiological perspective. Periodontitis and COPD may be associated or several reasons. First, both conditions share common risk factors, including smoking, age, and diabetes mellitus (Molina *et al*., 2023). Second, periodontitis is a chronic infectious disease of the periodontal tissues. The oral cavity is directly connected to the trachea, which increases the risk of pathogenic

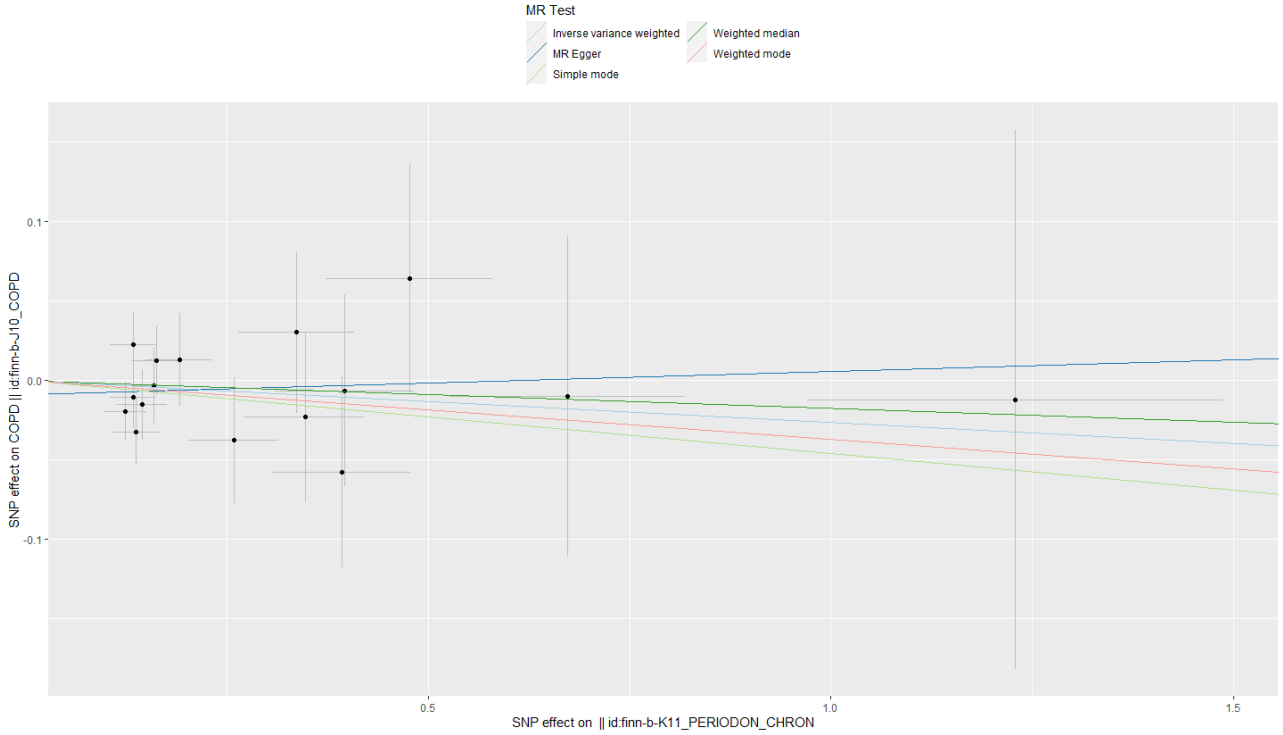

Figure 3. *The results of MR analysis in CP on COPD.*

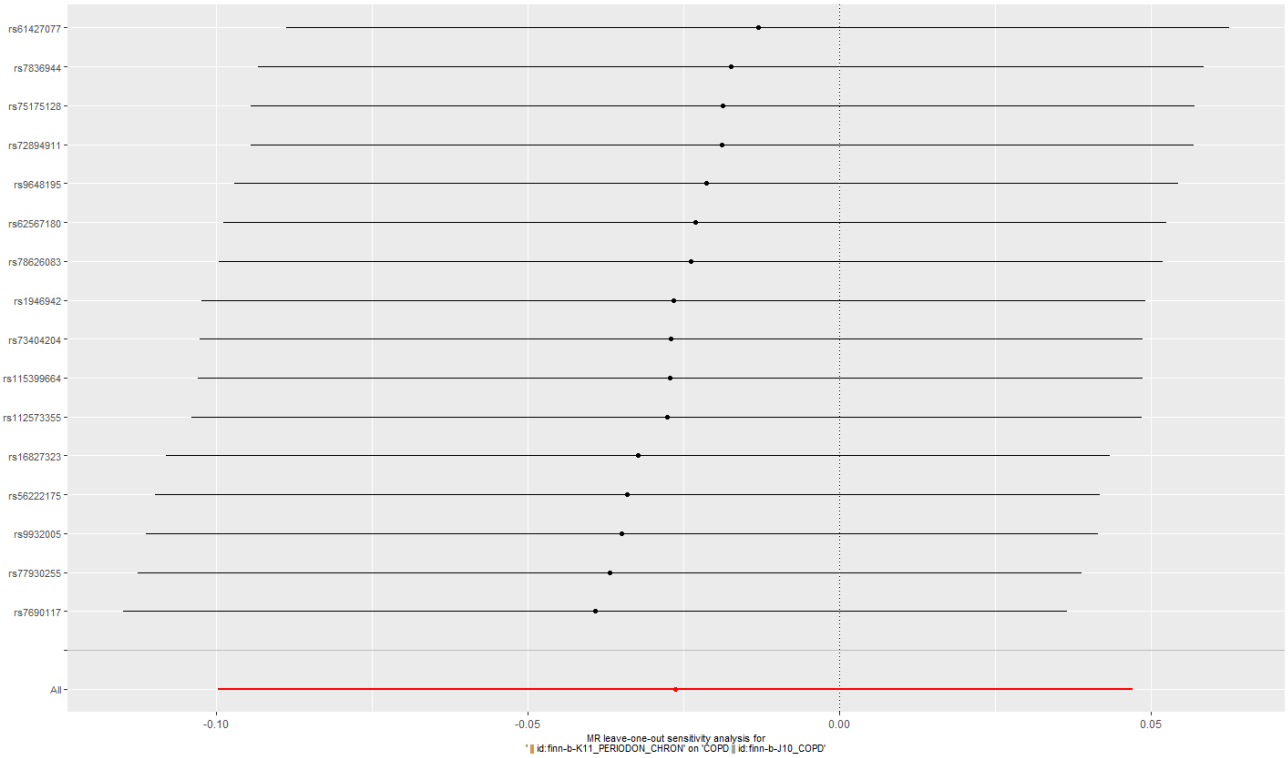

Figure 4. *The results of leave-one-out analysis in CP on COPD.*

microorganisms entering the respiratory tract and causing lung infection. Third, bacterial and viral infections can exacerbate COPD. Oral microorganisms present in patients with periodontitis can be inhaled through oral secretions. Contact with respiratory epithelial cells can induce the production of pro-inflammatory cytokines, which can exacerbate lung inflammation. The number of neutrophils, which are key effector cells involved in inflammation, is elevated in COPD and periodontitis. Th17 cells are immune cells that mediate defence responses when pathogens stimulate periodontal and lung tissues. Activated Th17 cells secrete pro-inflammatory cytokines to activate the Janus Kinase (JAK)/signal transducer and activator of transcription (STAT) signaling cascade (Liu *et al*., 2022). Furthermore, Th17 cells can directly activate the RANK/RANKL signaling pathway to increase the expression of RANKL, thereby stimulating inflammatory bone resorption (Kawai *et al*., 2006). Despite

both COPD and periodontitis involving inflammatory responses, and even sharing common immune pathways, the specific types of inflammatory cells, cytokines, and their interactions may differ significantly, leading to the unique pathological processes of each disease. Moreover, periodontitis is primarily caused by specific bacteria in the oral cavity. Although oral pathogens might be inhaled, damaging the barrier function of the bronchial and alveolar epithelium, allowing viruses and bacteria to invade lung tissue. This invasion could promote the excessive production of mucus in alveoli and bronchial cavities, thereby facilitating the development of COPD. However, if the evidence for this direct link is insufficient, the association between periodontitis and COPD could be considered nonspecific or indirect. Finally, it is widely recognised that oxidative stress is a significant factor in the pathophysiology of periodontitis and COPD. Ferroptosis is closely linked to the establishment of an oxidative stress microenvironment, characterized by the production of reactive oxygen species (ROS) and lipid peroxidation in inflammatory diseases (Zhang *et al*., 2022) hypothesized that ferroptosis promotes the development of periodontitis through oxidative stress-related ROS and nuclear factor kappa -B (NF-κB) -related pathways by synthesizing the bioinformatics data. Recent research has suggested that periodontitis can exacerbate the progression of COPD by promoting ferroptosis (Xiong *et al*., 2023). Deposition of particulate matter, including iron, in the lungs of smokers can cause increased oxidative stress and tissue damage in patients with COPD by disrupting iron homeostasis. These findings help to explain the findings of previous clinical trials that revealed a link between COPD and periodontitis

This research has several strengths. First, the bidirectional analysis ensured that causality between periodontitis and COPD could not be inferred in either direction. Second, large samples minimize the impact of confounding factors on the results. Finally, compared with traditional retrospective research, MRs are more effective at eliminating reverse causality and the effects of confounding factors. Simultaneously, this study has several limitations. The use of SNPs as genetic tools was weakly correlated with periodontitis and COPD, with a *p*-value threshold of less than 1×10^{-6}. The number of instrumental SNPs for COPD was less than 10 in reverse MR analyses. This may affect the statistical efficacy of causal evaluation. Additionally, this study used outcome data from European and American populations, and it is not possible to generalize the conclusions to other racial groups.

In summary, in this study, two-sample MR analysis of data from the GWAS summary database, did not demonstrate a causal relationship between genetically predicted CP and COPD, or between genetically predicted COPD and CP. To verify the results of this study, an updated MR analysis based on pooled data from larger GWASs and additional genetic instruments is warranted.

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Competing interests

No interests.

Author Contribution

MC and SC designed the experiments. YX and LZ searched for articles in the GWAS database. MC and SC wrote the manuscript. JL and HG checked the manuscript. All the authors reviewed and agreed with the content of the manuscript.

Ethics approval and consent to participate

Ethical approval and consent were not specifically for this study as we used summary data that is publicly available.

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