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A Causal Association Study Between Chronic Kidney Disease and Oral Health: A Mendelian Randomization Study

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ABSTRACT

Background and Aims: Previous studies have shown that chronic kidney disease (CKD) can lead to changes in oral health, but the conclusions remain controversial. Thus, we conducted a Mendelian randomization (MR) study from the perspective of genetic analysis to assess the causal association between CKD and oral health conditions, including dental caries, pulp diseases, periapical tissues, and diseases of the gum and periodontal tissues.

Methods: We performed inverse variance weighted (IVW) random effects MR analyses and several sensitivity MR analyses using summary statistics from genome-wide association studies (GWAS). The data were derived from the European population in 2021, which included 3902 cases of CKD, 4170 cases of dental caries, 5354 cases of diseases of the pulp and periapical tissues, and 4120 cases of gingivitis and periodontal diseases.

Results: We found a positive causal relationship between CKD and dental caries, and the effect odds ratio (OR) of CKD on dental caries was 1.368 (95% CI, 1.124–1.664; $p = 0.002$). There was no direct causal relationship between CKD and diseases of the pulp and periapical tissues and diseases of the gum and periodontal tissues, with the effect OR of 1.176 (95% CI, 0.973–1.420; $p = 0.094$) and 1.201 (95% CI, 0.977–1.477; $p = 0.08$).

Conclusions: Our findings suggest that CKD could affect oral health and only with a direct causal link to dental caries. However, pulp diseases, periapical tissues, and diseases of the gum and periodontal tissues have no direct causal relationship.

1 | Introduction

Chronic kidney disease (CKD) has become a global public health problem. Kidney Diseases: A Guide to Improving Global Outcomes defines CKD as "an abnormality in the structure or function of the kidney that persists for more than 3 months and has health implications" [1]. According to the latest estimates, more than 850 million people worldwide suffer from kidney disease [2]. The prevalence of CKD is 9% of the world's population and as high as 12% in some high-income countries [3]. CKD is also one of the fastest-growing causes of death [4]. Additionally, observational studies have shown that CKD can cause systemic changes, including oral changes such as dental caries [5], gingivitis [6], periodontitis [7], enamel hypoplasia, and changes in saliva flow and composition [8, 9]. Notably, the oral effects correspond to the age of the CKD patient and their duration, and the effects include both deciduous teeth and permanent teeth [10]. Thus, proper oral care and preventive measures should be taken to avoid potentially severe oral concerns in patients with CKD. In contrast, oral health problems, such as pain, swelling, infection, and bacteremia, can cause lesions in other body parts and negatively affect quality of life

and systemic health [11]. Therefore, increasing awareness of related oral diseases in patients with CKD, especially those with terminal disease [12], will improve the quality of life of these patients and the effectiveness of multidisciplinary diagnostic and treatment approaches. Currently, there is no definitive consensus regarding the changes in dental caries among patients with CKD. The potential association between diseases of the pulp and periapical tissues and CKD has been rarely investigated, with insufficient evidence available. A limited number of studies have suggested a link between CKD and periodontitis, but the strength of evidence remains weak. Few studies have comprehensively evaluated the association between CKD and oral conditions. Therefore, after retrieving the latest statistical data from genome-wide association studies (GWAS), we conducted Mendelian randomization (MR) analysis, using genetic variation as an instrumental variable. MR analysis is less susceptible to the influence of environmental factors. Utilizing genetic variants as instrumental variables enables the unbiased detection of causal effects, thereby circumventing the confounding factors typically encountered in conventional observational studies. This study hypothesized that there was a potential association between CKD and oral health conditions, including dental caries, diseases of the pulp and periapical tissues, and gingival and periodontal diseases.

2 | Materials and Methods

2.1 | Study Design

Data was derived from the IEU database for the European population, including men and women, in 2021 (Table 1). CKD exposure data included 216,743 subjects (3902 cases and 212,841 controls) and 16,380,459 single-nucleotide polymorphisms (SNPs). Outcome data of oral diseases were from the same population, including 199,565 subjects (dental caries 4170 cases with 16,380,411 SNPs, diseases of the pulp and periapical tissues 5354 cases with 16,380,387 SNPs, gingivitis and periodontal diseases 4120 cases with 16,380,400 SNPs). The analysis in this study was based on individual-level data, with additional details regarding the data provided in the Supporting Information. Following quality control, the causal relationship between CKD and oral diseases was analyzed using MR analyses.

2.2 | Instrumental Variable Selection

We first screened out the SNPs associated with CKD, and their significance threshold was $p < 5 \times 10^{-8}$. The F-statistic was used to assess the strength of genetic variables. When $F > 10$, the correlation was strong, and the analysis results could avoid the influence of weak tool bias. We conducted a linkage disequilibrium threshold of $r^2 < 0.01$ to remove the linkage imbalance in a 500-kb window. These selected SNPs must satisfy three core assumptions. Assumption 1: SNPs significantly correlate with exposure, meaning SNPs could effectively predict exposure. Assumption 2: SNPs must be independent of the outcome. That is, SNPs could only affect the outcome through exposure. Assumption 3: SNPs must be independent of confounding factors associated with exposure or outcomes (Figure 1). To eliminate SNPs that do not meet Assumptions 2 and 3, we conducted separate screening for them through the Phenoscanner database for SNP validation.

2.3 | MR

All analyses were performed in R 4.3.0 using the Two Sample MR package. Five analysis methods were included in the package: inverse variance weighted (IVW), MR Egger, Weighted median, Simple mode, and Weighted mode. Among them, we chose IVW analysis as the primary method to evaluate the causal effect. Other methods were used as complementary methods. When all IVW instruments are valid instrumental variables, the IVW method possesses high statistical power and is capable of more accurately detecting the causal effects between exposure and outcome. In scenarios where there are multiple instrumental variables with small effects, IVW performs robustly, effectively mitigating the undue influence of individual instrumental variables on the results.

TABLE 1 | IEU database details.

	Chronic kidney disease	Dental caries	Diseases of the pulp and periapical tissues	Diseases of the gum and periodontal tissues
Dataset	finn-b-N14_CHRONKIDNEYDIS	finn-b-K11_CARIES	finn-b-K11_PULP_PERIAPICAL	finn-b-K11_GINGIVITIS_PERIODONTAL
Year	2021	2021	2021	2021
Population	European	European	European	European
Sex	Males and females	Males and females	Males and females	Males and females
Case	3902	4170	5354	4120
Control	212,841	195,395	195,395	195,395
Number of SNPs	16,380,459	16,380,411	16,380,387	16,380,400

Abbreviation: SNP, single-nucleotide polymorphism.

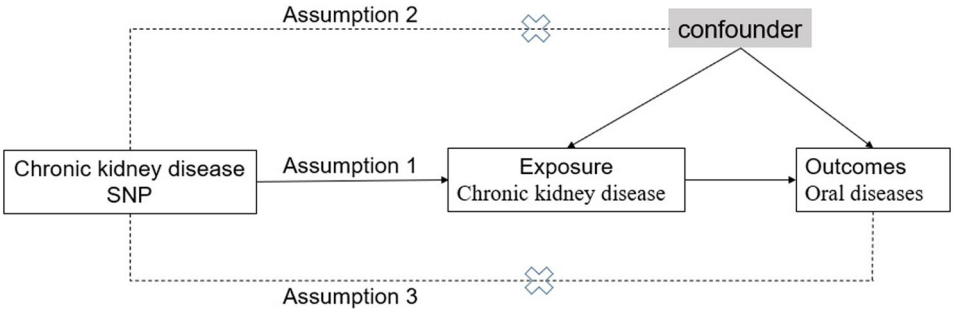

FIGURE 1 | Schematic overview of the SNP selection hypothesis.

2.4 | Sensitivity Analyses

The primary objective of sensitivity analysis is to assess the robustness of the results. We used the MR Egger regression to assess whether directional pleiotropy was present. MR-PRESSO was used to verify the presence of heterogeneity among the instruments. The leave-one-out method was employed to investigate the influence of individual genetic variants on the results, with the aim of assessing the potential undue impact of single genetic variants.

3 | Results

3.1 | Instrumental Variable Selection

Through screening three hypotheses, three SNPs were selected: rs17220157, rs9271365, and rs77924615. The minimum *F*-statistic was 20.3, indicating a strong association with the exposure. By systematically filtering through the PhenoScanner database, it was confirmed that the SNPs influence the outcome solely through the exposure factor, thereby avoiding pleiotropy. Additional details regarding the SNPs can be found in Table S1.

3.2 | MR

In both IVW and Weighted Median analyses, a positive causal relationship was observed between CKD and dental caries. In the IVW analysis, the odds ratio (OR) of CKD on dental caries was 1.368 (95% CI, 1.124–1.664; $p = 0.002$) (Table 2) (Figure 2A). A positive correlation was also between CKD and dental caries ($b = 0.313$). In Weighted median analysis, the OR was 1.292 (95% CI, 1.032–1.616; $p = 0.025$), and CKD was also positively correlated with caries ($b = 0.256$). However, the OR of CKD on diseases of the pulp and periapical tissues and the OR of CKD on diseases of the gum and periodontal tissues were not found to be statistically significant ($p = 0.094$; $p = 0.082$) (Table 2) (Figure 2B,C).

3.3 | Sensitivity Analyses

The results of this study demonstrated robustness, thereby providing robust support for the reliability of the causal effects. Neither horizontal pleiotropy was detected by MR-Egger (Table 3), nor heterogeneity was found by MR-PRESSO detection (Table 3). No significant outlier in the leave-one-out analysis indicated that our causal estimation was not driven by specific SNPs (Figure 3).

4 | Discussion

Our study provides evidence of a direct causal relationship between CKD and dental caries but not between CKD and other oral diseases, such as pulp or periodontal diseases. Integrating the results of MR analysis from a genetic perspective with those of traditional observational studies can provide a more comprehensive exploration of the patterns of disease changes.

This study was the first to find that CKD may directly lead to an increased incidence of dental caries through genetic analysis. However, the relevant clinical studies were still inconclusive. Scholar Kapellas found that a higher proportion of Indigenous Australians with kidney disease had untreated dental caries and a lower rate of tooth restoration [13]. However, other studies have found that patients with CKD had changes in the microbiota, fewer teeth filled, and lower dental caries scores [5]. Similarly, Indian scholars found no significant association between the stage of kidney disease and dental caries, but the dental caries rate in CKD patients was significantly lower than that in the control group [14]. A systematic review and meta-analysis report in 2018 found that CKD patients had lower dental caries scores in 14 studies, but only five studies showed statistically significant differences between observed groups [15]. Another literature review on patients with end-stage kidney disease showed lower salivary flow rates and recorded higher dental caries scores, but no differences were found between groups [16]. However, methodological deficiencies still made the evaluated studies prone to bias. Moreover, the disease's stage or onset could profoundly impact the outcome or detection of the cause. Especially in patients with CKD, subjects receiving different treatment regimens may exhibit various oral manifestations [17]. There is also still a lack of well-designed studies, such as longitudinal and multicenter studies, to fully support this scientific evidence.

The increased risk of dental caries in CKD patients may be associated with altered mineral metabolism, alterations in saliva composition, and reduced salivary flow. In patients with renal dysfunction, vitamin D absorption is reduced, calcium level is reduced, and mineral metabolism is affected [18]. Unfortunately, if the metabolism changes occur at the stage of tooth

TABLE 2 | MR analysis of CKD and oral diseases.

		b	*p* value	OR	OR_lci95	OR_uci95
Dental caries	Inverse variance weighted	0.313	0.002**	1.368	1.124	1.664
	MR Egger	−0.141	0.796	0.869	0.379	1.994
	Weighted median	0.256	0.025*	1.292	1.032	1.616
	Simple mode	0.242	0.249	1.274	0.948	1.712
	Weighted mode	0.224	0.202	1.251	0.990	1.582
Diseases of the pulp and periapical tissues	Inverse variance weighted	0.162	0.094	1.176	0.973	1.420
	MR Egger	0.004	0.996	1.004	0.317	3.181
	Weighted median	0.192	0.039*	1.211	1.009	1.454
	Simple mode	0.285	0.210	1.329	0.979	1.805
	Weighted mode	0.014	0.911	1.014	0.814	1.264
Diseases of the gum and periodontal tissues	Inverse variance weighted	0.183	0.082	1.201	0.977	1.477
	MR Egger	−0.302	0.617	0.739	0.312	1.750
	Weighted median	0.123	0.239	1.131	0.921	1.388
	Simple mode	0.106	0.557	1.112	0.826	1.497
	Weighted mode	0.087	0.557	1.091	0.854	1.394

Abbreviations: SD, standard deviation.
*$p < 0.05$; **$p < 0.01$.

development, it will subsequently affect the formation of tooth hard tissue. Studies have also reported that the incidence of enamel hypoplasia in patients with CKD was higher than that in normal people [15]. Enamel hypocalcification would reduce the resistance to dental caries, which may cause the incidence of dental caries to increase. The permeability of the glomerular filtration membrane increased, resulting in the loss of a large amount of protein in the plasma, causing changes in the composition and secretion of saliva in patients with kidney disease [19]. The decrease in saliva flow reduces the cleaning and scouring effect on the tooth surface, causing plaque accumulation and increasing the possibility of caries. However, it has also been reported that the increase of urea in saliva indirectly caused an increase in saliva pH [20]. If the pH value is maintained above the critical level of enamel demineralization, it may not increase the occurrence of caries.

There is a four-factor theory of caries. That is, time, host, diet, and bacteria jointly determine the occurrence of dental caries [21]. This article did not discuss the host factors determined by time and parental genetics. Patients with CKD should eat a carbohydrate-rich diet to reduce the load on the kidneys, which may increase the risk of tooth decay. The use of glucocorticoids and cytotoxic drugs in CKD treatment has the potential to affect the stability of the oral microenvironment. It has been reported that the number of *Streptococcus mutans*, one of the pathogens causing dental caries, has decreased [22]. Dysbiosis of the microbiota may also be a cause of changes in the oral environment, leading to oral diseases. However, the microbial population is large and complex, and more comprehensive and overall research is still needed. As a comprehensive whole, the final result is the result of multiple interactions between positive and negative feedback loops. Furthermore, our study investigated the direct causal relationship between CKD and dental caries, helping to identify the fundamental problems that lead to the disease and find clear targets to achieve good treatment results.

In this study, no direct relationship was found between diseases of the pulp and periapical tissues and CKD. There are few clinical studies on this issue. It has been reported that pulp necrosis may be the source of systemic microinflammation in patients with CKD [23]. Scholars have also found that the incidence of apical periodontitis was significantly increased in patients with CKD, and there was a correlation between the severity of apical periodontitis and CKD markers, but these findings did not establish a causal relationship [24]. Root canal therapy is a routine treatment for pulpitis and apicitis. A Taiwan report identified that root canal therapy could reduce mortality in patients with end-stage renal disease [25, 26]. Moreover, pulpitis and apical periodontitis occur when dental caries progress to a later stage, mainly because they do not skip dental caries in most cases, except for atretic pulpitis and retrograde periapical periodontitis. However, there is a current lack of research and exploration in this area.

In this study, no direct causal relationship between CKD and gingivitis was found by genetic analysis. There are few clinical studies on the effects of CKD on gingivitis. Some scholars have reported that with the increase in the stage of CKD patients, the gum index would also increase [14]. Studies have shown that some medications taken for kidney disease, such as calcium channel blockers, could cause drug-induced gum hyperplasia [27]. Some patients with end-stage renal disease required

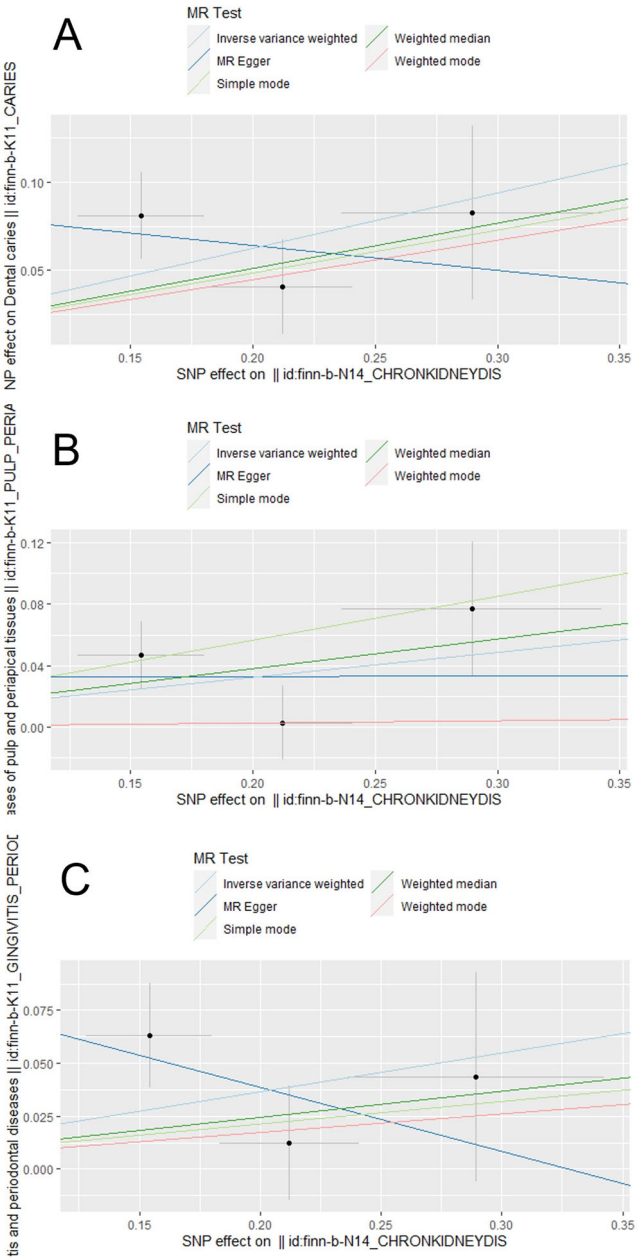

FIGURE 2 | MR analysis of CKD and oral diseases. (A) MR analysis of CKD and dental caries. (B) MR analysis of CKD and diseases of the pulp and periapical tissues. (C) MR analysis of CKD and diseases of the gum and periodontal tissues. The light blue lines were IVW analysis and MR Fitting results. A showed that with the increase of CKD, the risk of caries was also increased, and it was statistically significant.

peritoneal dialysis, and the gum was prone to bleeding and inflammation due to decreased coagulation function [12, 28]. Most studies have shown that gingival inflammation is caused by changes related to CKD, and more extensive research is needed.

A genetic analysis of CKD and periodontitis was done in 2019, and they did not find a causal relationship [29]. Notably, our study reached the same conclusion using updated GWAS data in 2021. Additionally, relevant clinical studies are abundant. According to the latest systematic review analysis in 2023, 60% of these reports showed a link between CKD and periodontitis. The prevalence of periodontitis in patients with CKD varies widely, ranging from 34.35% to 93.65%, and the strength of evidence is low [30]. This can be explained by the different diagnostic criteria and methods used to assess periodontitis.

Although the genetic analysis of CKD could not directly affect the occurrence of periodontitis, the indirect effect of CKD may impact periodontitis. Periodontal disease is a multifactor disease [31]. On the one hand, microorganisms are the starting factor of periodontal disease. It has been reported that increased glomerular filtration rate in CKD patients leads to protein loss, indirectly causing changes in saliva flow rate and composition, which may exert strong selection pressure on oral microbiota and lead to changes in community structure [32]. Changes in the blood composition of patients with CKD indirectly caused changes in saliva pH, which provided more favorable growth conditions for several periodontal pathogens such as *Porphyromonas gingivalis*, *Prevotella intermedia*, and *Clostridium nucleatum* [33]. Shiyuan Guo also found that patients with CKD had increased oral microbial diversity compared to the control group [26]. On the other hand, periodontitis is mainly due to the loss of alveolar bone. Calcium loss in CKD patients is often accompanied by mineral metabolism disorders, affecting all aspects of bone physiology, including bone volume, turnover, and mineralization [34]. It has also been reported that failing kidneys were unable to hydroxyl inactive vitamin D (25-hydroxyvitamin D) into its active form calcitriol (1,25-dihydroxycholecalciferol) [35]. Meanwhile, vitamin D played an important role in the host immune response and was associated with kidney disease and periodontitis [36]. In addition, systemic hypocalcemia and hyperphosphatemia caused by CKD were associated with impaired renal phosphate excretion, leading to the development of periodontal disease [37]. Studies have also revealed an association between CKD patients undergoing hemodialysis and periodontal disease, with alterations observed in their serum biomarkers, such as protein, phosphorus, and calcium [38]. Finding the real cause of the disease, whether direct or indirect, will help us to treat the disease.

Unlike traditional observational epidemiology, MR analysis is less susceptible to environmental factors, and genetic variation as an instrumental variable allows unbiased detection of causal effects. Because alleles are randomly assigned during conception, this random process occurs among individuals with different genetic backgrounds. The confounding factors are evenly distributed among these individuals. The analysis in this paper was carried out using Two Sample MR Software packages, including five analysis methods. Among them, IVW was more suitable for this study as the most effective analysis method, and the other four methods served as supplements [39]. IVW is the most effective analytical method because all variance-weighted inverse variables are effective instrumental variables. The IVW method uses the Wald ratio to correlate individual SNPs and then selects a fixed effects model or random effects model to mate aggregate the effects at multiple sites. When pleiotropy does not exist, the IVW method is more suitable than the MR Egger method. The Weighted median method is a supplement to MR Egger. The weighted median is used to combine data from multiple genetic variations into a single causal estimate, which is a supplement to the MR Egger regression method. Also, it provides stable results provided that at least 50% of the weight comes from a valid Instrumental variable.

TABLE 3 | *p* values of pleiotropy and heterogeneity analysis of CKD and oral diseases.

		Dental caries	Diseases of the pulp and periapical tissues	Diseases of the gum and periodontal tissues
Heterogeneity	MR-PRESSO	0.266	0.084	0.252
	Inverse variance weighted	0.256	0.202	0.224
Pleiotropy	MR Egger	0.470	0.829	0.461

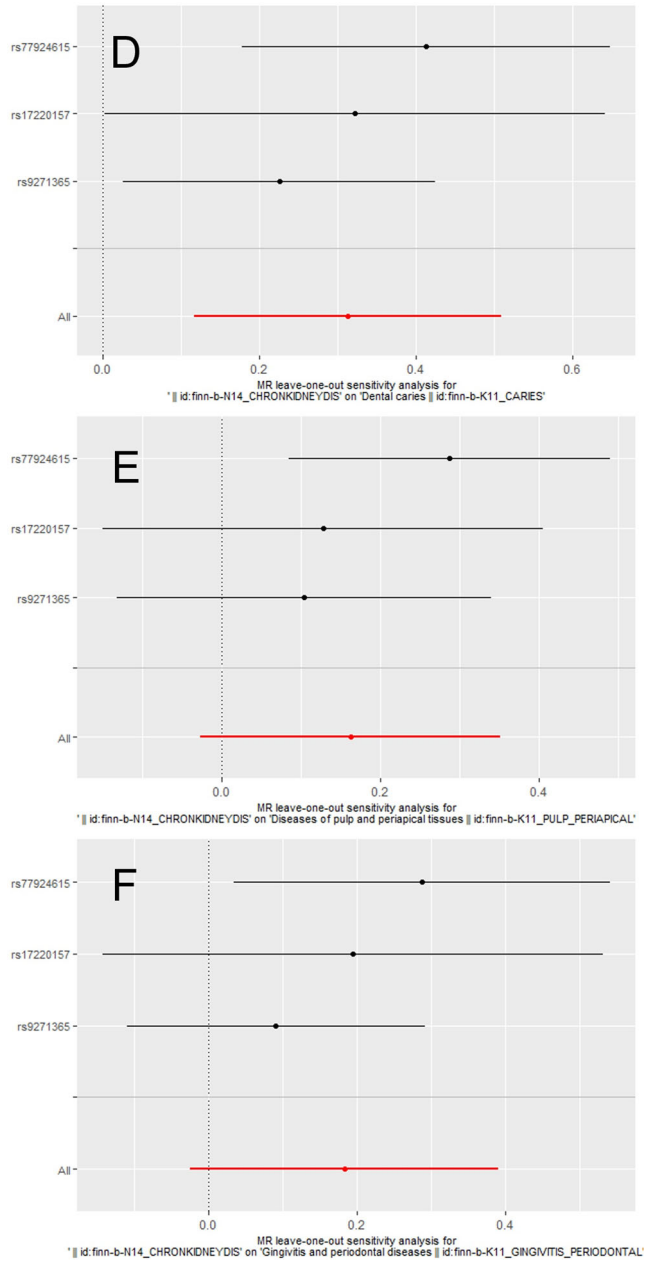

FIGURE 3 | MR leave-one-out sensitivity analysis of CKD and oral diseases. (D) Leave-one-out analysis of CKD and dental caries. (E) Leave-one-out analysis of CKD and diseases of the pulp and periapical tissues. (F) Leave-one-out analysis of CKD and diseases of the gum and periodontal tissues. Leave-one-out analysis showed that the results did not change much after removing any SNP, and the results of MR analysis were robust without potential bias.

In the data on CKD and dental caries, the IVW method showed that CKD would increase the incidence of dental caries, and Weighted median analysis also confirmed this possibility to a certain extent. However, other analytical methods did not find this association. Although other analytical methods were not as suitable and comprehensive as the IVW method, there were still doubts about the association between CKD and dental caries. Therefore, we should look at this problem critically and perhaps design other analytical methods to further study from different perspectives in the future. In the analysis of diseases of the pulp and periapical tissues and diseases of the gum and periodontal tissues, no correlation was found in the five analysis methods, but the possibility could not be completely ruled out.

Our two-sample MR study utilized a wide range of recent GWAS data to explore the oral health status of patients with CKD. However, due to the lack of relevant data on Asian people with CKD, the data on European populations was used in this paper and may be biased. Future studies should include diverse populations to validate these findings. GWAS data are generally large datasets, and with the efforts of scholars around the world, new and more comprehensive data is constantly accumulating. Another disadvantage was that endodontic and periapical diseases were grouped without further detailed grouping when collecting GWAS data, which lacked accuracy to some extent. However, these two diseases belong to a large group of diseases, and the treatment methods are also the same. Furthermore, the practice of data consolidation was acceptable. As such, the data for gingivitis and periodontitis showed a similar pattern. Further exploration is still needed after improving the defects of the data.

5 | Conclusion

In conclusion, our MR study found that CKD may have a direct causal relationship with dental caries but may not have a direct causal relationship with diseases of the pulp and periapical tissues and diseases of the gum and periodontal tissues. The occurrence of diseases results from the combination of direct and indirect factors. Combining MR with observational studies allows an in-depth analysis of the direct and indirect factors contributing to the disease. Future research could further investigate the role of the microbiome and dietary factors in the relationship between CKD and oral health. Therefore, finding targeted approaches will improve the oral health of patients with CKD and the effectiveness of diagnostic and treatment approaches in both disciplines.

Author Contributions

Guilian Zhang: investigation, writing – original draft, methodology, visualization, formal analysis, data curation, validation, resources. **Duojiao Xu:** software, writing – original draft. **Guoxia Yu:** conceptualization, writing – review and editing, funding acquisition, project administration, supervision.

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Ethics Statement

Ethical approval is not required because this study was based on a public GWAS database.

Conflicts of Interest

No conflict of interest exists in the submission of this manuscript, and the manuscript is approved by all authors for publication.

Data Availability Statement

The corresponding author, Guoxia Yu, had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis. These data were derived from the following resources available in the public domain: the IEU Open GWAS project (https://gwas.mrcieu.ac.uk/) and the FinnGen database (https://www.finngen.fi/en).

Reference numbers and their corresponding links are as follows:

Chronic kidney disease (N14_CHRONKIDNEYDIS)

https://risteys.finngen.fi/endpoints/N14_CHRONKIDNEYDIS#dialog-table-case-counts

Dental caries (K11_CARIES_DENTIN)

https://risteys.finngen.fi/endpoints/K11_CARIES_DENTIN

Diseases of pulp and periapical tissues (K11_PULP_PERIAPICAL)

https://risteys.finngen.fi/endpoints/K11_PULP_PERIAPICAL

Gingivitis and periodontal diseases (K11_GINGIVITIS_PERIODONTAL)

https://risteys.finngen.fi/endpoints/K11_GINGIVITIS_PERIODONTAL

Transparency Statement

The lead author, Guoxia Yu, affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.