

## Research Article Periodontal Science



**Received:** May 15, 2022  
**Revised:** Sep 27, 2022  
**Accepted:** Oct 12, 2022  
**Published online:** Nov 16, 2022

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### Conflict of Interest

No potential conflict of interest relevant to this article was reported.

### Author Contributions

Conceptualization: Eun-Kyoung Pang; Formal analysis: Min-Ho Kim, Eun-Kyoung Pang;

# Association of periodontitis with menopause and hormone replacement therapy: a hospital cohort study using a common data model

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## ABSTRACT

**Purpose:** The present study was designed to compare the incidence of periodontitis according to menopausal status and to investigate the possible effect of hormone replacement therapy (HRT) on periodontitis in postmenopausal women using a common data model (CDM) at a single institution.

**Methods:** This study involved retrospective cohort data of 950,751 patients from a 20-year database (2001 to 2020) of Ewha Womans University Mokdong Hospital converted to the Observational Medical Outcomes Partnership CDM. One-way analysis of variance models and the  $\chi^2$  test were used to analyze the statistical differences in patient characteristics among groups. A time-dependent Cox regression analysis was used to calculate hazard ratios and 95% confidence intervals, and *P* values less than 0.05 were considered to indicate statistical significance.

**Results:** Of the 29,729 patients, 1,307 patients were diagnosed with periodontitis and 28,422 patients were not. Periodontitis was significantly more common among postmenopausal patients regardless of HRT status than among the non-menopausal group (*P*<0.05).

Time-dependent Cox regression analysis showed that the postmenopausal patients had a significantly higher chance of having periodontitis than non-menopausal patients (*P*<0.05), but after adjustment for age, body mass index, and smoking status, the difference between the non-menopausal and post-menopausal HRT-treated groups was insignificant (*P*=0.140).

**Conclusions:** Postmenopausal women had a significantly greater risk of periodontitis than non-menopausal women. Additionally, the use of HRT in postmenopausal women could reduce the incidence of periodontitis.

**Keywords:** Hormone replacement therapy; Menopause; Periodontitis

## INTRODUCTION

Menopause is the loss of ovarian follicular function resulting in a permanent termination of menstruation. Menopause is clinically diagnosed after 12 months of amenorrhea [1]. Menopause usually occurs in patients aged 45–55 years, and the estimated median age at

Investigation: Min-Ho Kim, Ki-Yeol Park,  
Eun-Kyoung Pang; Methodology: Min-Ho  
Kim, Ki-Yeol Park, Eun-Kyoung Pang; Project  
administration: Eun-Kyoung Pang; Writing -  
original draft: Ki-Yeol Park; Writing - review &  
editing: Seong-Ho Choi, Eun-Kyoung Pang.

menopause is approximately 51 years [2,3]. Estrogen has been demonstrated to act on the hypothalamus, pituitary, ovaries, and other reproductive organs, and it is also engaged in a variety of non-reproductive processes, such as bone mineral metabolism, immune system function, memory and cognition, and cardiovascular function [4].

After menopause, low estrogen levels cause serious adverse systemic and oral changes, increasing the risk of coronary heart disease, osteoporosis, and other chronic diseases such as arthritis, cognitive decline, Alzheimer disease, tooth loss, and periodontal disease [5]. Estrogen deficiency decreases bone metabolism, causes bone density loss, and affects immunological responses and inflammation, which may cause the bone-resorptive disease periodontal disease [6-11]. Hormone replacement therapy (HRT), which is intended to replace the deficient hormones, has been suggested as a treatment for menopausal symptoms in postmenopausal women, including hot flashes, mood swings, and decreased libido. HRT also reduces loss of bone mass and can prevent postmenopausal osteoporosis [12-14].

Common data models (CDMs), which are standardized data structures defined to efficiently utilize data from multiple hospitals, are increasingly used for worldwide cooperative research. A CDM represents healthcare data from diverse sources in a standardized format, and the integration and standardization of these data sources into the same CDM vocabulary allows for multicenter data analysis in a variety of clinical studies. Use of a CDM avoids certain ethical issues because each institution controls its own data, which is provided in an encrypted format without patient information. Additionally, research with large sample sizes attained through multicenter collaboration and research using diagnosis and prescription codes, including for non-reimbursed items, are both feasible with CDMs. However, additional costs and time are required to convert the data into a standardized format [15-19]. Examples of CDMs include the Observational Medical Outcomes Partnership (OMOP) CDM, the Sentinel CDM, and the National Patient-Centered Clinical Research Network CDM. The OMOP CDM, managed by Observational Health Data Sciences and Informatics, best satisfied the requirements for supporting data sharing from longitudinal electronic health record-based studies because of its superiority in content coverage, case characterization, and data accessibility for researchers [19-21].

According to several studies, postmenopausal women on HRT have greater tooth retention and lower rates of periodontal disease than untreated postmenopausal women, but conflicting findings exist regarding the effect of HRT on periodontal disease. Limitations of previous studies include the inconsistent impact of HRT on periodontal disease as well as small sample size. Additionally, cross-sectional research, including studies with large sample sizes and nationally representative data, is also limited in that cross-sectional causal inference was challenging, data depended on survey questionnaires, or researchers lacked information on diagnostic and drug prescription codes [6,10,11,22-25]. Although various studies have reported the associations among periodontal disease, menopause, and HRT mentioned above, to the best of our knowledge, no longitudinal study using CDM data with a large sample size has been conducted. Therefore, we hypothesized that menopause could be a risk factor for periodontitis and that HRT may reduce the risk of periodontitis in postmenopausal women. In accordance with this hypothesis, the aim of our study was to compare the incidence of periodontitis by menopausal status and to investigate the possible effect of HRT on periodontitis in postmenopausal women using a CDM at a single institution.

## MATERIALS AND METHODS

### Data sources

Our results were obtained from the CDM database of Ewha Womans University Medical Center (EUMC). This database was based on the OMOP CDM (version 5.0) and included data from 2001 to 2020 from 1,931,245 patients. The items present in the CDM data from EUMC included the patient's information; visit record; death record; procedure, drug, and device record; clinical test results; information obtained through surveys, such as family history, smoking, and allergies; and hospital information. The condition occurrence table specified diseases based on International Classification of Diseases, 10th Revision (ICD-10) codes. In this study, diseases were defined as follows: menopause, N950–N959; diabetes, E10–E14; osteoporosis, M80–M82; rheumatism, M05–M06 and M080; and periodontitis, K052–K056. This study was approved by the Institutional Review Board (IRB) of EUMC (IRB number: EUMC 2021-05-033).

### Study design and cohort definition

We conducted this longitudinal cohort study of all outpatients who visited the Department of Obstetrics and Gynecology at Ewha Womans University Mokdong Hospital in Seoul, Korea between January 2001 and December 2020.

Of the 950,751 Korean female patients, 154,958 patients were 40 to 69 years old during the observation period. A total of 7,834 patients were diagnosed with menopause, whereas 147,124 were not. Patients with menopause were identified by diagnosis. After eliminating postmenopausal patients who did not visit the Department of Obstetrics and Gynecology from the total of 147,124 patients, 37,159 individuals remained. Among the 7,834 patients diagnosed with menopause, those who were diagnosed within 1 year of the end of the observation period (the washout period) were excluded. The remaining 5,396 patients consisted of 3,357 patients who received HRT and 2,039 who did not.

For the independent variable, the patients were divided into 3 groups.

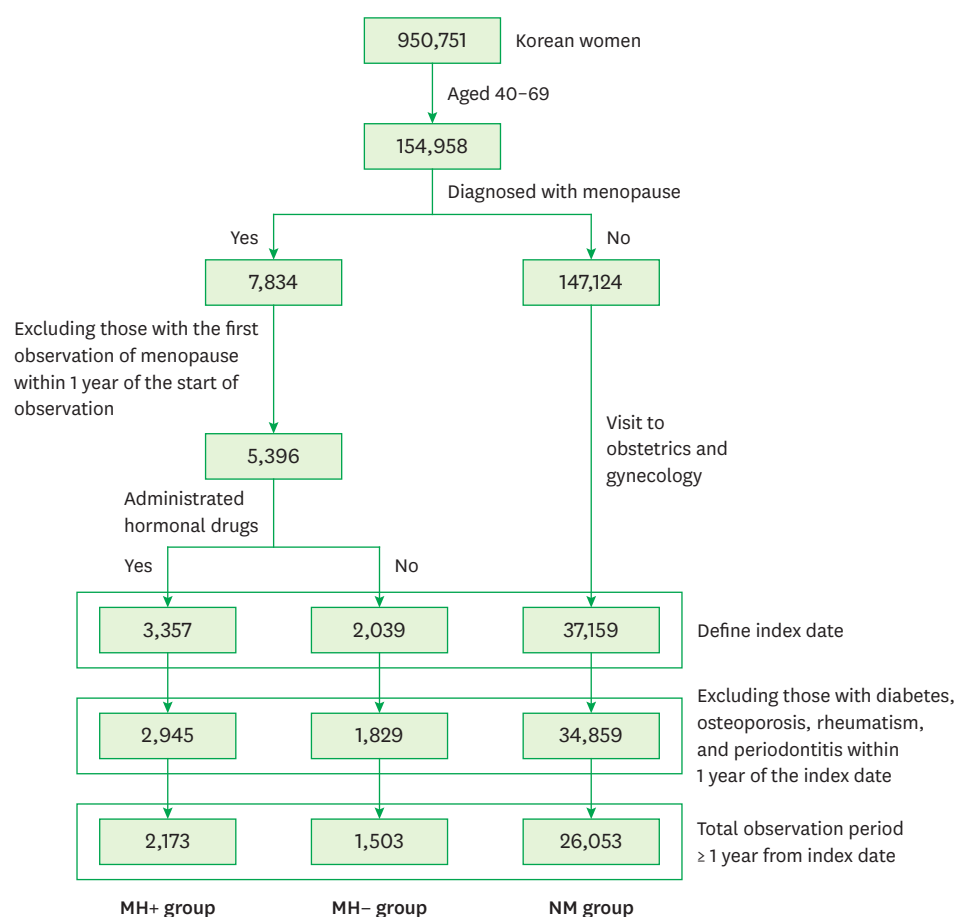
- The NM group included patients who visited Obstetrics and Gynecology but were not diagnosed with menopause.
- The MH+ group included those who were diagnosed with menopause and were administered hormonal drugs.
- The MH– group included those who were diagnosed with menopause and were not administered hormonal drugs.

The NM group's index date was defined as the 365th day from the first visit to Obstetrics and Gynecology. The MH+ group's index date was defined as the date of the first hormonal drug administration. The MH– group's index date was defined as the date when first diagnosed with menopause.

Patients were excluded from any group if they were diagnosed with diabetes, osteoporosis, rheumatism, or periodontitis within 1 year of the index date. Additionally, those whose total observation periods were shorter than 1 year from the index date were excluded. **Figure 1** shows a detailed flow chart of the inclusion and exclusion process for patients in this study.

### Identification of patients with periodontitis and severity classification

Patients with periodontitis were defined by diagnosis, with the first occurrence after the index date considered in cases of multiple occurrences (ICD code K05.2, acute periodontitis;



**Figure 1.** Flow chart of the inclusion and exclusion criteria for the study participants.

NM group: non-menopausal, MH+ group: postmenopausal with hormone replacement therapy, MH- group: postmenopausal without hormone replacement therapy.

K05.3, chronic periodontitis; K05.5, other periodontal diseases; K05.6, periodontal disease unspecified). Patients diagnosed with gingivitis were not included (K05.0, acute gingivitis; K05.1, chronic gingivitis) [26,27].

The periodontitis group was further classified into subgroups (mild, moderate, or severe) based on periodontitis treatment under the assumption that treatment would differ by severity. This was necessary because the CDM data did not include probing depth, bleeding on probing, tooth mobility, or clinical attachment level. Each group was classified by 1 or more of the following procedure codes. The mild periodontitis group included patients who underwent scaling alone after periodontitis diagnosis (H506212, H506212H, H506244, H506244H, H509058, H5090561, J123B, J123C, JEP410R, and JEP410A). The moderate periodontitis group included patients who underwent root planing or subgingival curettage procedures (H506221, H509057, H506231, H506231s, J2240, J2240, J260B1, and J260A2). The severe periodontitis group included patients who underwent the following periodontal procedures: simple or complicated periodontal flap operation (H506351, H506351S, H506353, H506353S, J260C1, and J260C2); periodontal bone graft for alveolar bone defects with an autograft or an allogeneic, xenogeneic, or substitute graft (H506271, H506271S, H506272, H506366, J5071, J5072, J5083, J5083-1, JEP210, and JEP211R); or guided tissue regeneration with or without bone grafting (H506365, H506359, H506365, H506365, J5082,

J5020, JEP310A, JEP310R, J5081, and JEP310B). Because it was not possible to identify whether a tooth extraction was the result of periodontitis, tooth extraction cases were excluded. Patients without a periodontal treatment code were also excluded.

### HRT

The MH+ group included only patients who were exposed to HRT as indicated by prescription codes. HRT was considered to include estrogen or progesterone supplements. Various routes and regimens, such as oral, topical, percutaneous, or transvaginal methods, were included [12,22,28]. In this study, hormone therapy was performed according to patient choice. Although the recent consensus on menopausal hormone therapy indicates that HRT is effective in women under the age of 60 years or within 10 years after menopause, the number of patients refusing HRT has increased due to the controversial relationship between HRT and breast cancer documented in the past. Therefore, if postmenopausal symptoms are severe, HRT is recommended by clinicians, and the final decision is made by the patient [14].

### Statistical analysis

Data were expressed as mean±standard deviation for continuous variables and as number and percentage for categorical variables. One-way analysis of variance models and the  $\chi^2$  test were used to analyze the statistical significance of differences in patient characteristics among the 3 groups.

Kaplan-Meier curves were used to assess the assumption of proportional hazards. Because a crossed line was observed in the Kaplan-Meier curves at around 6 years, time-dependent Cox proportional hazards models were used to avoid deviating from the assumption of proportional hazards and to compare periodontitis incidence. In this study, age at index date, body mass index (BMI), and smoking status were used as confounders in the Cox regression analysis, with BMI chosen based on the suggested positive association between obesity and periodontal disease. BMI was calculated as weight (kg) divided by the square of height (m<sup>2</sup>). Height and weight were calculated as averages of the measured values within 365 days from the index date. Patients were classified by smoking status as nonsmokers, past smokers, or current smokers. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated, and *P* values less than 0.05 were considered to indicate statistical significance. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

## RESULTS

### Demographic distribution according to menopause and HRT status

Of the total database of 1,931,245 patients, 29,729 patients were included in the study. The distribution of these patients by menopause diagnosis and HRT treatment status is illustrated in **Table 1**. Of the 29,729 patients, 3,676 (12.37%) were diagnosed with menopause, of whom 2,173 (7.31%) received HRT and 1,503 (5.06%) did not. The patients' overall average age was 46.04 years, and the average age of each group was 45.00 years (NM), 54.72 years (MH+), and 51.55 years (MH-) (*P*<0.001). Overall, only 7,839 of the patients had a BMI on record. The overall average BMI was 23.18 kg/m<sup>2</sup>, and the average BMI for each group was 23.19 kg/m<sup>2</sup> (NM), 23.08 kg/m<sup>2</sup> (MH+), and 23.16 kg/m<sup>2</sup> (MH-) (*P*=0.787). Only 1,320 of the patients had a smoking status on record. Specifically, 1,000 patients in the NM group, 137 patients in the MH+ group, and 119 patients in the MH- group were nonsmokers. Previous smokers included 27 patients in the NM group, 4 patients in the MH+ group, and 3 patients in the MH- group.

**Table 1.** Demographic distribution by menopause and hormone replacement therapy status

Variables	Total	NM group	MH+ group	MH- group	P value
Total	29,729 (100)	26,053 (87.63)	2,173 (7.31)	1,503 (5.06)	
Age (yr)	46.04±9.73	45.00±9.60	54.72±7.42	51.55±6.26	<0.001
BMI (kg/m <sup>2</sup> )	23.18±3.71	23.19±3.74	23.08±3.35	23.16±3.61	0.787
Smoking					0.690
No	1,256 (95.15)	1,000 (94.88)	137 (96.48)	119 (95.97)	
Past	34 (2.58)	27 (2.56)	4 (2.82)	3 (2.42)	
Current	30 (2.27)	27 (2.56)	1 (0.70)	2 (1.61)	
Periodontitis					<0.001
No	28,422 (95.60)	24,975 (95.86)	2,038 (93.79)	1,409 (93.75)	
Yes	1,307 (4.40)	1,078 (4.14)	135 (6.21)	94 (6.25)	
Severity					0.415
Mild	399 (89.87)	334 (90.03)	36 (83.72)	29 (96.67)	
Moderate	43 (9.68)	35 (9.43)	7 (16.28)	1 (3.33)	
Severe	2 (0.45)	2 (0.54)	0 (0)	0 (0)	

Values are presented as mean±standard deviation or number (%).

BMI: body mass index, NM group: non-menopausal, MH+ group: postmenopausal with hormone replacement therapy, MH- group: postmenopausal without hormone replacement therapy.

Finally, 27 patients in the NM group, 1 patient in the MH+ group, and 2 patients in the MH- group were current smokers ( $P=0.690$ ).

Of the total of 29,729 patients, 1,307 had periodontitis (4.4%), while 28,422 did not (95.6%). In the NM group, 1,078 patients (4.14%) had periodontitis, while 24,975 (95.86%) did not. In the MH+ group, 135 patients (6.21%) had periodontitis and 2,038 patients (93.79%) did not, while in the MH- group, 94 patients (6.25%) had periodontitis and 1,409 patients (93.75%) did not. The incidence of periodontitis was significantly higher in the MH+ (6.21%) and MH- groups (6.25%) than in the NM group (4.14%) ( $P<0.001$ ).

Overall, only 444 patients had periodontal treatment codes recorded; 399 were considered to indicate mild periodontitis, 43 moderate periodontitis, and only 2 severe periodontitis. In the NM group, 334 patients had mild periodontitis, 35 patients had moderate periodontitis, and 2 patients had severe periodontitis. In the MH+ group, 36 patients had mild periodontitis, 7 patients had moderate periodontitis, and no patients had severe periodontitis. In the MH- group, 29 patients had mild periodontitis, 1 patient had moderate periodontitis, and no patients had severe periodontitis ( $P=0.415$ ).

### Observation and survival periods of each cohort group

**Table 2** shows the observation and survival periods by group. The average observation period across all patients was 7.61 years, with a minimum of 1 year and a maximum of 19.11 years. The average observation period by group was 7.69 years for the NM group, 6.98 years for the MH+ group, and 7.17 years for the MH- group. The average survival period for all patients was 11.65 years, with a range of 1.03 years to 19.00 years. By group, the average survival period was 11.85 years for the NM group, 10.69 years for the MH+ group, and 10.80 years for the MH-

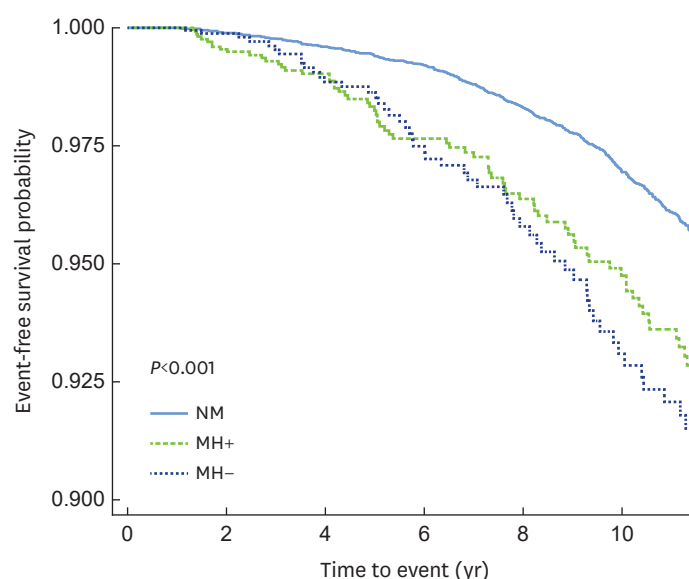
**Table 2.** Observation and survival periods of each cohort group

Periods	Total	NM group	MH+ group	MH- group
Observation period (yr)	7.61 (1.00–19.11)	7.69 (1.00–19.11)	6.98 (1.00–18.87)	7.17 (1.00–18.84)
Survival period (yr)	11.65 (1.03–19.00)	11.85 (1.03–19.00)	10.69 (1.32–18.87)	10.80 (1.17–18.84)

Values are presented as mean (minimum to maximum).

NM group: non-menopausal, MH+ group: postmenopausal with hormone replacement therapy, MH- group: postmenopausal without hormone replacement therapy.





**Figure 2.** Kaplan-Meier curves illustrating survival distributions. Significant differences in survival distributions were found ( $P<0.001$ ). Time to a periodontitis event is shown on the x-axis, while event-free survival probability is shown on the y-axis.

NM group: non-menopausal, MH+ group: postmenopausal with hormone replacement therapy, MH- group: postmenopausal without hormone replacement therapy.

group. To illustrate the survival distributions, Kaplan-Meier curves are provided in **Figure 2**. Time to a periodontitis event is shown on the x-axis, while event-free survival probability is shown on the y-axis. Significant differences in survival distributions were found ( $P<0.001$ ).

### Associations of menopause, HRT, and periodontitis

The distribution of periodontitis by group is shown in **Table 3**. Model 1 (adjusted for age) showed that the MH+ group (HR, 1.414; 95% CI, 1.166–1.714;  $P<0.001$ ) and MH- group (HR, 1.262; 95% CI, 1.013–1.572;  $P=0.038$ ) had significantly elevated likelihoods of periodontitis. Model 2 included only 7,839 patients with a recorded BMI and was adjusted for age and BMI. In model 2, the MH+ group had an elevated likelihood of periodontitis (HR, 1.543; 95% CI, 1.018–2.339;  $P=0.041$ ), but less so than the MH- group (HR, 2.915; 95% CI, 1.933–4.395;  $P<0.001$ ). Only 1,320 patients with a smoking status record were included in model 3, which was adjusted for age, BMI, and smoking status. In model 3, the MH+ group had an increased chance of periodontitis relative to the MN group, but the difference between the groups was insignificant (HR, 1.937; 95% CI, 0.805–4.664;  $P=0.140$ ). The MH- group also had an increased likelihood of periodontitis (HR, 2.666; 95% CI, 1.288–5.521;  $P=0.008$ ).

**Table 3.** HRs and 95% CIs for periodontitis in postmenopausal patients with or without hormone replacement therapy based on a time-dependent Cox regression analysis

Groups	Model 1 (n=29,729)			Model 2 (n=7,839)			Model 3 (n=1,320)		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
NM group	1.000	Reference		1.000	Reference		1.000	Reference	
MH+ group	1.414	1.166–1.714	<0.001	1.543	1.018–2.339	0.041	1.937	0.805–4.664	0.140
MH- group	1.262	1.013–1.572	0.038	2.915	1.933–4.395	<0.001	2.666	1.288–5.521	0.008

Model 1: adjusted for age; Model 2: adjusted for age and body mass index; Model 3: adjusted for age, body mass index, and smoking status.

NM group: non-menopausal, MH+ group: postmenopausal with hormone replacement therapy, MH- group: postmenopausal without hormone replacement therapy, HR: hazard ratio, CI: confidence interval.

## DISCUSSION

In this study, the OMOP CDM database from EUMC was used. In this database, disparate observational databases are systematically combined into a common format using a library of standardized analytic forms. The database contains order communication system and electronic medical record data from EUMC patient records from between 2001 and 2020. The advantage of using a CDM for research is that large-sample cohort studies can be conducted using diagnosis and prescription codes, including for non-reimbursement items. Because postmenopausal HRT is often not fully covered by insurance in South Korea, non-reimbursement medical data may be relevant; therefore, using a CDM to evaluate the effect of HRT on periodontitis may be beneficial. To our knowledge, this is the first observational cohort study to evaluate the causal relationship among menopause, periodontitis, and HRT with large samples and long observation periods.

The results of this cohort study show that the incidence of periodontitis was significantly higher among the postmenopausal patients, regardless of HRT treatment, than among non-menopausal patients. The group receiving HRT had a slightly decreased incidence of periodontitis relative to the group with no HRT administered. Additionally, in the time-dependent Cox regression analysis adjusted for age, BMI, and smoking status (model 3), patients with menopause had an elevated chance of having periodontitis. Notably, however, the difference between the NM and MH+ groups was insignificant ( $P=0.140$ ) in that model, suggesting that HRT may impact the incidence of periodontitis.

Several previous studies have indicated a relationship between menopause and certain periodontal conditions, although the methodologies differed. While some research suggests that menopause is not a significant risk factor for periodontitis, most studies have noted the link between menopause and periodontal disease, and this study supports that link.

Previous studies on the effect of HRT on the relationship between menopause and periodontal disease have also shown inconsistent results. Pizzo et al. [23] indicated that clinical periodontal parameters did not significantly differ by HRT treatment status, and thus HRT could be irrelevant for protection against periodontitis in postmenopausal women. In contrast, Haas et al. [11] suggested that menopause may be a risk factor for periodontal attachment loss and that HRT could have a beneficial effect on periodontal health. Their results indicate that postmenopausal women without hormonal therapy had a greater chance of having periodontitis than premenopausal women. However, postmenopausal women with hormonal therapy had a similar likelihood to premenopausal women. Ronderos et al. [22] investigated the possible association between HRT and periodontal disease using the third United States National Health and Nutrition Examination Survey. They suggested that among women with high calculus scores, those with osteoporosis had an elevated risk of attachment loss, and that risk decreased when estrogen replacement therapy was administered. Grossi [24] found that patients treated with estrogen replacement therapy showed less clinical attachment loss and alveolar bone loss than untreated patients. They suggested that estrogen replacement therapy appears to have a beneficial effect on the severity of periodontal disease. Research using data from the fourth and fifth Korea National Health and Nutrition Examination Survey also supports the relationship between periodontal disease and HRT [25]. The findings of the present study similarly support the hypothesis that HRT impacts postmenopausal women's risk of periodontitis.



This study had several limitations. First, as shown in **Table 1**, significant differences in age were present between the non-menopausal and postmenopausal groups. The younger age of the non-menopausal group could explain why the risk of periodontitis was lower in that group. In addition, the relevant CDM data coverage is still insufficient, and detailed information was not included, such as probing depth, bleeding on probing, clinical attachment loss, and mobility for each tooth. The analysis was therefore based on periodontitis diagnosis. Furthermore, a discrepancy in the number of subjects was present between models in the time-dependent Cox regression analysis because only a limited number of confounders were available, and information about BMI and smoking status was not accessible for all patients. Due to the small number of patients classified by the severity of periodontitis, it also was not possible to analyze the relationship between HRT and periodontitis severity.

In conclusion, despite these limitations, this study revealed that postmenopausal women had a significantly greater risk of periodontitis than non-menopausal women. Additionally, the use of HRT in postmenopausal women could reduce the incidence of periodontitis.

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