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Association between oral health conditions and the risk of major noncommunicable diseases: A protocol for systematic review and meta-analysis

Natchanon Promruck[1,2], Chidchanok Ruengorn[2,3], Kednapa Thavorn[2,4,5,6], Panwadee Bandhaya[1,2] and Surapon Nochaiwong[2,3]

Abstract

Objective: Although epidemiological studies suggest that oral health conditions may be associated with an increased risk of noncommunicable diseases, the findings have yet to be comprehensively synthesized, particularly for a major noncommunicable diseases-related health and economic burden. Therefore, we will perform a systematic review and meta-analysis of all available observational studies investigating the association between oral health conditions and subsequent risk of major noncommunicable diseases.

Methods: With limited English publications, we will search electronic databases, including MEDLINE, Embase, PubMed, Cochrane Library, Scopus, and CINAHL. Based on the temporal properties and natural course of disease progression, we will seek cohort or case–control studies that investigate the association between oral disease conditions and the risk of noncommunicable diseases. Regarding the World Health Organization agenda, oral health conditions will include dental caries, periodontal disease, oral cancer, edentulism, other oral conditions (i.e., oro-dental trauma, cleft lip and palate, and noma), and endodontic lesions. Based on the global disease burden, primary outcomes of interest will include the four major systemic noncommunicable diseases: cardiovascular diseases, cancers, chronic respiratory diseases, and type 2 diabetes mellitus. Random-effects meta-analysis will be used to estimate pooled effects estimate and 95% confidence intervals. Statistical heterogeneity will be investigated using the I^2 index and τ^2 statistics. Preplanned subgroup and sensitivity analyses and random-effects meta-regression analyses will be performed to address possible heterogeneity and establish the robustness of the meta-analytic estimates. The prediction intervals, expected (*E*)-value, and evidence certainty will be appraised to synthesize the findings and draw evidence-based conclusions.

Conclusion: This systematic review will summarize all available evidence regarding the association between oral health conditions and the risk of major noncommunicable diseases. The findings will encourage collaboration between oral health and primary care professionals for early detection and management of noncommunicable diseases and promote oral health well-being.

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[1]Faculty of Dentistry, Department of Restorative Dentistry and Periodontology, Chiang Mai University, Chiang Mai, Thailand
[2]Pharmacoepidemiology and Statistical Research Center, Chiang Mai University, Chiang Mai, Thailand
[3]Faculty of Pharmacy, Department of Pharmaceutical Care, Chiang Mai University, Chiang Mai, Thailand
[4]Ottawa Hospital Research Institute, Ottawa Hospital, Ottawa, ON, Canada
[5]Institute of Clinical and Evaluative Sciences, ICES uOttawa, Ottawa, ON, Canada
[6]Faculty of Medicine, School of Epidemiology and Public Health, University of Ottawa, Ottawa, ON, Canada

Corresponding authors:
Panwadee Bandhaya, Faculty of Dentistry, Department of Restorative Dentistry and Periodontology, Chiang Mai University, Chiang Mai 50200, Thailand.
Email: panwadee.b@cmu.ac.th

Surapon Nochaiwong, Faculty of Pharmacy, Department of Pharmaceutical Care, Chiang Mai University, Suthep Road, Chiang Mai 50200, Thailand.
Email: surapon.nochaiwong@gmail.com

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Noncommunicable diseases, NCD, oral health, public health, systematic review, meta-analysis

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Introduction

In 2022, the World Health Organization (WHO) defined "oral health conditions" as a group of diseases with different causes, epidemiology, disease management, and treatments that affect the oral disease conditions of the worldwide population.[1] Oral health conditions not only significantly strain physical health and economic burdens but also impair the health-related quality of life and mental health well-being of those affected.[2] Globally, it has been estimated that oral health conditions affect approximately 3.5 billion people, mainly in lower- and upper-middle-income countries.[1] Regarding public health concerns, five main oral health conditions include dental caries, severe periodontal disease, edentulism, oral cancer, and other oral conditions (i.e., oro-dental trauma, cleft lip and palate, and noma). However, other oral disease conditions (e.g., endodontic infection) that impact the health of teeth and mouth are not comprehensively estimated.[3]

Over the past decades, literature evidence has suggested that people living with systemic noncommunicable diseases (NCDs) are at risk of oral disease conditions, particularly among those with multimorbidity or limited general health and/or oral health self-care.[4–6] On the contrary, based on the bidirectional association aspect, the causal role of oral health conditions and subsequent risk of NCDs has been suggested in recent years. Although the mechanisms underlying an interconnected between oral diseases and the development of NCDs are not well established, several pathways have been proposed, both biological pathways (e.g., the interaction of oral microbiome and host immune system, bacteria-derived chronic inflammation)[7,8] and non-biological pathways (e.g., social determinants of health inequalities, nutrition, and dietary patterns).[2,9,10] In 2022, the WHO called for urgent action by incorporating oral health conditions into NCDs, public oral healthcare services, and universal health coverage programs.[1,11]

On the basis of the contemporary available systematic reviews regarding the association between oral health conditions and subsequent risk of systemic NCDs, several major limitations have been identified. First, the effect estimates of existing reviews are generally synthesized based on cross-sectional studies or mixed designs,[12–14] which may be subject to judging the evidence-based conclusion regarding the temporal relationship. Moreover, the risk estimates based on a previous umbrella review by Botelho et al.[12] may have been affected by the methodological inconsistencies and the quality of evidence findings, especially those poor methodological designs, relatively small number of longitudinal studies, and heterogeneity of definitions of oral health conditions. Second, previous evidence explicitly focused on particular conditions of oral health or NCDs, with the majority of reviews being focused on periodontitis populations.[12–14] Moreover, evidence regarding these issues has been accumulating, particularly in longitudinal studies, and expanded to other conditions than periodontitis populations. Finally, multiple recent studies in the area of oral health conditions and major NCDs-related health and economic burdens (i.e., cardiovascular diseases, cancers, chronic respiratory diseases, and type 2 diabetes mellitus) have yet to be investigated comprehensively.[12–14] Based on several compelling reasons, we propose to perform a comprehensive systematic review and meta-analysis to reevaluate and summarize all available evidence regarding the association of oral disease conditions and subsequent risk of major systemic NCDs.

Methods and analysis

Protocol and registration

The prespecified protocol for this systematic review and meta-analysis was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42021274184). This study protocol has been drafted and is in line with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) reporting guidance (Supplemental Online, Appendix I).[15] Based on the rationale to conduct the replicate systematic reviews,[16] there is a need for the replication and updated evidence-based to investigate the association of oral disease conditions and subsequent risk of major systemic NCDs (Supplemental Online, Appendix II).

Patient and public involvement

Patients and the public had no role in this study.

Information sources and systematic search strategy

Based on the consultation with the experienced information medical specialist, we will search for English articles in MEDLINE, Embase, PubMed, Cochrane Library (CENTRAL), Scopus, and CINAHL databases from inception. Search strategies will utilize a combination of Medical Subject Headings terms, main keywords, or controlled vocabulary regarding oral health conditions and NCDs (e.g., ("Oral Health," "Dental Caries," "Periodontal Diseases," "Edentulism," "Oral Neoplasm," "Cleft Lip," "Cleft Palate," "Noma," "Maxillofacial Injuries," "Dental Pulp Diseases")

Table 1. Study inclusion/exclusion criteria.

Study elements	Criteria for inclusion	Criteria for exclusion
Populations	• Adult participants aged 18 years or older • Other subgroups analysis will be included if studies provide data to calculate the measure of effect of the outcome of interest	• In vitro or animal studies • Studies including less than 50 participants will be excluded owing to they lacked statistically significant power
Interventions	• Major oral health conditions based on WHO definition, including dental caries (tooth decay), periodontal disease, oral cancer, edentulism, other oral conditions that have public health relevance (oro-dental trauma, cleft lip and palate, noma) and endodontic lesion at baseline	• Unclear definition for each condition • Self-reported status
Comparators	• No major oral health conditions status	• Studies without control groups
Outcomes	• Primary outcomes: Level 1 of NCDs (major NCDs-related health and economic burden ❖Association between oral disease conditions and cardiovascular disease, cancers, chronic respiratory diseases, type 2 diabetes mellitus • Secondary outcomes: Level 2 of NCDs ❖Association between oral health conditions and chronic kidney disease, metabolic syndrome, and rheumatoid arthritis • Additional outcomes ❖Inflammation in diseases (e.g., bleeding on probing) ❖Laboratory markers (e.g., blood glucose level, blood pressure and body mass index)	• Studies not providing data to calculate the measure of effect of the outcome of interest • Unclear definition for each condition • Studies with a follow-up period of less than 3 months
Time frame	• From the inception dates of each database to current (an updated search will be conducted before formal analyses)	• No restrictions were imposed on timing of start date
Study design	• Observational nonrandomized trial (cohort and case–control studies) • Gray literature will be browsed • Studies will be limited to English language	• RCTs design, cross-sectional, N-of-one, case series/case reports, narrative review, systematic review, meta-analysis, guidelines, and opinion/editorials

WHO: world health organization; RCTs: randomized controlled trial.

AND "NCDs"). Vocabulary, syntax, and filters for study design and study population will be applied and adjusted across the selected electronic databases. The predefined search was conducted on 10 October 2023 and cross-checked by two investigators (PB and SN). Details of the search strategy for each database are described in Supplemental, Table S1. To identify all relevant articles, we will also manually search gray literature from Google Scholar, reference lists of included studies, and prior systematic reviews.

Process of study selection and eligible criteria

All retrieved citations will be collated and deduplicated using a citation manager (EndNote). The unique citations will be then uploaded to the Rayyan platform, a web application for systematic reviews.[17] For stage I—screening, a team of investigators (NP and PB) will be screened based on the title/abstract of citations in order of likelihood of inclusion. In stage II, potentially eligible articles will be further independently reviewed in duplicate by a team of investigators based on full-text articles against the inclusion and exclusion criteria (Table 1). Any disagreement will be reached by a team discussion.

Regarding the study eligibility criteria, we predefined the NCDs based on the global disease burden into two levels of outcomes of interest. For level 1 of NCDs (primary outcomes: major NCDs-related health and economic burden), we will include the outcomes of interest, including cardiovascular diseases, cancers, chronic respiratory diseases, and type 2 diabetes mellitus, because these particular groups of diseases account for about 80% of all worldwide premature NCD mortality.[18] Level 2 of NCDs (secondary outcomes) will be other chronic diseases, including chronic kidney disease, metabolic syndrome, and rheumatoid arthritis. Unlike randomized trials and intervention studies, we will include only observational studies (case–control or cohort studies) to draw the evidence findings regarding the natural course of disease progression. Moreover, we excluded evidence from cross-sectional studies, which may be subject to causal relationships as temporal properties of the study design. Details of the eligible criteria based on the population, intervention, comparison, outcome, timing, and setting framework are provided in Table 1.

Data collection and risk of bias assessment

A pilot test of the data collection using a predefined extraction form will be independently performed by two investigators (NP and PB) based on five included studies. We will

then refine the standardized extraction form based on a pilot test data collection accordingly. We will extract data in relation to study characteristics (e.g., study population, study design, study location, sample size, setting, study period, and analysis method); patient characteristics (e.g., number of patients, definitions and criteria of oral health conditions, severity of oral health conditions, age, sex, body mass index, race and ethnicity, comorbid conditions, and laboratory results); outcomes of interests (individual definitions of NCDs and outcomes measurements). In case of missing data or uncertain information, we will email the corresponding author of the particular article for further clarification. However, if the authors do not respond within two attempts, we will report the potentially eligible article as data insufficient, excluded, or handled with imputed information based on the quality of available data. Before the formal analysis, the extracted data will be reviewed and cross-checked by a third party (CR, KT, and SN).

The risk of bias in each included study will be independently appraised by two investigators (NP and PB) and verified by methodologists (CR, KT, and SN) using the Newcastle–Ottawa Scale (NOS).[19] The NOS evaluates the quality of nonrandomized studies based on three domains, including selection (4 points), comparability (2 points), and exposure (for case-control studies; 3 points) or outcome (for cohort studies; 3 points). The summary NOS scores ranged from 0 to 9 points, with the higher scores indicating the higher quality of the study. In this circumstance, the overall risk of bias will be classified as the highest quality if the NOS score is $\geqslant$8 points.[20,21] Any discrepancies in the data collection process and risk of bias assessment will be resolved through team discussion.

Data analysis and evidence synthesis

All analyses and graph visualization will be performed using Stata software version 16.0 (StataCorp LLC, College Station, TX, USA). Two-tailed with p-values less than 0.05 will be considered statistically significant. Ultimately, only aggregate risk estimates based on the greatest degree of adjustment will be pooled and summarized to account for potential confounders in nonrandomized studies. We anticipate pooling the effect estimates for each oral health condition and the particular NCD outcomes using a random-effects model regardless of the degree of statistical heterogeneity to address further methodological heterogeneity between the included studies.[22] The common effect estimates will be summarized as adjusted hazard ratios, odds ratios, or standard mean differences with corresponding 95% confidence intervals. Furthermore, we will estimate 95% prediction intervals for all outcomes of interest (individual NCDs regarding each oral health condition) to account for the expected uncertainty based on a new study.[23]

Statistical heterogeneity will be investigated using the Cochran Q test with $p < 0.10$. The degree of inconsistency will be estimated using the I^2 index and τ^2 statistics. We will then classify the degree of heterogeneity as low ($I^2 = 25.0\%$ and $\tau^2 = 0.01$), moderate ($I^2 = 50.0\%$ and $\tau^2 = 0.06$), and high ($I^2 = 75.0\%$ and $\tau^2 = 0.16$).[24] In case of sufficient data, a small study effect will be explored using funnel plots inspection for each outcome of interest. Statistical publication bias will be tested using Egger's methods, with $p < 0.10$.[25] The trim and fill method will also be calibrated for publication bias and address the number of included studies.[25]

Preplanned subgroup and random-effects univariate meta-regression analyses will be performed to address possible heterogeneity using the prespecified study and patient characteristics as effect modifiers. A set of sensitivity analyses will be assessed to establish the robustness of the meta-analytic estimates as follows: calculate the expected (E)-value to address the potential residual confounders,[26] limiting the analysis to studies that are classified as having highest quality (NOS $\geqslant$ 8 points), including the analysis to studies that only represent the directness of effect estimates, and post-hoc analysis based on the "leave-one-out" approach (excluding individual included studies one at a time of analysis).

To synthesize the evidence findings, we will employ assessment evidence certainty regarding oral health conditions for each outcome of interest (individual NCDs) using the modified Grading of Recommended Assessment, Development, and Evaluation approach and the United States Agency for Healthcare Search and Quality.[27,28] For evidence synthesis conclusions, we will grade the strength of body evidence into insufficient, very low, low, moderate, or high quality. In case of disagreement, the judging evidence certainty will be resolved by a team consensus.

Ethics and dissemination

Indeed, the approach regarding systematic reviews involves information based on existing published literature. Moreover, patients or the public had no role or direct involvement in this study. As such, this systematic review and meta-analysis does not require formal ethical approval. However, the Ethical Committee of the Faculty of Dentistry, Chiang Mai University, has granted an ethical exemption for this review (No. 44/2023). The final review findings and any amendments to the study protocol as needed will be reported in accordance with the PRISMA 2020 reporting guidelines.[29] Strategies for formal dissemination will comprise peer-reviewed journals and scientific meeting conferences.

Discussion

In recent decades, there has been a substantial improvement and growing evidence-based healthcare treatment interventions; however, NCDs remain the leading cause of chronic illness in our society and account for seven of ten global deaths, as well as premature avertable mortality.[18,30]

Of these, the four major, including cancers, cardiovascular diseases, chronic respiratory diseases, and diabetes, account for about 80% of NCD deaths.[18] Concerning the global oral health crisis, the WHO has issued and developed the global initiative agenda by incorporating an action plan by 2023 aligned with NCD and universal health coverage agendas.[11,31] With respect to limited evidence consistency, a systematic review by Botelho et al.[12] found that the overall strength of a body of evidence of the association between oral health conditions and NCDs was unfavorable owing to poor meta-synthesizing or methodological inconsistencies. Furthermore, the findings are prominently based on prevalent associations (e.g., cardiovascular diseases or diabetes mellitus) owing to the nature of the cross-sectional study design.[12]

To better understand the global impact of oral health conditions as a potential prognostic risk for the development of systemic NCDs, particularly the major burden NCDs (i.e., cancers, cardiovascular diseases, chronic respiratory diseases, and diabetes), we will summarize all available observational studies that account for the temporal relationship (i.e., cohort or case–control studies). Our systematic review and meta-analysis will use a comprehensive evidence-based synthesis approach. Given that we plan to perform a rigorous and updated systematic review and meta-analysis, including all available evidence from the contemporary literature, some study limitations must be acknowledged. As we limited our search strategy to studies published in the English language, non-English evidence may limit our findings. In addition, apart from the methodological differences, heterogeneity in study-specific effect estimates regarding differences in definitions of oral health conditions and outcomes of interest and degree of controlling for confounders across the included studies may also affect our results.

Collectively, our findings will promote a proactive collaboration between oral health professionals and primary care professionals for early detection and management of NCDs and promote public oral health well-being to align among NCDs and risk-factor advocates. Ultimately, findings from the evidence-based synthesis will further inform the WHO Global Strategy for Oral Health agenda for effective coverage surveillance of public oral health conditions and oral health literacy promotion among individuals at risk of NCDs.

Conclusion

This systematic review and meta-analysis will summarize all available evidence regarding the association between oral health conditions and the subsequent risk of systemic major NCDs-related health and economic burden. Evidence from this review can be used in the risk assessment of major NCDs among people with oral health conditions for proper public surveillance and disease prevention. In addition, the results of this review will enhance medical personnel's awareness and lead to collaborative treatment planning for comprehensive care.

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Author contributions

NP, CR, KT, PB, and SN contributed to the study concept and design, and conducting the process evaluation. NP and SN designed the search strategy. CR and PB support study management and coordination. CR, KT, and SN provided critical revision of the manuscript for important intellectuals. NP and PB drafted the manuscript. SN is the chief of study investigators. All authors reviewed the approval of the version to be published.

Availability of data materials

No data was generated or analyzed during this study protocol.

Declaration of conflicting interests

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Informed consent

NA.

ORCID iD

Surapon Nochaiwong https://orcid.org/0000-0003-1100-7171

Supplemental material

Supplemental material for this article is available online.

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