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Determinants and Potential Influence of Oral Health on Cardiometabolic Conditions

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Introduction

Oral diseases represent a global health issue, affecting roughly 3.5 billion people globally in 2017. The number of people with untreated dental caries in permanent and deciduous teeth was 2.3 billion and 532 million, respectively. Around 796 million suffered from severe periodontitis, and 267 million had complete tooth loss (edentulism). The global disability-adjusted life years (DALYs) that could be attributed to oral diseases rose by 64% from 1990 to 2015.

Oral diseases enormously impact general health and well-being and impose social and economic burdens. Current epidemiological findings have indicated that oral diseases are linked to a wide variety of chronic diseases (e.g., diabetes mellitus (DM), cardiovascular diseases, neurocognitive disorders, rheumatic diseases, respiratory diseases) and metabolic syndrome (MetS). The global cost attributable to oral diseases was estimated to reach $544 billion in 2015, consisting of nearly $357 billion direct cost and $188 billion indirect cost.

The burden of oral diseases is disproportionately borne by disadvantaged and deprived communities, especially occurring in low- and middle-income countries (LMICs), where there are scarce resources and a high level of social inequalities. Oral diseases are the fourth most costly disease to treat in developed nations. In low-income countries (LICs), treatment is often unavailable, and the cost of dental caries treatment alone in children exceeds the entire healthcare budget designated for children. The prevalence of oral diseases is especially rising in developing countries due to shifts in broader social, economic, and commercial factors, potentially influencing lifestyle.

At present, established and standardised surveillance data on oral diseases is lacking in LMICs, such as in Indonesia, hindering the progress towards achieving global oral health. This information is vital to understanding the disease burden in the population, tracking progress, and informing decision-making. Furthermore, most studies investigating the determinants of oral health have been from developed countries. Since Indonesia is a developing nation with disparities in healthcare resource distributions, rapid economic change and modernisation leading to social transition, oral health status and practice among Indonesian populations, as well as their risk factors, might differ from those in developed nations. The magnitude of the chronic-oral diseases associations, such as MetS and periodontal diseases might also differ according to the study population or ethnicity. Identifying factors that influence oral diseases in the population is necessary for establishing interventions. Given that the main oral health behaviour is oral hygiene

practice, and the most prevalent oral disease is periodontal diseases, studying these two can bring valuable contributions to the literature. Finally, ascertaining the current evidence of the potential influence of oral health on cardiometabolic conditions, such as oral hygiene and MetS, could be useful, as it may provide more substance for developing public health policies and programs, notably strategies for preventing and managing chronic diseases.

Objectives

The overall aim of this thesis is to map the oral health status and practice and their determinants in the Indonesian population and to examine the global association between oral hygiene and MetS.

The specific objectives are to:

1. Investigate the prevalence and factors associated with oral hygiene practice among Indonesian adolescents.
2. Investigate the prevalence and factors associated with periodontitis among Indonesian adults.
3. Quantitatively synthesize the current body of evidence of the associations between oral hygiene status and care and MetS.

Materials and Methods

This thesis employed two general approaches to attain the research aims. The first approach was empirical-analytical research methodology, employing data from two Indonesian national health surveys, whereas the second approach was a systematic review and meta-analytic methodology.

Study 1 – Prevalence and determinants of oral hygiene practice among Indonesian adolescents

This study was a secondary analysis of the 2015 Indonesia Global School-based Health Survey (GSHS), covering 11,142 school adolescents aged 11-18 years. The outcome variable was oral hygiene practice (frequency of tooth brushing), which was dichotomised into less than twice a day and a minimum of twice a day. The independent variables included sociodemographic (age, gender, and hunger status (proxy for socioeconomic status (SES)), lifestyle (dietary practice, physical activity, sedentariness, nutritional status, cigarette smoking, consumption of alcohol, and drug use), and psychosocial variables (psychological distress and peer and parental support).

The characteristics of the sample were summarised by conducting descriptive statistics. The adjusted F (a variant of the second-order Rao-Scott adjusted chi-square statistic) and its degrees of freedom were used to statistically test the differences in the frequency of tooth-brushing among the selected variables. We used multiple logistic regression to examine the relationship between independent variables and tooth-brushing frequency and reported the resulting odds ratios (ORs) and the corresponding 95% confidence intervals (CIs). Following the GSHS guidance, weighting was applied to make the findings representative of the target population, taking into account the sampling design, non-response, and distribution of the population by gender and grade. Data analysis was conducted using the complex samples module of the SPSS 23.0 (IBM Corp., Armonk, New York, USA). We set the statistical significance at a *p*-value <0.05.

Study 2 – Prevalence and determinants of periodontitis among Indonesian adults

This study was a secondary analysis of the Indonesian Basic National Health Research (Riset Kesehatan Dasar / Riskesdas), covering 13,359 dentate adults aged 35+ years. The outcome variables related to periodontitis were the number of teeth with bleeding on probing (BOP), the number of teeth with pocket depth (PD) ≥4 mm, and the number of sextants with clinical attachment loss (CAL) ≥4 mm. The independent variables included sociodemographic (age, gender, residential location, education, and occupation), health behaviours (cigarette smoking,

tobacco chewing, tooth-brushing habits, and dental attendance), access to health care, and biological variables (MetS or its components (abdominal obesity, hyperglycaemia, hypertension, elevated triglycerides (TG), reduced high-density lipoprotein cholesterol (HDL-C)).

The characteristics of the sample were summarised by conducting descriptive statistics. Negative binomial regression models were used to evaluate the relationship between the independent and outcome variables, incorporating an offset variable for the natural logarithm of the number of examined teeth (for the outcomes of BOP and PD) and the number of examined sextants (for the outcome of CAL). We reported rate ratios (RRs) and the corresponding 95% CIs. Weighting was used to make the findings representative of the target population. Data analyses were performed using the "svyset" command in STATA (version 13.0, Stata Corp, College Station, TX, USA). We set the statistical significance at a *p*-value <0.05.

Study 3 – Global association between oral hygiene and metabolic syndrome

This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, with the registered protocol on the PROSPERO No. CRD42021243292. The research question was, "Is better oral hygiene status or care associated with a reduced MetS risk?". The inclusion criteria included observational studies, assessing the exposure of oral hygiene status (e.g., plaque index (PI), plaque score (PSc), oral hygiene index (OHI)) or care (i.e., tooth brushing, interdental cleaning, and dental attendance) and the outcome of MetS in multiple analyses. There were no restrictions on the study population characteristics. Animal studies, clinical trials, case series, case reports, commentaries, editorial letters, and reviews were excluded.

We searched PubMed and Web of Science databases until March 17th, 2021, with restrictions on articles published in English. Reference lists of eligible studies and relevant systematic reviews were further examined to capture additional relevant studies.

Two authors independently screened all titles and abstracts to determine eligibility, extracted the data from the included studies, and assessed the studies' quality. We used a data extraction form to collate the following data: first author, publication year, study country, study design, sample size, age, gender, type of oral hygiene assessment, diagnostic criteria employed for defining MetS, number of MetS cases, OR or risk ratio with their 95% CIs from the most adjusted model, and factors adjusted in the analysis. The included studies' quality was assessed by employing the

Newcastle–Ottawa Scale (NOS) tools for cross-sectional, case-control, and cohort studies. In the presence of discrepancies, they were resolved through consensus discussion.

Separate meta-analyses were performed for distinct types of exposure (i.e., oral hygiene status, tooth brushing, and interdental cleaning). We used OR as the common measure for the relationship between oral hygiene and MetS. We considered the reported RR approximately as OR. In the meta-analysis, the data utilised were the estimates and the 95% CIs from the most adjusted model in the included studies.

The categorisation of exposure differed across studies. The reference group was poor oral hygiene status or care, corresponding to the greatest score of OHI, PI, and PSc, or the least category of tooth-brushing frequency, interdental cleaning, and dental visit in every study. In the case of a study categorising the exposure into three or more groups, a fixed-effects (FE) model was employed to combine the findings of the categories, generating a single effect estimate. We employed a random-effects (RE) model for the primary analysis to compute an overall pooled OR (DerSimonian and Laird). The I^2 statistic was computed to evaluate heterogeneity, with a value of 50% or greater indicating substantial heterogeneity. Pre-specified subgroup analyses by study design and country were performed to evaluate sources of heterogeneity. Publication bias assessment employing funnel plot and Egger's test was only recommended when there was a sufficient number of studies (>10).

Meta-analysis was performed employing the generic inverse variance method in Review Manager (RevMan) 5.4 software (The Cochrane Collaboration, 2020).

Results

Study 1 – Prevalence and determinants of oral hygiene practice among Indonesian adolescents

The weighted average (±SD) age of the sample was 14.0 (±1.6) years, 48.9% were male, and 4.1% had lower SES (mostly/always being hungry). The prevalence of students with tooth-brushing frequency less than twice a day was 10.8%.

In the multiple logistic regression model, male (adjusted OR (aOR) = 0.36; 95% CI 0.30-0.43), lower SES (aOR = 0.60; 95% CI 0.46-0.79), sedentary behaviour (aOR = 0.64; 95% CI 0.52-0.79), drug use (aOR = 0.52; 95% CI 0.27-0.99), and psychological distress (aOR = 0.71; 95% CI 0.58-0.88) were associated with infrequent tooth brushing. Healthy dietary practice (aOR = 1.65; 95% CI 1.39-1.96), peer support (aOR = 1.23; 95% CI 1.03-1.47), and parental support (aOR = 1.33; 95% CI 1.07-1.66) were associated with frequent tooth brushing. The relationships between age, physical activity, nutritional status, cigarette and alcohol use and tooth-brushing frequency were not shown.

Study 2 – Prevalence and determinants of periodontitis among Indonesian adults

The weighted average (±SD) age of the sample was 50.3 (±10.4) years. Most samples were female, resided in urban regions, had their highest educational attainment level of primary school or lower, worked in an occupation categorised as ‘others’, had never smoked or chewed tobacco, brushed their teeth daily but at the incorrect timings, had not visited a dental professional in the past year, and had convenient access to medical facilities. In addition, most of them suffered from hypertension, but not abdominal obesity, hyperglycaemia, or MetS, and had normal HDL-C and TG levels. The respective prevalence of respondents with a minimum of one tooth with BOP, one tooth with PD ≥4 mm, or one sextant with CAL ≥4 mm was 74.9%, 40.7%, and 40.6%.

In the models adjusted by MetS, increasing age was associated with more teeth with BOP (aOR = 1.01; 95% CI 1.00-1.01), more teeth with PD ≥4 mm (aOR = 1.02; 95% CI 1.01-1.02), and more sextants with CAL ≥4 mm (aOR = 1.03; 95% CI 1.03-1.03). Male was associated with more teeth with BOP (aOR = 1.08; 95% CI 1.01-1.15), more teeth with PD ≥4 mm (aOR = 1.19; 95% CI 1.07-1.32), and more sextants with CAL ≥4 mm (aOR = 1.19; 95% CI 1.09-1.30). Compared to those whose highest educational attainment level was elementary school or lower, those with higher education were associated with fewer teeth with BOP (aOR = 0.79; 95% CI 0.71-0.88),

fewer teeth with PD ≥4 mm (aOR = 0.74; 95% CI 0.61-0.91), and fewer sextants with CAL ≥4 mm (aOR = 0.82; 95% CI 0.71-0.95). Compared to those whose occupations were listed as 'others', manual workers were associated with more teeth with BOP (aOR = 1.08; 95% CI 1.02-1.15), while non-manual workers were associated with fewer sextants with CAL ≥4 mm (aOR = 0.89; 95% CI 0.82-0.97).

Compared to never smokers, former smokers were associated with fewer teeth with BOP (aOR = 0.88; 95% CI 0.80-0.97), while current smokers were associated with more sextants with CAL ≥4 mm (aOR = 1.14; 95% CI 1.04-1.25). Compared to non-daily tooth brushing, daily tooth brushing, regardless of the timing, was associated with fewer teeth with BOP (aOR for correct timing = 0.82; 95% CI 0.69-0.97; aOR for incorrect timing = 0.86; 95% CI 0.76-0.97). Likewise, daily and correct timing of tooth brushing was associated with fewer sextants with CAL ≥4 mm (aOR = 0.74; 95% CI 0.57-0.96). Both dental attendance (aOR = 0.92; 95% CI 0.87-0.98) and convenient access to medical facilities (aOR = 0.93; 95% CI 0.87-0.98) were associated with fewer teeth with BOP. Residential location, chewing tobacco status, and MetS were not demonstrated to be associated with any of the periodontal health indicators.

Turning to the models adjusted by the independent component of MetS, hyperglycaemia was associated with more teeth with BOP (aOR = 1.06; 95% CI 1.01-1.11), more teeth with PD ≥4 mm (aOR = 1.13; 95% CI 1.03-1.23), and more sextants with CAL ≥4 mm (aOR = 1.15; 95% CI 1.08-1.23). Central obesity, hypertension, declined HDL-C, and increased TG were not shown to be associated with any periodontal health indicators.

Study 3 – Global association between oral hygiene and metabolic syndrome

There was a total of 595 articles identified from the search. Of these, 144 duplicates and 380 irrelevant studies were removed. Following full-text review of the 71 studies, thirteen satisfied the eligibility criteria and were included in the review and meta-analysis.

There were seven studies with a cross-sectional design, three with a case-control design, and three with a cohort design. A study conducted by Shearer et al. (2018) used data originally from a longitudinal study. Nonetheless, as our exposure of interest (modified OHI-S) was assessed with the outcome (MetS) simultaneously at age 38, this study was considered cross-sectional, and the findings of their cross-sectional model were reported.

There were eleven studies conducted in nations in Asia. One study was performed in New Zealand and one in Finland. The study populations of all studies were adults, and the year of publication varied from 2009 to 2020. The average sample size across studies was 4251.

Six studies reported oral hygiene status, six reported tooth-brushing frequency, two reported interdental cleaning, and one reported dental attendance as the independent variables in the studies. In the meta-analysis, we considered a study by Tsutsumi and Kakuma (2015) as two separate studies since it reported the findings for females and males separately rather than as total samples. We used a similar approach for research by Kim et al. (2013) since it reported distinct findings for interdental brushing and flossing.

All studies conducted health examinations to ascertain MetS conditions. There were four studies employing the NCEP ATP III criteria or its modified version to define MetS, five employing JIS criteria, two employing IDF criteria, and two employing other criteria. The most common controlled variables of all included studies were age, gender, SES, smoking status, alcohol use, physical activity, and periodontal parameters. All studies, except one, reported OR as a measure of the relationship. The studies' qualities ranged from moderate to high.

Findings from meta-analyses showed that overall improved oral hygiene status (pooled OR = 0.30; 95% CI 0.13–0.66; I^2 = 91%), brushing teeth frequently (pooled OR = 0.68; 95% CI 0.58–0.80; I^2 = 89%), and interdental cleaning (pooled OR = 0.89; 95% CI 0.81–0.99; I^2 = 27%) were associated with a reduced MetS risk. Although there was minimal heterogeneity for interdental cleaning, there was substantial heterogeneity for the exposure of oral hygiene status and tooth-brushing frequency. The relationship between dental attendance and MetS was investigated only in a study by Tanaka et al. (2018), which showed no relationship (OR = 1.10; 95% CI 0.77–1.55).

Turning to oral hygiene status, in the subgroup analysis of study design, the relationship between better oral hygiene status and a reduced MetS risk was only noted in the subgroup of case-control studies (pooled OR = 0.11; 95% CI 0.06–0.20; I^2=39%). The pooled effect estimates of cross-sectional studies indicated no relationship (pooled OR = 0.72; 95% CI 0.41–1.26; I^2=46%). There was not enough study to pool an effect estimate for cohort studies. The subgroup analysis by study design decreased heterogeneity to below 50%.

Turning to tooth-brushing frequency, brushing teeth frequently was associated with a reduced MetS risk in all subgroup analyses. In the subgroup analysis by study design, the pooled OR (95%

CI) of cross-sectional studies was 0.67 (0.55–0.81), with I^2=93%, whereas the pooled OR (95% CI) of cohort studies was 0.74 (0.62–0.89), with I^2=0%. In the subgroup analysis by country, the pooled OR (95% CI) of studies in Japan was 0.61 (0.52–0.70), with I^2=55%, whereas the pooled OR (95% CI) of studies in Korea was 0.85 (0.78–0.93), with I^2=73%. Although subgroup analysis by country decreased heterogeneity, they remained over 50%. High heterogeneity remained noted in cross-sectional studies.

Discussion

Main discussion

Overall, both of our empirical studies noted the existence of social disparities and gender differences in oral health in Indonesian populations. While hyperglycaemia was associated with periodontitis among Indonesian adults, the association between MetS and periodontitis could not be demonstrated. Similarly, the current global evidence in our review indicated the need for further well-designed longitudinal studies to confirm the relationship between poor oral hygiene and MetS risk.

Our first empirical study investigated the prevalence and determinants of oral hygiene practice among Indonesian school adolescents. Around a tenth had poor oral hygiene practice. Male gender, lower SES, poor dietary practice, sedentariness, drug use, psychological distress, less peer support, and no parental support were associated with poor oral hygiene practice.

Both oral and general health habits are shaped by the complex interaction between individual attributes and family, social, cultural and environmental determinants. Our study showed a positive relationship between the male gender and poor oral hygiene practice. Males might be less concerned about aesthetics and have a lower level of oral health awareness than females. Our study could not find any relationship between age and oral hygiene practice, similar to a study by Peltzer and Pengpid (2014). Regarding SES, our findings demonstrated that higher SES was associated with better oral hygiene. Higher SES adolescents typically have greater resources, access to dental care, environments encouraging healthy habits, and higher levels of educational attainment, resulting in better health consciousness.

Our study found that adolescents with better dietary practices typically adopt better oral hygiene practice. The family environment influences the adoption of these two behaviours since tooth brushing and meal consumption are often conducted at home. In particular, parents substantially influence these behaviours, as children tend to imitate them. Similarly, our findings demonstrated that sedentariness was associated with brushing teeth infrequently. Children's sedentary behaviours, such as screen-based activities or electronic media use, often depend on the family environment. Furthermore, Tsuchiya et al. (2017) suggested that excessive game players might have less spare time for tooth brushing since they would rather choose to play video games. They might also have a low sense of coherence, representing poor oral health behaviours.

Nutritional status and physical activity could represent the disposition toward a healthy lifestyle and the ability to preserve health and well-being. Nonetheless, our study could not find any relationships between nutritional status and physical activity and oral hygiene practice, corroborating the results of a study by Peltzer and Pengpid (2014). This finding might be due to the low awareness of the physical activity level recommended by the World Health Organisation (WHO), as only roughly a tenth of students were physically active for at least 60 minutes daily.

Existing literature has demonstrated a relationship between substance use (e.g., cigarettes, alcohol, and cannabis) and worse tooth-brushing behaviours, as health risk behaviours often exist in the same social context. Our study only found a borderline relationship between drug use and brushing teeth infrequently but could not show any relationships between cigarette smoking, consumption of alcohol, and the frequency of tooth brushing. Drug abusers might view oral health as a low priority. It was plausible that smokers might not have differing tooth-brushing habits in frequency but rather in duration compared to non-smokers, as Macgregor (1984) found. The low alcohol consumption prevalence might also account for the different results in our study. Alcohol use might not be prevalent in the country due to cultural and religious reasons.

Our study found a positive relationship between peer and parental support and better oral hygiene practice. Regular tooth-brushing behaviours are typically formed in a home with a set routine and positive family relationships. Children having high parental support receive better supervision and reinforcement to engage in healthy behaviours and have sound psychological health. A high level of parental support may also reflect better monitoring of their children's tooth-brushing habits. Besides family, peers influence identity formation in adolescents by influencing social norms and values. These influences may also include oral health habits since they usually relate to appearance, which adolescents consider important. Stronger interpersonal relationships influenced adolescents more because they tried to adapt to the behavioural characteristics of their peer groups. It is also known that adolescents typically befriend those with similar behavioural characteristics to theirs. Our study demonstrated a relationship between psychological distress and brushing teeth infrequently. Several depressive symptoms, including fatigue, psychomotor impairment, and demotivation, might undermine the oral health behaviours of individuals.

Oral hygiene practice adopted in adolescence is usually sustained into adulthood and is the primary risk factor for oral diseases. Among the most prevalent oral diseases are periodontal diseases, common in adults. In our second empirical study, we examined the prevalence and determinants of periodontitis among adults in Indonesia. We found over 40% of adults had

periodontitis. Increasing age, male gender, lower education and occupation status, worse tooth-brushing habits, less dental attendance and healthcare access, and hyperglycaemia were associated with worse statuses of at least one periodontal health indicator. Compared to never smoking, former smoking was inversely associated with BOP, while current smoking was positively associated with CAL. Residential location, tobacco chewing, MetS, central obesity, hypertension, and dyslipidaemia were not found to be associated with any periodontal health indicators.

Our findings showed that increasing age was associated with periodontitis. Older adults might have more severe periodontitis than younger adults due to lifetime cumulative tissue destruction and increased periodontal susceptibility due to alteration in tissue repair capacity and exposure to pro-inflammatory conditions. Our study found that the male gender was associated with periodontitis. Shiau and Reynolds (2010) suggested that the difference might not only be due to behavioural and environmental characteristics, but also sexual dimorphism in host immunity.

Our study found that educational attainment and occupation were associated with periodontitis. Lower education is often associated with worse coping strategies and oral health awareness, less dental care access, smoking, and having a higher body mass index (BMI) and type 2 DM (T2DM), which are the risk factors for periodontitis. Occupation might influence the social environment, behaviours, and psychosocial factors of individuals. For example, compared to non-manual workers, manual workers tend to have less income and dental care access, experience more psychosocial hazards, stress, and poorer sleep quality, and exhibit health-risk behaviours. Lack of flexibility in daily life may also lead to reduced frequency and effectiveness of tooth cleaning.

Our study demonstrated the associations of worse tooth-brushing behaviours and less dental attendance and access to healthcare facilities with BOP. Furthermore, daily and correct timing of tooth brushing was inversely associated with CAL. Improper tooth-brushing behaviours often result in poor oral hygiene, which is a risk factor for periodontitis. Our study could not show associations between smoking status and PD. Compared to never smoking, former smoking was inversely associated with BOP, while current smoking was positively associated with CAL. It was suggested that nicotine might induce gingival vasoconstriction, resulting in reduced signs of inflammation, such as redness and bleeding. The suppressed inflammatory reaction might also indicate reduced host defence capacity. Other effects of smoking might involve enhancing pathogen-enriched microflora in the subgingival, suppressing fibroblast proliferation and attachment, and promoting collagen breakdown and bone resorption, which might lead to CAL.

Our study showed a positive relationship between hyperglycaemia and periodontitis, which was in line with a joint statement by the International Diabetes Federation (IDF) and the European Federation of Periodontology (EFP). Hyperglycaemia influences periodontitis through several pathways. Firstly, it promotes the generation of irreversible advanced glycation end-products (AGEs) and their interactions with RAGEs (receptors of AGEs), resulting in the dysfunction of immune cells and changes in the phenotypes and functions of certain cells. It also causes cytokine imbalance – that is, enhanced pro-inflammatory cytokines levels, including tumour necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and IL-6. Diabetic patients with periodontitis are known to have polymorphonuclear leukocytes (PMNs) with declined chemotaxis and phagocytosis and changed superoxide production; these attributes lead to their accumulation in the periodontium and the formation of structures resembling abscess. Secondly, hyperglycemia raises reactive oxygen species (ROS) and oxidative stress levels directly and indirectly through the AGE-RAGE axis, promoting changes in cytokine profiles. Lastly, hyperglycemia raises receptor activator of nuclear factor-kappa B ligand to osteoprotegerin ratios (RANKL/OPG) directly and indirectly through the AGE-RAGE axis, stimulating inflammation and destruction. In addition, the majority of elements in these pathways have a bidirectional relationship. The pro-inflammatory condition creates AGEs, ROS, and adipokines. It also raises the RANKL/OPG ratio and induces the proliferation of pathogenic bacteria in the subgingival.

On the other hand, MetS, central obesity, hypertension, and dyslipidaemia were not shown to be associated with periodontal status, which was similar to findings from studies by LaMonte et al. (2014) and Zuk et al. (2017). The inconsistent findings might be a result of variation in confounders, study populations (e.g., age, gender, and genetic background), and the diagnostic and clinical criteria for defining MetS and periodontitis. Nascimento et al. (2019) also showed that the relationship between MetS and periodontitis depended on analytical methods. Furthermore, it was suggested that hypertension and dyslipidaemia might only have an additive effect on the risk of periodontitis if they are complemented with hyperglycaemia and/or obesity. Benguigui et al. (2010) argued that insulin resistance, rising with obesity, plays a more prominent role since it might mediate the association between obesity and periodontitis.

Poor oral hygiene is the main cause of oral diseases, including periodontitis. In our meta-analysis, we investigated whether poor oral hygiene was associated with MetS. While we found that better status of oral hygiene, brushing teeth frequently, and interdental cleaning were generally associated with a reduced MetS risk, the high heterogeneity for the exposure of tooth-brushing

frequency and an inconsistent finding for oral hygiene status in the subgroup analyses were noted. Only one study examined the relationship between dental attendance and MetS and showed no relationship.

Our primary analysis demonstrated an overall negative relationship between oral hygiene status and the risk of developing MetS. However, the findings were not consistent in subgroup analysis by study design. We further noted that of all research included in the meta-analysis for oral hygiene status, only those by Pussinen et al. (2020) and Shearer et al. (2018), which were performed in Finland and New Zealand, respectively, did not show a relationship. There are some possible explanations for the dissimilarities in their findings from those of other studies. First, it might be due to the context of the study populations. Both studies were conducted in high-income countries among Caucasian populations, while the others were in Asian populations. Second, it could be attributed to differences in the age of the study samples. The two studies had a relatively younger age study sample than the other studies, whose average age of study samples was 50+ years. Shearer et al. (2018) argued that it might only be in later life that the influence of periodontal inflammation on cardiometabolic health becomes apparent. Furthermore, Pussinen et al. (2020) showed the findings of both the adjusted RRs for the outcome of MetS and the adjusted β values for the outcome of the number of MetS components. Although there was no relationship between the presence of visible plaque and MetS, there was a positive relationship between the number of teeth with visible plaque and the number of MetS components.

Our study revealed negative associations between tooth-brushing frequency and interdental cleaning and the risk of developing MetS. While the results across all subgroup analyses of tooth-brushing frequency were consistent, there was substantial heterogeneity. Tooth brushing is known as the most vital measure of oral self-care for plaque control and is a protective factor against periodontal diseases. Although a suggestion for proper tooth-brushing frequency could not be provided, most included studies in the review employed a threshold of at least twice a day. Another systematic review by Fu et al. (2019) also demonstrated similar findings, suggesting that brushing teeth less frequently than twice a day might not benefit DM prevention. Furthermore, interdental cleaning is recommended to preserve oral health. Using interdental brushes daily has been shown to reduce periodontal bacteria, stimulate symbiotic microbiota, and decrease interdental inflammation.

Poor oral hygiene has been suggested to worsen MetS by raising local and systemic inflammation. Periodontal bacteria in plaque, their products, and local inflammatory response may gain entry

into the circulation and contribute to systemic inflammation. Chronic exposure to pro-inflammatory cytokines may change the metabolism of lipids, leading to hyperlipidemia. In addition, TNF-α could promote insulin resistance by directly affecting target organs (e.g., liver, muscle, and adipocytes) and indirectly stimulating adipocytes to release free fatty acids. Increased pro-inflammatory cytokines levels may also contribute to the dysfunction of pancreatic β-cells, resulting in the occurrence of T2DM. Moreover, infection with *Porphyromonas gingivalis* has been shown to promote metabolic disorders through gut microbiome alteration.

Alternatively, an explanation for the relationship between oral hygiene care and MetS might be attributed to common risk factors or biased health consciousness. It is plausible that people adopting healthier lifestyles might also have improved oral hygiene care. It was argued that oral hygiene care might only be a reflection of general health awareness or behaviours, underlining the complexity of oral epidemiology. Nonetheless, in our review, most included studies adjusted for crucial confounders, for example, age, gender, SES, smoking status, alcohol use, and physical activity, which minimised the bias.

The relationship between dental attendance and MetS was not shown in the study conducted by Tanaka et al. (2018). Their findings were consistent with research showing no relationship between dental attendance and professional dental cleaning and DM. Other confounders were suggested to have more crucial roles in DM occurrence than the professional dental cleaning. On the other hand, a review by Baeza et al. (2020) has shown that scaling and root planning could be beneficial for metabolic control and decreasing systemic inflammation in T2DM patients.

Strength, limitations, and consideration for future research

Our empirical studies had several strengths. First, they were the first to estimate the prevalence and determinants of oral hygiene practice among school adolescents and periodontitis among adults at a national level in Indonesia. Second, we used two recent national health surveys in Indonesia that followed international guidelines, facilitating international comparison. The 2015 Indonesia GSHS is part of an international effort to monitor health behaviours among adolescents in multiple countries. The GSHS covered various health behaviours, allowing us to investigate lifestyle in a comprehensive manner. The 2018 Riskesdas was also the first Indonesian national health survey that clinically measured oral health status, adopting the WHO Oral Health Survey. Third, our study was among the few that explored the relationship between MetS and periodontitis in Southeast Asian populations. Fourth, the relatively large sample size in our empirical studies

provided favourable statistical power to obtain reliable estimates.

Furthermore, our systematic review and meta-analysis was the first to provide global evidence of the relationship between oral hygiene and MetS. This topic is considered novel and closely linked to a growing scientific interest in the interrelationships between oral pathogens, oral microbiome dysbiosis, and systemic diseases. Furthermore, studying this topic is important for developing strategies that target common risk factors for oral and general health. Finally, the included studies in this review had moderate to high quality.

Nevertheless, there were several general limitations of both of our empirical studies. First, they were cross-sectional, limiting our ability to establish causation. Second, some variables were based on self-reported information that might be susceptible to inaccuracy. There was the possibility of social desirability bias in responding to behavioural questions. However, this bias in the GSHS might be reduced by informing the participants that the questionnaire was anonymous and confidential. Third, there might be the effects of unobserved confounders since the analyses were restricted to the available data in the survey.

Turning to the empirical studies, the first study was only concerned with tooth-brushing frequency, but its effect on oral health status was unknown since there were no assessments of timing, duration, and method of tooth brushing and the use of fluoridated toothpaste. Therefore, high self-reported tooth-brushing frequency in this study cannot be directly translated into enhanced oral health status. A generalisation of our findings to out-of-school adolescents or children in the younger age groups should also be considered with caution. Future studies should capture more psychosocial, family, and wider socioeconomic determinants (e.g., residential areas) to further explore determinants of oral hygiene practice. Investigating weekday-to-weekend differences in oral hygiene practice might also be worthwhile.

Similarly, in the second empirical study, the analysis was based on secondary data, and hence there might have been effects from unmeasured confounders (e.g., income or wealth, nutrition, consumption of alcohol, and physical activity). In addition, several dimensions of tobacco use are suggested to be evaluated from several dimensions, including type, dose, duration, and time since cessation. Other limitations originated from the survey protocol to collect information concerning periodontal health. Firstly, the survey recorded both PD and CAL in the form of scores (ranges); thus, determining the severity of periodontitis (the average of PD and CAL) in a person was not possible. A person's full extent of CAL could not be known since the measurements were

restricted to sextants, mainly based on using index teeth. Nevertheless, partial CAL recording remained decent in assessing the population's past periodontitis experience. Secondly, developing a periodontitis case definition by integrating data regarding CAL and PD or CAL and BOP on the index teeth was not possible. According to the protocol, if the sextant's index tooth was absent, all teeth present in that sextant were measured, and the greatest score was noted as the sextant's score. The tooth eventually used to record the sextant's CAL was not noted. Future studies might consider adopting a recording protocol that could allow the development of a periodontitis case definition. However, despite being unable to develop a periodontitis case definition, the evaluated three periodontal disease parameters complemented one another in providing insight into the population's periodontal condition. BOP and PD represent periodontal inflammation, and CAL represents the accumulation of periodontal destruction.

Turning to our systematic review and meta-analysis, several limitations arose from the methods employed and the included studies. First, a grey literature search was not performed, and only English-language studies were considered, which might introduce bias. Second, a publication bias assessment could not be undertaken as it was not suggested for a review with an inadequate number of studies (<10). Third, besides study design and country, other heterogeneity sources could be the variety of evaluation methods of oral hygiene status (e.g., using different indices), the reporting of tooth-brushing frequency and interdental cleaning, and MetS diagnostic criteria.

Further limitations in the review stemmed from the inherent limitations of the included studies. First, there was a limited number of longitudinal studies. The methodological limitations of the studies employing cross-sectional design could influence the findings. Second, tooth-brushing frequency and interdental cleaning variables were based on self-reported information, which might be susceptible to bias. Nevertheless, it could simply be a case of nondifferential misclassification, resulting in underestimating the true effect estimates. Third, regular tooth brushing did not necessarily represent better oral health status because the included studies did not account for the timing, duration, and method of tooth brushing, as well as the type of dentifrice used. Fifth, the majority of the included studies were performed in the Asian population, which might affect the generalisability of the results globally. Additional studies performed on other populations are encouraged to generate more evidence. Better comparison between studies may also be achieved by the use of a standardised protocol to report oral hygiene (e.g., tooth-brushing frequency).

Conclusions, study implications and recommendations

Overall, both of our empirical studies indicated a need to improve oral health in Indonesia. The findings that poor oral hygiene practice and periodontitis were more common among males and those with lower SES suggested the existence of social disparities and gender differences in oral health in Indonesian populations. Intersectoral interventions that target not only individuals (e.g., by placing greater emphasis on the male and low SES populations) but also upstream social, political, and economic factors might be beneficial to reducing oral health inequalities.

Among Indonesian school adolescents, there were positive relationships between some lifestyle and psychosocial factors and oral hygiene practice. These findings support the hypothesis that oral health shares common risk factors with other NCDs behaviours. Developing interventions targeting the underlying social context of adolescents may enhance not only oral health but also general health. Incorporating oral health into general health promotions could be useful and avoid duplication of efforts. The targets may include schools, families, and other social environments where adolescents live, learn and play. Furthermore, the findings that peer and parental support were associated with better oral hygiene might indicate the potential for leveraging social support to increase the uptake of oral health preventive behaviours. Besides schools, our study supports the evidence for the potential roles of parents in promoting oral health in Indonesia.

Among Indonesian adults, the prevalence of periodontal diseases is high. While the relationship between MetS and periodontitis was not shown, there was a positive association between hyperglycaemia and periodontitis. Since there is considerable evidence of a DM-periodontitis link, the IDF and the EFP developed consensus guidelines for medical and oral health practitioners and patients to improve the prevention, early detection, and co-management of periodontitis and DM. Periodontal therapy is linked with a short-term decrease in glycated haemoglobin (HbA1c) and is recommended as safe and effective in diabetic individuals. Adoption of the guidelines into the healthcare context in Indonesia might be beneficial. Hyperglycemic patients should be checked for periodontitis. Integrating oral health into routine DM care could reduce the disease burden. Regarding MetS, future well-designed longitudinal studies are needed to examine its temporal relationship with periodontal diseases.

Similarly, in our meta-analysis, while we found overall negative relationships between oral hygiene status, tooth-brushing frequency, and interdental cleaning and MetS, substantial heterogeneity for the exposure of tooth-brushing frequency and inconsistent findings for oral

hygiene status in the subgroup analyses were noted. Inadequate evidence exists on the relationship between dental attendance and MetS. Additional high-quality longitudinal studies are needed to explore the relationships between oral hygiene status and care and MetS, and to examine their underlying mechanism. Studying this topic will contribute to understanding the interrelationship between oral health and MetS.

New Findings

Study 1. Prevalence and determinants of oral hygiene practice among Indonesian adolescents

- ***Tooth-brushing behaviours among adolescents in Indonesia could still be improved***
  The prevalence of school adolescents in Indonesia not adhering to the recommended twice-a-day tooth brushing was 10.8%.

- ***Male gender and lower SES were associated with poor oral hygiene practice among adolescents in Indonesia***
  Male (aOR 0.36; 95% CI 0.30-0.43) and lower SES (aOR 0.60; 95% CI 0.46-0.79) were associated with lower odds of frequent tooth brushing.

- ***There is the potential to leverage social support to increase the uptake of oral health preventive behaviours***
  Peer support (aOR = 1.23; 95% CI 1.03-1.47) and parental support (aOR =1.33; 95% CI 1.07-1.66) were associated with higher odds of frequent tooth brushing.

Study 2. Prevalence and determinants of periodontitis among Indonesian adults

- ***The prevalence of periodontitis among Indonesian adults is high***
  The respective prevalence of adults with a minimum of one tooth with BOP, one tooth with PD ≥4 mm, and one sextant with CAL ≥4 mm was 74.9%, 40.7%, and 40.6%.

- ***Male gender and lower SES were associated with periodontitis in Indonesian adults***
  Male was associated with more teeth with BOP (aOR = 1.08; 95% CI 1.01-1.15), more teeth with PD (aOR = 1.19; 95% CI 1.07-1.32) and more sextants with CAL (aOR = 1.19; 95% CI 1.09-1.30).

  Compared to individuals with primary school or lower as their highest educational attainment, those with a higher education degree were associated with fewer teeth with BOP (aOR 0.79; 95% CI 0.71-0.88), fewer teeth with PD (aOR 0.74 95% CI 0.61-0.91), and fewer sextants with CAL (aOR = 0.82; 95% CI 0.71-0.95).

  Compared to an occupation listed as ‘others’, those with manual occupation were associated with more teeth with BOP (aOR 1.08 95% CI 1.02-1.15), while those with non-manual occupation were associated with fewer sextants with CAL (aOR 0.89; 95% CI 0.82-0.97).

- ***MetS was not found to be associated with periodontitis in Indonesian adults***

  The associations between MetS and the number of teeth with BOP, the number of teeth with PD, and the number of sextants with CAL were aOR = 1.02 (95% CI 0.98-1.07), aOR =1.08 (95% CI 0.99-1.18), and aOR = 1.05 (95% CI 0.99-1.13), respectively.

- ***Hyperglycaemia was the only component of MetS associated with periodontitis in Indonesian adults***

  The associations between hyperglycemia and more teeth with BOP, more teeth with PD, and more sextants with CAL were aOR = 1.06 (95% CI 1.01-1.11), aOR = 1.13 (95% CI 1.03-1.23), and aOR = 1.15 (95% CI 1.08-1.23), respectively.

Study 3. Global association between oral hygiene and metabolic syndrome

- ***The potential influence of oral hygiene on MetS needs further investigation***

  Our overall meta-analysis found that better oral hygiene status (pooled OR = 0.30; 95% CI 0.13–0.66), frequent tooth brushing (pooled OR = 0.68; 95% CI 0.58–0.80), and interdental cleaning (pooled OR = 0.89; 95% CI 0.81–0.99) were associated with a reduced MetS risk. However, high heterogeneity for the exposure of tooth-brushing frequency (I^2 = 89%) and an inconsistent finding for oral hygiene status in subgroup analyses were noted. Only one study examined the relationship between dental attendance and MetS and showed no relationship (OR = 1.10; 95% CI 0.77–1.55). Further high-quality longitudinal studies are needed to explore the relationships.

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List of publications related to the dissertation

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   J. Clin. Periodontol. 49 (6), 562-572, 2022.
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2. **Santoso, C. M. A.**, Ketti, F., Bramantoro, T., Zsuga, J., Nagy, A. C.: Association between Oral Hygiene and Metabolic Syndrome: a Systematic Review and Meta-Analysis.
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List of other publications

4. Nguyen, C. M., **Santoso, C. M. A.**, Vu, D. T. H., Szőllősi, G. J., Bata, R., Zsuga, J., Nagy, A. C.: Awareness Related to Cardiometabolic Diseases: a Cross-Sectional Study in Southern Vietnam.
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