DISSERTATION FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

Determinants and Potential Influence of Oral Health on Cardiometabolic Conditions

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DOCTORAL SCHOOL OF HEALTH SCIENCES

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List of Abbreviations

AGE	: advanced glycation end-product
aOR	: adjusted odds ratio
BMI	: body mass index
BOP	: bleeding on probing
CAL	: clinical attachment loss
CDC	: Centers for Disease Control and Prevention
CEJ	: cementoenamel junction
CHC	: community health centre
CI	: confidence interval
COVID-19	: coronavirus disease 2019
CVD	: cardiovascular disease
DALY	: disability adjusted life years
DBP	: diastolic blood pressure
DM	: diabetes mellitus
DMFT / dmft	: Decayed, Missing and Filled Teeth
FPG	: fasting plasma glucose
GSHS	: Global School-based Health Survey
HbA1c	: glycated haemoglobin
HDL-C	: high-density lipoprotein cholesterol
HIC	: high-income country
IDF	: International Diabetes Federation
IL	: interleukin
JIS	: Joint Interim Statement
LIC	: low-income country
LMIC	: low- and middle- income country
MetS	: metabolic syndrome
MMP	: matrix-metalloproteinases
NCD	: non-communicable disease
NCEP ATP III	: National Cholesterol Education Program Adult Treatment Panel III
NHI	: National Health Insurance
NIHRD	: National Institute of Health Research and Development
NOS	: Newcastle–Ottawa Scale

OHI	: oral hygiene index
OHI-S	: simplified oral hygiene index
OPG	: osteoprotegerin
OR	: odds ratio
PD	: pocket depth
PI	: plaque index
PMN	: polymorphonuclear leukocyte
PRISMA	: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSc	: plaque score
RAGE	: receptor of advanced glycation end-product
RANKL	: receptor activator of nuclear factor-kappa B ligand
RevMan	: Review Manager
RR	: rates ratio
Riskesdas	: Riset Kesehatan Dasar (Indonesian Basic National Health Research)
ROS	: reactive oxygen species
SBP	: systolic blood pressure
SBDP	: school-based dental program
SD	: standard deviation
SES	: socioeconomic status
T2DM	: type 2 diabetes mellitus
TG	: triglycerides
TNF	: tumor necrosis factor
WC	: waist circumference
WHO	: World Health Organisation

1. Introduction

Oral diseases represent a global health issue, affecting roughly 3.5 billion people globally in 2017 (1,2). Despite being preventable, the total global prevalence of dental caries, periodontal diseases, and tooth loss has remained constant for the past three decades at 45%, higher than other chronic diseases (3). 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) (2). The global disability-adjusted life years (DALYs) that could be attributed to oral diseases rose by 64% from 1990 to 2015 (4).

Oral diseases enormously impact general health and well-being and impose social and economic burdens (5). Oral diseases negatively affect people's quality of life, disrupting their oral functions and social relationships. The impacts can be in the form of pain, discomfort, reduced self-esteem, chewing impairment, reduced appetite, sleep disturbances, loss of productivity or reduced performance at school or the workplace (6-9), loneliness (10), and depression (11). Furthermore, despite lacking causal evidence (12,13), current epidemiological findings have indicated that oral diseases are linked to a wide variety of chronic diseases (e.g., diabetes mellitus (DM) (14), cardiovascular diseases (15), neurocognitive disorders (16), rheumatic diseases (17), respiratory diseases (18)) and metabolic syndrome (MetS) (19-21). 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 (22).

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 (5,23). 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 (24,25). The prevalence of oral diseases is especially rising in developing countries due to shifts in broader social, economic, and commercial factors, potentially influencing lifestyle (5).

Although there has been an estimation of the global distribution and disease burden of oral diseases (2,4), established and standardised surveillance data on oral diseases is lacking in LMICs (1,26). This information is vital to understanding the disease burden in the population,

tracking progress, and informing decision-making (26). It is especially recommended to have evidence based on the local context to influence policy (27). Identifying factors that influence oral diseases in the population is necessary for establishing interventions. Furthermore, ascertaining the current evidence of the potential influence of oral health on cardiometabolic conditions could be useful, as it may provide more substance for developing public health policies and programs.

2. Literature Review

Common types of oral diseases

Dental caries

Dental caries is a multifactorial and dynamic disease mediated by biofilm and driven by sugar, leading to interchange periods between demineralization and remineralization of dental hard tissues (28). Following the consumption of free sugars, the pH of the biofilm can become lower than a critical threshold, leading to the dissolution of the hard tissues. Sufficient loss of minerals in the tooth may initially present as a white spot on the surface of the tooth. If they progress to cavitation, it can cause pain and discomfort. The progression to the dental pulp may further result in infection, sepsis, and tooth loss (5).

Balancing the pathological and protective factors that can cause caries is paramount to preventing the occurrence of the disease. Pathological factors leading to demineralisation and caries lesion progression are poor oral hygiene, insufficient fluoride exposure, frequent sugar intake, and salivary dysfunction. Meanwhile, protective factors that lead to remineralisation and lesion arrest include a healthy diet, twice-a-day tooth brushing with fluoridated toothpaste, application of professional topical fluoride and sealants, and normal salivary function (28).

The dental caries index generally used to estimate cumulative experience of caries is the Decayed, Missing and Filled Teeth (DMFT / dmft) index, which is defined as the combined number of decayed, missing, and filled teeth attributable to dental caries. If the index is written in capital letters (DMFT), it refers to permanent dentition. If it is written in lowercase letters (dmft), it refers to primary dentition. Untreated caries can be reflected by the number of decayed teeth, while treated caries can be reflected by the number of filled or missing teeth that are extracted due to caries (5).

Periodontal diseases

Periodontal diseases consist of inflammatory conditions affecting periodontium (gingiva, alveolar bone, and periodontal ligament). The condition often begins with gingivitis, characterized by bleeding and swollen gingiva. If left unaddressed, they progress to periodontitis, characterized by the irreversible loss of bone and ligament, creating periodontal pockets, potentially leading to tooth loss (29).

Periodontitis is among the commonest diseases globally, affecting 20-50% of the world population (15). In 2010, the prevalence of severe periodontitis alone reached almost 11% worldwide, affecting roughly 743 million individuals and being listed as the 6th most common disease (30). There was a 25.8% rise in the global burden of periodontal diseases from 2006 to 2016 (31). Periodontal diseases have significant impacts on oral and overall health and life quality. The diseases are the main cause of tooth loss and are associated with chronic diseases through infection, inflammation, and shared risk factors (32). Furthermore, the diseases were estimated to cause an economic loss of more than $150 billion in the United States or Europe in 2018 (33).

Clinical variables that are often used to measure an individual's periodontal status, evaluate treatment outcome, and monitor population periodontal health includes bleeding on probing (BOP), pocket depth (PD), and clinical attachment loss (CAL) (34). BOP and PD indicate periodontal inflammation, while CAL estimates cumulative periodontal damage (35-37). A periodontal probe is used to measure these indices. BOP indicates the presence of a bleeding response after inserting the probe between the tooth and gingiva (38). PD indicates the distance from the free gingival margin to the base of the pocket (39), with the normal value of <4mm (40). CAL indicates the distance from the cementoenamel junction (CEJ) of the tooth to the bottom of the pocket (39), with the range of normal value <3-4 mm (41,42).

The aetiology of periodontitis is multifactorial. Pathogenic bacteria are known as the primary aetiological agents. Nevertheless, the destruction of periodontium is mostly due to the host immune response to microbial infection, often determined by genetic and environmental factors. Activated leucocytes in the periodontal tissues generate a range of inflammatory mediators, such as cytokines-chemokines and matrix-metalloproteinases (MMPs), causing tissue destruction (15). That said, several risk factors of periodontitis that have been identified include age, gender, ethnicity, genetics, socioeconomic status (SES), oral hygiene, smoking, stress, systemic conditions, and medication (43,44).

Treatment of periodontal diseases begins with initial non-surgical therapy, encompassing home care review, scaling, and root planning. During the periodontal re-evaluation phase, sites with the remaining active periodontitis may be treated with surgical therapy. Regular periodontal maintenance therapies are paramount for treatment success and long-term teeth retention (45). Moreover, interventions to change behaviours, such as individually customised oral-hygiene instructions, smoking cessation programs, and dietary modification, should also be part of the intervention (46).

Tooth loss

Tooth loss represents the endpoint of oral diseases, most commonly caries and periodontitis, and the history or paucity of dental treatments (5). The biggest burden of total tooth loss was borne in developed nations (2). Proximal risk factors for tooth loss include oral diseases (e.g., dental caries and periodontal diseases), dental trauma, and dental treatments (47). Intermediate risk factors include age, DM, oral and general health behaviours (e.g., smoking, diet, tooth brushing, dental attendance), while distal risk factors include SES (e.g., income, education) (47,48), community water fluoridation, social relationships, among others (47).

Determinants of oral health

Addressing oral health is complex, as multiple factors influence them (49,50). Oral diseases share common risk factors with NCDs. They are influenced by proximal determinants (i.e., individual's biological and behavioural factors), which are sequentially shaped by intermediate and structural determinants (i.e., broader social, political, cultural, and environmental factors that the individual does not directly control) (5,51).

Turning to the proximal determinants, biological factors include inflammation, infection, and immune response, while behavioural factors include oral hygiene, dietary practices, substance use, physical activity, and sedentariness (5,51,52). Intermediate determinants represent individuals' social position and circumstances, such as income, education, occupation, social relationships, and psychosocial factors (5,51). Income reflects material circumstances and social position influencing people's ability to access health resources. Occupation relates to working conditions (control, autonomy, stress), represents people's relationship to work, and may affect support networks. Education indicates a lifetime measure of SES and captures knowledge that influences their ability to make health-conscious decisions (53,54). Meanwhile, structural determinants refer to socioeconomic, political, and environmental contexts, such as macroeconomic, social and welfare policies and globalisation (5,51). All of

these determinants, however, can also be influenced by commercial determinants (5,55), referring to any corporate activities that can influence health, including marketing campaigns to promote harmful products (e.g., unhealthy diet, tobacco, and alcohol) (55,56).

Besides the broader social environment context, the timing of exposure to risk factors, particularly in early life, is crucial in determining health in later life (57). Incorporating a time element, Fisher-Owens et al. (2007) developed a conceptual framework of children's oral health determinants, which can also be distinguished according to their level of influence. They are child-level influence (e.g., genetics, biology, health behaviours), family-level influence (e.g., SES, parental health status, family functioning, social support, family health behaviours), and community-level influence (e.g., characteristics of the health care system, physical environment and safety) (58). Social support can indirectly influence children's health through their parents, especially mothers. Parents with a high level of social support in their community might be more able to have more friends, relatives, and access to professionals and community resources (59).

Oral hygiene status and care

Oral hygiene is among the most proximal determinants of oral health (5,51). Good oral hygiene is primarily achieved by adopting proper tooth brushing and flossing habits, complemented with regular professional dental cleaning (60-62). Regular preventive dental visits are critical as they enable dental professionals to assess the risk of oral diseases, deliver preventive and restorative treatments, and screen for systemic diseases (63). In a clinical setting, several indices have been developed to measure oral hygiene status, including plaque index (PI), plaque score (PSc), oral hygiene index (OHI), and simplified oral hygiene index (OHI-S), with higher scores indicate worse oral hygiene (64,65).

While the more accurate indicators to assess oral health are through clinical assessment, they might not be feasible to be used in wide-scale population-based studies (66). Given that the main indicator of oral hygiene is the frequency of tooth brushing (67), this measure can also be used to represent the person's oral hygiene (68). Moreover, a previous study has indicated the correlation between self-report oral hygiene measures and clinically confirmed periodontal diseases (66,69).

Metabolic syndrome

MetS, also called insulin resistance syndrome or syndrome X, was first named by Gerald Reaven (70). It represents a clustering of factors (i.e., abdominal obesity, insulin resistance, hypertension, and dyslipidemia) that raise type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) risk occurrence (71,72). MetS is currently becoming a worldwide epidemic (73,74). Despite the MetS prevalence varying according to the use of diagnostic criteria, age group, and ethnicity (74,75), approximately 25% of the global population has the condition (73,75).

MetS imposes a burden on the individual and society. For example, studies showed that MetS was associated with unfavourable quality of life (76), worse hospitalisation (77), severe complications (78), and mortality rates due to coronavirus disease 2019 (COVID-19) (77,78). Another study demonstrated that individuals with MetS had 1.6 times higher mean annual total healthcare costs than those without MetS, with a mean cost rise per additional risk factor of 24% (79).

Several risk factors associated with MetS that have been demonstrated include SES (80), diet (81), smoking (82), physical activity (83), and oral diseases, including periodontal diseases and dental caries (19-21).

Interrelationship between oral health and metabolic syndrome

MetS or its components have been suggested to have an interrelationship with oral diseases (84-87). First, MetS or its components may influence the development of periodontitis through a common pathway of oxidative stress (88,89). They can create a pro-oxidant state that impairs the antioxidant capacity of the periodontal tissues and their responses to bacterial challenges (89). A study by Katz et al. (2005) has shown high expression of receptors of advanced glycation end-product (RAGE) in the periodontal tissues (89,90), indicating the tissues' sensitivity to oxidative damage products. Moreover, since advanced glycation end-products (AGEs) might stimulate apoptosis in osteoblasts (89,91) and fibroblasts (89,92), they might also affect the homeostasis of alveolar bone and the advancement of periodontitis. Both MetS and periodontitis enhance serum levels of oxidative damage products, generating a pro-inflammatory condition (89). Second, MetS or its drug treatments may influence oral health through their effects on salivation (93,94). A meta-analysis found that MetS was associated with tooth loss, which is the end phase of dental diseases, including periodontal diseases and caries (93). Oxidative stress may lead to hyposalivation, resulting in an

increased caries risk (93,95). Several MetS components, including hyperglycemia and hypertension, were also associated with decreased salivary flow rate (93,96).

In addition, the association between oral and systemic diseases could be attributed to the role of oral pathogen and periodontium in the inflammation processes and common risk factors (97). Poor oral hygiene, the main cause of oral diseases, may result in the accumulation of dental plaque, including subgingival biofilm harbouring gram-negative bacteria. The resulting chronic periodontitis could eventually lead to bacteraemia and systemic inflammation (97-101), especially considering periodontium as a cytokine reservoir (97). Invading bacteria originating from severe dental caries or endodontic infections has also been hypothesised to promote similar mechanisms (20,102-104). Finally, the presence of chronic low-grade inflammation corroborates the occurrence of metabolic impairment (104-107).

Poor oral hygiene has been shown to be linked to low-grade inflammation (66), indicating its potential relationship with MetS (108). A study has also shown a relationship between systemic exposure to periodontal bacteria and MetS risk (99). Moreover, the relationships between poor oral hygiene and increased risks of the MetS components, such as obesity (109), DM (110,111), hypertension (111,112), and dyslipidaemia (111,113), have also been demonstrated.

Global overview of oral health status and practice among adolescents

Adolescence is defined as a life period between the age of 10 and 19 years (114). It is a transitional stage from childhood to adulthood, characterised by physical, psychological, and social shifts. During this period, social interaction becomes increasingly crucial, with adolescents spending more time with their peers (115-117). Transformations occurred in this phase may thus affect not only adolescents' oral health status but also behaviours (58,118).

Physical changes during adolescence include physical growth spurt and fat and muscle distribution changes, among others. In terms of dentition, this period usually starts with late transitional dentition and concludes with full permanent dentition. Jaw development follows the course of overall body growth. Malocclusion may become more apparent at this time (119). Furthermore, hormonal changes during puberty could influence the response of periodontal tissues to local factors. Exaggerated response to plaque may occur, resulting in gingival hyperplasia, known as puberty gingivitis (120,121).

Meanwhile, psychologically, peer influence becomes stronger during adolescence as they try to adjust to their peers' behaviours (122,123). Adolescents may also view oral health as important as it relates to appearance and their interactions with others (124,125). A study found that interventions to improve oral health among adolescents should also involve peers and the wider community (126). Finally, given that habits formed during adolescence tend to last until adulthood, this period offers a crucial opportunity for interventions (8,127).

Turning to current oral health status among global adolescents, a review found that the prevalence of cavitated dentine carious lesions among those aged 12 years was above 41%. The mean DMFT scores varied depending on the developmental status of the countries, ranging from roughly 0.9 to 2.1. Of this, the proportion of the decayed component was high, with the lowest prevalence observed in high-income countries (HICs) (128). Furthermore, about 79% of adolescents worldwide had periodontal disease, 19% had BOP, and 50% had calculus (129).

Regarding oral health behaviours, over 5% of school adolescents in 23 LMICs had never or less than once-daily tooth brushing (130). Another study found that the prevalence of twice-daily tooth brushing among school adolescents in Europe and North America ranged from 50% to 81% in 2010 (131). Finally, the prevalence of unmet dental needs among adolescents worldwide was 34%, with the highest prevalence in Southeast Asia and Africa and the lowest in Europe (132).

Indonesian context

Indonesia is an LMIC (133) with over 240 million people, listed as the fourth biggest populous nation in the world. The health system in Indonesia is a combination of public and private providers and financing, with a decentralization policy in the public sector. The Ministry of Health manages several tertiary and specialist hospitals and provides a strategic direction for the health system. Provincial governments direct hospitals at the provincial level, oversee district health services, and manage cross-district health problems within the province, while district/municipal governments direct hospitals at the district/city-level, community health centres (CHCs, or Puskesmas), and other subdistrict facilities. CHCs are responsible for delivering primary care and public health promotion at the community level (134).

One of the responsibilities of CHCs is to organise school-based dental programs (SBDP). It is also the standard to have a dental clinic run by a dentist to provide dental services in the

CHCs (135-138). Nevertheless, in 2011, only 4.8% of CHCs in Indonesia ran comprehensive oral health programs (delivering dental services and organising both SBDP and village community dental health efforts) (139). Limited resources, including shortage and uneven distribution of oral health practitioners, weakness in the management process, and policy orientation of oral health towards curative rather than preventive care, were suggested to undermine the provision of SBDP (135,137,140).

In 2014, Indonesia established the National Health Insurance (NHI, or Jaminan Kesehatan Nasional). The NHI covers dental services in primary care as part of the benefit packages, including counselling, dental scaling, curative care (i.e., dental restoration and minor surgery), and dental emergency care (137,141,142).

Despite the expansion of Indonesian healthcare and improvement in overall health status in recent years (134,135), oral diseases remain a public health challenge (134). The prevalence of self-report oral health problems was 23.4% in 2007 (all ages) (143), 25.9% in 2013 (all ages) (144), and 57.6% in 2018 (aged ≥3 years) (145). The prevalence of active dental caries increased from 43.4% (aged ≥12 years) in 2007 to 53.2% (aged ≥12 years) in 2013, corresponding to over 93 million people with active dental caries in 2013 (143,144,146). In 2018, around 89% had experienced caries and 74% suffered from periodontal diseases. The average DMF-T index was high (7.1), with D-T and M-T serving as the biggest components (145). Such a high prevalence of oral diseases may indicate poor oral hygiene in society (134) and low public awareness of the importance of oral health (147). Only roughly 3% of the population brushed their teeth correctly in 2018, and approximately 5% had a dental visit in the year preceding the survey (145).

Research rationale

This thesis identified several research gaps in the literature. First, regarding global oral health, established and standardised surveillance data on oral diseases at a national level is lacking in LMICs (1,26), such as in Indonesia (133). Most existing oral health studies in Indonesia were based on small sample sizes or limited geographical areas (148-152). Second, most studies investigating the determinants of oral health status and practice have been from developed countries. Since Indonesia is a developing nation with disparities in healthcare resource distributions (153), rapid economic change and modernisation leading to social transition, oral health status and practice among Indonesians, as well as their risk factors,

might differ from those in developed nations. Third, the magnitude of the chronic-oral disease association, such as MetS and periodontal diseases, has been suggested to differ according to the study population or ethnicity (19). There is a dearth of studies on Southeast Asian populations. Asians may have metabolic traits that are distinct from Caucasians who have the same body mass index (BMI), such as elevated percentages of body fat, increased abdominal and visceral fat deposition, and decreased muscle mass and connective tissue (154).

Against this backdrop, investigation of the distribution of oral health status and practice in Indonesian populations, and their risk factors, is of utmost importance for formulating oral health programs and policies in the nation. Given that the main oral health behaviour is oral hygiene practice, and among the most prevalent oral diseases are periodontal diseases (155,156), studying these two can bring valuable contributions to the literature.

Finally, while oral hygiene has been suggested to be associated with cardiometabolic conditions, such as MetS or its components (108-113), epidemiological findings are rather mixed, with some studies found no association (157,158). Ascertaining the current global evidence of the potential influence of oral hygiene on MetS could be useful, as it may aid healthcare practitioners in delivering more holistic care. It may also provide more substance for developing public health policies and programs, notably chronic disease prevention and management strategies.

3. Aims and 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.

Study hypothesis:

1. We hypothesised that better lifestyle and psychosocial factors were associated with better oral hygiene practice among Indonesian adolescents.
2. We hypothesised that better statuses of an individual's biological, behavioural, and social factors were associated with reduced periodontitis risk among Indonesian adults.
3. We hypothesised that improved oral hygiene status and care were associated with reduced MetS risk.

4. 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. The second approach was a systematic review and meta-analytic methodology.

4.1 Prevalence and determinants of oral hygiene practice among Indonesian adolescents

Data source

The Global School-based Health Survey is a survey project fielded in schools. It was established by the World Health Organisation (WHO) and the United States Centers for Disease Control and Prevention (CDC) to examine health behaviour risk and protective factors among in-school adolescents, primarily aged 13-17 years (159,160). The 2015 Indonesia GSHS collected samples using a two-stage cluster sampling design. After selecting schools by applying a probability-proportional-to-size sampling method, the classrooms were systematically sampled. The entire students in the appointed schools and classrooms were asked to complete unidentified, self-administered questionnaires within a regular class period. There was a total of 75 schools chosen, spreading across three regions (Sumatra, Java-Bali, and outside of Sumatra, Java-Bali) in 26 provinces and 68 districts or cities (159,161). The survey had 100% and 94% response rates for schools and students, respectively, with a total number of 11,142 students aged 11-18 years (160). The survey received ethical approval from the Indonesian national government administration and institutional review board or ethics committee (No. LB.02.01/5.2/KE.158/2015). The survey obtained informed consent from students and their parents (161). The dataset can be publicly downloaded from the WHO website (162).

Measurements

Outcome variable

The outcome variable was oral hygiene practice, which was evaluated by asking the frequency of tooth brushing per day. The response options were dichotomised into less than twice a day and a minimum of twice a day. This cut-off point was selected based on the recommendations to maintain optimal oral health (131).

Independent variables

This study included four broad categories of independent variables, including sociodemographic, lifestyle (health status and behaviours), psychological, and social support variables. The sociodemographic variables included age, gender (female/male), and hunger status, which was considered a proxy for measuring SES (163).

The lifestyle variables included dietary practice, physical activity, sedentariness, nutritional status, cigarette smoking, consumption of alcohol, and drug use. We developed the variable of dietary practice from items related to diet available in the survey. We gave one point for each of the following responses: at least twice a day fruit intake, at least three times a day vegetable intake, less than once a day soft drink intake, and less than three times a week fast food intake. We followed the cut-off values employed in a previous study to categorise these responses (164). We summed the points and dichotomised the total score based on the midpoint value into; unhealthy (score 0-2) and healthy (score 3-4) dietary practices. Following the WHO recommendation, physical activity was defined as being physically active for a minimum of one hour a day (165). We defined sedentary behaviour as more than three hours a day spent "sitting and watching television, playing computer games, talking with friends, or doing other sitting activities, such as playing PlayStation" (162,164). The students' body weight and height were assessed to compute BMI, representing their nutritional status. The BMI was then classified into underweight, normal weight, and overweight/obese (159). Cigarette smoking was determined as having smoked cigarettes in the past 30 days, and alcohol consumption as having a minimum of one alcoholic drink in the last 30 days. We defined drug use as having ever used marijuana in life.

The psychological variable included psychological distress. It was assessed using five indicators. We gave one point for each of the following responses: having zero close friends, mostly/always feeling lonely, mostly/always feeling anxious, having suicidal ideations, and having attempted suicide (166). We summed the points and dichotomised the total score according to the midpoint value into; no (score 0) and yes (score 1-5).

The social support variables included peer and parental support. We considered having peer support if students in the school are mostly/always kind and helpful. We constructed the variable of parental support from three questions related to parents or guardians. We gave one point for each of the following responses: mostly/always parental/guardian checking homework, mostly/always parental/guardian understanding children's problems and worries, and mostly/always parental/guardian knowing children's activities in their spare time (164).

We summed the points and dichotomised the total score according to the midpoint value into; no (score 0) and yes (score 1-3).

The variables and their categorisations are shown in detail in Appendix Table 1.

Statistical analysis

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 between 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 (159,167). 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.

4.2 Prevalence and determinants of periodontitis among Indonesian adults

Data source

The Indonesian Basic National Health Research (Riset Kesehatan Dasar / Riskesdas) was a quinquennial, cross-sectional, nationally representative survey aiming to evaluate the health indicators of the population living in Indonesia (145). The 2018 Riskesdas applied a two-stage sampling design, targeting 25,000 households for biomedical and oral health examinations. The first stage was to systematically choose 2,500 census blocks across 26 provinces by taking into account the distribution of samples in each province and stratum at the district/city level. The following stage was to choose ten households in every census block. Entire individuals in the appointed households were included as samples. The survey methodology and sampling procedure have been detailed in previous studies. The 2018 Riskesdas received ethical approval from the Health Research Ethics Commission (Komisi Etik Penelitian Kesehatan / KEPK) of the National Institute of Health Research and Development (NIHRD), Ministry of Health, Indonesia (No. LB.02.01/2/KE.267/2017). The survey obtained informed consent from the participants (145,168).

This study obtained permission from the Data Management Laboratory of NIHRD to use a subset of data of 18,370 non-pregnant adults aged 35 years or older undergoing physical, biomedical, and dental examinations. In this study, we excluded participants who had lost all their teeth (edentulous) (n = 298), had all teeth excluded or not recorded from the periodontal examination (n = 247), had inadequate diagnostic information on hypertension and DM (n = 4322), or had missing information on confounders (n = 144). Of the 13,359, there were three missing values for BOP and 86 for PD. Therefore, the final samples for the outcome of the number of teeth with BOP and PD were 13,356 and 13,273, respectively Almost 359 individuals had all six sextants excluded or not recorded from the CAL examination, and thus the final sample for the outcome of the number of sextants with CAL 13,000.

Measurement

Outcome variables

The outcome variables related to periodontitis in this study were the number of teeth with BOP, the number of teeth with PD, and the number of sextants with CAL. Following the WHO Oral Health Surveys guidelines, trained and calibrated dentists conducted clinical oral examinations at the study site (145). All teeth present, including third molars, were examined for BOP and PD. For every tooth, the BOP status was noted as 0 (no bleeding), 1 (bleeding), 9 (tooth excluded) or X (tooth not present), and the PD status was noted as 0 (no pocket), 1 (pocket 4–5 mm), 2 (pocket 6 mm or greater), 9 (tooth excluded) or X (tooth not present). A tooth was categorised as having PD if the score was 1 or 2. The CAL measurement was only performed on the index teeth (17/16, 11, 26/27, 36/37, 31, 47/46) and was noted as 0 (0–3 mm), 1 (4–5 mm), 2 (6–8 mm), 3 (9–11 mm), 4 (12 mm or greater), X (excluded sextant) or 9 (not recorded) (38,145). A sextant was classified as having CAL if the score was 1, 2, 3, or 4.

Independent variables

This study included four broad categories of independent variables, including sociodemographic, health behaviours, access to health care, and biological variables.

Sociodemographic variables included age, gender (female/male), residential location (urban/rural), education, and occupation. The highest educational attainment level was categorised into primary school or lower, junior and senior high school, and higher education. The occupation type was categorised into non-manual occupation (private or government

employees, entrepreneurs), manual occupation (farmers, fishermen, labourers, drivers, domestic helpers), and 'others' (unemployed individuals, students, others).

Health behaviour variables included cigarette smoking, tobacco chewing, tooth-brushing habits, and dental attendance. Cigarette smoking status was assessed by inquiring whether respondents ever had cigarette smoking, followed by whether they had smoked in the one month preceding the survey. Similarly, respondents were also asked about their tobacco chewing status. According to the responses, we classified cigarette smoking and tobacco chewing statuses as never, past, and current. The measurement of tooth-brushing behaviours was performed by asking respondents whether they had daily tooth brushing. Individuals responding 'yes' were then inquired about their timing of tooth brushing: prior to breakfast, following breakfast, following lunch, during morning shower, during evening shower, and prior to bedtime. We considered those answering 'yes' to the timing of 'following breakfast' and 'prior to bedtime' as having correct brushing time (169). Based on the answers, tooth-brushing behaviours were classified as 'non-daily tooth brushing, 'daily tooth brushing, incorrect timing', and 'daily tooth brushing, correct timing'. The measurement of dental attendance was performed by asking respondents about the frequency of their visits to a dental professional in the year preceding the survey. The answers were classified as less than one time and at least one time.

The variable of overall access to healthcare facilities was created based on index access to three types of healthcare facilities, including hospitals, CHCs, and private practices (145). It was dichotomised into easy (at least one of the three healthcare facility types was considered easy to access) and difficult (none of them was considered easy to access).

The biological factors were MetS or their components. The definition of MetS followed the Joint Interim Statement (JIS), employing the waist circumference (WC) cut-off points for Asian ethnicity (71). MetS was defined if the respondents had three of the following five components: WC ≥90 cm in males and ≥80 cm in females; high-density lipoprotein cholesterol (HDL-C) <40 mg/dL in males and <50 mg/dL in females; triglycerides (TG) ≥150 mg/dL; systolic blood pressure (SBP) ≥130 mmHg and/or diastolic blood pressure (DBP) ≥85 mmHg or prior hypertension diagnosis or consuming antihypertensive drugs; fasting plasma glucose (FPG) ≥100 mg/dL or DM. Respondents were classified as having DM if they had any of the following: prior DM diagnosis; post-load 2-hour plasma glucose ≥200 mg/dL; or random plasma glucose ≥200 mg/dL with classic hyperglycaemia symptoms (polyuria,

polyphagia, polydipsia, and weight loss) (170). The criteria for diagnosing increased TG and decreased HDL-C depended only on biochemical assessments since the survey did not obtain information on drugs consumed for treating these conditions.

Statistical analysis

The characteristics of the sample were summarised by conducting descriptive statistics. Since all the outcome variables (the number of teeth with BOP, the number of teeth with PD, and the number of sextants with CAL) were count data with skewed distributions, the models that could be employed to evaluate the relationship between the independent and outcome variables were Poisson or negative binomial regression. The latter was then chosen due to the over-dispersion of the data. Moreover, considering the variations of the number of teeth and sextants assessed between individuals, the negative binomial models were computed by applying 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). This facilitated the number of possible adverse outcomes to be compared fairly between individuals. We reported rate ratios (RRs) and the corresponding 95% CIs. Weighting was used to make the findings representative of the target population.

For sensitivity analyses of the associations between MetS or its components with periodontitis, we calculated E-values to evaluate the robustness of the findings to potential unobserved confounders. The E-values represent the least risk ratio magnitude of the relationship that an unobserved confounder would require to have with both the exposure and the outcome to negate the observed effect, given the observed covariates. The E-values for both the relationship estimate and the CI bound nearest to the null were computed (171).

Data analyses were performed by applying 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.

4.3 Global association between oral hygiene and metabolic syndrome

We performed the study following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (172). We registered the study protocol on the PROSPERO, with record No. CRD42021243292 (173). This study had the following research question: “Is better oral hygiene status or care associated with a reduced MetS risk?”

Eligibility Criteria

We applied the following inclusion criteria:

1. The study design was cross-sectional, case–control, or cohort.
2. The exposure was 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).
3. The outcome was MetS, which was determined using clear diagnostic criteria (e.g., National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), International Diabetes Federation (IDF), Joint Interim Statement (JIS))
4. The study evaluated the relationship between exposures and outcomes in multiple analyses.

No restrictions on the study population characteristics were applied. Animal studies, clinical trials, case series, case reports, commentaries, editorial letters, and reviews were excluded.

Search Strategy

We searched PubMed and Web of Science databases using the following keywords: oral hygiene, dental deposit, OHI, PI, PSc, tooth brushing, interdental cleaning, dental visit, and MetS. Our search was limited to research published in English and did not impose any restrictions on the date of publication. We conducted our last search on the 17th of March 2021. Our search strategy is shown in detail in Appendix Table 3. We also examined reference lists of eligible studies and relevant systematic reviews to capture additional pertinent studies.

Study Selection and Data Extraction

Two authors screened all titles and abstracts separately to determine eligibility. Relevant studies were further assessed for full-text review. In the presence of discrepancies, they were resolved through consensus discussion. This study used JabRef 5.2 for the review process.

Following the study selection, the two authors separately extracted the data from the studies. 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 measurement, 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. In case of discrepancies, they were resolved through consensus discussion.

Quality Assessment

The two authors separately assessed the included studies' quality by employing the Newcastle–Ottawa Scale (NOS) tools for cross-sectional, case-control, and cohort studies. The scale assessed three primary aspects: the selection of respondents, comparability of the study groups, and the evaluation of the exposure/outcome of interest. For studies with case-control or cohort design, the total score was 9 points, whereas for studies with cross-sectional design was 8 points (174,175). The quality of studies was further categorised into low (0-3 points), moderate (4-6 points), or high (7-9 points). In the presence of discrepancies, they were resolved through consensus discussion.

Statistical Analyses

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 (176). 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 an effect estimate (177). We employed a random-effects (RE) model for the primary analysis to compute an overall pooled OR (DerSimonian and Laird) (178).

The I^2 statistic was computed to evaluate heterogeneity. A value of 50% or greater indicates substantial heterogeneity (176,178). 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 suggested when there was a sufficient number of studies (>10) (179,180).

Meta-analysis was performed employing the generic inverse variance method in Review Manager (RevMan) 5.4 software (The Cochrane Collaboration, 2020) (178,181).

5. Results

5.1. Prevalence and determinants of oral hygiene practice among Indonesian adolescents

Table 1 displays the sociodemographic, lifestyle, and psychosocial attributes of the samples. The weighted average (±SD) age of the students was 14.0 (±1.6) years. Males and those with lower SES (mostly/always being hungry) comprised 48.9% and 4.1% of the samples, respectively. The prevalence of students with tooth-brushing frequency less than twice a day was 10.8%.

Turning to bivariate analysis, compared to students who brushed their teeth frequently, infrequent tooth brushers tended to be male, have lower SES, and have poor dietary practice and longer duration of sedentariness. They also tended to smoke cigarettes, drink alcohol, use drugs, experience psychological distress, receive less peer support, and have no parental support. We found neither significant difference in the percentage of tooth-brushing frequency within the age groups, physical activity levels or nutritional status groups.

Table 1. Distribution of sociodemographic, lifestyle, and psychosocial characteristics of the study population by tooth-brushing frequency

	Total Unweighted N (weighted %)	**<2 times/day Unweighted N (weighted %)**	**≥2 times/day Unweighted N (weighted %)**	**P-value[a]**
Tooth-brushing frequency				
Less than twice daily	1191 (10.8)			
At least twice daily	9873 (89.2)			
Sociodemographic				
Age				
≤11 year old	251 (2.2)	35 (11.4)	216 (88.6)	
12 year old	1796 (17.3)	203 (11.6)	1578 (88.4)	0.714
13 year old	2502 (24.2)	279 (10.6)	2204 (89.4)	
14 year old	2565 (24.1)	280 (11.0)	2263 (89.0)	
15 year old	1943 (14.7)	203 (11.4)	1727 (88.6)	
16 year old	1113 (8.5)	99 (10.1)	1008 (89.9)	
17 year old	776 (7.5)	67 (8.3)	708 (91.7)	
≥18 year old	178 (1.6)	22 (11.7)	155 (88.3)	
Gender				
Male	5090 (48.9)	807 (15.7)	4241 (84.3)	<0.001
Female	6020 (51.1)	381 (6.1)	5604 (93.9)	
Hunger status (proxy for SES)				
Never/rarely/sometimes	10609 (95.9)	1095 (10.4)	9444 (89.6)	<0.001
Mostly/always	482 (4.1)	87 (18.3)	389 (81.7)	
Lifestyle				
Dietary practice				
Unhealthy (score 0-2)	7476 (66.9)	892 (12.2)	6532 (87.8)	<0.001
Healthy (score 3-4)	3453 (33.1)	269 (7.8)	3164 (92.2)	
Physical activity				
0-6 day/week	9594 (87.8)	1039 (11.0)	8490 (89.0)	0.603
7 days/week	1316 (12.2)	135 (10.4)	1175 (89.6)	
Sedentary behaviour				
≤1-2 hour/day	8016 (72.7)	792 (9.8)	7164 (90.2)	0.001
≥3-4 hour/day	2906 (27.3)	373 (13.3)	2519 (86.7)	
Nutritional status				
Normal weight	8139 (76.3)	842 (10.5)	7242 (89.5)	0.312
Underweight	863 (7.9)	102 (12.0)	755 (88.0)	
Overweight/obese	1552 (15.8)	142 (9.4)	1400 (90.6)	
Current smoking				
0 day	9813 (88.4)	963 (9.9)	8797 (90.1)	<0.001
≥1 day	1172 (11.6)	195 (16.1)	958 (83.9)	
Current alcohol use				
0 day	10448 (95.6)	1066 (10.4)	9315 (89.6)	<0.001
≥1 day	473 (4.4)	85 (17.0)	379 (83.0)	
Drug use				
0 time	10771 (98.3)	1109 (10.4)	9596 (89.6)	<0.001
≥1 time	172 (1.7)	47 (28.5)	120 (71.5)	
Psychological factor				
Psychological distress				
No (score 0)	9117 (84.5)	893 (9.9)	8171 (90.1)	0.001
Yes (score 1-5)	1705 (15.5)	234 (13.8)	1460 (86.2)	
Social support				
Peer support				
Never/rarely/sometimes	6695 (60.9)	818 (12.3)	5830 (87.7)	<0.001
Mostly/always	4282 (39.1)	353 (8.4)	3904 (91.6)	
Parental support				
No (score 0)	3907 (35.6)	540 (14.0)	3343 (86.0)	<0.001
Yes (score 1-3)	6900 (64.4)	616 (9.0)	6242 (91.0)	

[a]Differences in the distribution of variables across the frequency of tooth brushing were statistically tested by the adjusted F (a variant of the second-order Rao-Scott adjusted chi-square statistic) and its degrees of freedom.

Table 2 displays the findings of the multiple logistic regression of the relationships between sociodemographic, lifestyle, and psychosocial factors and tooth-brushing frequency. Male, lower SES, sedentary behaviour, drug use, and experiencing psychological distress were associated with brushing teeth infrequently. Healthy dietary practice and peer and parental support were associated with frequent tooth-brushing. The relationships between age, physical activity, nutritional status, cigarette smoking, consumption of alcohol and tooth-brushing frequency were not shown.

Table 2. Associations of sociodemographic, lifestyle, and psychosocial factors with tooth-brushing frequency

Variables	OR (95% CI)
Sociodemographic	
Age	1.06 (0.97-1.15)
Gender	
Female	Ref.
Male	0.36 (0.30-0.43)**
Hunger status (proxy for SES)	
Never/rarely/sometimes	Ref.
Mostly/always	0.60 (0.46-0.79)*
Lifestyle	
Dietary practice	
Unhealthy (score 0-2)	Ref.
Healthy (score 3-4)	1.65 (1.39-1.96)**
Physical activity	
0-6 day/week	Ref.
7 days/week	1.01 (0.78-1.29)
Sedentary behaviour	
≤1-2 hour/day	Ref.
≥3-4 hour/day	0.64 (0.52-0.79)**
Nutritional status	
Normal weight	Ref.
Underweight	0.97 (0.68-1.38)
Overweight/obese	1.15 (0.91-1.47)
Current smoking	
0 day	Ref
≥1 day	1.07 (0.78-1.47)
Current alcohol use	
0 day	Ref
≥1 day	0.99 (0.63-1.56)
Drug use	
0 time	Ref.
≥1 time	0.52 (0.27-0.99)*
Psychological factor	
Psychological distress	
No (score 0)	Ref.
Yes (score 1-5)	0.71 (0.58-0.88)*
Social support	
Peer support	
Never/rarely/sometimes	Ref.
Mostly/always	1.23 (1.03-1.47)*
Parental support	
No (score 0)	Ref.
Yes (score 1-3)	1.33 (1.07-1.66)*

OR (odds ratios) and 95% CI (confidence intervals) were derived from a multiple logistic regression analysis, with tooth-brushing frequency <2 times/day as a reference group. Age was treated as a continuous variable. The model was adjusted for all variables simultaneously.

* P-value <0.05 ** P-value <0.001

5.2 Prevalence and determinants of periodontitis among Indonesian adults

Table 3 displays the characteristics of the samples. The weighted average (±SD) age of the samples 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, and worked in an occupation categorised as ‘others’. The majority were never smokers, were never tobacco chewers, had daily but incorrect timing of tooth brushing, 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%.

Table 3. Characteristics of the study participants

	Unweighted N (Weighted %)	Mean (95% CI) percentage of teeth with BOP	Mean (95% CI) percentage of teeth with PD ≥4 mm	Mean (95% CI) percentage of sextants with CAL ≥4 mm
Total subjects	13359 (100)	30.3 (29.2-31.5)	11.1 (10.3-11.9)	20.3 (19.4-21.2)
Age				
35-64 years	11963 (89.8)	29.8 (28.6-30.9)	10.7 (9.9-11.5)	18.7 (17.8-19.6)
65+ years	1396 (10.2)	35.4 (33.0-37.8)	15.0 (13.3-16.8)	35.3 (32.7-37.9)
Gender				
Male	5137 (37.9)	31.0 (29.6-32.4)	12.8 (11.7-13.8)	23.8 (22.6-25.0)
Female	8222 (62.1)	29.9 (28.8-31.1)	10.1 (9.4-10.9)	18.1 (17.2-19.1)
Residential location				
Rural	6452 (46.4)	32.7 (31.1-34.3)	11.6 (10.4-12.8)	22.1 (20.7-23.5)
Urban	6907 (53.7)	28.3 (26.8-29.8)	10.7 (9.6-11.8)	18.8 (17.6-19.9)
Educational attainment				
Primary school or lower	7881 (60.3)	32.8 (31.4-34.1)	12.1 (11.2-13.1)	22.7 (21.6-23.8)
High school	4602 (33.7)	27.3 (25.9-28.7)	9.9 (8.9-10.9)	16.9 (15.8-18.1)
Higher education	876 (6.1)	22.9 (20.5-25.2)	7.8 (6.4-9.2)	15.4 (13.4-17.4)
Occupation				
Non-manual workers	3377 (24.7)	26.6 (25.1-28.1)	9.7 (8.6-10.7)	17.0 (15.8-18.2)
Manual workers	4716 (34.4)	34.0 (32.3-35.6)	12.9 (11.7-14.0)	23.7 (22.3-25.1)
Others	5266 (40.9)	29.5 (28.2-30.8)	10.5 (9.7-11.4)	19.5 (18.4-20.6)
Cigarette smoking				
Never	9127 (68.2)	30.3 (29.2-31.5)	10.3 (9.6-11.1)	18.6 (17.7-19.5)
Past	940 (7.0)	27.8 (25.4-30.2)	10.6 (9.0-12.2)	19.7 (17.5-22.0)
Current	3292 (24.8)	31.0 (29.4-32.7)	13.4 (12.1-14.6)	25.2 (23.8-26.7)
Tobacco chewing				
Never	12902 (96.9)	30.3 (29.2-31.5)	11.1 (10.3-11.9)	20.1 (19.2-21.0)
Past	170 (1.2)	25.3 (20.7-30.0)	9.5 (6.2-12.7)	24.5 (18.5-30.5)
Current	287 (2.0)	33.8 (28.8-38.8)	12.4 (9.3-15.4)	27.5 (22.8-32.2)
Tooth-brushing behaviour				
Not daily	375 (2.6)	40.6 (35.9-45.4)	14.6 (11.7-17.5)	33.4 (28.5-38.3)
Daily, incorrect time	12600 (94.8)	30.1 (29.0-31.3)	11.1 (10.3-11.9)	20.1 (19.2-21.0)
Daily, correct time	384 (2.6)	27.3 (23.7-31.0)	9.2 (6.5-11.9)	14.9 (11.8-18.0)
Dental visit				
<1 time	11137 (83.4)	30.9 (29.8-32.1)	11.3 (10.4-12.1)	20.6 (19.6-21.5)
≥1 time	2222 (16.7)	27.3 (25.7-29.0)	10.2 (9.2-11.3)	18.9 (17.4-20.4)
Access to healthcare facilities				
Easy	7938 (57.2)	28.8 (27.5-30.1)	10.8 (9.8-11.7)	19.7 (18.7-20.8)
Difficult	5421 (42.9)	32.4 (30.9-34.0)	11.6 (10.6-12.6)	21.0 (19.7-22.3)
MetS				
No	7879 (59.0)	30.4 (29.2-31.6)	11.1 (10.2-12.0)	20.3 (19.2-21.4)
Yes	5480 (41.0)	30.2 (28.9-31.6)	11.1 (10.2-12.1)	20.3 (19.2-21.4)
Hyperglycemia				
No	7376 (55.8)	29.2 (28.0-30.4)	10.2 (9.3-11.1)	18.3 (17.2-19.3)
Yes	5983 (44.2)	31.8 (30.4-33.1)	12.3 (11.3-13.3)	22.9 (21.8-24.0)
Abdominal obesity				
No	7099 (53.0)	31.7 (30.4-33.0)	12.2 (11.2-13.2)	22.4 (21.3-23.5)
Yes	6260 (47.0)	28.8 (27.6-30.1)	9.9 (9.1-10.8)	18.0 (17.0-19.0)
TG				
Normal	9692 (72.7)	30.2 (29.0-31.4)	10.8 (10.0-11.6)	19.8 (18.9-20.8)
Elevated	3667 (27.3)	30.7 (29.2-32.2)	11.9 (10.8-13.0)	21.5 (20.2-22.8)
HDL-C				
Normal	8065 (60.2)	30.4 (29.2-31.6)	11.2 (10.3-12.1)	21.1 (20.0-22.1)
Reduced	5294 (39.9)	30.2 (28.8-31.6)	11.0 (10.1-12.0)	19.2 (18.1-20.3)
Hypertension				
No	4625 (33.7)	30.0 (28.6-31.4)	10.5 (9.6-11.4)	18.5 (17.3-19.6)
Yes	8734 (66.3)	30.5 (29.3-31.7)	11.4 (10.5-12.3)	21.2 (20.2-22.2)

CI = confidence interval; BOP = bleeding on probing; PD = pocket depth; CAL = clinical attachment loss; TG = triglycerides; HDL-C = high density lipoprotein cholesterol; MetS = metabolic syndrome.

Table 4 displays the unadjusted analyses of the associations of sociodemographic and behavioural factors, access to healthcare facilities, MetS and their components with BOP, PD, and CAL. Increasing age, lower level of educational attainment, worse tooth brushing behaviours, hyperglycaemia, and not being abdominally obese were associated with more teeth with BOP, more teeth with PD ≥4 mm, and more sextants with CAL ≥4 mm. Male gender and having elevated TG and hypertension were associated with more teeth with PD ≥4 mm and more sextants with CAL ≥4 mm. Residing in an urban area was associated with fewer teeth with BOP and fewer sextants with CAL ≥4 mm. Compared to those occupations listed as 'others', manual workers tended to have more teeth with BOP, more teeth with PD ≥4 mm, and more sextants with CAL ≥4 mm, while non-manual workers tended to have fewer teeth with BOP and fewer sextants with CAL ≥4 mm. Compared to never smokers, ex-smokers were associated with fewer teeth with BOP, while current smokers were associated with more teeth with PD ≥4 mm and more sextants with CAL ≥4 mm. Compared to never tobacco chewers, former tobacco chewers were associated with fewer teeth with BOP, while current tobacco chewers were associated with more sextants with CAL ≥4 mm. Dental attendance and convenient access to medical facilities were associated with fewer teeth with BOP. MetS was not demonstrated to be associated with BOP, PD, and CAL. Reduced HDL-C was associated with fewer sextants with CAL.

Table 4. Unadjusted associations of sociodemographic and behavioural factors, access to healthcare facilities, MetS, and their components with BOP, PD, and CAL

Variables	Number of teeth with BOP (N=13,356)	Number of teeth with PD (N=13,273)	Number of sextants with CAL (N=13,000)
	Crude RR (95% CI)	Crude RR (95% CI)	Crude RR (95% CI)
Age	1.01 (1.01-1.01)**	1.02 (1.02-1.02)**	1.03 (1.03-1.04)**
Gender (ref: female)			
Male	1.03 (1.00-1.07)	1.26 (1.19-1.34)**	1.33 (1.26-1.40)**
Residential location (ref: rural)			
Urban	0.87 (0.80-0.93)**	0.91 (0.79-1.06)	0.85 (0.78-0.93)*
Education (ref: primary school or lower)			
High school	0.83 (0.79-0.88)**	0.82 (0.74-0.90)**	0.76 (0.70-0.81)**
Higher education	0.70 (0.63-0.78)**	0.65 (0.54-0.79)**	0.70 (0.61-0.80)**
Occupation (ref: others)			
Manual workers	1.15 (1.09-1.22)**	1.23 (1.11-1.36)**	1.23 (1.15-1.32)**
Non-manual workers	0.90 (0.85-0.95)**	0.92 (0.83-1.02)	0.88 (0.82-0.95)*
Smoking (ref: never)			
Former	0.91 (0.84-1.00)*	1.03 (0.88-1.19)	1.09 (0.97-1.22)
Current	1.02 (0.97-1.07)	1.29 (1.19-1.40)**	1.37 (1.29-1.46)**
Chewing tobacco (ref: never)			
Former	0.83 (0.69-0.99)*	0.86 (0.61-1.22)	1.16 (0.89-1.50)
Current	1.12 (0.96-1.29)	1.11 (0.88-1.41)	1.37 (1.15-1.63)**
Tooth brushing (ref: not daily)			
Daily, incorrect	0.75 (0.67-0.85)**	0.78 (0.63-0.95)*	0.60 (0.52-0.70)**
Daily, correct	0.69 (0.58-0.81)**	0.64 (0.46-0.90)*	0.47 (0.36-0.60)**
Dental visit (ref: no)			
Yes	0.88 (0.83-0.93)**	0.91 (0.82-1.01)	0.93 (0.86-1.01)
Access to healthcare (ref: difficult)			
Easy	0.88 (0.83-0.94)**	0.93 (0.83-1.04)	0.94 (0.87-1.02)
MetS (ref: no)			
Yes	0.99 (0.95-1.04)	1.01 (0.92-1.10)	1.01 (0.95-1.08)
Hyperglycaemia (ref: no)			
Yes	1.08 (1.04-1.13)**	1.20 (1.10-1.31)**	1.27 (1.20-1.35)**
Abdominal obesity (ref: no)			
Yes	0.91 (0.87-0.95)**	0.82 (0.75-0.89)**	0.82 (0.77-0.87)**
Elevated TG (ref: no)			
Yes	1.01 (0.97-1.06)	1.11 (1.02-1.21)*	1.10 (1.03-1.17)*
Reduced HDL-C (ref: no)			
Yes	0.99 (0.95-1.04)	0.98 (0.91-1.07)	0.90 (0.85-0.96)*
Hypertension (ref: no)			
Yes	1.01 (0.97-1.06)	1.09 (1.00-1.18)*	1.15 (1.07-1.22)**

BOP = bleeding on probing; PD = pocket depth; CAL = clinical attachment loss; MetS = metabolic syndrome; TG = triglycerides; HDL-C = high density lipoprotein cholesterol. The outcomes were the number of teeth with BOP, the number of teeth with PD, and the number of sextants with CAL. RRs (rate ratios) and 95% CIs (confidence intervals) were derived from negative binomial regression analyses. The log form of the number of examined teeth for BOP and PD was used as an offset variable for the analyses of BOP and PD outcomes, respectively, while the log form of the number of examined sextants was used as an offset variable for the analysis of CAL outcome.

* P-value <0.05 ** P-value <0.001

Table 5 displays the adjusted analyses of the associations between sociodemographic and behavioural factors, access to healthcare facilities, MetS, and their components with BOP, PD, and CAL. In the models adjusted by MetS, increasing age, male, and lower educational attainment levels were demonstrated to be associated with more teeth with BOP, more teeth with PD ≥4 mm, and more sextants with CAL ≥4 mm. Compared to those whose occupations were listed as 'others', manual workers were associated with more teeth with BOP, while non-manual workers were associated with fewer sextants with CAL. Compared to never smokers, former smokers were associated with fewer teeth with BOP, while current smokers were associated with more sextants with CAL ≥4 mm. Compared to non-daily tooth brushing, daily tooth brushing, regardless of the timing, was associated with fewer teeth with BOP, and daily and correct timing of tooth brushing was associated with fewer sextants with CAL ≥4 mm. Both dental attendance and convenient access to medical facilities 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 found to be associated with more teeth with BOP, more teeth with PD ≥4 mm, and more sextants with CAL ≥4 mm. Central obesity, hypertension, declined HDL-C, and increased TG were not shown to be associated with any periodontal health indicators.

Table 5. Adjusted associations of sociodemographic, behavioural factors, access to healthcare facilities, MetS, and their components with BOP, PD, and CAL

Variables	Number of teeth with BOP (N=13,356)		Number of teeth with PD (N=13,273)		Number of sextants with CAL (N=13,000)	
	Adjusted RR (95% CI) †	Adjusted RR (95% CI) ‡	Adjusted RR (95% CI) †	Adjusted RR (95% CI) ‡	Adjusted RR (95% CI) †	Adjusted RR (95% CI) ‡
Age	1.01 (1.00-1.01)**	1.00 (1.00-1.01)**	1.02 (1.01-1.02)**	1.02 (1.01-1.02)**	1.03 (1.03-1.03)**	1.03 (1.03-1.03)**
Gender (ref: female)						
Male	1.08 (1.01-1.15)*	1.06 (0.99-1.14)	1.19 (1.07-1.32)*	1.14 (1.03-1.28)*	1.19 (1.09-1.30)**	1.16 (1.06-1.26)*
Residential location (ref: rural)						
Urban	0.95 (0.88-1.03)	0.96 (0.88-1.03)	1.02 (0.88-1.19)	1.03 (0.88-1.20)	0.93 (0.84-1.03)	0.93 (0.85-1.03)
Education (ref: primary school or lower)						
High school	0.92 (0.87-0.97)*	0.93 (0.88-0.98)*	0.94 (0.84-1.04)	0.94 (0.85-1.05)	0.94 (0.87-1.02)	0.95 (0.88-1.03)
Higher education	0.79 (0.71-0.88)**	0.79 (0.71-0.89)**	0.74 (0.61-0.91)*	0.75 (0.62-0.92)*	0.82 (0.71-0.95)*	0.83 (0.72-0.95)*
Occupation (ref: others)						
Manual workers	1.08 (1.02-1.15)*	1.08 (1.02-1.15)*	1.09 (0.98-1.22)	1.09 (0.97-1.21)	1.04 (0.96-1.13)	1.04 (0.96-1.12)
Non-manual workers	0.95 (0.89-1.00)	0.95 (0.89-1.01)	0.92 (0.82-1.03)	0.92 (0.82-1.03)	0.89 (0.82-0.97)*	0.89 (0.82-0.97)*
Smoking (ref: never)						
Former	0.88 (0.80-0.97)*	0.89 (0.80-0.98)*	0.89 (0.75-1.06)	0.90 (0.76-1.07)	0.89 (0.78-1.01)	0.90 (0.79-1.02)
Current	0.93 (0.86-1.00)	0.93 (0.86-1.00)*	1.10 (0.97-1.25)	1.10 (0.97-1.24)	1.14 (1.04-1.25)*	1.14 (1.04-1.25)*
Chewing tobacco (ref: never)						
Former	0.85 (0.70-1.03)	0.85 (0.71-1.03)	0.81 (0.55-1.18)	0.82 (0.56-1.22)	0.98 (0.76-1.26)	0.98 (0.76-1.27)
Current	1.05 (0.90-1.22)	1.05 (0.90-1.22)	0.99 (0.78-1.24)	0.99 (0.79-1.25)	1.09 (0.91-1.30)	1.10 (0.92-1.31)
Tooth brushing (ref: not daily)						
Daily, incorrect	0.86 (0.76-0.97)*	0.86 (0.77-0.97)*	1.04 (0.84-1.28)	1.04 (0.84-1.28)	0.91 (0.78-1.07)	0.91 (0.78-1.07)
Daily, correct	0.82 (0.69-0.97)*	0.83 (0.70-0.98)*	0.93 (0.66-1.30)	0.93 (0.66-1.31)	0.74 (0.57-0.96)*	0.75 (0.58-0.97)*
Dental visit (ref: no)						
Yes	0.92 (0.87-0.98)*	0.92 (0.87-0.98)*	0.95 (0.86-1.06)	0.96 (0.86-1.07)	1.00 (0.92-1.09)	1.01 (0.93-1.09)
Access to healthcare (ref: difficult)						
Easy	0.93 (0.87-0.98)*	0.93 (0.88-0.98)*	0.99 (0.88-1.10)	0.99 (0.89-1.10)	1.03 (0.95-1.11)	1.02 (0.95-1.11)
MetS (ref: no)						
Yes	1.02 (0.98-1.07)	N/A	1.08 (0.99-1.18)	N/A	1.05 (0.99-1.13)	N/A
Hyperglycaemia (ref: no)						
Yes	N/A	1.06 (1.01-1.11)*	N/A	1.13 (1.03-1.23)*	N/A	1.15 (1.08-1.23)**
Abdominal obesity (ref: no)						
Yes	N/A	0.96 (0.91-1.00)	N/A	0.91 (0.83-1.00)	N/A	0.94 (0.88-1.01)
Elevated TG (ref: no)						
Yes	N/A	1.02 (0.98-1.07)	N/A	1.07 (0.98-1.16)	N/A	1.04 (0.97-1.11)
Reduced HDL-C (ref: no)						
Yes	N/A	1.02 (0.98-1.07)	N/A	1.05 (0.97-1.14)	N/A	0.99 (0.93-1.06)
Hypertension (ref: no)						
Yes	N/A	0.99 (0.95-1.04)	N/A	1.05 (0.96-1.14)	N/A	1.04 (0.97-1.11)

BOP = bleeding on probing; PD = pocket depth; CAL = clinical attachment loss; MetS = metabolic syndrome; TG = triglycerides; HDL-C = high density lipoprotein cholesterol. N/A = not applicable. The outcomes were the number of teeth with BOP, the number of teeth with PD, and the number of sextants with CAL. RRs (rate ratios) and 95% CIs (confidence intervals) were derived from negative binomial regression analyses. The log form of the number of examined teeth for BOP and PD was used as an offset variable for the analyses of BOP and PD outcomes, respectively, while the log form of the number of examined sextants was used as an offset variable for the analysis of CAL outcome.

† Model was simultaneously adjusted for age, gender, residential location, education, occupation, smoking status, chewing tobacco status, tooth-brushing behaviour, dental visit, access to healthcare facilities, and MetS.

‡ Model was simultaneously adjusted for age, gender, residential location, education, occupation, smoking status, chewing tobacco status, tooth-brushing behaviour, dental visit, access to healthcare facilities, hyperglycemia, abdominal obesity, elevated TG, reduced HDL-C, and hypertension.

* P-value <0.05 ** P-value <0.001

The E-values for the point estimates of the relationships between hyperglycaemia and BOP, PD, and CAL were 1.31, 1.51, and 1.57, respectively. Meanwhile, the E-values for the lower CIs were 1.11, 1.21, and 1.37, respectively. The interpretation of these findings would be unobserved confounders could only explain the observed effects when they had a magnitude of RR relationship with both exposure and outcome of a minimum of 1.31 each for BOP, 1.51 each for PD, and 1.57 each for CAL, conditional on the observed confounders. Likewise, the required magnitude of RR for an unobserved confounder to shift the lower CI to 1.00 would be 1.11 for BOP, 1.21 for PD, and 1.37 for CAL, conditional on the observed confounders. The E-values findings can be seen in detail in Appendix Table 2.

5.3 Global association between oral hygiene and metabolic syndrome

5.3.1 Literature search

Figure 1 displays the flowchart of the study selection process. Our search identified a total of 595 articles. Following the removal of 144 duplicates and 380 irrelevant studies, 71 studies were chosen for full-text review. Finally, thirteen studies satisfied the eligibility criteria and were included in the review and meta-analysis.

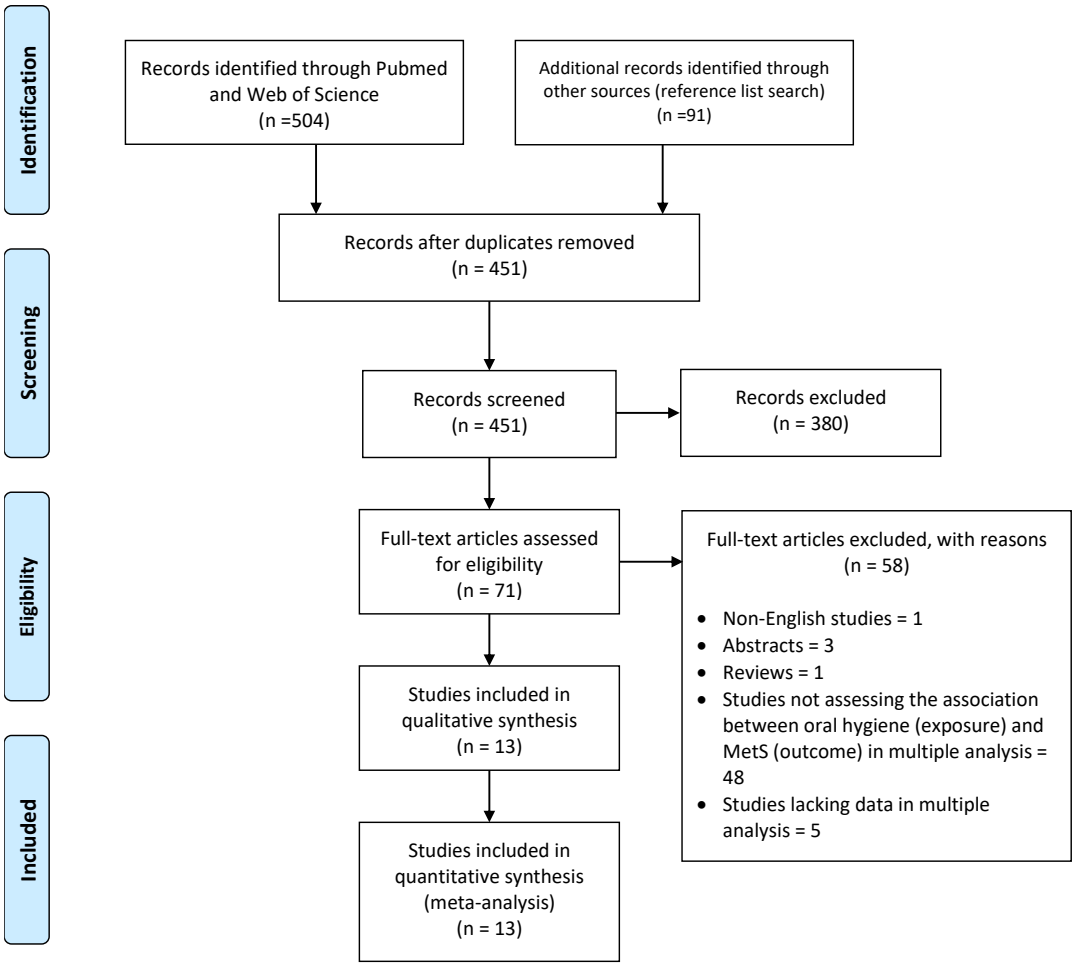


Figure 1. PRISMA flowchart of the literature search and study selection (172). MetS, metabolic syndrome.

5.3.2. Characteristics of studies

Table 6 displays the primary characteristics of the thirteen included studies. 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) (158) 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.

There were six studies reporting oral hygiene status, six reporting tooth-brushing frequency, two reporting interdental cleaning, and one reporting dental attendance as the independent

variables in the studies. In the meta-analysis, we considered a study by Tsutsumi and Kakuma (2015) (182) as two different studies since it calculated the findings for females and males separately rather than as total samples. We used a similar approach for research by Kim et al. (2013) (183) since it reported distinct findings for interdental brushing and flossing.

All studies conducted health examinations to determine 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. The entire included studies, except one (157), used OR as a measure of the relationship.

Table 6. Main characteristics of thirteen studies included in the systematic review and meta-analysis

Author, Publication Year	Country	Study Design	Sample Size (M, F)	Age Range	Type of Oral Hygiene	Diagnostic Criteria for MetS	Number of Cases	Statistical Analysis; Adjustments	Association
Fukui et al., 2012 (184)	Japan	Cross-sectional	6421 (M: 4944, F: 1477)	34–77	Tooth-brushing frequency (times/day)	Modified NCEP ATP III *, except the use of BMI ≥ 25 kg/m^2 to define obesity. Treatments for raised TG and reduced HDL were not recorded.	958	Logistic regression; age, gender, smoking habit, alcohol consumption, C-reactive protein, number of teeth, and periodontal parameter (PD or CAL).	OR (95% CI) Adjusted by PD: ≤1 time daily [reference] 2 times daily = 0.67 (0.57–0.78) ≥3 times daily = 0.50 (0.40–0.64) Adjusted by CAL: ≤1 time daily [reference] 2 times daily = 0.66 (0.57–0.77) ≥3 times daily = 0.50 (0.39–0.63)
Kim et al., 2013 (183)	South Korea	Cross-sectional	18742 (M: 8034, F: 10708)	≥19	Tooth-brushing frequency (times/day), use of dental floss (yes or no), use of interdental brush (yes or no)	Modified NCEP ATP III * for Asians.	5878	Logistic regression; age, gender, income, education, smoking, alcohol intake, and physical activities.	OR (95% CI) Tooth-brushing frequency: ≥3 times daily [reference] 2 times daily = 1.23 (1.12–1.34) ≤1 time daily = 1.23 (1.04–1.47) Use of dental floss: Yes [reference] No = 1.23 (1.07–1.41) Use of interdental brush: Yes [reference] No = 1.05 (0.92–1.20)
Tsutsumi and Kakuma, 2015 (182)	Japan	Cross-sectional	12548 (M: 7703, F: 4845)	30–59	Tooth-brushing frequency (times/day)	Obesity (body mass percentage ≥ 20% in men or ≥30% in women, and/or BMI ≥ 25 kg/m^2) and at least one of the following: TG ≥ 150 mg/dL and/or low HDL < 40 mg/dL or drug for hypertriglyceridemia, SBP ≥ 130 mm Hg and/or DBP ≥ 85 mm	3624	Logistic regression; Males: age, exercise during holidays, favorite seasoning, eating soup, sugar in coffee, having an interest in losing weight, and housekeeping during holidays; Females: age, favorite seasoning, worrying about job, sugar in	OR (95% CI) Males: None [reference] 1 time daily = 0.57 (0.40–0.81) 2 times daily = 0.50 (0.35–0.71) ≥3 times daily = 0.42 (0.29–0.61) Females: ≤1 time daily [reference] 2 times daily = 0.65 (0.48–0.87) ≥3 times daily = 0.44 (0.32–0.62)

Author, Publication Year	Country	Study Design	Sample Size (M, F)	Age Range	Type of Oral Hygiene	Diagnostic Criteria for MetS	Number of Cases	Statistical Analysis; Adjustments	Association
						Hg or drug for hypertension, FPG ≥ 110 mg/dL or drug for diabetes).		coffee, pickles and food boiled in soy sauce, exercise during holidays, eating quickly, preparation of dinner, and solving problems immediately.	
Kim et al., 2019 (185)	South Korea	Cross-sectional	8314 (M: 3860, F: 4454)	35–79	Tooth-brushing frequency (times/day)	Three or more of the following five: WC ≥ 90 cm in men or ≥85 cm in women, TG > 150 mg/dL or treatment for raised TG, HDL < 40 mg/dL in men or <50 mg/dL in women or treatment for reduced HDL, SBP ≥ 130 mm Hg and DBP ≥ 85 mm Hg or antihypertensive medication, FPG ≥ 100 mg/dL or current use of antidiabetic medication.	2834	Logistic regression; age, gender, household income, education, smoking, alcohol intake, physical activity, and periodontitis.	OR (95% CI) Frequency of daily tooth-brushing (continuous) = 0.887 (0.84–0.94)
Saito et al., 2019 (186)	Japan	Cross-sectional	2379 (M: 960, F: 1419)	75 and 80	Use of secondary oral hygiene products, such as dental floss or interdental brushes (none or sometimes or every day)	JIS [ǂ], except the use of BMI ≥ 25 kg/m^2 to define obesity and the use of HbA1c levels ≥ 5.6% to additionally define elevated glucose. Treatments for raised TG and reduced HDL were not included.	563	Logistic regression; age, gender, smoking, exercise, weight gain, eating speed, cholesterol drug intake, community periodontal index, and the number of teeth.	OR (95% CI) None [reference] Sometimes = 1.19 (0.92–1.54) Everyday = 0.71 (0.55–0.92)
Shearer et al.,	New	Cross-sectional	836	38	Modified	NCEP ATP III [¤],	152	Logistic regression;	OR (95% CI)

Author, Publication Year	Country	Study Design	Sample Size (M, F)	Age Range	Type of Oral Hygiene	Diagnostic Criteria for MetS	Number of Cases	Statistical Analysis; Adjustments	Association
2018 (158)	Zealand				OHI-S (very low (0–0.5) or low (>0.5–1.0) or moderate (>1.0–1.5) or high (>1.5))	except the use of HbA1c ≥ 5.7% (≥39 mmol/mol) to define elevated glucose and the use of antihypertensive drugs to additionally define elevated blood pressure.		gender, low socioeconomic status, smoking, dysglycemia, and inflammatory load.	Low [reference] High = 0.95 (0.44, 2.01)
Chen et al., 2011 (187)	Taiwan	Cross-sectional	253 (M:117, F: 136)	>18	PI	Modified NCEP ATP III * for Asians, except the use of FPG ≥ 110 mg/dL or previously diagnosed T2DM to define elevated glucose.	145	Logistic regression; age, gender, education, smoking, high-sensitivity C-reactive protein, and serum albumin.	OR (95% CI) PI score (continuous) = 1.724 (1.135–2.615)
Kobayashi et al., 2012 (188)	Japan	Cohort prospective, 3-year follow-up	685 (M: 513, F: 172)	-	Tooth-brushing frequency (times/day)	JIS ǂ for Asians, except not including treatments for raised TG, reduced HDL, and elevated glucose.	99	Logistic regression; age, gender, smoking status, drinking status, breakfast eating, educational level, occupation (desk work or non-desk work), depressive symptoms, physical activity, and total caloric consumption.	OR (95% CI) ≤1 time daily [reference] 2 times daily = 0.80 (0.49–1.31) ≥3 times daily = 0.43 (0.19–0.97)
Tanaka et al., 2018 (108)	Japan	Cohort retrospective, 5-year follow-up	3722 (M: 2897, F: 825)	35–64	Tooth-brushing frequency (times/day), dental check-ups (regular or irregular)	JIS[ǂ] for Asians, except the use of BMI ≥ 25 kg/m^2 to define obesity.	412	Logistic regression; age, gender, periodontal status, number of present teeth, occupational status, smoking quantity, alcohol consumption, physical activity, dietary behavior, food	OR (95% CI) Tooth-brushing frequency: ≤1 time daily [reference] 2 times daily = 0.83 (0.65–1.05) ≥3 times daily = 0.64 (0.45–0.91) Dental check-ups: Irregular [reference] Regular = 1.10 (0.77–1.55)

Author, Publication Year	Country	Study Design	Sample Size (M, F)	Age Range	Type of Oral Hygiene	Diagnostic Criteria for MetS	Number of Cases	Statistical Analysis; Adjustments	Association
								preference, tooth-brushing frequency, dental check-ups, and number of MetS components at baseline.	
Pussinen et al., 2020 (157)	Finland	Cohort prospective, 21-, 27-, 31-year follow-up	586 (M: 270, F: 316)	27–43	Presence of visible plaque (yes or no)	JIS ǂ for Europeans.	153	Poisson regression; age, gender, childhood BMI, family income, adulthood smoking (ever) and socioeconomic status (education), and interaction terms between caries and periodontal parameters.	RR (95% CI) No [reference] Yes = 1.21 (0.87–1.86)
Pham, 2018 (189)	Vietnam	Case–control (case = 206, control = 206)	412 (M: 114, F: 298)	50–78	PI (≤2.5 or 2.51–2.90 or 2.91–3.26 or ≥3.27)	JIS ǂ for Asians.	206	Logistic regression; age and gender.	OR (95% CI) ≤2.5 [reference] 2.51–2.90 = 4.81 (1.74–13.27) 2.91–3.26 = 6.12 (2.24–16.70) ≥3.27 = 7.50 (2.80–20.12)
Li et al., 2009 (190)	China	Case–control (case = 152, control = 56)	208 (M: 85, F: 123)	37–78	PI (≤1 or >1–1.5 or >1.5–2 or >2)	IDF §	152	Logistic regression; age, gender, and smoking.	OR (95% CI) ≤1 [reference] >1–1.5 = 4.81 (0.81–28.63) >1.5–2 = 13.06 (2.24–76.18) >2 = 47.4 (6.94–323.68)
Li et al., 2020 (191)	China	Case–control (case = 114, control = 49)	163 (M: 60, F: 103)	37–78	PI	IDF §	114	Logistic regression (backward); age, gender, smoking habits, bleeding index, PD, and biomarkers (serum C-reactive protein, salivary IL-6, and IL-1β).	OR (95% CI) PI score (continuous) = 14.69 (5.56–38.84)

M = male; F = female; MetS = metabolic syndrome; WC = waist circumference; BMI = body mass index; TG = triglycerides; HDL = high-density lipoprotein; SBP = systolic blood pressure; DBP = diastolic blood pressure; FPG = fasting plasma glucose; HbA1c = glycated haemoglobin; T2DM = type 2 diabetes mellitus; OHI-S = simplified oral hygiene index; PI = plaque index; PD = probing depth; CAL = clinical attachment level; OR = odds ratio; RR = risk ratio; CI = confidence interval.

[¤] The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) (2001) definition is any three of the following five: WC > 102 cm (>40 in) in men or >88 cm (>35 in) in women, TG ≥ 150 mg/dL, HDL < 40 mg/dL in men or <50 mg/dL in women, blood pressure ≥ 130/85 mm Hg, FPG ≥ 110 mg/dL (192).

* The modified NCEP ATP III (2005) definition is any three of the following five: WC ≥ 102 cm (≥40 in) in men or ≥88 cm (≥35 in) in women (for Asians: ≥90 cm (≥35 in) in men and ≥80 cm (≥31 in) in women), TG ≥ 150 mg/dL (1.7 mmol/L) or treatment for raised TG, HDL < 40 mg/dL (1.03 mmol/L) in men or <50 mg/dL (1.3 mmol/L) in women or treatment for reduced HDL, SBP ≥ 130 mm Hg or DBP ≥ 85 mm Hg or treatment for hypertension, FPG ≥ 100 mg/dL or treatment for elevated glucose (193).

[§] The International Diabetes Federation (IDF) (2005) definition is increased WC (ethnicity-specific) plus any two of the following four: TG ≥ 150 mg/dL (1.7 mmol/L) or treatment for raised TG, HDL <40 mg/dL (1.03 mmol/L) in men or <50 mg/dL (1.29 mmol/L) in women or treatment for reduced HDL, SBP ≥ 130 mm Hg or DBP ≥ 85 mm Hg or treatment for hypertension, FPG ≥ 100 mg/dL (5.6 mmol/L) or previously diagnosed T2DM (194).

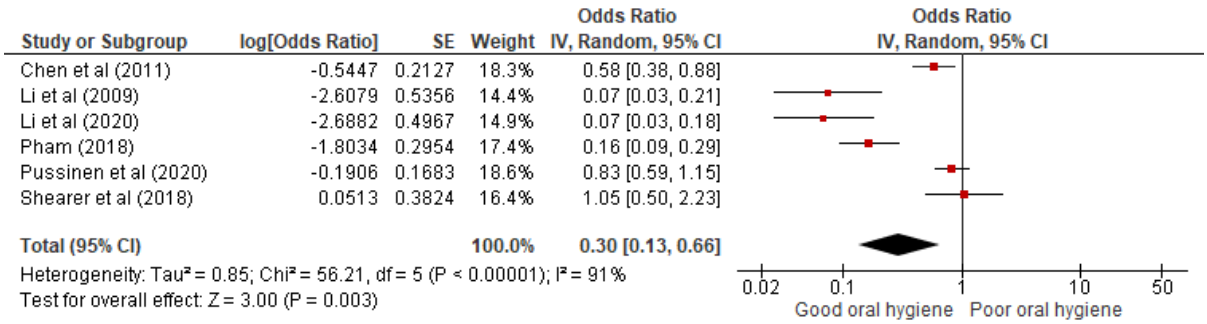
[ǂ] The Joint Interim Statement (JIS) (2009) definition is any three of the following five: increased WC (population- and country-specific), TG ≥ 150 mg/dL (1.7 mmol/L) or treatment for raised TG, HDL <40 mg/dL (1.0 mmol/L) in men or <50 mg/dL (1.3 mmol/L) in women or treatment for reduced HDL, SBP ≥ 130 mm Hg and/or DBP ≥ 85 mm Hg or treatment for hypertension, FPG ≥100 mg/dL or treatment for elevated glucose (71).

5.3.3. Quality studies

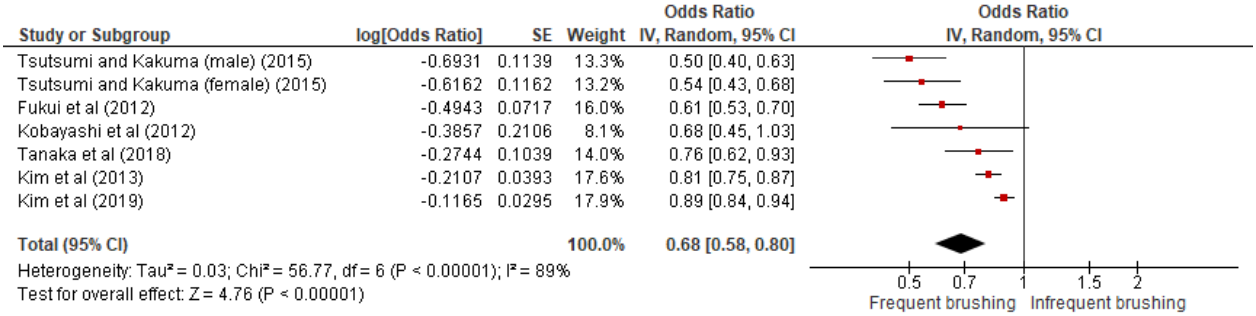
The included studies' qualities ranged from moderate to high. There was one study with a cross-sectional design, two with a case-control design, and three with a cohort design rated as high quality. There were six studies with a cross-sectional design and one study with a case-control design rated as moderate quality. The quality evaluation of the included studies is depicted in detail in Appendix Table 4.

5.3.4. Associations of oral hygiene status and care with MetS

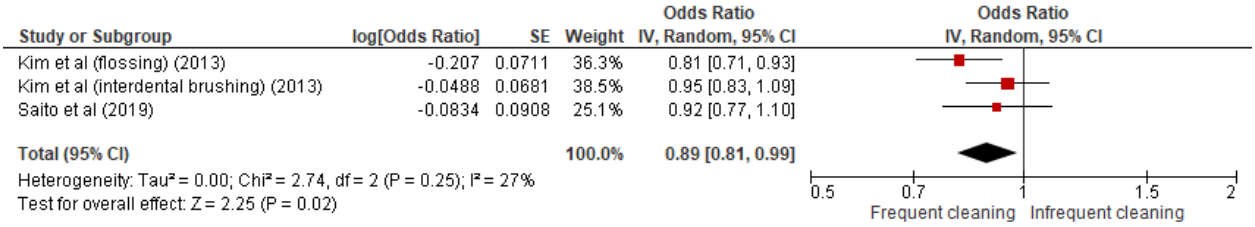
Figure 2 displays the findings of the meta-analysis of the associations of oral hygiene status, tooth-brushing frequency, and interdental cleaning with MetS. Improved oral hygiene status (pooled OR = 0.30; 95% CI 0.13–0.66), brushing teeth frequently (pooled OR = 0.68; 95% CI 0.58–0.80), and interdental cleaning (pooled OR = 0.89; 95% CI 0.81–0.99) were associated with a reduced MetS risk. Although there was minimal heterogeneity for interdental cleaning (I^2 = 27%), there was substantial heterogeneity for the exposure of oral hygiene status (I^2 = 91%) and the frequency of tooth brushing (I^2 = 89%).



(**a**) Good versus poor oral hygiene status



(**b**) Frequent versus infrequent tooth brushing



(**c**) Frequent versus infrequent interdental cleaning

Figure 2. Meta-analysis of the associations of (**a**) oral hygiene status, (**b**) tooth-brushing frequency, and (**c**) interdental cleaning with metabolic syndrome.

The relationship between dental attendance and MetS was investigated only in one study, performed by Tanaka et al. (2018). They showed no relationship between dental attendance and MetS (OR = 1.10; 95% CI 0.77–1.55) (108).

5.3.5. Subgroup analyses

Table 7 depicts the findings of subgroup analysis for the relationship between oral hygiene status and MetS by study design. The relationship between better oral hygiene status and a reduced MetS risk was only noted in the subgroup of case-control studies. The pooled effect estimates of cross-sectional studies indicated no significant relationship. There was not enough study to pool an effect estimate for cohort studies. The subgroup analysis by study design decreased heterogeneity to below 50%.

Table 7. Subgroup analysis by study design for the association between oral hygiene status and MetS.

Subgroup	Number of Studies	OR (95% CI)	I^2 (%)	*p*
Cross-sectional	2	0.72 (0.41–1.26)	46	0.17
Case–control	3	0.11 (0.06–0.20)	39	0.19
Cohort	1	0.83 (0.59–1.15)	-	-

MetS = metabolic syndrome; OR = odds ratio; CI = confidence interval; I^2 = percentage of variation due to heterogeneity; *p* = p-value for heterogeneity.

Table 8 displays the findings of subgroup analyses for the relationship between the frequency of tooth brushing and MetS. In all subgroup analyses, brushing teeth frequently was associated with a reduced MetS risk. Nevertheless, high heterogeneity remained noted in cross-sectional studies. Although subgroup analyses by country decreased heterogeneity, they remained over 50%.

Table 8. Subgroup analyses for the association between tooth-brushing frequency and MetS.

Subgroup	Number of Studies	OR (95% CI)	I^2 (%)	*p*
Study design				
Cross-sectional	5	0.67 (0.55–0.81)	93	<0.001
Cohort	2	0.74 (0.62–0.89)	0	0.64
Country				
Japan	5	0.61 (0.52–0.70)	55	0.06
Korea	2	0.85 (0.78–0.93)	73	0.06

MetS = metabolic syndrome; OR = odds ratio; CI = confidence interval; I^2 = percentage of variation due to heterogeneity; *p* = p-value for heterogeneity.

6. Discussion

6.1 Main discussion

This thesis aimed to map the oral health status and practice and their determinants in the Indonesian populations and to investigate the global relationship between oral hygiene and MetS. To achieve these aims, we conducted two empirical studies employing data from Indonesian national health surveys and a systematic review and meta-analysis study. 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 of them had poor oral hygiene practice. We found that 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.

The prevalence of school adolescents in Indonesia brushing their teeth a minimum twice a day was similar to the figures reported in other nations, such as Malaysia (87%) (195) and the Philippines (89%) (130). Conversely, our study's prevalence was smaller than those in South Korea (93%) (196) but greater than those in the United Arab Emirates (57%) (130), China (44%) (197), and the average in Europe and North America (65%) (198), and nine nations in Africa (77%) (199).

Both oral and general health habits are shaped by the complex interaction between individual attributes and family, social, cultural and environmental determinants (200,201). Our study showed a positive relationship between the male gender and poor oral hygiene practice, corroborating the findings of other studies (199,202). Males might be less concerned about aesthetics and have a lower level of oral health awareness than females (203). Our study could not find any relationship between age and oral hygiene practice, which was in line with findings from previous studies (199,202). 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 (204,205).

Our study found that adolescents with better dietary practices typically adopt better oral hygiene practice, which was consistent with previous studies (202,206). 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 (204,206). 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 (207). Furthermore, a study 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, which simultaneously represents poor oral health behaviours (208).

Prior research among adolescents in Finland has demonstrated that nutritional status and physical activity were associated with oral hygiene practice (209). Nutritional status and physical activity could represent the disposition toward a healthy lifestyle and the ability to preserve health and well-being (210,211). Nonetheless, our study could not find any relationships between nutritional status and physical activity and oral hygiene practice, corroborating the results of another study (202). This finding might be due to the low awareness of the physical activity level recommended by WHO, as only roughly a tenth of students were physically active for a minimum of one hour per day in our study.

Previous studies have found a relationship between substance use (e.g., cigarettes, alcohol, and cannabis) and worse tooth-brushing behaviours (68,212). Health risk behaviours often exist in the same social context. Smokers might brush their teeth for appearance rather than for oral health maintenance (213). Those consuming alcohol might have ignored tooth brushing after drinking (214), whereas drug abusers might view oral health as a low priority (215). Our study could only observe 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. As found by another study, smokers might not have differing tooth-brushing habits in respect of frequency but rather in duration compared to non-smokers (212). 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 (216).

Our study found a positive relationship between 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 (204). 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 (217,218). Furthermore, our study found a positive relationship between peer support and brushing teeth frequently, as confirmed by a prior study (219). 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 (124,219). 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 (219,220). Our study demonstrated a relationship between psychological distress and brushing teeth infrequently, as confirmed by another study. Several depressive symptoms, including fatigue, psychomotor impairment, and demotivation, might undermine the oral health behaviours of individuals (221).

Oral hygiene practice adopted in adolescence is usually sustained into adulthood (127) and is the primary risk factor for oral diseases (222). Among the most prevalent oral diseases are periodontal diseases, which are common among adults (155,156). Our second empirical study examined the prevalence and determinants of periodontitis among adults in Indonesia. We found that more than 40% of adults had periodontitis. Increasing age, male gender, lower educational attainment and occupation status, worse tooth-brushing habits, less dental attendance and access to healthcare, 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, chewing tobacco status, MetS, central obesity, hypertension, and dyslipidaemia were not shown to be associated with any of the periodontal health indicators.

Our findings showed that increasing age was associated with periodontitis, as reported by previous studies (35,223). Older adults might have more severe periodontitis than younger adults due to lifetime cumulative tissue destruction (35,224) and increased periodontal

susceptibility due to alteration in tissue repair capacity and exposure to pro-inflammatory conditions (225). Similar to previous studies, our study found that the male gender was associated with periodontitis (35,226). It was suggested that the difference might not only be due to behavioural and environmental characteristics, but also sexual dimorphism in host immunity (227,228). Although current evidence remains inconclusive, sex-specific genetic architecture, sex steroid modulation, or their combination were hypothesised to play a role in the sex differences in immunity (228-230). X-linked genes have been found to regulate pattern recognition receptors, cytokine synthesis, and transcriptional factors (227,231). Sex steroid hormones may affect immunity. It is suggested that estrogen tends to enhance immune response, while testosterone suppresses them (227,232,233).

In line with previous studies, educational attainment and occupation were associated with periodontitis (35,223,234). Lower educational attainment is often associated with worse coping strategies, poorer awareness of periodontal health and oral hygiene, less access to dental care, being a smoker, and having a higher BMI and T2DM, which are the risk factors for periodontitis (234). Occupation might influence the social environment, behaviours, and psychosocial factors of individuals (235). For example, compared to non-manual workers, manual workers tend to have less income (236) and less access to dental care (237), experience more psychosocial hazards (238), have a higher level of stress (239) and poorer sleep quality (240), and exhibit health-risk behaviours (i.e., smoking and drinking alcohol) (241). Lack of flexibility in day-to-day life may also lead to reduced frequency and effectiveness of tooth-cleaning (235,242).

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 (243). 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. Our results were consistent with those found in prior research (244,245). Nicotine might induce gingival vasoconstriction, resulting in reduced signs of inflammation, such as redness and bleeding. It was also suggested that the suppressed inflammatory reaction might indicate reduced host defence capacity (244). Other effects of smoking might involve enhancing pathogen-enriched microflora in the subgingival

(246), suppressing fibroblast proliferation and attachment (247,248), and promoting collagen breakdown (248) and bone resorption (249,250), which might lead to CAL (250,251).

Our study showed a positive relationship between hyperglycaemia and periodontitis, as confirmed by prior studies (252,253) and a joint statement by the International Diabetes Federation (IDF) and the European Federation of Periodontology (EFP) (254). Hyperglycaemia influences the development of periodontitis through several pathways. Firstly, it promotes the generation of irreversible AGEs and their interactions with RAGEs, 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 (254,255). 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 (256,257). 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 (255).

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 previous studies (258-262). 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 (253,263). Moreover, a study by Nascimento et al. (2019), employing structural equation modelling, showed that the relationship between MetS and periodontitis depended on analytical methods. There was no relationship between MetS and periodontitis when both diseases were considered as observed categorical variables, but there was a positive relationship when multiple dimensions of both diseases were considered as latent or construct variables (264). Similarly, hypertension and dyslipidaemia

might only have an additive effect on the risk of periodontitis if they are complemented with hyperglycaemia and/or obesity (256). Furthermore, a study suggested that insulin resistance, rising with obesity, plays a more prominent role since it might act as a mediator for the association between obesity and periodontitis (262).

Poor oral hygiene is the main cause of oral diseases, including periodontitis (243,265). 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 (108). Our findings indicated the need for further well-designed longitudinal studies to confirm the association between oral hygiene and MetS.

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 (157,158). There are some possible explanations for the dissimilarities in their findings from those of other studies. First, it might be due to differences in 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 or older. Shearer et al. (2018) argued that it might only be in later life that the influence of periodontal inflammation on cardiometabolic health becomes apparent (158). 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 (157).

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 for 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 (243,266). 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 also demonstrated similar findings, suggesting that brushing teeth less frequently than twice a day might not benefit DM prevention (176). 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 (267).

Poor oral hygiene has been suggested to worsen MetS by raising local and systemic inflammation (268). Periodontal bacteria in plaque, their products, and local inflammatory response may gain entry into the circulation and contribute to systemic inflammation (269). Exposure to pro-inflammatory cytokines (e.g., TNF-α and IL-1β) in the long term may change the metabolism of lipids, leading to hyperlipidemia (270). 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 (271). Increased pro-inflammatory cytokines levels may also contribute to the dysfunction of pancreatic β-cells, resulting in the occurrence of T2DM (270,272,273). Moreover, a recent study demonstrated that infection with *Porphyromonas gingivalis* could promote the development of metabolic disorders through gut microbiome alteration (274).

Alternatively, an explanation for the relationship between oral hygiene care and MetS might be attributed to common risk factors (98) or biased health consciousness. It is plausible that people adopting healthier lifestyles might also have improved oral hygiene care (275). It was argued that oral hygiene care might only be a reflection of general health awareness or behaviours, underlining the complexity of oral epidemiology (276). 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) (108). 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 (110). On the other hand, a review has shown that scaling and root planning could be beneficial for metabolic control and decreasing systemic inflammation in T2DM patients (277).

6.2 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 (159,160). 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 (38). 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 meta-analysis study was the first to provide global evidence of the relationship between oral hygiene and MetS. Following a systematic review, we conducted a meta-analysis to assess the strength of evidence (278), providing a summary estimate of the effect size (178). 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 (279). Furthermore, studying this topic is important for developing strategies that target common risk factors for oral and general health (93). 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 the 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. The latter is a crucial feature of oral health behaviours owing to its caries prevention effectiveness (280). 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 adolescents who are out of school or children in the younger age groups should also be proceeded with caution. Future studies should capture more psychosocial indicators, including sense of coherence, and 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 (269,281,282). For instance, longer dip duration and cumulative exposure to smokeless tobacco products in South Asia (e.g., Naswar) were associated with an elevated oral cancer risk (283), which is a crucial dimension of the periodontal assessment. However, the calculated E-values for the relationship between hyperglycaemia and CAL were relatively higher than other known confounders of periodontitis, for example, age and smoking (Appendix Table 2). This finding might indicate that bias originating from unobserved confounders would not be large.

Other limitations in this study 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 (38). Future studies might consider adopting a recording protocol that could allow the development of a case definition for periodontitis. 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. The parameters of BOP and PD represent periodontal inflammation, and CAL represents the accumulation of periodontal destruction (35-37).

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, an assessment of publication bias could not be undertaken as it was not suggested for a review with an inadequate number of studies (<10). Low test power might lead to misleading interpretation (179,180,284). Third, besides study design and country, other sources of heterogeneity in our meta-analysis 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 criteria used to define MetS.

Further limitations in our review and meta-analysis 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 (254). 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 (adjusted OR (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 higher education degrees 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), brushing teeth frequently (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 the 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.

Summary

Standardised surveillance data on oral health is lacking in LMICs, such as Indonesia, hindering the progress towards achieving global oral health. Furthermore, there was no summary of evidence on the relationship between oral hygiene and MetS. The aims of this thesis were: 1) to investigate the prevalence and factors associated with oral hygiene practice among Indonesian adolescents; and 2) periodontitis among Indonesian adults; 3) to quantitatively synthesize the body of evidence of the association between oral hygiene and MetS.

This thesis consisted of two empirical studies and a systematic review and meta-analysis. The first study used cross-sectional data from the 2015 Indonesia GSHS, covering 11,142 students aged 11-18 years. Logistic regression was employed to compute the ORs and 95% CIs. Around 10.8% of the students had less than twice a day tooth-brushing. Male gender, lower SES, poor dietary practice, sedentariness, drug use, psychological distress, less peer support, and no parental support were associated with brushing teeth infrequently. The second study used cross-sectional data from the 2018 Indonesia National Health Survey, covering 13,359 dentate individuals aged 35+ years. Negative binomial regression was applied to compute the RRs and 95% CIs. Over 40% of adults had periodontitis. Increasing age, male gender, lower educational attainment and occupation status, worse tooth-brushing habits, less dental attendance and access to healthcare, and hyperglycemia 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, chewing tobacco status, MetS, central obesity, hypertension, and dyslipidaemia were not found to be associated with any periodontal health indicators. The third study was a systematic review and meta-analysis. A search on PubMed and Web of Science databases until March 17th, 2021, was undertaken to identify eligible studies on the relationship between oral hygiene and MetS. Random-effect models were employed to pool the effect estimates. We found overall negative relationships between oral hygiene status, the frequency of tooth brushing, interdental cleaning and MetS. Nevertheless, substantial heterogeneity for the exposure of tooth-brushing frequency and inconsistent findings for oral hygiene status in subgroup analyses were noted. There was inadequate evidence on the relationship between dental attendance and MetS.

Overall, our empirical studies indicated a need to improve oral health in Indonesia. The existence of social disparities and gender differences in oral health was observed. Intersectoral interventions targeting not only individuals, but also upstream social, political, and economic factors could be beneficial in reducing inequalities. Specifically, integrating oral health promotion into general health actions addressing adolescents' families, schools, and social environments is warranted to promote healthier behaviours. Furthermore, our findings confirmed the evidence of the potential roles of hyperglycemia on periodontitis. Integrating oral health into routine DM care could reduce the disease burden. Regarding MetS, further studies examining its role in periodontitis would be worthwhile. Similarly, high-quality longitudinal studies are needed to confirm the relationship between oral hygiene and MetS.

Keywords

Oral health, oral hygiene, tooth brushing, periodontitis, dental health surveys, cardiometabolic condition, metabolic syndrome, hyperglycaemia

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Appendix

Appendix Table 1. List of the GSHS variables used in this study

Variables	Questions	Categories
Oral hygiene practice		
Tooth-brushing frequency	During the past 30 days, how many times per day did you usually brush your teeth?	1 = ≥2 times/day 0 = <2 times/day
Demographics		
Age	How old are you?	≤11 – ≥18 year old
Sex	What is your sex?	1 = male, 0 = female
Hunger status (proxy for SES)	During the past 30 days, how often did you go hungry because there was not enough food in your home?	1 = mostly/always 0 = never/rarely/sometimes
Dietary Practice[a]: created by adding the results of the coding below		
Fruits	During the past 30 days, how many times per day did you usually eat fruit, such as pineapples, bananas, oranges, or watermelons?	1 = ≥2 times/day 0 = <2 times/day
Vegetables	During the past 30 days, how many times per day did you usually eat vegetables, such as carrots, cabbage, or spinach?	1 = ≥3 times/day 0 = <3 times/day
Soft drinks	During the past 30 days, how many times per day did you usually drink carbonated soft drinks?	1 = <1 time/day 0 = ≥1 time/day
Fast food	During the past 7 days, on how many days did you eat food from a fast food restaurant?	1= <3 d/week 0 = ≥3 d/week
Physical activity	During the past 7 days, on how many days were you physically active for a total of at least 60 minutes per day?	1 = 7 days 0 = <7 days
Sedentary behaviour	How much time do you spend during a typical or usual day sitting and watching television, playing computer games, talking with friends, or doing other sitting activities such as playing PlayStation?	1 = ≥3-4 hours/day 0 = <3 hour/day
Nutritional status (BMI):		
Height	How tall are you without your shoes on?	used for BMI calculation
Weight	How much do you weigh without your shoes on?	used for BMI calculation
Current smoking	During the past 30 days, on how many days did you smoke cigarettes?	1 = ≥1 day 0 = 0 day
Current alcohol use	During the past 30 days, on how many days did you have at least one drink	1 = ≥1 day 0 = 0 day

Variables	Questions	Categories
	containing alcohol?	
Drug use	During your life, how many times have you used marijuana?	1 = ≥1 times 0 = 0 times
Psychological Distress[b]: created by adding the results of the coding below		
Close friends	How many close friends do you have?	1= 0 friends 0 = ≥1 friends
Loneliness	During the past 12 months, how often have you felt lonely?	1 = mostly/always 0 = never/rarely/sometimes
Anxiety	During the past 12 months, how often have you been so worried about something that you could not sleep at night?	1 = mostly/always 0 = never/rarely/sometimes
Suicidal ideation	During the past 12 months, did you ever seriously consider attempting suicide?	1 = yes 0 = no
Suicidal attempt	During the past 12 months, how many times did you actually attempt suicide?	1 = ≥1 times 0 = 0 time
Peer support	During the past 30 days, how often were most of the students in your school kind and helpful?	1 = mostly/always 0 = never/rarely/sometimes
Parental Support[c]: created by adding the results of the coding below		
Parental/guardian supervision	During the past 30 days, how often did your parents or guardians check to see if your homework was done?	1 = mostly/always 0 = never/rarely/sometimes
Parental/guardian connectedness	During the past 30 days, how often did your parents or guardians understand your problems and worries?	1 = mostly/always 0 = never/rarely/sometimes
Parental/guardian's knowledge of their free time	During the past 30 days, how often did your parents or guardians really know what you were doing with your free time?	1 = mostly/always 0 = never/rarely/sometimes

GSHS = Global School-based Health Survey; SES = socioeconomic status; BMI = body mass index.
[a]The scores were summed and categorised based on the median value into unhealthy (score 0-2) and healthy (score 3-4) dietary practice.
[b]The scores were summed and categorised based on the median value into no (score 0) and yes (score 1-5).
[c]The scores were summed and categorised based on the median value into no (score 0) and yes (score 1-3).

Appendix Table 2. E-values for observed associations of MetS and its components with the number of teeth with BOP, the number of teeth with PD, and the number of sextants with CAL

	Number of teeth with BOP RR (95% CI)	**Number of teeth with PD ≥4 mm RR (95% CI)**	**Number of sextants with CAL ≥4 mm RR (95% CI)**
	N = 13,356	**N = 13,273**	**N = 13,000**
MetS			
Observed association	1.02 (0.98-1.07)	1.08 (0.99-1.18)	1.05 (0.99-1.13)
E-value for point estimate	1.16	1.37	1.28
E-value for CI	1.00	1.00	1.00
Hyperglycaemia			
Observed association	1.06 (1.01-1.11)	1.13 (1.03-1.23)	1.15 (1.08-1.23)
E-value for point estimate	1.31	1.51	1.57
E-value for CI	1.11	1.21	1.37
Abdominal obesity			
Observed association	0.96 (0.91-1.00)	0.91 (0.83-1.00)	0.94 (0.88-1.01)
E-value for point estimate	1.25	1.43	1.32
E-value for CI	1.00	1.00	1.00
Elevated TG			
Observed association	1.02 (0.98-1.07)	1.07 (0.98-1.16)	1.04 (0.97-1.11)
E-value for point estimate	1.16	1.34	1.24
E-value for CI	1.00	1.00	1.00
Reduced HDL-C			
Observed association	1.02 (0.98-1.07)	1.05 (0.97-1.14)	0.99 (0.93-1.06)
E-value for point estimate	1.16	1.28	1.11
E-value for CI	1.00	1.00	1.00
Hypertension			
Observed association	0.99 (0.95-1.04)	1.05 (0.96-1.14)	1.04 (0.97-1.11)
E-value for point estimate	1.11	1.28	1.24
E-value for CI	1.00	1.00	1.00

RR = rate ratio; CI = confidence interval; BOP = bleeding on probing; PD = pocket depth; CAL = clinical attachment loss; MetS = metabolic syndrome; TG = triglycerides; HDL-C = high density lipoprotein cholesterol.

Appendix Table 3. Database search strategy

Database		Search strategy	Number of studies
PubMed		("oral hygiene"[Mesh] OR "toothbrushing"[Mesh] OR "Dental Devices, Home Care"[Mesh] OR "oral hygiene" OR "tooth brush*" OR "toothbrushing" OR "interdental cleaning" OR "interdental brush*" OR floss* OR "dental visit" OR "dental attendance" OR "dental deposits"[Mesh] OR "dental plaque"[Mesh] OR "dental deposit*" OR "dental plaque" OR "oral plaque" OR "Dental plaque index"[MeSH] OR "Oral hygiene index"[MeSH] OR "plaque score" OR "oral hygiene index" OR "plaque index" OR "oral health"[Mesh] OR "mouth diseases"[Mesh] OR "oral health behavior" OR "dental health behavior" OR "oral hygiene practice") AND ("metabolic syndrome"[Mesh] OR "metabolic syndrome" OR "metabolic syndrome X" OR "Metabolic X Syndrome" OR "Cardiometabolic Syndrome" OR "Dysmetabolic Syndrome X" OR "dysmetabolic syndrome" OR "Insulin Resistance Syndrome X" OR "Metabolic Cardiovascular Syndrome" OR "Reaven Syndrome X" OR "Syndrome X" OR "insulin resistance syndrome" OR "plurimetabolic syndrome") Filters: English	271
Web of Science	1	ALL FIELDS: (“oral hygiene” OR “tooth brush*” OR “toothbrushing” OR “interdental cleaning” OR “interdental brush*” OR floss* OR “dental visit” OR “dental attendance” OR “dental deposit*” OR “dental plaque” OR “oral plaque” OR “plaque score” OR “oral hygiene index” OR “plaque index” OR “oral health behavior” OR “dental health behavior” OR “oral hygiene practice”) OR TOPIC: (“oral health” OR “mouth disease*”) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years	59,826
	2	ALL FIELDS: (“metabolic syndrome” OR “metabolic syndrome X” OR “Metabolic X Syndrome” OR “Cardiometabolic Syndrome” OR “Dysmetabolic Syndrome X” OR "dysmetabolic syndrome" OR “Insulin Resistance Syndrome X” OR “Metabolic Cardiovascular Syndrome” OR “Reaven Syndrome X” OR “Syndrome X” OR “insulin resistance syndrome” OR “plurimetabolic syndrome”) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years	109,997
	3	#1 AND #2 Refined by: LANGUAGES: (ENGLISH) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years	233

Note: The date of the last search was March 17, 2021.

Appendix Table 4. Quality assessment of the 13 included studies

Study	Study design	Selection	Comparability	Outcome / Exposure	Total score
Fukui et al, 2012 (184)	Cross-sectional	1	2	2	5 / 8
Kim et al, 2013 (183)	Cross-sectional	2	2	2	6 / 8
Tsutsumi and Kakuma, 2015 (182)	Cross-sectional	0	2	2	4 / 8
Kim et al, 2019 (185)	Cross-sectional	2	2	2	6 / 8
Saito et al, 2019 (186)	Cross-sectional	1	2	2	5 / 8
Shearer et al, 2018 (158)	Cross-sectional	3	2	2	7 / 8
Chen et al, 2011 (187)	Cross-sectional	1	2	2	5 / 8
Kobayashi et al, 2012 (188)	Cohort	2	2	3	7 / 9
Tanaka et al, 2018 (108)	Cohort	2	2	3	7 / 9
Pussinen et al, 2020 (157)	Cohort	3	2	3	8 / 9
Pham, 2018 (189)	Case-control	3	1	1	5 / 9
Li et al, 2009 (190)	Case-control	3	2	2	7 / 9
Li et al, 2020 (191)	Case-control	3	2	2	7 / 9

Note: The quality of the included studies was assessed using Newcastle-Ottawa Scale for cross-sectional, case-control, and cohort studies, as applicable. The maximum score for cross-sectional studies was 8 points (4 for selection, 2 for comparability, and 2 for outcome). The maximum score for case-control studies was 9 points (4 for selection, 2 for comparability, and 3 for exposure). The maximum score for cohort studies was 9 points (4 for selection, 2 for comparability, and 3 for outcome) (174,175).

Publication List

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Registry number: DEENK/407/2022.PL
Subject: PhD Publication List

Candidate: Cornelia Melinda Adi Santoso
Doctoral School: Doctoral School of Health Sciences

List of publications related to the dissertation

1. **Santoso, C. M. A.**, Bramantoro, T., Kardos, L., Szakács, D. F., Nagy, A. C.: Metabolic syndrome and periodontitis among adults: the 2018 Indonesia National Health Survey.
   J. Clin. Periodontol. 49 (6), 562-572, 2022.
   DOI: http://dx.doi.org/10.1111/jcpe.13622
   IF: 7.478 (2021)
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.
   J Clin Med. 10 (13), 1-16, 2021.
   DOI: http://dx.doi.org/10.3390/jcm10132873
   IF: 4.964
3. **Santoso, C. M. A.**, Bramantoro, T., Nguyen, M. C., Nagy, A. C.: Lifestyle and psychosocial correlates of oral hygiene practice among Indonesian adolescents.
   Eur. J. Oral. Sci. 129 (1), 1-10, 2021.
   DOI: http://dx.doi.org/10.1111/eos.12755
   IF: 2.16

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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.
   Int. J. Environ. Res. Public Health. 18 (19), 10209-, 2021.
   DOI: http://dx.doi.org/10.3390/ijerph181910209
   IF: 4.614
5. Bramantoro, T., **Santoso, C. M. A.**, Hariyani, N., Setyowati, D., Zulfiana, A. A., Nor, N. A. M., Nagy, A. C., Pratamawari, D. N. P., Irmalia, W. R.: Effectiveness of the school-based oral health promotion programmes from preschool to high school: a systematic review.
   PLoS One. 16 (8), 1-16, 2021.
   DOI: http://dx.doi.org/10.1371/journal.pone.0256007
   IF: 3.752
6. **Santoso, C. M. A.**, Bramantoro, T., Nguyen, M. C., Bagoly, Z., Nagy, A. C.: Factors Affecting Dental Service Utilisation in Indonesia: a Population-Based Multilevel Analysis.
   Int. J. Environ. Res. Public Health. 17 (15), 1-11, 2020.
   DOI: http://dx.doi.org/10.3390/ijerph17155282
   IF: 3.39

Total IF of journals (all publications): 26,358
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