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Epidemiology of Periodontal Health

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EPIDEMIOLOGY OF PERIODONTAL HEALTH

Diagnosis, trends, and systemic relationships

Epidemiology of Periodontal Health

Diagnosis, trends, and systemic relationships

PhD thesis

to obtain the degree of PhD at the University of
Groningen on the authority of the Rector
Magnificus Prof. C. Wijmenga and in accordance
with the decision by the College of Deans.

This thesis will be defended in public on
13 October 2021 at 9:00 (am)

by

An Li

born on 24 August 1988
in Anhui, China

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Dedicated to my beloved parents

Epidemiology of Periodontal Health

diagnosis, trends, and systemic relationships

1. There is a critical need for universally standardizing the definition of periodontal health to make comparison with different studies valid. This thesis
2. Periodontal status of a tooth is more correlated to that of adjacent teeth compared to non-adjacent teeth. This thesis
3. Socioeconomic inequalities in periodontal health tended to enlarge in the Netherlands over the past two decades. This thesis
4. Individuals subsisting on a pro-inflammatory diet are more likely to have poor periodontal health. This thesis
5. A systemic biomarker of inflammation may mediate the associations between periodontal inflammation and cognitive function among older adults. This thesis
6. Concomitant presence of cognitive impairment and periodontitis/edentulism was associated with a higher risk of mortality in the geriatric population. This thesis
7. Learn how to see. Realize that everything connects to everything else. Leonardo da Vinci
8. Eind goed, al goed. (All's well that ends well.) Dutch proverb
9. 非宁静无以致远。(Slow and steady wins the race.) Zhuge Liang, a Chinese statesman

TABLE OF CONTENTS

Chapter 1	General introduction	13
Chapter 2	Definitions used for a healthy periodontium: a systematic review <i>International Journal of Dental Hygiene, 2020</i>	35
Chapter 3	Periodontal breakdown inter-tooth relationships in estimating periodontitis-related tooth loss <i>Journal of Dentistry, 2021</i>	63
Chapter 4	Trends in socioeconomic inequality of periodontal health among Dutch adults <i>BMC Oral Health, 2021</i>	81
Chapter 5	Dietary inflammatory potential is associated with poor periodontal health <i>Journal of Clinical Periodontology, 2021</i>	103
Chapter 6	White blood cell count mediates the association between periodontal inflammation and cognitive performance <i>The Journals of Gerontology. Series A, 2021</i>	125
Chapter 7	Combined association of cognitive impairment and poor oral health on mortality risk in older adults <i>Journal of Periodontology, 2021</i>	143
Chapter 8	General discussion, summary, and conclusions	165
Appendices	List of frequently used abbreviations Curriculum vitae & publications Acknowledgement	175

CHAPTER 1

General introduction

GENERAL INTRODUCTION

Periodontalepidemiology is the study of distribution (i.e., prevalence and incidence) and determinants (i.e., etiology and risk factors) of periodontal health problems in the population and its application to prevent and control the problems [1, 2]. Periodontal epidemiology is a subdiscipline of epidemiology that is considered an indispensable part of the biomedical triad (**Figure 1**). The evolving knowledge in periodontology has been aided by the mutual promotion of basic, clinical, and epidemiological sciences. Two fundamental assumptions in epidemiology are: 1) diseases do not occur at random; in other words, there exist factors that protect populations from diseases or predispose them to diseases; 2) these factors can be identified via systematic investigation of populations [3]. Epidemiology is a population science that studies the distribution and determinants of disease at the population level rather than individual or micro-level [4]. Agreeably, the era of Big Data has arrived in epidemiological studies. As one of the important characteristics of Big Data, high variety in data can be achieved by merging the datasets from different sources [5]. For example, the researchers try to add mortality data to health survey participants to detect unexpected associations. As the public-use data are increasingly made available online, merging these existing

Figure 1. Triad of biomedical science [3]

datasets becomes more common and easier [6]. However, working with such high variety datasets reinforces the validity challenges due to measurement errors [5]. Thus, the robustness of the findings is often assessed by sensitivity analyses or validation analyses in epidemiological research.

In medical research, a paradigm refers to a shared understanding of thought patterns that provide a coherent theory regarding the domain under study and occupy the dominant position. From a historical perspective, the understanding of periodontitis has changed over time and led to the formation of different paradigms [7]. The paradigms can roughly classify different eras as follows: focal infection ear (1900–1950), periodontal indices ear (1956–1982), risk assessment ear (1982–1996), and periodontal medicine ear (1996–present) [7]. These changes were promoted by the evolving knowledge of periodontitis and the advancing measurement methodologies [8]. Periodontal investigators correspondingly encountered several methodological issues and challenges [9], such as a plethora of case definitions and biased estimations of disease severity, extent, and distribution. In this introduction, the methodological challenges in epidemiology are presented. The history of periodontal epidemiology will be reviewed characterized by several paradigms. The valid concepts or lack of knowledge in different paradigms will be also pinpointed. Finally, the research purposes of the PhD thesis will be introduced.

Renewed Understanding of Periodontal Health

The World Health Organization defines health as “a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity [10, 11].” This definition of health is considered as no longer suitable for managing chronic diseases and conditions in this aging society [12]. In the dental context, periodontal health can be interpreted as either the natural concept or the holistic concept [13]. In the natural concept, periodontal health and disease seem to be mutually exclusive [14]. Specifically, periodontal health is defined as the absence of periodontal breakdown and no evidence of periodontal inflammation. In the holistic concept [15], individuals are considered periodontally healthy if they had effective chewing without pain and stable gingival status. The natural and holistic concepts give rise to a debate regarding whether periodontal health status can exist before the onset of disease and be restored from a reduced periodontium (e.g., alveolar bone loss, loss of attachment, and gingival recession). However, complete health on a pristine periodontium seems relatively strict and simplistic. The complete periodontal health definition is not sufficiently pragmatic to serve as a preventive starting point and a therapeutic endpoint [13, 16]. What constitutes

a healthy periodontium is far more sophisticated than initially supposed. It is necessary to consider not only the historical lesion but also to observe the current status. A renewed understanding of periodontal health helps confirm a reference point for assessing disease as well as a realistic treatment target and strategy.

From a conventional viewpoint, periodontal health refers to a state free from periodontal disease [13]. A series of clinically measured indicators and parameters are used to assess periodontal disease based on various case definitions [17–19]. However, the case definitions of periodontitis and assessment protocols in periodontal epidemiology are highly diverse [20]. The diversity across studies included the lack of consensus concerning the teeth examined, probe used, and number of sites per tooth. The inconsistencies in the disease parameters and measurement criteria reduce the likelihood of valid comparisons between different studies [20]. To address the problems, efforts have been made toward standardizing the definition for periodontal health [21] and the classification system for periodontitis [22] by the World Workshop of the European Federation of Periodontology and the American Academy of Periodontology (EFP/AAP). Periodontal health has been defined as a stable and non-inflammatory status, irrespective of intact or reduced periodontium [16, 21]. Although EFP/AAP released the first official definition of periodontal health, the characteristics of existing definitions are unknown. **Chapter 2** of this thesis systematically reviews the used definitions for a healthy periodontium in the current scientific literature to investigate explicitness and variability.

Era of Focal Infection (1900–1950)

An iterative process of different paradigms keeps evolving and changing the periodontology knowledge over time. During the first half of the 20th century, the “focal infection” paradigm was a mainstream theory. In 1918, Arthur D. Black noted that dentists have a duty to free the patients’ mouths from infection, even if it requires extracting teeth [23]. Dental therapy at that moment was often intense; dentists directly pulled out the decayed or infected teeth. Even “therapeutic edentulation” was viewed as preventive dentistry to cut off the pathogen source (i.e., oral infection) of systemic diseases. Dentures were widely used in young adults in that “blood and vulcanite” era [24]; it now seems incomprehensible. At that time, there was a belief that periodontal disease was the leading cause of tooth loss among adults and the elderly. Nowadays, some epidemiological research has been following this belief and considered lost teeth in persons aged ≥ 50 years as periodontitis-related tooth loss [25]. Periodontitis-caused tooth loss as a natural consequence of aging has been questioned increasingly.

In contrast, other reasons for extracted teeth should be considered, such as caries, orthodontic interventions, and trauma.

A methodological problem regarding periodontitis severity has remained in periodontal research for decades. Missing data owing to extracted teeth affect estimation accuracy. Specifically, the study by Hugoson and Jordan in 1982 revealed that severe destructive periodontitis was observed in remarkably few cases (at most 8%) in the age groups 50 years and older [26]. A higher prevalence of severe periodontitis in the elderly would be masked by the high prevalence of edentulism or significant tooth loss [27]. Failing to determine periodontitis as reason for tooth loss has long impacted the estimation of severe periodontitis, leading to over-estimation or under-estimation. Notably, tooth loss due to periodontal disease was an essential component of the staging aspect of the 2018 classification to assess periodontitis severity more accurately [22]. The reasons for tooth loss were often not registered or otherwise neglected in relevant population datasets [28]. Therefore, **Chapter 3** proposes a reference indicator to estimate periodontitis-related tooth loss when tooth extraction causes are not recorded or uncertain.

Era of Periodontal Indices (1956–1982)

Periodontal epidemiology did not gain momentum until the era of “periodontal indices”. Landmark indices were proposed to score periodontal disease and oral hygiene, including Russell’s Periodontal Index [29], Ramfjord’s Periodontal Disease Index [30], and Greene and Vermillion’s Oral hygiene Index [31]. Russell stated that the combined effect of age and oral hygiene could explain more than 90% of the occurrence of periodontal disease [32]. The theory laid a strong foundation for professional plaque removal and optimal oral hygiene in periodontal therapy. Personal oral hygiene is also viewed as a crucial element of periodontitis prevention and control. Furthermore, periodontal epidemiology has benefited from such evolving measurements as they assess periodontitis from three dimensions and levels: prevalence (number of individuals affected), extent (number of teeth and sites affected), and severity (degree of destruction at the lesions). Using standardized periodontal indices facilitates reporting the global trends in periodontitis prevalence [8, 33]. Nationwide oral health surveys are an important tool for descriptive epidemiology in the field of disease control. Data from the survey studies are used to measure periodontal health and disease trends, identify the most susceptible target populations in need of treatment intervention, and reallocate resources for vulnerable subgroups.

Several studies providing trend data indicate improvements in oral hygiene and mild/moderate periodontitis—but not severe periodontitis—among adults during the past decades [34, 35]. The overall prevalence of periodontitis decreased between 1988 (7.3%) and 2000 (4.2%) in the U.S. population [36]. Repeated cross-sectional studies performed in 35-year-old Oslo citizens [37] indicate that the percentage of individuals with deep periodontal pockets (≥ 6 mm) decreased significantly from 21.8% in 1984 to 8.1% in 2003. Similarly, in a study on periodontitis trends from Sweden, the proportion of individuals having healthy or almost healthy periodontal status in the whole population increased from 43% in 1983 to 60% in 2013 [27]. In the Asian countries, the age-standardized incidence and prevalence of periodontitis decreased in South Korea and Thailand while increasing in China, Japan, and India from 1990 to 2017 [38]. In a trend study from 1983 to 1995 [39], Kalsbeek et al. described changes in periodontal status among Dutch adults aged 25–54 years. There were significant improvements in gingival bleeding, oral hygiene, and buccal root exposure but no changes in the percentage of individuals with periodontal pockets (>3.5 mm). The Dutch national oral health surveys of 2002, 2007, and 2013 were performed [40–43]. In **Chapter 4**, trends in the oral hygiene and periodontal health of the Dutch population are investigated in the repeated cross-sectional studies.

Era of Risk Assessment (1982–1996)

The “risk assessment” paradigm in periodontal epidemiology has emerged with epidemic risk in medical studies [44]. Until then, the paradigm of periodontal indices believed that untreated gingivitis would inevitably progress to periodontitis, and the process would continue to progress linearly [7]. In contrast, burst theory noted that periodontitis progression could be characterized by episodes of disease activity followed by periods of remission [45]. Gingival bleeding and swelling were regarded as clinical features of active inflammation inside the periodontal tissue. Correspondingly, Nesse et al. developed a quantifiable parameter to quantify the surface area of the ulcerating wound caused by both gingivitis and periodontitis: i.e., Periodontal Inflamed Surface Area (PISA) [46]. PISA is calculated as the sum of periodontal pocket depth per bleeding teeth to estimate the periodontal inflammatory burden and activity at the individual level. To date, an increasing number of studies have used PISA to measure focal inflammatory burden and indirectly reflect an elevated systemic inflammation [47–51]. Gingival bleeding and periodontal pockets may be viewed as key indicators of periodontal health and stability [52].

Landmark studies improved the understanding of the inter-individual variation in periodontitis susceptibility [53–55]. The findings showed that susceptible individuals have a high risk of periodontitis, even if the levels of oral hygiene and gingivitis are similar. The “susceptible individuals” theory sparked extensive research into the potential risk factors for periodontitis. Notably, smoking and diabetes were identified as critical risk factors for periodontitis not until the era of risk assessment [56–59]. Focusing on maintaining periodontal health, Mariotti et al. proposed a three-layer model to understand a series of host-environmental factors related to periodontal health comprehensively and hierarchically [13]. As depicted in **Figure 2**, the three-layer model closely connects these factors and includes 1) host biological factors that directly affect the periodontium (e.g., genetic background, inflammatory and immune response, anatomical characteristics, and microbial biofilm) [60, 61], 2) environmental and systemic factors that indirectly affect the biological layer (e.g., smoking, physical activity, alcohol intake, dietary nutrients, and mental stress) [62], and 3) general factors that can influence both the biological and environmental/systemic factors (e.g., education, socioeconomic status, health awareness, and medical resources) [63].

Figure 2. Three-layered periodontal health model. The inner layer indicates directly contributing factors; the middle layer indicates oral environment and systemic factors, and the outer layer indicates personal factors [13].

Most host biological factors are seen as non-modifiable risk factors for periodontitis. Periodontitis is an oral inflammatory disease associated with complex interactions between bacteria and immune response [64,65]. Specifically, periodontal pathogens and oral microorganisms are regarded as the triggers of periodontitis. The form and severity of disease are largely dependent on the host defense to these periodontal pathogens. Environmental factors modulate the host's immune and inflammatory system [66-68]. Modifiable risk factors contribute to the maintenance of periodontal health, for example, smoking cessation, stress reduction, and moderate-to-vigorous physical activity [69]. Although several animal studies have shown that nutritional deficiencies have a deleterious effect on periodontal health, population-based epidemiological evidence has rarely been reported [70]. As important modifiable risks, dietary intake and nutrition may play a contributory role in the innate and adaptive immune responses and then affect the onset and development of periodontitis [71, 72]. Dietary deficiency of vitamins A, C, and D and calcium promotes gingival and periodontal inflammation [72]. Numerous studies have reported that various macronutrients or micronutrients influence periodontal health, such as dietary fiber [73], antioxidants [74, 75], sugars [76], refined carbohydrates [77], and saturated fats [78]. These studies have focused on the effect of individual nutrients or a set of related nutrients on periodontal status.

Dietary guidelines could be used as host-modulating approaches to promote and maintain periodontal health. However, studying a single or a few nutrients has several methodological and conceptual limitations [79-81]: 1) such a study is unlikely to detect the synergistic and cumulative effects of complex combinations of nutrients; 2) when correlated nutrients are simultaneously entered into a model, their separate effects are difficult to examine; and 3) some statistically significant findings may be obtained by random chance when a large number of food items or nutrients are analyzed. Dietary pattern analysis—for example, analysis based on Healthy Eating Index (HEI) [82], Alternative HEI [83], and Western Dietary Pattern [84]—which represents a broader picture of food and nutrient consumption, has recently emerged as a complementary approach to examining the relationship between unhealthy dietary habits and gingival bleeding, periodontitis, and periodontal tooth loss. Nevertheless, these index-based dietary patterns were not designed to capture the diet-borne systemic inflammation. The dietary inflammatory index was developed to measure an individual's dietary inflammatory potential [85]. **Chapter 5** explores the possible positive relationship between the higher dietary inflammatory index and poor periodontal health.

Era of Periodontal Medicine (1996–present)

From the mid-1990s onward, the “periodontal medicine” paradigm focusing on the periodontal–systemic link was initiated and gained momentum [86, 87]. Periodontal pathogens are not restricted to the oral cavity. Oral bacteria and their toxins may be disseminated via several routes (e.g., circulation, oropharyngeal, and orodigestive) to reach distal sites, where they induce low-grade inflammation and metabolic alterations [88-90]. An elevated systemic pro-inflammatory state (e.g., peripheral blood leukocytes, interleukin, and inflammatory mediators) increases the risk of other chronic inflammatory diseases [91-93]. The inflammatory comorbidities include but are not limited to diabetes [94-96], cardiovascular diseases [97-99], stroke [100], Alzheimer's disease (AD) [101], rheumatoid arthritis [102], pregnancy complications [103, 104], respiratory disease [105], cancer [106], obesity, and metabolic syndrome [107], as summarized in **Figure 3**. Although the directions and causal mechanisms of the periodontal-systemic links have remained elusive, many reports indicate that periodontal therapy ameliorates the symptoms and surrogate markers of comorbid conditions [108]. Understanding the effect of periodontal inflammation on overall systemic health may provide insights into the periodontitis-associated comorbidities and help in providing better and comprehensive care to patients [109, 110].

Figure 3. Periodontal inflammation and associated inflammatory comorbidities [110]

Pietropaoli et al. recently found that PISA, as a continuous variable, showed a significant association with hypertension in a large nationally representative population [111]. This association was mediated by the inflammatory markers to various extents. C-Reactive Protein (CRP), White Blood Cell (WBC) count, and ferritin mediated 5.4%, 4.2%, and 10.2%, respectively, of the association between PISA and high or uncontrolled blood pressure. Two independent large-scale surveys showed that both CRP and WBC acted as mediating factors in the association between periodontitis and hypertension in the U.S. and Korean populations [112]. The importance of periodontal therapy to regulate the systemic inflammatory response has been emphasized by Christan et al. [113], who showed that periodontal treatment reduced WBC count in patients with aggressive periodontitis. Assessing the inflammatory burden caused by periodontitis may be beneficial for monitoring at the individual patient level and evaluating the risks of systemic diseases at the population level. This thesis has focused on studying the association of periodontitis with cognitive impairment in the elderly population.

Longer life expectancy and lower birth rates have been increasing the proportion of elderly individuals in industrialized countries [114]. To promote and initiate healthy ageing has become an important public health priority. The increase in life expectancy has seen a commensurate increase in oral health problems that directly impact the life quality of the elderly and indirectly give rise to other health problems [115]. Poor periodontal health is commonly observed in elderly individuals [116, 117]. The prevalence of moderate-to-severe periodontitis increases with increasing age, affecting approximately two-thirds (64%) of the older population of the US [118]. Aging itself could be closely associated with a low-grade inflammatory status and impaired autophagic capacity [119, 120]. Periodontitis and dementia are considered disorders driven by chronic inflammation [110]. It is widely accepted that periodontitis is associated with an increased risk for neurodegenerative diseases [101, 121].

There is a continuous spectrum of impairment of cognitive function from normal aging to dementia in older adults [122]. Cognitive impairment is regarded as an early stage of dementia [123]. Delaying the onset and progression of AD, the most prevalent form of dementia, has become an intense research focus [124]. The 2020 Lancet Commission has recently identified 12 modifiable risk factors for dementia [125], suggesting that addressing these risk factors prevent or delay approximately 40% of dementia cases. Notably, in a large-scale cohort study, dental prophylaxis and periodontal treatment had beneficial effects in terms of reducing or delaying the onset and development of dementia [126].

Numerous studies on the neuroinflammatory pathogenesis of AD suggest that systemic pro-inflammatory molecules and bacteria or bacterial products contribute to the onset and development of dementia [127-129]. Periodontal pathogens may increase incident dementia and, potentially, the risk of AD-associated mortality through a low-grade inflammatory response, oral microbial dysbiosis, and bacterial invasion [130, 131]. These findings may support an immune response role of periodontitis in AD pathogenesis. Therefore, **Chapter 6** investigates whether systemic inflammation has a mediation effect in the association between periodontal inflammation and cognitive impairment among older adults.

Cognitive impairment has emerged as a major contributing factor to mortality in the elderly [132]. A systematic review showed that smoking, diabetes mellitus, and cardiovascular disease (CVD) may substantially contribute to the increased mortality in individuals with dementia [133]. Moreover, a pooled analysis of two large cohorts showed that impaired cognition is associated with an increased risk of stroke, congestive heart failure, and CVD death [134]. These cardiometabolic complications may partially explain the increased mortality associated with dementia. Exploring comorbidity development trends is instructive in promoting successful aging because comorbidity may affect the life span of elderly individuals with declined cognition [135, 136]. Poor periodontal health is a common comorbidity in cognitive dysfunction among the elderly [137, 138] and could increase the risk of overall and cause-specific mortality [139]. A considerable proportion of the increased mortality risk is attributed to CVD risk factors and other chronic diseases [140]. Considering that periodontal disease and impaired cognition are closely intertwined, the overlap between cardiometabolic risk factors associated with two diseases may increase the mortality rate of the elderly. **Chapter 7** examines the combined effect of periodontal health and cognitive function on mortality in the elderly population.

RESEARCH GOALS

Overall, the two main types of study design used in epidemiology are descriptive and analytical studies. The purpose of this thesis is to understand periodontal health at a population level on the basis of epidemiological principles and methods. More specifically, this thesis has focused on periodontal health diagnosis, temporal trends, dietary patterns, and effects of periodontal inflammation on systemic health.

The specific aims of this thesis (**Figure 4**) are as follows:

1. To investigate the current scientific literature related to the definition of periodontal health (**Chapter 2**)
2. To estimate tooth loss related to periodontal disease by assessing the periodontal inter-tooth relationships (**Chapter 3**)
3. To assess differences in oral hygiene and periodontal status among people of different socioeconomic status in the Netherlands over two decades (**Chapter 4**)
4. To investigate the association between dietary inflammatory potential and poor periodontal health (**Chapter 5**)
5. To examine whether systemic inflammatory factors mediate the association between periodontal inflammation and cognitive function (**Chapter 6**)
6. To evaluate whether cognitive impairment with poor oral health increases the risk of mortality in an older adult population (**Chapter 7**)

Figure 4. Schematic diagram illustrating the contents of the thesis

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CHAPTER 2

Definitions used for a healthy periodontium: A systematic review

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ABSTRACT

Introduction: There is no standard reference for periodontal health, and the diagnostic properties of the various definitions have not been studied. This review investigates the explicitness and variability of defining periodontal health in the current scientific literature.

Methods: The authors conducted a systematic literature review using PubMed and CENTRAL (2013-01/2019-05) according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the guidelines of the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) statement.

Results: A total of 51 papers met the predefined inclusion criteria. Of these, 13 papers did not report any explicit definitions of periodontal health. Half of the 38 remaining articles used a reference to support their definition, and half of them not. The studies published in periodontics-related journals or those that scored a low risk of bias for the methodical quality presented more explicit and valid definitions. Probing pocket depth was the most frequently used individual parameter for defining periodontal health. However, there were substantial variations in the methods of measurement and cut-off values.

Conclusions: Given the diversity of periodontal health definitions, a cross-study comparison is difficult. This review's results may be useful in making others aware of the significance of standardizing the definition of a healthy periodontium.

INTRODUCTION

The main objective of periodontal care is to reach and maintain a healthy periodontium. Definition of periodontal health plays a crucial role in population surveillance, and it also determines therapeutic targets for clinicians [1]. Most studies traditionally define the opposite of periodontal disease as a healthy periodontal status, regarding health as an absence of illness, as does the World Health Organization (WHO) [2]. Specifically, periodontal health refers to a state free from inflammation and characterized by shallow pockets and the absence of gingival bleeding [3]. Nevertheless, there are various case definitions of periodontal disease [4-6], and these definitions refer to an array of clinical signs and symptoms (e.g., probing pocket depth [PPD], clinical attachment loss [CAL], and bleeding on probing [BOP]) [7]. The definition of periodontal health should be consistent and standardized, facilitating comparison of clinical studies [8]. Periodontal health was recently defined as the absence of clinically detected inflammation by the 2018 World Workshop of the European Federation of Periodontology and the American Academy of Periodontology (EFP/AAP) [9]. This EFP/AAP definition is mainly based on PPD and BOP scores.

We hypothesize that there is substantial heterogeneity in the existing definitions of periodontal health. To date, no overview of periodontal health definitions has been conducted. Therefore, this systematic review (SR) investigates current scientific literature related to the definition of periodontal health.

METHODS

Protocol Development

The protocol for this SR was developed "a priori," following an initial discussion among members of the research team according to the Cochrane Handbook for Systematic Reviews of Interventions and the guidelines of PRISMA and MOOSE.

Search Strategy

A structured literature search of the National Library of Medicine, Washington, D.C. (PubMed-MEDLINE) and the Cochrane Central Register of Controlled Trials (Cochrane-CENTRAL) was performed up to May 2019. Since the Centers for Disease Control and the American Academy of Periodontology (CDC/AAP) case definition of periodontal disease was updated in 2012, this report covers all studies published and cited since January 2013. We hand-searched all of the

reference lists of selected papers. This forward citation check was carried out in four rounds to identify additional published work that could meet the eligibility criteria of the study, so called “snowball procedure”. For details regarding the search terms used, see **Table S1**.

Eligibility Criteria

Publications were included only when they (1) were original studies, (2) were conducted in a human population, (3) were published in English, (4) contained the group of periodontal health or the control group as the opposite of periodontal disease, and (5) the definitions described measurements and identified thresholds.

Screening and Selection

Two reviewers (A.L. and R.Z.T.) screened the titles and abstracts of the studies obtained during the search for eligible papers independently. After the screening, the reviewers read the full texts of eligible papers in detail. Any disagreement concerning eligibility was resolved by consensus, and if conflict persisted, the decision was settled through arbitration led by a third reviewer (D.E.S.). The papers that met all the selection criteria were processed for data extraction.

Assessment of Heterogeneity

Heterogeneity across studies was detailed according to the following factors: study design, published journal type, participants’ characteristics, potential confounding factors, measurement tools and procedures, explicit definitions, clinical parameters, and cut-off values.

Methodological Assessment Risk of Bias

The two reviewers (A.L. and R.Z.T.) independently scored the methodological qualities of each study as well. The appropriate critical appraisal checklists from the Joanna Briggs Institute were used depending on the study design [10]. Studies that met 80% of the criteria were considered to have a low risk of bias. And 60% to 79% was a moderate risk of bias; 40% to 59% criteria was substantial risk of bias; and less than 40% high risk of bias [11].

Data Extraction and Analysis

The characteristics of the published journal type, study design, country, sample frame, sample size, group, age, gender, smoking status, medical condition, examination area, measurement tool, probing location, and definition of periodontal health were extracted. Papers that included detailed measuring parameters and clear cut-off values were regarded as having an “explicit

definition” [12]. Moreover, the “explicit definition” papers that used references to support their definitions were considered as having a “valid definition” [13]. The extracted criteria for periodontal health were recorded with Microsoft Excel 2017 (Microsoft, Redmond, WA, USA). All quantitative analyses were conducted with SPSS Statistics 25 (SPSS Inc., Chicago, IL, USA).

RESULTS

Search Results

The search through online databases resulted in 1,236 unique studies (**Figure 1**). The titles and abstracts’ initial screening resulted in 49 studies that went on to the full-text review. Then, a detailed reading of the full texts was performed. Two independent reviewers excluded 20 studies (**Table S2**), leaving 29 eligible papers. Furthermore, a manual search through the reference list of the 29 papers led reviewers to identify 22 additional relevant studies (**Figure S1 & Table S3**). Finally, a total of 51 studies were included in the evaluation of the definition of periodontal health. Among the selected papers, 38 defined periodontal health. Thirteen studies did not report an explicit periodontal health definition and rather referenced periodontal health as the opposite of disease. This study outlines the characteristics of the included papers. These characteristics are summarized in **Table 1**.

Study Characteristics

The papers were published in journals of different categories, targeting periodontology (29%), dentistry (29%), and general medicine (41%). The studies were designed as cross-sectional studies (37/51), longitudinal studies (4/51), and randomized or non-randomized allocated control studies (10/51). A total number of 372,983 individuals were enrolled in the studies, ranging from 18 to 354,850 individuals for each one (mean: 7,313, SD 49,660, median; 78). Most publications were authored by research groups in India (14%) and the United States (12%). Most studies (82%) recruited patients from a hospital setting with comorbidities such as diabetes [46], chronic kidney disease [29], or chronic hemodialysis [53]. Concerning confounding factors, such as smoking habits and medical conditions, 28 of the studies excluded participants with smoking habits. Those with complicated medical conditions were excluded from 45 studies (**Table 1**).

Figure 1. Flow of information through the different phases of the systematic review.
* see Table S2, **see Figure S1 & Table S3.

Table 1. Overview of the studies processed for data extraction

Reference (Year) Type of journal Risk of bias	Study design Sample frame Country	Sample size of all Healthy Group: Number / Age / Gender	Smoking status Medical condition	Examination area Measurement tool Probing location	Explicit definition of periodontal health or Opposite of periodontal disease
Mourao et al., 2013 [14] Medical journal Substantial	RCT Study Dental clinic Brazil	ALL: (n=60) Periodontal health group: (n=20) 48.6 ± 7.4, ♀: 12 / ♂: 8	Not Recorded Not Recorded	Full mouth Probe Type Unclear Inter-proximal Sites	Explicit definition of periodontal health
Jones et al., 2013 [15] Dental journal Substantial	RCT Study General Population United Kingdom	ALL: (n=369) 6-Month Group: (n=125) 37.1 ± 10.4, ♀: 68 (54.4%) / ♂: 57 (45.6%) 12-Month Group: (n=122) 39.6 ± 10.8, ♀: 79 (64.8%) / ♂: 43 (35.2%) 24-Month Group: (n=122) 36.4 ± 10.6, ♀: 88 (72.1%) / ♂: 34 (27.9%)	Recorded Excluded	Full mouth WHO Probe Six Sites	Basic Periodontal Examination (BPE) Explicit definition of periodontal health
Graziani et al., 2018 [16] Periodontal journal Moderate	RCT Study Dental hospital Italy	ALL: (n=60) Group 1: (n=15) 28.7 ± 9.8, ♀: 6 (40%) / ♂: 9 (60%) Group 2: (n=14) 26.1 ± 3.7, ♀: 8 (57%) / ♂: 6 (43%) Group 3: (n=16) 26.4 ± 5.2, ♀: 9 (56%) / ♂: 7 (44%) Group 4: (n=15) 26.4 ± 5.4, ♀: 8 (53%) / ♂: 7 (47%)	Excluded Excluded	Full mouth UNC-15 Probe Six Sites	Consensus report of the 5th European Workshop in periodontology [17] Explicit definition of periodontal health
Sukhtankar et al., 2013 [18] Medical journal Moderate	Non-randomized experimental study Department of Periodontics and oral implantology India	ALL: (n=40) (24-55), ♀: 20 / ♂: 20 Periodontal health group: (n=20)	Excluded Excluded	Full mouth UNC-15 Probe Site Unclear	Explicit definition of periodontal health
Sharma et al., 2014 [19] Medical journal Moderate	Non-randomized experimental study Dental hospital India	ALL: (n=60) Periodontal health group: (n=20) 25-60	Excluded Excluded	Full mouth Probe Type Unclear Six Sites	WOOD classification: [20] Opposite of periodontal disease

Table 1. (Continued)

Guentsch et al., 2014 [21] Periodontal Journal Moderate	Non-randomized experimental study Dental hospital Germany	ALL: (n=30) Periodontal health group: (n=15) 26 (23-39), ♀: 11 / ♂: 4	Excluded Excluded	Full mouth UNC-15 Probe Six Sites	Armitage classification: [22] Explicit definition of periodontal health
Hassan et al., 2015 [23] Medical Journal Moderate	Non-randomized experimental study General Population Egypt	ALL: (n=30) Periodontal health group: (n=10) 37.81 ± 8.3, ♀: 6 / ♂: 4	Excluded Excluded	Full mouth Michigan 0 Probe Six Sites	Explicit definition of periodontal health
Leite et al., 2014 [24] Medical Journal Low	Non-randomized experimental study General hospital Brazil	ALL: (n=55) Periodontal health group: (n=55) 33.18 ± 6.42, ♀: 67% / ♂: 33%	Excluded Excluded	Full mouth Michigan 0 Probe Four Sites	Armitage classification: [22] Explicit definition of periodontal health
Al-Hamoudi et al., 2018 [25] Dental Journal Low	Non-randomized experimental study Dental hospital Saudi Arabia	ALL: (n=137) Obese patients without CP: (n=34) 37.5 (31-42), ♀: 2 / ♂: 32 Non-obese patients without CP: (n=33) 36.2 (33-42), ♀: 0 / ♂: 33	Excluded Excluded	Full mouth UNC-15 periodontal probe Six Sites	Armitage classification: [22] Opposite of periodontal disease
Muthu et al., 2015 [26] Dental Journal Moderate	Non-randomized experimental study Dental hospital India	ALL: (n=220) (35-50), ♀: 96 / ♂: 124 Control group: (n=90)	Excluded Excluded	Examination area unclear Probe Type Unclear Site Unclear	Explicit definition of periodontal health
Lee et al., 2017 [27] Medical Journal Substantia	Cohort General Population Korea	ALL: (n=354,850) Periodontal health group: (n=154,824) 40-49: 46.8%, 50-59: 27.6%, 60-69: 19.6%, 70-79: 6%, ♀: 49.2%, ♂: 50.8%	Recorded Excluded	Full mouth Probe Type Unclear Inter-proximal Sites	Armitage classification: [22] Opposite of periodontal disease
Raber-Durlacher et al., 2013 [28] Medical Journal High	Cohort Study Dental hospital Netherlands	ALL: (n=18) 41.8 ± 13.4 (19-64) ♀: 11 (61%) / ♂: 7 (39%) Periodontal Health Group: (n=5)	Not Recorded Not Recorded	Full mouth Probe Type Unclear Four Sites	Explicit definition of periodontal health
Ricardo et al., 2015 [29] Medical Journal Moderate	Cohort Study Population United States	ALL: (n=10,755): 41.5 ± 0.5, ♀: 50% / ♂: 50% CKD (+) without Periodontitis group: (n=1,142): 51.9 ± 1.2, ♀: 62.1% / ♂: 37.9% CKD (-) without Periodontitis group: (n=8,795): 39.6 ± 0.4, ♀: 49.8% / ♂: 50.2%	Recorded Chronic kidney disease (CKD) patients	Full mouth Probe Type Unclear Site Unclear	CDC/AAP case definition: [6] Opposite of periodontal disease

Table 1. (Continued)

Lourenco et al., 2014 [30] Periodontal Journal Moderate	Case-Control Study Division of Graduate Periodontics Brazil	ALL: (n=97) Periodontal health group: (n=27) 24.2 ± 6.9, ♀: 77.8% / ♂: 22.2%	Recorded Excluded	Full mouth UNC-15 Probe Site Unclear	Armitage classification: [22] Explicit definition of periodontal health
Zimmermann et al., 2013 [31] Periodontal Journal Low	Cross-Sectional Dental hospital Brazil	ALL: (n=78) NW non-periodontitis (NP) Group: (n=20) 42.9 ± 7.2, ♀: 14 / ♂: 6 Obese non-periodontitis Group: (n=18) 43.2 ± 7.4, ♀: 14 / ♂: 4	Excluded Excluded	Full mouth UNC-15 Probe Six Sites	Armitage classification: [22] Explicit definition of periodontal health
Apatzidou et al., 2013 [32] Dental Journal Moderate	Cross-Sectional Department of periodontology Greece	ALL: (n=78) Healthy individuals: (n=27) 31 ± 5, ♀: 15 / ♂: 12	Excluded Excluded	Full mouth UNC-15 Probe Six Sites	Explicit definition of periodontal health
Ebersole et al., 2013 [33] Medical Journal Low	Cross-Sectional Population United States	ALL: (n=80) Healthy adults: (n=30) 31.4 ± 6.8, ♀: 46.7% / ♂: 53.3%	Recorded Excluded	Full mouth UNC-15 Probe Inter-proximal Sites	Armitage classification: [22] Explicit definition of periodontal health
Rathnayake et al., 2013 [34] Periodontal Journal Low	Cross-Sectional Dental hospital Sweden	ALL: (n=451) PD- group: (303) 42.6 ± 15.5, gender unclear	Recorded Recorded	Full mouth UNC-15 Probe Four Sites	Explicit definition of periodontal health
Wang et al., 2013 [35]B Medical Journal High	Cross-Sectional Dental hospital China	ALL: (n=16) 30-65, gender unclear	Excluded Excluded	Examination Area Unclear Probe Type Unclear Site Unclear	Explicit definition of periodontal health
Gursoy et al., 2013 [36] Periodontal Journal Moderate	Cross-Sectional Population Finland	ALL: (n=230) Control subject group: (n=81) 47.9 ± 5.7, ♀: 64.2% / ♂: 35.8%	Recorded Excluded	Full mouth Probe Type Unclear Four Sites	Explicit definition of periodontal health
Kebschull et al., 2013 [37] Dental Journal Substantial	Cross-Sectional Clinic of post-doctoral periodontics United States	ALL: (n=310) 'Healthy' group: (n=69) 45.7 ± 11.6 (24-76), ♀: 50.8% / ♂: 49.2%	Excluded Excluded	Full mouth Probe Type Unclear Six Sites	Armitage classification: [22] Explicit definition of periodontal health
Salazar et al., 2013 [38] Periodontal Journal Moderate	Cross-Sectional Population Germany	ALL: (n=400) Healthy periodontium group: (n=20) 48.6 ± 11.4, ♀: 50% / ♂: 50%	Recorded Excluded	Examination Area Unclear SHIP-2: PCP11 probe; SHIP-TREND: PCPUNC probe15 Site Unclear	Explicit definition of periodontal health

Table 1. (Continued)

Gokhale et al., 2013 [39] Medical Journal Low	Cross-Sectional Department of Periodontics India	ALL: (n=120) 30-60 Periodontal health group: (n=30)	Excluded Excluded	Full mouth UNC-15 Probe Four Sites	Armitage classification: [22] Explicit definition of periodontal health
Pansezai et al., 2018 [40] Medical Journal Low	Cross-Sectional Dental hospital Pakistan	ALL: (n=86) Healthy group: (n=14) 44.4 ± 6.6, ♀: 5 / ♂: 9	Recorded Excluded	Full mouth Hu-Friedy Probe Four Sites	Explicit definition of periodontal health
Pushparani et al., 2014 [41] Periodontal Journal Low	Cross-Sectional Department of periodontology India	ALL: (n=600) Control healthy individual: (n=150) 35.46 ± 6.10.74, ♀: 70 / ♂: 80 Type 2DM without periodontitis: (n=150) 46.26 ± 10.02, ♀: 72 / ♂: 78	Excluded Excluded	Area Unclear Probe Type Unclear Site Unclear	Armitage classification: [22] Opposite of periodontal disease
Shetty et al., 2016 [42] Medical Journal moderate	Cross-Sectional Dental hospital India	ALL: (n=120) Healthy group: (n=30)	Excluded Excluded	Area Unclear Probe Type Unclear Site Unclear	Explicit definition of periodontal health
Huang et al., 2018 [43] Medical Journal Moderate	Cross-Sectional Dental hospital China	ALL: (n=68) ♀: 31 (43 ± 12.1) / ♂: 37 (47 ± 11.7) Healthy group: (n=20)	Not Recorded Excluded	Area Unclear Probe Type Unclear Site Unclear	Armitage classification: [22] Explicit definition of periodontal health
Papathanasiou et al., 2014 [44] Periodontal Journal Moderate	Cross-Sectional Population United States	ALL: (n=42) periodontally healthy group: (n=14) 26.3 ± 2.6, ♀: 78.6% / ♂: 21.4%	Excluded Excluded	Full mouth UNC-15 Probe Six Sites	Explicit definition of periodontal health
Mesa et al., 2014 [45] Periodontal Journal Low	Cross-Sectional Dental hospital Spain	ALL: (n=77) Periodontal health group: (n=36) 46.25 (19-79), ♀: 46 / ♂: 31	Recorded Excluded	Full mouth UNC-15 Probe Six Sites	Explicit definition of periodontal health
Schjetlein et al., 2014 [46] Medical Journal Moderate	Cross-Sectional Study General hospital Diabetes patients Denmark	ALL: (n=62) 57.0 (51-60), ♀: 28 / ♂: 34 Without periodontitis group: (n=49) 57.0 (51-61), ♀: 24 / ♂: 25	Recorded Excluded	Full mouth WHO Probe Site Unclear	Periodontal Screening Index Explicit definition of periodontal health
Ramirez et al., 2014 [47] Dental Journal Low	Cross-Sectional General hospital Colombia	ALL: (n=44) Periodontal health group: (n=22) 40.6 ± 8.6, ♀: 17 (77.3%) / ♂: 5 (22.7%)	Recorded Excluded	Full mouth Probe Type Unclear Site Unclear	Armitage classification: [22] Explicit definition of periodontal health

Table 1. (Continued)

Beklen et al., 2014 [48] Medical Journal Substantial	Cross-Sectional General Hospital Turkey	ALL: (n=20) Periodontal health group: (n=10) 33-39, gender unclear	Excluded Excluded	Full mouth Probe Type Unclear Inter-proximal Sites	Explicit definition of periodontal health
Singh et al., 2014 [49] Periodontal Journal Low	Cross-Sectional Department of periodontics and oral implantology India	ALL: (n=106) Periodontally healthy individuals: (n=22) 27.5 (22-50), ♀: 16 / ♂: 6	Excluded Excluded	Full mouth Probe Type Unclear Six Sites	Explicit definition of periodontal health
Duran-Pinedo et al., 2014 [50] Medical Journal Substantial	Cross-Sectional General hospital United States	ALL: (n=13) Periodontally healthy individuals: (n=6) Age unclear, gender unclear	Excluded Excluded	Examination Area Unclear Probe Type Unclear Site Unclear	Explicit definition of periodontal health
Tabari et al., 2013 [51] Dental Journal Moderate	Cross-Sectional Department of Periodontology Iran	ALL: (n=50) Individuals with a healthy periodontium: (n=25) 20-45, ♀: 11 (44%) / ♂: 14 (56%)	Excluded Excluded	Full mouth UNC-15 probe Four Sites	Armitage classification: [22] Explicit definition of periodontal health
Tabari et al., 2014 [52] Periodontal Journal Low	Cross-Sectional Department of Periodontology Iran	ALL: (n=40) Periodontally healthy individuals: (n=20) 33.85 ± 6.84, ♀: 65% / ♂: 35%	Excluded Excluded	Full mouth UNC-15 Probe Four Sites	Armitage classification: [22] Explicit definition of periodontal health
Gameata et al., 2015 [53] Medical Journal Moderate	Cross-Sectional Study General hospital Romania	ALL: (n=238) 57.0 (50.0-64.8), ♀: 40% / ♂: 60% Periodontal health group: (n=58) 55.5 (42.3-61.0), ♀: 43% / ♂: 57%	Recorded Stable chronic hemodialysis patients	Full mouth Probe Type Unclear Site Unclear	Explicit definition of periodontal health
Ozcan et al., 2015 [54] Dental Journal Moderate	Cross-Sectional Department of periodontology Turkey	ALL: (n=72) Healthy subjects: (n=23) 34.50 ± 7.09 (35-75), ♀: 11 / ♂: 12	Excluded Excluded	Examination Area Unclear Michigan 0 Probe Site Unclear	Explicit definition of periodontal health
Kirst et al., 2015 [55] Medical Journal Substantial	Cross-Sectional General hospital United States	ALL: (n=50) Healthy controls: (n=25)	Not recorded Excluded	Examination Area Unclear Probe Type Unclear Site Unclear	Explicit definition of periodontal health

Table 1. (Continued)

Velosa-Porras et al., 2016 [56] Dental journal Low	Cross-Sectional Dental hospital Colombia	ALL: (n=150) Mean=50.2 Periodontal health group: (n=75) ♀: 44 / ♂: 31	Recorded Excluded	Full mouth Electronic probe Site Unclear	Armitage classification: [22] Opposite of periodontal disease
Prodan et al., 2016 [57] Medical journal Moderate	Cross-Sectional Population Netherlands	ALL: (n=261) 22.6 (18.0-32.0) ♀: 116 / ♂: 145	Excluded Excluded Student of university	Full mouth Probe Type Unclear Site Unclear	Dutch periodontal screening index (DPSI) [58] Explicit definition of periodontal health
Noguera-Julian et al., 2017 [59] Medical journal Moderate	Cross-Sectional Dental hospital United States	ALL: (n=50) 45.3 (37.0-53.0) ♀: 17 / ♂: 32 / Trans: 1	Recorded Excluded	Full mouth Probe Type Unclear Inter-proximal Sites	CDC/AAP case definition: [6] Opposite of periodontal disease
Saglam et al., 2017 [60] Dental journal Moderate	Cross-Sectional Dental Hospital Turkey	ALL: (n=60) ♀: 33 / ♂: 27 Periodontal health group: (n=20) 30.62 ± 7.65	Excluded Excluded	Full mouth Probe Type Unclear Six Sites	Explicit definition of periodontal health
Lavu et al., 2015 [61] Medical journal Moderate	Cross-Sectional Dental hospital India	ALL: (n=400) Periodontal health group: (n=200) 29.64 ± 5.5 (20-55), ♀: 52.4% / ♂: 47.5%	Excluded Excluded	Full mouth UNC-15 Probe Six Sites	Armitage classification: [22] Explicit definition of periodontal health
Kursunlu et al., 2015 [62] Dental journal Moderate	Cross-Sectional Study Department of periodontology Turkey	ALL: (n=80) Periodontally healthy subjects (n=20)	Excluded Excluded	Full mouth Probe Type Unclear Site Unclear	Armitage classification: [22] Explicit definition of periodontal health
Chaiyapit et al., 2015 [63] Dental journal High	Cross-Sectional General hospital Thailand	ALL: (n=90) Healthy subjects: (n=30) 54.4 ± 11.03 (35-75), ♀: 17 / ♂: 13	Not recorded Excluded	Examination Area Unclear Probe Type Unclear Site Unclear	Armitage classification: [22] Explicit definition of periodontal health
Wara-aswapati et al., 2013 [64] Periodontal journal Moderate	Cross-Sectional General Hospital Thailand	ALL: (n=35) Control individuals without periodontitis: (n=16) 34.0 ± 15.8, ♀: 14 / ♂: 2	No Recorded Excluded	Area Unclear UNC-15 Probe Site Unclear	Armitage classification: [22] Opposite of periodontal disease
Javed et al., 2014 [65] Periodontal journal Low	Cross-Sectional Dental hospital Pakistan	ALL: (n=88) Controls: (n=28) 51.7 ± 12.9, ♀: 0 / ♂: 28	Excluded Excluded	Full mouth Hu-Friedy Probe Six Sites	Armitage classification: [22] Opposite of periodontal disease

Table 1. (Continued)

Kim et al., 2013 [66] Dental journal Low	Cross-Sectional Dental hospital Korea	ALL: (n=125) 57.85 ± 1.03, ♀: 48 / ♂: 77	Recorded Excluded	Area Unclear WHO-probe Six Sites	WHO community periodontal index of treatment needs [67] Explicit definition of periodontal health
Torrunguang et al., 2015 [68] Medical journal Substantial	Cross-Sectional Study Population Thailand	ALL: (n=1,362) No/mild periodontitis: (n=479) 46.6 ± 4.4, ♀: 211 / ♂: 268	Recorded Not Recorded	Full mouth Probe Type Unclear Six Sites	CDC/AAP case definition: [6] Opposite of periodontal disease
Ghailab et al., 2015 [69] Periodontal journal Moderate	Cross-Sectional Dental hospital Egypt	ALL: (n=50) Periodontal health group: (n=10) 47.8 ± 2.9, ♀: 5 / ♂: 5	Excluded Excluded	Full mouth Michigan 0 Probe Six Sites	Armitage classification: [22] Explicit definition of periodontal health

Methodological Quality Assessment

The included studies’ methodological quality was used to estimate the potential risk of bias and is presented in detail in **Table S4.1–5**. The estimated potential risk of bias was low for 15 studies, moderate for 25 studies, substantial for eight studies, and high for three studies.

Measurement Methods

In 39 out of the 51 papers, a full-mouth assessment was conducted (**Table 1**). Various types of periodontal probes were used. Twenty-four studies did not report the probe’s details, 16 studies used the UNC-15 probe, and four studies used the Michigan 0-probe. The number and location of probing sites varied. Four sites (mesio-buccal, mesio-lingual, disto-buccal, and disto-lingual) per tooth were used in 8 studies, and six sites (mesio-buccal, mid-buccal, disto-buccal, mesio-lingual, mid-lingual, and disto-lingual) per tooth were used in 17 studies. Moreover, five studies specifically measured the indicators at the location of the interproximal sites.

Presence of An Explicit or Valid Definition

A precise definition of periodontal health is offered in 38 (75%) of the included studies. The remaining 13 papers provided the references and defined the opposite of disease as periodontal health (**Table 2**). An explicit definition with a supporting disease as periodontal health (**Table 2**). An explicit definition with a supporting reference was reported in 19 papers. In contrast, the other 19 studies only used a definition rather than indicating any reference (**Table 2**, for details see **Figure S2**). The two most frequently used references were the Armitage classification (1999) [22], used in 22 papers, and the CDC/AAP case definition [6], used in five papers. None of the papers reporting details of the classification followed the original proposed definition strictly, but a wide variance was applied (**Table S5.1–2**).

Table 2. Classification of included papers according to explicit and valid definitions

ALL = 51	Full text reading	N (%)	Definition analyzing	N (%)
1	Definition of health ^a	38 (74.5)	1.1 Definition of health with reference ^b	19 (37.25)
			1.2 Definition of health without reference	19 (37.25)
2	Disease to define health	13 (24.5)	2.1 Definition of disease with reference	12 (23.5)
			2.2 Definition of disease without reference	1 (2)

^aThe “only definition” and “reference and definition” groups were regarded as explicit definitions of periodontal health.

^bthe “reference and definition” group was regarded as a valid definition of periodontal health

The number of explicit and valid periodontal health definitions was sub-analyzed according to journal categories, study designs, and resource of patients as well as assessed methodological risk of bias. In the periodontal journals, the definitions used were more explicit (87%) than those used in the dental or medical journals (**Table S6.1**). Moreover, the papers collected from a department of periodontology tended to provide explicit definitions (91%) compared to other studies. The studies scoring a low risk of bias for the methodical quality had more valid definitions (**Table S6.2**).

Clinical Parameters and Cut-off Values

Table 3 summarizes the different periodontal health definitions used (38 studies). Notably, Loureco provided two definitions of periodontal health in the one study [30]. Therefore, the table contains 39 definitions. The table also presents the differences regarding cut of points, PPD, CAL, BOP, and other relevant information for each study. Probing pocket depth was almost used for all definitions ($n = 35$), whereas BOP was used in less than half of the cases ($n = 16$). Probing pocket depth appeared in nine studies used as a single criterium. A combination of PPD with CAL appeared in 10 studies. A combination of PPD with BOP appeared in five studies, and a triple set of PPD, CAL, and BOP was used in 10 papers.

Figure 2A–C presents the numbers of papers using a threshold. The most frequently used PPD cut-off was ≤ 3 mm, which appeared in 20 studies. However, 11 studies reported a threshold of 3.5 mm or higher. A considerable amount of variety was observed concerning the CAL threshold, ranging from 0 to 4 mm. Nine studies reported the absence of CAL, and 15 studies did not report CAL (**Figure 2B**). Figure 2 C demonstrates that among the reported BOP thresholds, the most commonly used was 10% sites, but the majority of the included papers ($n = 23$) did not report BOP.

Table 3. Summary of periodontal health definitions

Papers (N) / Definitions (n)	PPD (mm)	CAL (mm)	BOP (%)	Other	Reference
N = 38/ n = 39	n = 35	n = 24	n = 16		
1	≤3				Beklen et al, 2014 [48]
2	≤3				Ozcan et al., 2015 [54]
3	≤3				Duran-Pinedo et al., 2014 [50]
4	<3.5				Jones et al., 2013 [15]
5	<3.5				Schjetlein et al., 2014 [46]
6	<4				Garneata et al., 2015 [53]
7	<4				Gursoy et al., 2013 [36]
8	≤4			No clinical sign + no X-ray bone loss	Ramirez et al., 2014 [47]
9	<5				Prodan et al., 2016 [57]
10		≤3			Kirst et al., 2015 [55]
11		≤3			Kim et al., 2013 [66]
12		<3			Graziani et al., 2018 [16]
13				No X-ray bone loss	Rathnayake et al., 2013 [34]
14	=0	=0		No clinical sign + no X-ray bone loss	Huang et al., 2018 [43]
15	<3	<3			Wang et al., 2013 [35]
16	≤3	=0			Guentsch et al., 2014 [21]
17	≤3	=0			Tabari et al., 2014 [52]
18	≤3	=0			Pushparani et al., 2014 [41]
19	≤3	=0		GI = 0 + PI = 0	Ghallab et al., 2015 [69]
20	≤3	=0		GI = 0 + PI = 0	Hassan et al., 2015 [23]
21	≤3	≤2			Mesa et al., 2014 [45]
22	≤3	≤3			Zimmermann et al., 2013 [31]
23	≤4	≤4			Kebschull et al., 2013 [37]
24	≤3		≤10		Tabari et al., 2013 [51]
25	≤3		≤10		Apatzidou et al., 2013 [32]
26	≤3		≤30		Salazar et al., 2013 [38]
27	<4		≤15		Muthu et al., 2015 [26]
28	≤4		≤10		Raber-Durlacher et al., 2013 [28]
29	<3	=0	=0		Kursunlu et al., 2015 [62]
30	<3	<3	=0		Mourao et al., 2013 [14]
31	≤3	=0	=0	No clinical sign + no history	Lavu et al., 2015 [61]
32	≤3	=0	≤10		Singh et al., 2014 [49]
33	≤3	≤1	≤10		Sukhtankar et al., 2013 [18]

Table 3. (Continued)

34	≤3	≤2	≤20	No X-ray bone loss	Saglam et al., 2017 [60]
35 ^a	≤3	≤3	≤10		Lourenco et al., 2014 [30]
	≤4	≤4	≤5		Lourenco et al., 2014 [30]
36	≤3	≤3	≤10	No X-ray bone loss	Leite et al., 2014 [24]
37	≤3	≤3	≤20		Papathanasiou et al., 2014 [44]
38	≤4	≤2	≤10		Ebersole et al., 2013 [33]

Abbreviations: BOP, bleeding on probing; CAL, clinical attachment level; PDD, probing pocket depth.

^aLourenço et al provided two sets of periodontally healthy definition in one paper. 'Gray shades' means a single criterion or combination involving PPD/CAL/BOP to define periodontal health.

Figure 2. Distribution of severity and extent for PPD (A), CAL (B) and BOP (C) used to define periodontal health among 36 studies showed by number. Notably, one of studies provided two definitions of periodontal health. Therefore, the total number of definitions is 37.

DISCUSSION

This systematic review aims to conduct an exploratory analysis of periodontal health definitions and the methods used to measure a healthy periodontium. To the best of our knowledge, this is the first SR exclusively dedicated to exploring various periodontal health definitions. Although the significance of periodontal health is well known, a universal and formal definition did not exist until the World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions, which was organized by the EFP and the AAP [9]. The main findings of this review were that (1) there is a lack of an explicit definition of periodontal health and consequently, a lack of application of references, (2) there is significant heterogeneity in measuring methods, and (3) there are considerable inconsistencies in the different periodontal parameters and cut-off values used.

Operational definitions and consistent criteria for a healthy periodontium were not provided in the majority of papers. The studies that did not provide a definition or a reference were excluded (**Table S2**). Some did provide a definition but lacked a reference, and some only gave a reference but lacked a definition. Only 37% (19 of 51) of the papers included in this study reported an explicit definition with detailed clinical parameters and cited a reference. The two most commonly cited references were the 1999 International Workshop for the Classification of Periodontal Disease [22] (21 out of 31) and the CDC/AAP case definition for population-based studies of periodontitis [6] (5 out of 31) (**Table S5**). Even when a proper reference was used, there existed a variety of interpretations. Misuse of the original criteria of the references created even more heterogeneity and introduces inevitable bias. As with the definition of periodontitis, it was difficult to achieve the goal of reproducing and analyzing the results from different studies [7].

A periodontal pocket is the most common sign of periodontitis and easy to detect and assess in the clinical practice using various periodontal probes. The regularization of using periodontal probes will raise the accuracy of the process of diagnosing the condition and evaluating the treatment outcome [70, 71]. The present SR has identified a great amount of variety in the methods and materials used, such as the periodontal probing methods, particularly the type of probe and probing site. The procedure of measuring PPD and CAL was described as being assessed by either four or six sites per tooth. The number of sites used and especially the proportion of interdental sites assessed may influence the outcome. In any case, uniformity in material and methods can reduce the measurement bias. The EFP/AAP workshop recommended the use of an International Organization for Standardization (ISO) periodontal probe [9].

A cut-off or a reference point is needed to distinguish health from recurring signs and symptoms of periodontal disease [8]. A wide range of parameters and cut-offs were identified in the present systematic review. Probing pocket depth was the most frequently used periodontal parameter. Given the fact that it is rather easy to detect and measure, PPD has been recognized for many years as the essential parameter for the diagnosis periodontal health and disease [72]. Half of the studies (51%) reported a threshold of PPD ≤ 3 mm. This cut-off value is also used to identify periodontal case types of health [73]. In contrast, there were still 11 (29%) definitions that used the threshold of 3.5mm PPD or deeper. The cut-off PPD ≤ 3 mm might be excessively strict if a population is assessed such that only a few end up in the category of healthy. This may be the reason that researchers in large epidemiology studies stretch the PPD cut-off point. For instance, Hugoson used the following cut-off of periodontal health and disease: $\leq 10\%$ sites with PPD ≥ 4 mm [74, 75]. Nevertheless, even the largest cut-off value of PPD did not exceed 5 mm in the current review. A systematic review reported that probing depth up to 6 mm or even more should be taken into account as a high-risk factor to predict further disease progression in periodontal patients [76].

Other frequently used parameters are CAL and BOP. Clinical attachment loss, the second most frequently used parameter, varies across studies. This was used in three (8%) studies as the single parameter and in 21 (55%) as an adjunct to PPD. The most commonly used threshold using CAL is the absence of attachment loss. As aging comes with natural bone loss, some CAL is physiological. Therefore, the absence of CAL is likely due to the outdated concept. Periodontal health is identified as the absence of any deficit of supporting tissues [8]. The strict and sometimes idealistic definition of absence of CAL can result in an overestimation of disease. The third most commonly used parameter, BOP, is never used alone, but serves as an adjunct. Notably, criteria consisting of BOP and PPD appeared in five (13%) articles, whereas BOP was only used in 16 out of 39 definitions (41%). The most frequently used BOP cut-off is less than 10%. Stable periodontium can manifest as the absence of extensive BOP [77]. The cut-off values of BOP used to identify health and disease vary. A large-scale epidemiological study used a cut-off of $<20\%$ BOP [74], without referencing evidence. Patients with BOP sites $\geq 16\%$ have a higher chance of losing attachment [78]. After active non-surgical treatment during the maintenance/supportive phase, the risk of tooth loss is considerably greater for patients with 30% bleeding [79]. Overall, a limited number of positive symptoms for BOP is accepted in the healthy periodontium. Interestingly, the most frequently used cut-off value (BOP $<10\%$) is consistent with the EFP/AAP classification. Nevertheless, there is no clear evidence to support the used cut-off values. Compared to previous values,

bleeding sites of 10% might underestimate the number of people with a healthy periodontium.

The current review is not without limitations. After a full-text reading and analysis of the reference lists, 22 extra papers were included (for details, see Figure 1). Although this snowball procedure was conducted carefully, it remains possible that some studies describing periodontal health were not included in our search. Searching for definitions of periodontal health is complicated as it is often used as a category describing the opposite of disease. Thus, periodontal health often does not appear as a search term in the title and abstracts of studies. This also explains why the snowball procedure reveals more papers than those obtained from the initial search and selected based on the given criteria. A recommendation for further studies is that there is a need for evaluations such as: What probe to use and what measurements to collect, in order to make a proper diagnosis for daily clinical practice and epidemiological studies.

The definition of periodontal health recommended by the EFP/AAP Workshop was defined as less than 10% of sites having BOP and PPD ≤ 3 mm in intact periodontium or ≤ 4 mm in reduced periodontium [9]. Previous studies took CAL into account as a critical factor in describing accumulated lesions and the susceptibility of the disease [17, 80]. However, loss of periodontal attachment has not been incorporated, partly because the newly proposed definition focuses on the current status of different periodontium. Periodontal inflammatory activity or inactivity can be identified according to the extent of BOP and PPD instead of CAL. Similar to the assessment of periodontal inflammatory burden [81], non-bleeding pockets are regarded as periodontal tissue without inflammation. The quantity of inflammation is related to the inflamed periodontal surface area, which is calculated by the PPD values of bleeding teeth.

Periodontal health can also present in an anatomically reduced periodontium [1]. In other words, periodontal health does not merely mean that there is an absence of supporting tissue deficit. It also refers to an individual's level of comfort, the stability of a functioning periodontium, and one's psychological and social well-being. This concept of holistic periodontal health has not been taken into account in this paper. Notably, the feasibility of directly regarding the definition of periodontal health in a reduced periodontium (PPD ≤ 4 mm and BOP $\leq 10\%$) as the treatment goal among patients remains uncertain. However, a certain PPD value after treatment needs be interpreted in light of variance in susceptibility and personalized medicine. Lang and Tonetti built a functional diagram to assess

periodontal risk in supportive periodontal therapy, which can help clinicians distinguish whether a treatment goal is reached or not [82]. Moreover, the number of residual pockets with a probing depth of ≥ 5 mm to a certain extent reflects the degree of success of periodontal treatment, which is different from the PPD threshold in the new definition. In the randomized clinical trial [83], the subjects presenting ≤ 4 sites with PD ≥ 5 mm at one year represented a successful treatment outcome. Therefore, the endpoint of therapy should seek the most optimal balance between over- and under-estimation of health status among treated periodontal patients. It is important to acknowledge the distinction between the diagnosis of periodontal health of initial patients versus treated patients. For the latter, a more flexible, comprehensive, and detailed assessment would be recommended.

CONCLUSION

This systematic review revealed a variety of definitions of periodontal health in existing scientific literature. This heterogeneity was measured according to study characteristics, measurement methods, explicit definitions, references, and cut-off values used. The definition of periodontal health proposed by the EFP/AAP Workshop offers an opportunity for the field to standardize and achieve uniformity in terms of methodologies in order to draw comparisons between different studies. This study also revealed that the number of people thought to have periodontal disease is likely overestimated due to the strict cut-off value.

SUPPLEMENTARY INFORMATION

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CHAPTER 3

Periodontal breakdown inter-tooth relationships in estimating periodontitis- related tooth loss

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ABSTRACT

Objectives: The reasons for tooth extraction are rarely recorded in epidemiological datasets. It poses a diagnostic challenge to determine if tooth loss is related to periodontal disease (TLPD). The present study aimed to assess the inter-tooth relationships based on the periodontal characteristics of existing teeth.

Methods: A cross-sectional dataset of 8,978 participants with complete periodontal examination (including probing pocket depth [PPD] and clinical attachment loss [CAL]) in the NHANES 2009–2014 was used in this study. Spearman rank correlation was applied to assess the inter-tooth correlations of PPD/CAL among 28 teeth after adjustment for relevant confounders. We further verify our findings in the Java Project on Periodontal Disease with TLPD information available (the number of TLPD = 12).

Results: Strong PPD/CAL correlations were observed in adjacent teeth (r for PPD = 0.652, r for CAL = 0.597; false discovery rate [FDR] < 0.05) rather than those on non-adjacent teeth (r for PPD = 0.515, r for CAL = 0.476; FDR < 0.05). The correlations increased among severe periodontitis cases (CAL $\geq$ 5 mm or PPD $\geq$ 6 mm). In line with this, we further observed that the teeth adjacent to the TLPD tooth had the most alveolar bone loss in the Java dataset.

Conclusion: The periodontitis parameters (PPD/CAL) of adjacent teeth could be a potential indicator to estimate TLPD when actual reasons for tooth extraction are unknown.

INTRODUCTION

Periodontitis is an oral infection resulting in the loss of tooth-supporting tissue, loosening of teeth, and tooth loss ultimately [1, 2]. In turn, when a large number of teeth are lost/extracted in a population, this could mask the potentially high prevalence of severe periodontitis [3, 4]. Knowledge of the reasons of missing teeth could contribute to assessing the severity of periodontitis more accurately. Therefore, tooth loss related to periodontal disease (TLPD) was an essential component of the staging dimension in the classification proposed at the 2018 World Workshop [5]. Nevertheless, the reasons for tooth loss were rarely registered or otherwise neglected in relevant population datasets [6].

The periodontal status of existing teeth might be a reference indicator for estimating TLPD. The higher correlation of the periodontal parameters [i.e., probing pocket depth (PPD) and clinical attachment loss (CAL)] between two teeth, the more representative they are for each other. More specifically, when these periodontal parameters of different teeth are highly correlated, one specific tooth's values could represent the correlated tooth's value. A recent cross-sectional study showed significant correlations between the adjacent tooth's periodontal status and the peri-implant condition [7]. Furthermore, the colonization by the microorganisms at the implant sulcus was influenced by the periodontopathic bacteria of adjacent teeth [8]. Therefore, we hypothesized the adjacent teeth that have PPD/CAL similarities as an indicator to help estimate the reason for tooth loss. The current study aims:

- 1) to assess in dentitions of a general population, for each tooth the correlation of PPD/CAL with corresponding teeth: i.e., the same tooth in the other quadrants as well as with adjacent teeth.
- 2) to determine the tooth pairs with the highest PPD/CAL correlation in this population.

METHODS

Study Design and Population

Three waves of survey data, acquired from the National Health and Nutrition Examination Survey (NHANES), were used to explore inter-tooth correlation. The NHANES is a national cross-sectional study administered by the National Center for Health Statistics (NCHS) to assess the health and nutritional status of the U.S.

population through a variety of questionnaires and examinations. The NCHS collected data from a stratified, multistage, clustered probability sample of the non-institutionalized civilians. Details regarding the NHANES protocol, testing procedures, and consent documents have been specified elsewhere [9]. The NCHS Ethics Review Board approved all NHANES protocols. Since this study analyzed public-use data, an additional research ethics review was not necessary for our analysis. Individuals who had fewer than 14 teeth and for whom no periodontal measurement data were available were excluded from our dataset [10]. In brief, the three waves from NHANES 2009–2014 enrolled 8,978 participants (**Fig. 1**). Two waves were used for a discovery dataset (NHANES 2009–2012, $n = 5,883$) and one wave for a validation dataset (NHANES 2013–2014, $n = 3,095$) to test the robustness and reproducibility of the results in the correlation analyses.

To verify the findings of the NHANES study, a dataset of a longitudinal study is necessary, which has a verified reason for extractions. Therefore, we used the data from the Java Project on Periodontal Diseases [11]. The study population consisted of 98 subjects from a tea estate on West Java, Indonesia, that had been part of a prospective longitudinal study and provided full datasets of clinical assessments from 1987, 1994 and 2002. In 2011, complete sets of dental radiographs were made which was combined with the survey forms and clinical slides from the previous assessments in order to estimate reasons for tooth loss. As previously described [11], a tooth was considered to be lost due to periodontitis if in the preceding examinations the presence of caries and/or root remnant of the tooth were never noted and if the tooth showed an increased pocket depth as well as attachment loss during the follow-up years, resulting in the last examination before the tooth was lost in pockets ≥ 6 mm with attachment loss ≥ 5 mm.

Demographics and Health-Related Variables

Demographic variables included age (year), gender, ethnicity/race (non-Hispanic white, Hispanic, African American, and other races), education (< high school, college, and > college), annual household income (<20,000\$, 20,000–75,000\$, and >75,000\$). Health-related characteristics included health behaviors such as smoking status (never smoked, former smoker, and current smoker), and medical history mainly comprised doctor-diagnosed diseases, such as arthritis, hypertension, hyperlipidemia, diabetes mellitus, and stroke. Physician-diagnosed myocardial infarction and coronary heart disease were defined as heart disease.

Figure 1. Population and analysis workflow of the present study using the National Health and Nutrition Examination Survey 2009–2014 dataset.

Periodontal Examination

Trained and calibrated dentists from the NCHS examined each patient's dentition and periodontal status. In the dentition assessment, the tooth-positions presenting edentulous or with dental implants were recorded as tooth loss [12]. The full mouth (four quadrants) was evaluated in each participant. The periodontal examination included probing assessments for PPD and CAL at six sites per tooth (mesio-, mid-, disto-buccal and mesio-, mid-, disto-lingual). As the third molars were excluded, a maximum of 28 teeth and 168 sites per individual could be examined to assess periodontal status. The maximum PPD and CAL per tooth were applied in the analyses to simplify the hierarchical structure of the periodontal data [13]. According to the 2018 World Workshop Classification System [5, 14], the patients with the maximum CAL of 1–2 mm were defined as stage I periodontitis, 3–4 mm as stage II, and ≥ 5 mm as stage III/IV. The complexity of management was also evaluated. The patients of stage II periodontitis were reclassified as stage III if the maximum PPD was ≥ 6 mm [15]. In the present study, we defined stage III/IV as severe periodontitis (CAL ≥ 5 mm or PPD > 6 mm); the others were set as non-severe periodontitis.

Data Analysis

For the present study correlation analyses were performed in the NHANES datasets regarding PPD and CAL. Since PPD and CAL may relate to the previously mentioned demographic and health-related variables [16, 17], we first inverse-rank transformed PPD and CAL values and further applied a linear regression model to adjust confounding factors [18], including age, sex, BMI, tooth number, ethnicity, education, income, smoking, alcohol intake, as well as presence of diseases (arthritis, hypertension, diabetes, dyslipidemia, and heart disease). Subsequently, we took residues of PPD and CAL generated from the linear regression model and determined the correlation of 28 teeth using Spearman rank correlation (378 random tooth pairs in total, $C2(28) = 378$). The Benjamini-Hochberg procedure was further applied to calculate the false discovery rate (FDR) [19]. Next a correlation matrix was built to present the results of all tooth pairs.

In the current dataset, 2,805 out of 8,978 participants (31%) had lost no teeth at all (**Fig. S1**). However, the missing teeth with unrecorded reasons in this population may bias the strength and direction of correlation. To further validate the representative of established correlations, we split the cohort into two parts (with and without tooth loss) to check whether there are significant differences in correlation strength and direction between two parts. Cochran-Q test was applied to assess the heterogeneity of effect sizes and direction between two

parts for each correlation coefficient [20]. The Cochran-Q test calculated the squared difference between individual study effect and the pooled effect using inverse variance weighting (**Fig. 1**).

Periodontitis severity could be a potential factor influencing the correlation of periodontal parameters. Since the findings from correlation analyses would be applied to periodontitis patients, subgroup analyses were performed to assess the variability of the PPD/CAL correlation coefficients across the tooth-relationships based on the degree of periodontitis severity. We divided the population into two groups: severe periodontitis (SP) and non-SP. The Cochran-Q test was further applied to assess the difference between the two groups (**Fig. 1**).

In the NHANES datasets, the normality of the continuous variables' distributions was assessed using a Kolmogorov-Smirnov test. Continuous variables with normal distribution were reported as mean (standard deviation [SD]), whereas non-normal variables were presented as median (interquartile range [IQR]). Categorical variables were described as number and frequency. Multiple imputation was used to handle the missing data of the covariables. Tooth-relationships are described as follows [21]: adjacent teeth (AD), contralateral teeth in the same jaw (CS) or the opposite jaw (CO), and ipsilateral opposing teeth (IO) (**Fig. 2A, B**). Evaluation of alveolar bone loss (ABL) was performed as described previously [22]. ABL of teeth in four relationships (AD, CS, CO, and IO) linked to each TLPD tooth was assessed radiographically. A one-way analysis of variance was used to compare the correlation coefficients and ABL of the four tooth-relationship categories. Significance was defined as $P < 0.05$ (two-tailed). All statistics were computed in R Project for Statistical Computing (version 3.6.0).

Figure 2. Diagram of the tooth-positions examples the lost lateral incisor (A) and the first molar (B) in the right maxillary quadrant. The positions of remaining teeth are classified into four categories: adjacent teeth (AD), the contralateral teeth in the same jaw (CS) and the opposite jaw (CO), and ipsilateral opposing teeth (IO). Spearman rank correlation matrices were used to present the correlation coefficients of PPD (C) and CAL (D) among all 28 teeth ($n = 378$) in the discovery dataset (NHANES 2009–2012). Abbreviations: NHANES, National Health and Nutrition Examination Survey; PPD, probing pocket depth; CAL, clinical attachment loss.

RESULTS

Characteristics of Study Populations

Of the 5,883 participants in the discovery dataset (NHANES 2009–2012), 2,962 (50.3%) were female, and 2,604 (44.3%) were non-Hispanic white. Subjects ranged in age from 30 to 85 years, with a mean (SD) age of 50.62 (13.85) (Table 1). The

characteristics of the population in the validation dataset (NHANES 2013–2014) are also shown in Table 1. Results of the Java data set showed that most teeth were lost due to caries or the co-occurrence of caries and periodontitis. Solely 12 missing teeth of only five subjects were assigned to be lost due to periodontal disease.

Table 1. Characteristic of the NHANES 2009–2014 subjects ($n = 8,978$)

VARIABLES	Discovery Dataset NHANES 2009–2012 ($n = 5,883$)	Validation Dataset NHANES 2013–2014 ($n = 3,095$)
Continuous variables, mean (SD)		
Age (year)	50.62 (13.85)	50.76 (13.90)
Body mass index (kg/m2)	29.27 (6.48)	29.46 (7.06)
Tooth number *	26 (5)	26 (5)
Categorical variables, n (%)		
Gender		
Male	2,921 (49.7)	1,480 (47.8)
Female	2,962 (50.3)	1,615 (52.2)
Ethnicity		
Non-Hispanic White	2,604 (44.3)	1,350 (43.6)
Hispanic	1,504 (25.6)	699 (22.6)
African American	1,126 (19.1)	566 (18.3)
Others	649 (11.0)	480 (15.5)
Education		
< high school	2,525 (43.0)	1,198 (38.7)
college	1,660 (28.3)	948 (30.6)
> college	1,690 (28.8)	948 (30.6)
Annual household income		
<20,000\$	1,006 (17.8)	448 (15.2)
20,000–75,000\$	2,929 (52.0)	1,476 (49.9)
>75,000\$	1,702 (30.2)	1,033 (34.9)
Smoking habit		
Non smoker	3,404 (57.9)	1,834 (59.3)
Former smoker	1,420 (24.1)	733 (23.7)
Current smoker	1,058 (18.0)	526 (17.0)
Arthritis	1,423 (24.2)	793 (25.7)
Hypertension	2,065 (35.1)	1,176 (38.0)
Hyperlipidemia	2,471 (42.0)	1,368 (44.2)
Diabetes mellitus	588 (10.0)	314 (10.1)

Table 1. (Continued)

Stroke	124 (2.1)	64 (2.1)
Heart disease	318 (5.4)	170 (5.5)

* Non-normal distribution continuous variable, median (interquartile range). Abbreviations: SD, standard deviation; NHANES, National Health and Nutrition Examination Survey

Inter-tooth PPD/CAL Correlations

Following the workflow presented in **Figure 1**, the Spearman rank correlation was applied to assess inter-tooth correlations of PPD and CAL. We observed significant PPD/CAL correlations (FDR <0.001) for all 378 tooth pairs in the discovery dataset (2009–2012, $n = 5,883$, **Fig. 2C, D** and **Supplementary Data 1**) with different confounding factors adjusted (age, gender, ethnicity, education, income, BMI, tooth number, smoking, alcohol intake, and chronic diseases). Strong PPD/CAL correlations were observed in adjacent teeth (r for PPD = 0.652, r for CAL = 0.597) instead of non-adjacent teeth (r for PPD = 0.515, r for CAL = 0.476, **Table S1**).

PPD/CAL correlations of tooth pairs in four tooth-relationships were further visualized in the tooth charts using a correlation network where the weight of each dash depended on the coefficient (AD-teeth, the number of tooth pairs [n] = 26; CS-teeth, $n = 12$; CO-teeth, $n = 14$; and IO-teeth, $n = 14$. **Fig. 3A, B**). The dashes of AD-teeth and CS-teeth are more evident in the tooth charts than those of CO-teeth and IO-teeth, particularly in the lower jaw. A stronger PPD/CAL correlation was seen for the AD-teeth when compared to the CS-teeth, IO-teeth, and CO-teeth ($P < 0.001$ for PPD and $P < 0.01$ for CAL, **Fig. 3C, D**). Consider tooth 16 as an example: the PPD correlation coefficients of AD-teeth include $16-17 = 0.678$ and $16-15 = 0.594$, CS-teeth is $16-26 = 0.549$, CO-teeth is $16-36 = 0.520$, and IO-teeth is $16-46 = 0.504$.

To further validate the robustness of all 378 significant periodontal correlations, another dataset (NHANES 2013–2014, $n = 3,095$) was included as replication, and all significant correlations in the discovery could be replicated at $P < 0.05$ (**Table S2** and **Supplementary Data 1**). Importantly, correlation strength was highest in the adjacent teeth when compared with other pairs (**Fig. S3**). Furthermore, 84.39% and 99.21% of correlations were comparable (Cochran-Q test FDR >0.05) between participants with ($n = 6,173$) and without ($n = 2,805$) tooth loss for PPD and CAL, respectively (**Supplementary Data 2**). This consistent effect was observed between participants with and without tooth loss (**Fig. S3**), indicating that the adjacent teeth were identified as the best correlated teeth in term of periodontal parameters.

Figure 3. Correlations of periodontal parameters among the tooth pairs were analyzed in the discovery dataset (NHANES 2009–2012). The tooth pairs in the four tooth-positions were shown in the tooth charts, with A for PPD and B for CAL. Teeth were identified using the FDI World Dental Federation notation. The correlation coefficients of PPD (C) and CAL (D) of tooth pairs in different positions were compared using a one-way analysis of variance. * $P < 0.01$, ** $P < 0.001$. Abbreviations: NHANES, National Health and Nutrition Examination Survey; PPD, probing pocket depth; CAL, clinical attachment loss; AD, adjacent teeth; CS, the contralateral teeth in the same jaw; IO, ipsilateral opposing teeth; CO, the contralateral teeth in the opposite jaw.

Inter-tooth PPD/CAL Correlations Increased in Severe Periodontitis

Since this general population contains both SP and non-SP participants, we further hypothesized that inter-tooth PPD and CAL correlations may show difference between SP and non-SP potentially due to disease severity. To assess this, we first divided the participants into severe and non-severe cases based

on the 2018 classification. As expected, similar results were obtained in the SP subgroup analyses (**Supplementary Data 3**) that adjacent teeth have higher PPD/CAL correlation coefficients than the other teeth among the participants with both non-SP and SP ($P < 0.001$ for PPD and $P < 0.05$ for CAL, **Fig. 4A, B**). Notably, the heterogeneity across two subgroups for each correlation coefficient shows stronger PPD/CAL correlations in patients with SP than individuals without SP ($P_{\text{heterogeneity}} < 0.001$ for PPD and $P_{\text{heterogeneity}} < 0.05$ for CAL, **Fig. 4C, D**). Again, consider tooth 16 as an example: the correlation coefficient of 16–17 (AD) increased from 0.659 in non-SP to 0.711 in SP, and 16–15 (AD) increased from 0.586 to 0.629. In brief, the adjacent tooth pairs had the highest PPD/CAL correlations; the correlation increased with increasing periodontitis severity. **Table S3** presents more detailed analyses.

Figure 4. Subgroup analyses were performed to assess the PPD/CAL correlation of the tooth pairs in different tooth-positions with periodontitis severity. Adjacent teeth have higher PPD (A) and CAL (B) correlation coefficients than the other teeth among participants with both non-severe and severe periodontitis. * $P < 0.05$, ** $P < 0.001$. Heterogeneity exists across two subgroups for each correlation coefficient, and the PPD (C) and CAL (D) correlations in severe periodontitis patients are stronger than those in the individuals with non-severe periodontitis. Circles represent tooth-position, and the lines indicate the different periodontitis severity of each tooth pair. Abbreviations: PPD, probing pocket depth; CAL, clinical attachment loss; AD, adjacent teeth; CS, the contralateral teeth in the same jaw; IO, ipsilateral opposing teeth; CO, the contralateral teeth in the opposite jaw; SP, severe periodontitis.

Periodontally Compromised Teeth Adjacent to TLPD tooth in the Java cohort

As found in the correlation analysis of the NHANES study, the adjacent teeth of TLPD tooth were found as to be the most correlated concerning PPD and CAL. We further investigated whether the teeth adjacent to the lost tooth have the greatest amount of bone loss compared to other teeth in the Java cohort. Given the highly correlated teeth clustered in the AD, CS, CO, and IO tooth-relationships (**Fig. 2C, D**), the teeth correlations analyzed in the Java study were only limited to these four categories. The other teeth (not AD, CS, CO, and IO) have lower correlation with each other from the statistical perspective, so they were not the focus of this study, even in case they had a more periodontal breakdown. In the Java study with twelve TLPD teeth from five subjects, the teeth adjacent to the TLPD tooth presented evident ABL, with a mean (SD) ABL of 45.6% (27.5%). In contrast, the mean (SD) ABL of CS is 36.6% (34.4%), CO is 43.82% (22.5%), and IO is 36.6% (17.8%). The teeth adjacent to TLPD tooth tended to have the most alveolar bone loss among the predefined four-relationship categories, although the difference did not reach statistical significance ($P > 0.05$). **Supplementary Data 4** displays more details.

DISCUSSION

The present study found that higher correlation coefficients of PPD and CAL were observed in adjacent teeth than those in the other tooth-relationships using NHANES data of a large-scale population. There was a consistent difference in the correlation network, both overall and in the subgroup with no tooth loss. More importantly, the periodontal correlation coefficients increased with increasing periodontitis severity. In addition, it was found that the teeth adjacent to TLPD tooth presented evident alveolar bone loss in the Java study. From this, we propose a potential indicator: the periodontally compromise adjacent teeth could help estimate whether tooth loss could be related to periodontitis.

The present study evaluated the correlations of periodontal parameters among 28 teeth after adjusting for potential confounders. It appeared that teeth have a higher correlation with their adjacent teeth than with other corresponding teeth. Notably, the PPD/CAL correlation coefficients of patients with severe periodontitis are significantly higher than those of individuals in the non-severe periodontitis group. Several possible explanations exist for the periodontal similarity of adjacent teeth. Teeth in poor condition result in a reduction of tooth-supporting

soft tissue and bone loss at interproximal sites, which have an impact on adjacent teeth [23, 24]. The bone-loss vulnerable interproximal alveolar sites may lead to the higher PPD/CAL correlations compared with the other, more distant tooth-relationships [25, 26]. The periodontal similarity between the adjacent teeth also could be relative with similar occlusion force, and masticatory function.

We revealed robust correlations between adjacent teeth in the severe periodontitis patients and confirmed the relationship between TLPD tooth and the adjacent teeth. In the Java project, the teeth adjacent to TLPD tooth presented moderate periodontal compromise, although the ABL of the teeth rarely reached a severe degree (i.e., >50%). From these results, we can reasonably infer that the more periodontal severe destruction of the teeth adjacent to the lost tooth, the higher probability that the reason for extraction was of periodontal origin.

When tooth extraction reasons are unknown, it is difficult to ascertain the number of TLPD teeth and accurately classify patients into severe periodontitis (stage III or IV). A recent cohort study compared the 2018 and 1999 systems for classifying periodontitis [27]. As no reasons for tooth extraction were provided in the dataset, the investigators considered all lost teeth in periodontitis patients as TLPD. However, even in periodontitis patients, other factors such as caries, orthodontic interventions, or trauma could have caused tooth loss. It is anticipated that this method could result in overestimating the counts of TLPD. The overestimation of TLPD will be corrected if, for each lost tooth, it is possible to identify whether the loss was periodontitis-related or not. Furthermore, the Fourth National Oral Health Survey of China recently showed the periodontal status in Chinese adults using the case definitions of the 2018 classification [28]. Because the reason for tooth loss was not available, the authors staged periodontitis using the method proposed in the comparative study [27]. They regarded all lost teeth as TLPD and classified the patients with 1–4 missing teeth as stage III and ≥ 5 missing teeth as stage IV. The prevalence of subjects with stage IV periodontitis was 14.9% in the total population. The prevalence of severe periodontitis (stage IV) was overestimated caused by neglecting other tooth loss reasons, compared with the age-standardized prevalence (9.8%) in the Global Burden of Disease 2017 Study [29]. From an epidemiological standpoint, the periodontal status of the adjacent teeth could be a reference indicator for estimating TLPD and a supportive tool for the 2017 World Workshop Classification System of periodontitis.

The limitations of the current study should be considered. Firstly, the high periodontal correlations between adjacent need to be interpreted cautiously.

The cross-sectional design of the NHANES study restricts causal inference. Despite this study employed rigorous statistical analyses and observed significant and robust correlations, we cannot make the causal interpretation (e.g., the periodontally compromised tooth directly affects the neighboring ones), although it may seem reasonable. Secondly, there is no large-scale dataset for validation, in which reasons for teeth extraction are recorded. We do not have such a dataset to evaluate the method's accuracy regarding sensitivity and specificity. The Java study dataset was the best available data we were able to retrieve. However, the Java study consists of only five patients who were exclusively determined to have twelve TLPD teeth. Although the difference of ABL among AD, CS, CO, and IO did not reach statistical significance (probably given the small sample size), there was a tendency for the teeth adjacent to the TLPD tooth to show the most periodontal breakdown. This preliminarily supports our theoretical principle. Thirdly, the measurements used to describe periodontal compromise in NHANES and Java studies are inconsistent. The former measures the PPD and CAL by probing examination, but the latter assesses the ABL by means of radiography. And the exact cutoff values of measurements may be influenced by various confounders and therefore remains ambiguous. We restricted the periodontal breakdown of adjacent teeth as moderate to severe periodontitis instead of a mild one. In other words, the specific definition of moderate-severe periodontitis needs to be flexibly adjusted according to the type of periodontal measurement in the used datasets. On the other hand, when teeth adjacent to a lost tooth showed minimal or no periodontal breakdown, it is unlikely that periodontal disease is the cause of that tooth loss.

In conclusion, we proposed a reference indicator for estimating TLPD based on the robust and significant correlations of periodontal parameters between adjacent teeth. The presence of moderate-severe periodontally compromised adjacent to absent teeth might help estimate the reasons for tooth loss.

SUPPLEMENTARY INFORMATION

<https://www.sciencedirect.com/science/article/pii/S0300571221001767>

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CHAPTER 4

Trends in socioeconomic inequality of periodontal health status among Dutch adults:

A repeated cross-sectional analysis over two decades

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ABSTRACT

Introduction: Studies exclusively focusing on trends in socioeconomic inequality of oral health status in industrialized countries are relatively sparse. This study aimed to assess possible differences in oral hygiene and periodontal status among people of different socioeconomic status (SES) in the Netherlands over two decades.

Methods: A repeated cross-sectional analysis of 3,083 participants aged 25–54 years was conducted on the Dutch National Oral Health Surveys of 1995, 2002, 2007, and 2013. Plaque-free was defined according to the Simplified Oral Hygiene Index (OHI-S = 0). Periodontal status was classified in two different ways, either periodontal health/disease (probing pocket depth index [PDI] = 0/≥1) or with/without deep pockets (PDI = 2). We used the regression-based absolute and relative effect index to measure the absolute and relative socioeconomic inequalities. Multivariable logistic regressions were used to explore temporal trends in oral hygiene and periodontal status by low- and high-SES groups.

Results: Age-standardized percentages of individuals with plaque-free increased in the whole population from 1995 to 2013 (12.7% [95% CI: 10.5–14.9] to 28.1% [24.8–31.5]). Plaque-free showed significant socioeconomic differences in absolute and relative inequalities in 2007 and 2013. Between 1995 and 2013, age-standardized percentage of periodontal health increased (from 51.4% [48.1–54.7] to 60.6% [57.0–64.1]). The significant absolute inequalities for periodontal health were seen in 2002 and 2013. The relative scale presented a similar pattern. Regarding deep pockets, there was little difference in the age-standardized overall prevalence in 1995 versus 2013 (from 6.5% [4.9–8.2] to 5.4% [3.7–7.0]). The significant absolute and relative inequalities in deep pockets prevalence were found in 1995. Yet, all interaction terms between survey year and SES did not reach significance (plaque-free: $P = .198$; periodontal health: $P = .490$; deep pockets: $P = .678$).

Conclusions: Socioeconomic inequalities in oral hygiene and periodontal status were present in the Netherlands in the last two decades.

Keywords: socioeconomic inequality, trends, oral hygiene, periodontal health, the Netherlands

INTRODUCTION

Periodontal disease is one of the most prevalent oral diseases; given that the severe case affected 796 million people worldwide and is associated with a variety of systemic conditions, it is considered a public health problem worldwide [1, 2]. Routine oral hygiene and effective plaque control have been identified as critical tools for achieving good periodontal health [3]. In recent decades, the periodontal health of adults has improved to varying degrees in Switzerland, Sweden, and Norway [4–7]. In contrast, the proportion of the severe periodontitis group did not decrease. Despite some progress achieved in periodontal prevention and care, social inequality in terms of periodontal health persists, and those on the lower rungs of the socioeconomic ladder still carry a substantial burden of periodontal disease and experience the poor oral health-related quality of life [8].

Socioeconomic inequality is thought to be socially unfair. More importantly, reducing disease burden of the lower socioeconomic population will largely improve the average health status of the overall population [9]. Therefore, reducing these inequalities is one of the primary goals of public health policies [10]. An understanding of the effects of socioeconomic changes on oral health over time can influence policymakers when revising policies, allocating budgets, and attempting to improve health quality [11]. Trends in terms of socioeconomic inequalities in children's oral health and adults' self-reported oral health, restorative dental treatment need, and tooth loss have been reported across the globe [12–17]. However, few nationally representative data have explored the effect of socioeconomic differences on temporal trends in oral hygiene and periodontal status among adults over time.

The existence of a national database on oral health in the Netherlands provides a unique opportunity to study trends in oral health disparities related to inequalities in socioeconomic status (SES) [18]. Hence, we examined the 1995–2013 trends in oral hygiene and periodontal status among Dutch adults and attempted to describe the possible inequalities in oral health linked to SES during the last two decades.

METHODS

Data Source and Study Population

The data used in this study were retrieved from a database developed by the Netherlands Organization for Applied Scientific Research (Toegepast Natuurwetenschappelijk Onderzoek, TNO). The Dutch National Oral Health Survey series has continuously gathered information on the oral health and oral health behavior of non-institutionalized civilian adult residents since 1995 [18]. The survey series was designed as a repeated cross-sectional study of the oral health status of the Dutch population over time based on a variety of oral health measures. More specifically, the Dutch National Oral Health Survey series used in this study were conducted among people living in the city of 's-Hertogenbosch, the Netherlands. This population is considered to be representative of the general Dutch population in terms of demographic distribution [19]. Under the National Health Care Institute's authority, Health Insurance Fund (HIF) companies were asked to provide the names and addresses of their clients. Since the HIF system focused on the relatively lower-income population before 2006 [20], people with low SES could be overrepresented. Therefore, the analyses were performed in the whole population and in the sub-populations stratified by SES. The stratification method facilitates making comparisons and conducting trend analyses about oral hygiene and periodontal status over time, in line with the approach adopted in a previous study on caries experience [13]. Central Committee on Research Involving Human Subjects concluded that no ethical approval was required for data collection for this purpose. Furthermore, it was determined that all of the requirements of the Personal Data Protection Act had been met (No. m1501261).

Data from four TNO survey cycles conducted between 1995 and 2013 were used. In 1995 and 2002, the sample included only persons aged 25–54 years [21, 22]. In 2007 and 2013, the scope was widened to 74 years [23, 24]. To conduct trend analyses in equal groups, we only included data of participants aged 25–54 years in this study. Information on sociodemographic characteristics and clinical examinations were from four surveys (1995, 2002, 2007, and 2013) while excluding those who were lacking dental measurement or SES data. In total, 3,083 respondents were included in the present study (see Fig. 1).

Socioeconomic Status and Covariates

Educational attainment was used as a proxy for socioeconomic status [13]. The level of education was divided into “low” (only having completed primary school or having received a lower-level general secondary education) and “high” (having

Figure 1 Flow chart indicating the subset of participants from 1995 to 2013 Dutch National Oral Health Survey included for analysis.

received a higher-level general secondary education or tertiary school) [25, 26]. Demographic variables, including age (25–34, 35–44, 45–54 years), gender and ethnic background, were collected via questionnaire and interview. Ethnicity (native/non-native Dutch) was determined on the participant's birth country (the Netherlands versus any other country). Oral hygiene behaviors included the time since the last dental visit, frequency of daily teeth brushing, using dental floss, using tooth pick, and mouthwash. We considered these covariates as potential confounders that were controlled in the multivariable regression models.

Assessment of Oral Hygiene and Periodontal Status

Oral health examinations were performed by a trained and qualified team of dentists and dental hygienists in a mobile research facility located in the municipalities in which the participants lived. The comprehensive oral health assessment included dentition status assessment, oral hygiene examination, and periodontal screening. Teeth missing (edentulous areas) or replaced by dental implants were recorded as lost teeth. To assess oral hygiene, the simplified oral hygiene index (OHI-S) was used to quantify dental plaque accumulation [27]. OHI-S was scored based on six index teeth: the buccal surfaces of teeth 16, 11, and 26 and the lingual surfaces of teeth 31, 36, and 46. Details concerning the criteria used in the OHI-S scoring can be found in **Table 1**. Oral hygiene was defined as “good” if all index teeth had OHI-S = 0, “fair” if at least one tooth with OHI-S = 1, and “poor” if at least one tooth with OHI-S = 2 to 3. In the current study, good oral hygiene (i.e., plaque-free [OHI-S = 0]) was considered as a binary outcome variable.

Periodontal status was assessed by probing pocket depth index (PDI), which is a standard periodontal parameter [18]. Periodontal examination was conducted on each tooth in two randomly selected quadrants (depending on the research ID number: ending with an odd number: we examined the 2nd and 4th quadrants; In case of an even number, we checked 1st and 3rd quadrants). This approach could minimize the burden of examination in large epidemiological studies. As third molars were excluded, a maximum of 14 teeth per individual could be examined. Three sites (buccal sites of maxillary vs. lingual sites of mandibular) were examined for each tooth using a Community Periodontal Index (CPI) probe recommended by the World Health Organization [28]. The highest score was recorded per tooth. The PDI scores were recorded as follows: PDI=0, pocket depth < 3.5 mm; PDI=1, pocket depth of 3.5–5.5 mm; and PDI=2, pocket depth > 5.5 mm (**Table 1**). We defined those individuals with PDI = 0 (all teeth have probing pocket depth <3.5 mm) as constituting the periodontal health group [29, 30]. Moreover, we defined PDI = 2 (≥1 tooth with probing pocket depth >5.5 mm) as deep pockets group. These approaches allowed for binary outcome variables [29, 30].

Table 1 Assessments and definitions of oral hygiene and periodontal status

Simplified Oral Hygiene Index (OHI-S)	Examination Protocol	Buccal surfaces of teeth 16, 11, 26 Lingual surfaces of teeth 31, 36, 46
	Score	0: no plaque 1: plaque on the gingival third of the surface 2: plaque on the middle third of the surface 3: plaque on the occlusal third of the surface
	Definition	Plaque-free was defined as all index teeth had OHI-S = 0
Pocket Depth Index (PDI)	Examination Protocol	Random half–mouth protocol Buccal surfaces of upper jaw Lingual surfaces of lower jaw
	Score	0: ≤ 3.5 mm 1: 3.5 – 5.5 mm 2: ≥5.5 mm
	Definition	1) Periodontal health was defined as all assessed teeth had pocket depth <3.5 mm (PDI = 0). 2) Deep pockets was defined as any assessed tooth had pocket depth >5.5 mm (PDI = 2).

Statistical Analysis

We calculated the means or the percentages of chosen population characteristics by survey year. The differences between survey years were analyzed by Chi-square test and one-way ANOVA. We calculated age-standardized percentages of oral hygiene (OHI-S = 0, 1, 2/3) and periodontal status (PDI = 0, 1, 2) using the direct method [31] with the data from Dutch population of 2006 as the standardized population. The age-standardized percentages with 95% confidence intervals (CIs) were presented for each study period.

We studied trends in socioeconomic inequality of oral hygiene and periodontal status in two steps. First, socioeconomic inequality was tested on the absolute and relative scales in each survey year (1995, 2002, 2007, 2013) [9]. We used multivariable logistic regressions to estimate the association of SES with oral health outcomes (i.e., plaque-free, periodontal health, and deep pockets). The logistic regressions were adjusted for potential confounders, including age, gender, ethnicity, SES, time since the last dental visit, number of teeth present, and oral hygiene behaviors (toothbrushing frequency, floss usage, and toothpick usage). Rate difference and odds ratio derived from the corresponding logistic model were used as the measure of absolute and relative effect [9, 32]. Rate

difference was defined as the difference between the predicted probability of the oral health outcome in high-SES group and that in low-SES group. The predicted probabilities for each outcome were calculated using marginal-effect estimation [33]. 95% CIs for the rate difference were estimated using the delta method [34]. As a second step, the adjusted percentages (i.e., predicted probabilities) of oral health outcomes were presented graphically to evaluate temporal trends using pooling data from four waves. We performed interaction analyses for each oral health outcomes in which the survey year (as a continuous variable) and the interaction between survey year and SES were additionally added into the logistic model in step one. A statistically significant interaction term (survey year × SES) indicated an increase or disease in socioeconomic inequalities of oral health outcomes over time [35]. Complete case analysis was used for handling missing data. R Project for Statistical Computing (version 3.6.0) was used to perform all analyses.

RESULTS

Characteristics of the Study Population

Participant characteristics aged 25–54 years by survey year are presented (Table 2). There were differences in the age and age composition of each survey year. The percentage of people with low-SES in 1995 and 2002 were higher than in 2007 and 2013. Compared to 1995 and 2007, the percentages of females in 2002 and 2013 were higher. Interdental hygiene behaviors (i.e., daily usage of floss and toothpick) improved over time. There were significant differences between survey years for these characteristics ($P < .01$).

Table 2. Characteristics of the Dutch population from the Dutch National Oral Health Survey 1995 to 2013

	1995 (n = 917)	2002 (n = 795)	2007 (n = 669)	2013 (n = 702)	P value ^b
Age year, Mean (SD)	38.1 (8.1)	40.7 (8.0)	41.1 (8.5)	40.2 (8.6)	.000
Age group, n (%)					
25–34 y	353 (38.5)	211 (26.5)	177 (26.5)	217 (30.9)	
35–44 y	317 (34.6)	310 (39.0)	227 (33.9)	235 (33.5)	.000
45–54 y	247 (26.9)	274 (34.5)	265 (39.6)	250 (35.6)	
Gender, n (%)					
Male	450 (49.1)	318 (40.0)	304 (45.4)	284 (40.5)	
Female	467 (50.9)	477 (60.0)	365 (54.6)	418 (59.5)	.000

Table 2. (Continued)

Ethnicity, n (%) ^a					
Native	831 (91.1)	639 (80.8)	576 (86.5)	636 (90.6)	
Non-native	81 (8.9)	152 (19.2)	90 (13.5)	66 (9.4)	.000
Socioeconomic status, n (%)					
Low	579 (63.1)	601 (75.6)	309 (46.2)	264 (37.6)	
High	338 (36.9)	194 (24.4)	360 (53.8)	438 (62.4)	.000
Time since the last dental visit, n (%) ^a					
More than 1 year	57 (6.2)	71 (8.9)	73 (10.9)	63 (9.0)	
Less than 1 year	859 (93.8)	723 (91.1)	595 (89.1)	638 (91.0)	.009
Toothbrushing frequency, n (%) ^a					
≤ once per day	254 (27.7)	218 (27.4)	122 (18.3)	182 (26.0)	
> twice per day	663 (72.3)	577 (72.6)	545 (81.7)	517 (74.0)	.000
Floss Usage, n (%) ^a					
Non-Daily	821 (89.5)	717 (90.2)	561 (84.4)	533 (75.9)	
Daily	96 (10.5)	78 (9.8v)	104 (15.6)	169 (24.1)	.000
Tooth Pick Usage, n (%) ^a					
Non-Daily	768 (83.8)	676 (85.0)	541 (81.5)	486 (69.2)	.000
Daily	149 (16.2)	119 (15.0)	123 (18.5)	216 (30.8)	
Number of teeth present, Mean (SD)	24.1 (5.3)	24.0 (5.4)	25.3 (4.1)	26.4 (3.1)	.000

^a Missing value for total study, ethnicity, $n = 12$ (0.4%); dental visit, $n = 4$ (0.1%); toothbrushing, $n = 5$ (0.2%); floss, $n = 4$ (0.1%); tooth pick, $n = 5$ (0.2%).
^b All P -values were calculated with a two-sided significance level of .05. Abbreviations: SD, standard deviation.

Simplified Oral Hygiene Index and Pocket Depth Index from 1995 to 2013

The age-standardized percentages of the OHI-S and the PDI in the total population can be found in Table 3. Between 1995 and 2013, there was a decrease in poor oral hygiene (OHI-S ≥2: from 41.1% [95% CI: 37.9–44.4] in 1995 to 10.9% [8.6–13.2] in 2013). Following this finding, the number of individuals with OHI-S = 0 showed an increasing trend over time. In contrast, no evident changes could be identified in the age-standardized percentages of individuals with deep pockets (PDI = 2) in the total population during the last two decades. Most of the changes in individuals with periodontal pockets (PDI = 1) occurred (from 42.0% [38.8–45.3] in 1995 to 34.0% [30.5–37.5] in 2013). This decreasing trend was accompanied by a steady increase (51.4% [48.1–54.7] to 60.6% [57.0–64.1]) in the proportion of individuals who exhibited periodontal health (PDI = 0, Table 3).

Table 3. Age-standardized percentage of oral hygiene and the periodontal status in the Dutch population from the Dutch National Oral Health Survey 1995 to 2013.

Age-standardized percentage (95% CI)	1995 (n = 917)	2002 (n = 795)	2007 (n = 669)	2013 (n = 702)
Oral Hygiene				
OHI-S = 0	12.7 (10.5–14.9)	8.9 (7.0–10.9)	20.6 (17.5–23.7)	28.1 (24.8–31.5)
OHI-S = 1	46.2 (42.9–49.4)	49.8 (46.4–53.3)	56.8 (53.0–60.6)	60.9 (57.3–64.5)
OHI-S = 2, 3	41.1 (37.9–44.4)	41.2 (37.8–44.6)	22.6 (19.4–25.8)	10.9 (8.6–13.2)
Periodontal Status				
PDI = 0	51.4 (48.1–54.7)	46.5 (43.0–49.9)	56.3 (52.6–60.0)	60.6 (57.0–64.1)
PDI = 1	42.0 (38.8–45.3)	45.0 (41.6–48.5)	36.8 (33.1–40.5)	34.0 (30.5–37.5)
PDI = 2	6.5 (4.9–8.2)	8.5 (6.6–10.4)	6.9 (5.1–8.7)	5.4 (3.7–7.0)

Percentages of oral hygiene and the periodontal status were age-standardized by the direct method, with the age distribution of the Dutch population in 2006 as the reference.

Relative and Absolute Socioeconomic Inequality of Oral Hygiene and Periodontal Status

Table 4 showed the relative and absolute socioeconomic inequality of plaque-free, periodontal health, and deep pockets in each survey year. For plaque-free, the significant absolute inequalities were observed in 2007 (absolute index = 8.4; 95% CI = 2.1, 14.7) and 2013 (absolute index = 8.6; 95% CI = 1.5, 15.7) while not in 1995 and 2002. When going from low-SES to high-SES, the adjusted percentage of plaque-free increased by 8.4 percentage points in 2007 and 8.6 percentage points in 2013, respectively. In the relative scale, the regression-based relative effect index presented a pattern similar to absolute inequality (1.698 [1.124 to 2.565] in 2007 and 1.561 [1.080 to 2.257] in 2013).

For the proportion of individuals having periodontal health, the significant absolute inequalities were seen in 2002 (10.0 [1.6 to 18.4]) and 2013 (9.6 [1.8 to 17.4]) (**Table 4**). We observed a similar pattern on the relative scale: moving from low-SES to high-SES was associated with a 1.5-fold increase in periodontal health's probability in 2002 and 2013. On the other hand, 1995 and 2007 did not show any significant inequality gap on absolute and relative inequality scales.

Compared with low-SES individuals, the prevalence of deep pockets in high-SES individuals was 4.2 percentage points lower in 1995 (**Table 4**). The relative scale finding was similar to the absolute inequality. The regression-based relative effect index decreased by almost 50% (0.216 to 0.869) in 1995, indicating that the high-SES individuals had half risk of deep pockets than those in the low-SES group. In contrast, we did not observe any significant absolute and relative inequality of deep pockets in 2002, 2007, and 2013.

Table 4. Absolute and relative socioeconomic inequality in plaque-free, periodontal health, and deep pockets in adults aged 25–54 from the Dutch National Oral Health Survey 1995 to 2013

Estimate (95% confidence interval)	1995 (n = 917)	2002 (n = 795)	2007 (n = 669)	2013 (n = 702)
Plaque-free				
Regression-based absolute effect index ^a	2.6 (-1.7 to 6.9)	1.9 (-2.1 to 6.0)	8.4 (2.1 to 14.7)	8.6 (1.5 to 15.7)
Regression-based relative effect index ^b	1.308 (0.819 to 2.090)	1.292 (0.674 to 2.477)	1.698 (1.124 to 2.565)	1.561 (1.080 to 2.257)
Periodontal health				
Regression-based absolute effect index ^a	3.7 (-3.5 to 10.8)	10.0 (1.6 to 18.4)	4.0 (-3.8 to 11.8)	9.6 (1.8 to 17.4)
Regression-based relative effect index ^b	1.163 (0.873 to 1.549)	1.516 (1.080 to 2.126)	1.188 (0.852 to 1.656)	1.516 (1.092 to 2.106)
Severe periodontitis				
Regression-based absolute effect index ^a	-4.2 (-7.1 to -1.3)	-2.3 (-5.9 to 1.3)	-3.1 (-5.4 to 0.7)	-2.6 (-5.6 to 0.3)
Regression-based relative effect index ^b	0.433 (0.216 to 0.869)	0.730 (0.382 to 1.396)	0.618 (0.325 to 1.176)	0.585 (0.290 to 1.177)

All logistic regression models were adjusted for including age, gender, ethnicity, SES, time since the last dental visit, number of teeth present, and oral hygiene behaviors (toothbrushing frequency, floss usage, and toothpick usage). Low-SES was regarded as reference.

^a Regression-based absolute effect index was estimated according to the SES difference of predicted probabilities of oral health outcomes. Absolute inequality was considered significant if the 95% confidence interval did not cross zero. Bold indicates *P* value < 0.05.

^b Regression-based relative effect index was estimated according to the adjusted odds ratio of SES for oral health outcomes. Relative inequality was considered significant if the 95% confidence interval did not cross one. Bold indicates *P* value < .05.

Trends in Socioeconomic Inequality of Oral Hygiene and Periodontal Status

Figure 2A illustrates the trends over time in the crude and adjusted percentages of individuals without detected plaque (OHI-S = 0) by SES-groups. In the 1995–2013 period, there was a significant increase in the adjusted percentage of individuals with OHI-S = 0 in both the low- and high-SES groups ($P_{\text{trend}} < .001$, Table 5), after adjusting for potential confounders. The slope of the high-SES group's temporal trend was slightly steeper than the corresponding slope for the low-SES group (**Fig. 2A**). However, the interaction effect of survey year × SES on plaque-free did not reach a significant level ($P_{\text{interaction}} = .198$, Table 5).

Figure 2 Adjusted percentage of plaque-free (A), periodontal health (B), and deep pockets (C) in adults aged 25–54 stratified by socioeconomic status from the Dutch National Oral Health Survey 1995 to 2013. All logistic regression models were adjusted for including age, gender, ethnicity, SES, time since the last dental visit, number of teeth present, and oral hygiene behaviors (toothbrushing frequency, floss usage, and toothpick usage). All P for trends were calculated using survey year as a continuous variable based on the multivariable regression model and with a two-sided significance level of .05.

The secular trends in the crude and adjusted percentage of periodontal health (PDI = 0) are shown in **Figure 2B**. After adjusting for confounders, the upward trends with respect to periodontal health were identified, with a percentage increase in the high-SES group ($P_{\text{trend}} < .001$, **Table 5**). In contrast, the percentage of periodontal health among the low-SES participants remained relatively constant ($P_{\text{trend}} = .083$, **Table 5**). Although SES inequality in periodontal health tends to widen increasingly over the last two decades (**Fig. 2B**), the SES group-by-time interaction did not reach statistical significance ($P_{\text{interaction}} = .490$, **Table 5**).

There was little difference in the adjusted percentage of individuals with deep pockets (PDI = 2) during all survey years, either in the high-SES or low-SES group (**Fig. 2C**). In the multivariable logistic regression models, no significant temporal trends were found for deep pockets between 1995 and 2013 (low-SES: $P_{\text{trend}} = .893$; high-SES group: $P_{\text{trend}} = .787$, **Table 5**). Additionally, the interaction term survey year $\times$ SES was not statistically significant ($P_{\text{interaction}} = .678$, **Table 5**).

Table 5. Trend analysis of plaque-free, periodontal health, and deep pockets in adults aged 25–54 from the Dutch National Oral Health Survey 1995 to 2013

Adjusted OR (95% CI)	Plaque-free	Periodontal health	Deep pockets
Total population			
Survey year			
1995	1 [reference]	1 [reference]	1 [reference]
2002	0.752 (0.539 to 1.048)	0.893 (0.733 to 1.090)	1.155 (0.792 to 1.686)
2007	2.073 (1.546 to 2.779)	1.289 (1.043 to 1.593)	1.102 (0.728 to 1.669)
2013	3.158 (2.372 to 4.206)	1.542 (1.242 to 1.913)	0.883 (0.562 to 1.388)
P for temporal trend ^a	.000	.000	.652
Low-SES population			
Survey year			
1995	1 [reference]	1 [reference]	1 [reference]
2002	0.754 (0.506 to 1.123)	.817 (0.645 to 1.036)	1.071 (0.703 to 1.631)
2007	1.730 (1.136 to 2.634)	1.248 (0.935 to 1.665)	1.038 (0.626 to 1.722)
2013	2.915 (1.914 to 4.438)	1.259 (0.922 to 1.718)	0.882 (0.502 to 1.548)
P for temporal trend ^a	.000	.083	.893
High-SES population			
Survey year			
1995	1 [reference]	1 [reference]	1 [reference]
2002	0.669 (0.353 to 1.266)	1.075 (0.741 to 1.559)	1.633 (0.690 to 3.865)
2007	2.525 (1.644 to 3.879)	1.359 (0.988 to 1.869)	1.410 (0.646 to 3.080)
2013	3.501 (2.316 to 5.292)	1.793 (1.312 to 2.449)	1.061 (0.470 to 2.397)

Table 2. (Continued)

<i>P</i> for temporal trend ^a	.000	.000	.787
<i>P</i> for interaction ^b	.198	.490	.678

All logistic regression models were adjusted for including age, gender, ethnicity, SES, time since the last dental visit, number of teeth present, and oral hygiene behaviors (toothbrushing frequency, floss usage, and toothpick usage). Low-SES was regarded as reference.
^a All *P* for trends were calculated using survey year as a continuous variable.
^b The interaction term indicated survey year × SES.
Bold indicates *P* value < .05.

DISCUSSION

This study tracked the trends in oral hygiene and periodontal status over the last two decades in a large sample of Dutch adults. Our data indicate that oral hygiene significantly improved over time in both the low- and high-SES groups and that the number of dental plaque-free individuals substantially increased as well. The improvement in periodontal health during the survey period slightly differed between high and low SES. In the low-SES group, the level of periodontal health remained almost constant. In contrast, our observations revealed a significant improvement in the percentage of periodontally healthy individuals in the high-SES population over time. Yet, within both SES groups, the prevalence of deep pockets over the last two decades remained the same.

We observed a significant decrease in the number of individuals with poor oral hygiene (OHI-S ≥2) since 1995. Concomitantly, there was an increase in the percentage of plaque-free individuals in the total sample. These findings regarding oral hygiene are similar to the trends identified in a previous Dutch dental health survey covering the period of 1983 to 1995 [18] and are aligned with the trends identified in studies conducted in other European countries. These findings reflect the remarkable improvements in oral hygiene that have occurred in most developed countries over the decades [4, 5, 7]. Notably, the improvements seen in oral hygiene among members of the low-SES group did not occur as rapidly as those in the high-SES group. These findings suggest that the previously noted persistence of socio-economic inequality was observed against a background of significantly improved oral hygiene over the last 20 years.

The current study focused on individuals with periodontal health, given that the main objective of dental care is to attain and maintain a healthy periodontium [36]. The definitions of periodontal disease that can be found among various clinical studies exhibit a high degree of heterogeneity [37]. Furthermore, the

varying degrees of severity of periodontitis and differences in the range of teeth affected lead to a series of “gray zones” in the classification system [38]. In contrast, the population consisting of individuals who exhibit healthy seems to show more homogeneity. Thus, tracking the percentage of individuals who exhibit periodontal health could also be an acceptable alternative in periodontal epidemiology.

The novel contribution of this study is the insight that socioeconomic inequality in periodontal health tends to widen in the Netherlands over the last two decades. To minimize the impact of the potential confounding factors, we attempted to control for the covariates using multivariable regressions and afterward analyzed the differentials in SES. The low-SES population did not significantly improve in periodontal health over time compared to their high-SES counterparts (*P* for trend = .083). Periodontal status is subject to periodontally accumulative defects, complex comorbidities, and multiple host risk factors [39]. Thus, the efficiency of measures intended to maintain periodontal health inferior to that designed to control plaque, suggesting that periodontal health is more challenging to change the SES inequality.

In the current study, education was used as a proxy for SES, as it has been documented to impact the ability to acquire and interpret periodontal health-related information [40]. Additionally, the level of education is also linked to a person’s position in his or her respective social structure. Individuals occupying higher social positions are hypothesized to have higher levels of social support, more control at work, and more job security than those of lower backgrounds in terms of SES [41]. All of the differentials in the high-SES group identified above facilitate access to costly dental services, particularly in developed countries. Another possible explanation for the widening differentials in SES is the changes that have occurred in oral health preventive programs, especially the 2006 health insurance reform in the Netherlands. Despite the fact that the mandatory basic dental insurance provides universal access to limited dental treatments to all Dutch citizens, most dental care requires supplementary insurance or out-of-pocket payment [20]. We assume that these financial barriers are more likely to be present in the low-SES group and that members of this group will therefore have more unmet dental care needs, which may explain the lack of improvement in periodontal health over time [42].

We did not observe the percentages of individuals with pocket depth >5.5 mm significantly decreased over time, even in the high-SES population. The prevalence

of deep pockets in the current study was 8.7% (low-SES) and 4.6% (high-SES), with a similar age-standardized prevalence in the high-income countries (6.6%, CI [5.5% to 7.8%]) [2]. Moreover, the unchanged prevalence of deep pockets over decades has been reported in previous studies in the Netherlands [18] as well as the other countries [6, 7, 43]. In the US, the prevalence of deep pockets nearly remained the same from 13.1% (CI, 11.7%-14.5%) in 1988 to 15.7% (CI, 13.8%-17.5%) in 2012 [43]. Similarly, no consistent trend of decreasing prevalence of deep pockets during either three- or four-decade intervals was found in Sweden [6, 7].

Several limitations of the current study should be considered. Firstly, the Dutch National Oral Health Survey employs the PDI for defining periodontal health and disease. Pocket depth index could cause misclassification and biased estimation as attachment loss is not assessed and a partial mouth recording protocol was used [44, 45]. There has been an updated classification system and case definition incorporating gingival bleeding, pocket depth, and attachment loss [46-48]. We conducted the analyses based on two different categorizing periodontal status methods (PDI = 0 and PDI = 2) to overcome this limitation partially. Secondly, this study selected education level as a single proxy for SES despite it would have been an acceptable and valid indicator [49]. Beyond education, other indicators related to socioeconomic inequalities include job position, income, tangible resources, or a combination of these variables [41, 50]. Since this information was not included in the TNO database, these additional indicators of SES were not considered in the analyses. Thirdly, the generalizability of the results to older populations may be limited, given that only young and middle-aged adults were included in the study. As the prevalence of periodontal disease increases with age, our results cannot necessarily be generalized across all age groups. Without the elderly, the prevalence of deep pockets in the current study could be underestimated compared to overall Swedish or the US population [6, 7, 43].

CONCLUSIONS

In conclusion, this study, using data from the Dutch National Oral Health Survey, demonstrated that socioeconomic inequalities in oral hygiene and periodontal status existed in the Dutch population in the last two decades. The trend in terms of improved periodontal health has not benefitted both SES groups equally, as the low-SES group has benefitted less than the high-SES group. The inequality identified in this study persisted between 1995 and 2013 in the Netherlands. It

is suggested that oral health workers should be aware that low-SES populations should be provided with more preventive care and dental education. Oral and dental policymakers may need to increasingly target socioeconomic inequality and tailor appropriate policies for different SES groups.

SUPPLEMENTARY INFORMATION

<https://bmcoralhealth.biomedcentral.com/articles/10.1186/s12903-021-01713-x>

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CHAPTER 5

Dietary inflammatory potential is associated with poor periodontal health:

A population-based study

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ABSTRACT

Background: Single nutrients may influence periodontal health, but its overall association with the inflammatory dietary pattern is still unclear. To investigate the association between dietary inflammatory potential and poor periodontal health.

Methods: A cross-sectional analysis of a nationally representative sample of participants was performed. NHANES 2011–2014 ($n = 7,081$) and NHANES 2001–2004 ($n = 5,098$) were used as discovery and validation datasets, respectively. The energy-adjusted dietary inflammatory index (E-DII) score was calculated for each participant based on 24-hr dietary recalls to assess diet-associated inflammation. Periodontitis was defined by the CDC/AAP using clinical periodontal parameters. Natural cubic spline was applied to identify any non-linear associations of the E-DII score with moderate/severe periodontitis. Furthermore, interaction analyses were performed by age, gender, and race/ethnicity to explore the moderating roles of these factors.

Results: In the discovery dataset, a non-linear positive relationship with periodontitis was identified for the E-DII score ($P_{\text{non-linearity}} < .001$) after adjustment for potential confounders. Compared with those individuals in the lowest tertile of E-DII, participants in the highest tertile who consumed a pro-inflammatory diet were 53% more likely to be periodontitis ($OR_{\text{tertile3vs1}} = 1.53$, 95% CI: 1.33–1.77). The validation dataset showed similar associations. Relatively stronger associations were seen in older adults and males.

Conclusions: Consuming a pro-inflammatory diet indicated by the E-DII score is associated with periodontal disease in the U.S. general adult population.

INTRODUCTION

Periodontitis is a prevalent oral inflammatory disease associated with complex interactions among plaque bacteria, environmental factors, and the host's immune system [1, 2]. The host-modulation imbalance between microbial factors and the immune-inflammatory response causes periodontitis onset and progression [3]. Conventional treatment and prevention of periodontitis mainly involve mechanical removal of the dental biofilm and calculus (i.e., professional cleaning and oral hygiene improvement). In complex cases, antibiotics and surgical treatment may be applied [4]. Additionally, healthy lifestyle changes should be incorporated in managing periodontal disease, including smoking cessation, stress reduction, and engaging in robust physical activity. Beyond these factors, adherence to a healthy diet plays an integral role in maintaining and promoting periodontal health [5].

A dietary index can be used to identify the synergistic effects among various nutrients and determine the overall healthy qualities of an individual's nutritional patterns [6-8], which is distinct from focusing solely on a specific macronutrient or micronutrient. Recent studies on various dietary indices have shown that unhealthy dietary patterns are associated with gingival bleeding and periodontal disease, including the Mediterranean diet, the Western diet, the Healthy Eating Index (HEI), and the Alternative HEI [9-13]. Nevertheless, these index-based dietary patterns were not designed to capture the inflammatory potential of diets. The energy-adjusted dietary inflammatory index (E-DII) was developed to measure an individual's dietary inflammatory potential [14]. There have been an increasing number of studies reporting the associations between the E-DII score and a variety of inflammatory diseases and conditions, including diabetes mellitus [15], cardiovascular disease [16], metabolic syndrome [17], cognitive impairment [18], and chronic kidney disease [19]. In a cross-sectional study conducted in the U.S. population, the E-DII score was positively associated with the number of missing teeth [20]. In the subgroup analysis, the significant association remained in persons aged >50 years who have suffered tooth loss primarily due to periodontitis. Adherence to a pro-inflammatory diet could result in a low-grade sustained inflammation, which could, in turn, exacerbate the progress of periodontitis through the regulation of immunity.

This study aimed to examine the relationship between the E-DII score and clinically determined periodontitis after adjusting for potential confounders (including sociodemographic factors, lifestyle, and periodontitis-related diseases). We also

explore differences in this association by age, gender, and race/ethnicity to determine the potential existence of subpopulations for dietary intervention.

METHODS

Study Design and Population

The current cross-sectional study uses two waves of survey data acquired from the National Health and Nutrition Examination Survey (NHANES). The NHANES is a stratified, multistage, clustered probability sampling study focusing on U.S. civilians' health and nutritional status; the NHANES is administered by the National Center for Health Statistics (NCHS). The survey consists of an in-home interview followed by physical examinations and biological sample collections at a mobile examination center. The NCHS Ethics Review Board approved all NHANES protocols and testing procedures, and all participants provided written informed consent [21]. Additional information including protocol numbers are available here (Protocol #98-12, <https://www.cdc.gov/nchs/nhanes/irba98.htm>).

NHANES 2011–2012 and 2013–2014 were merged as a discovery dataset for primary analysis; NHANES 2001–2002 and 2003–2004 were combined as a validation dataset to replicate the findings. The present study excluded individuals below 30 years of age, edentulous, and no data available on dietary or periodontal measurements. We also excluded individuals with extreme total energy intakes outside the range of 500–5,000 Kcal/day [22].

Exposure Variable

Dietary information was used to calculate the dietary inflammatory index score for each subject as an exposure variable. Trained interviewers conducted 24-hr dietary recalls to obtain dietary information using methods developed by the United States Department of Agriculture [23]. Dietary data consisted of all foods consumed and the quantities eaten. The dietary inflammatory index methodology was developed based on a systematic review of approximately 2,000 published research articles [14]. The dietary inflammatory index estimates dietary inflammatory potential based on the balance of pro- and anti-inflammatory properties of 45 different food components (mostly micro and macronutrients). For each food component, an inflammatory effect score was derived based on its pro-inflammatory effect (set to +1), anti-inflammatory effect (set to -1), or null effect (set to 0). These scores were weighted based on study design (i.e., randomized control trials received the greatest weight and cell culture studies received the lowest weight). The dietary

inflammatory index score was standardized to a representative world database from 11 populations worldwide, allowing the score to be used across different dietary patterns and cultures [14].

NHANES applies a total of 27 food components to calculate the E-DII score: carbohydrate; protein; total fat; dietary fiber; cholesterol; saturated, monounsaturated, and polyunsaturated fatty acids; omega-3 and omega-6 polyunsaturated fatty acids; vitamins A, B1, B2, B3 (niacin), B6, B9 (folic acid), B12, C, D, and E; alcohol; beta-carotene; caffeine; iron; magnesium; zinc; and selenium. A z-score for each food parameter was computed by subtracting the world standard means and then dividing it by its standard deviation. Thereafter, each food parameter's z-score was converted to a centered percentile score and multiplied by the literature-derived inflammatory effect score. All of the specific food parameters' dietary inflammatory index scores were then summed to create each participant's overall score. To control the total energy intake effect, the dietary inflammatory index was calculated per 1,000 calories of food consumed (i.e., E-DII). Higher E-DII scores correspond to more pro-inflammatory diets, whereas more negative values are more anti-inflammatory [14].

Outcome Variable

The primary outcome of interest was moderate or severe periodontitis. In the discovery dataset (NHANES 2011–2014), the full mouth (four quadrants) was evaluated in each participant. Trained and calibrated dentists examined the periodontal status of each participant. Probing pocket depth (PPD) and clinical attachment loss (CAL) have shown good reliability, with Inter-class Correlation Coefficients (ICCs) ranging from 0.80–0.90 and 0.79–0.86, respectively [24]. The periodontal examination included probing assessments at six sites per tooth (mesio-, mid-, disto-buccal and mesio-, mid-, disto-lingual). As the third molars were excluded, a maximum of 28 teeth and 168 sites per individual could be examined to assess periodontal status.

We used the CDC/AAP case definition (Centers for Disease Control & Prevention and American Academy of Periodontology) to categorize periodontal disease [25]. No or mild periodontitis was defined as no evidence of moderate, or severe periodontitis; Moderate: ≥ 2 inter-proximal site with ≥ 4 mm CAL (not on the same tooth), or ≥ 2 interproximal site with ≥ 5 mm PPD; Severe: ≥ 2 interproximal site with ≥ 6 mm CAL (not on the same tooth) and ≥ 1 interproximal site with ≥ 5 mm PPD. The participants were dichotomized as no/mild periodontitis and moderate/severe periodontitis [26]. The periodontal examination protocol and periodontitis definition in the validation dataset were provided in the **Supplemental Method**.

Potential Confounders

Sociodemographic variables were age, gender, race/ethnicity, educational level, and annual household income. We categorized race/ethnicity into non-Hispanic Whites and others. Educational level and annual household income were grouped into three categories: less than high school, some college, or college graduate or more and <20,000\$, 20,00–75,000\$, or >75,000\$, respectively. Behavioral variables included smoking status (current, former, or never), the average number of alcoholic drinks consumed in past year (0, <1, 1–8, and >8 drinks per week) [27], level of physical activity (low, moderate, or high), and time since last dental visit (<1, 1–3, >3 years). Moreover, smoking intensity was quantitated among current smokers (in the last 30 days) and former smokers (before quitting) by calculating the average number of cigarettes smoked per day [28].

Systemic biomarkers of inflammation, including C-reactive protein (CRP, only for NHANES 2001–2004) and white blood cell (WBC) count, were measured using blood samples taken from the participants. As done in a previous study [29], we used the following eight variables to characterize systemic diseases: abdominal adiposity, obesity, hypertension, dyslipidemia, dysglycemia, cardiovascular diseases, and arthritis (**Table S1**). Since both periodontal disease and E-DII could be related to the above covariates, we decided to adjust our analyses for these potential confounders.

Statistical Analysis

Descriptive statistics were calculated to describe the characteristics of participants overall and by the E-DII tertiles. The Kolmogorov-Smirnov test was used to test the normality of the distribution of the continuous variables. Continuous variables with normal distribution were reported as mean with standard deviation and compared among tertile groups using a one-way ANOVA test. Non-normal variables were presented as median with interquartile range and compared using an independent-samples Kruskal-Wallis test. Categorical variables were described as numbers with frequencies and compared using a Chi-square test.

In the discovery dataset, a multivariable logistic model was used to study the association between the E-DII score and moderate/severe periodontitis after adjusting for age, gender, race/ethnicity, education, income, smoking habit, alcohol consumption, physical activity, dental visit, abdominal adiposity, obesity, hypertension, dyslipidemia, dysglycemia, WBC count, cardiovascular, arthritis, total energy intake, and the number of teeth present. To avoid arbitrary categorization, we explored the relationship between continuous E-DII and

periodontitis. Natural cubic splines with two knots equally spaced within the range of E-DII were used to examine the potential non-linear relationships. Secondly, we examined the association between the E-DII tertiles and periodontitis. We performed interaction analyses to determine whether the association between the E-DII score tertiles and periodontitis differed by age group (<60 and ≥60), gender, and race/ethnicity (Whites and others). Furtherly, the robustness of the total and subgroup associations between E-DII tertiles and moderate/severe periodontitis was validated using data from the NHANES 2001–2004.

We performed a sensitivity analysis in the discovery dataset to investigate effect modification by total energy intake (< median and ≥ median). In additional sensitivity analyses using data from the NHANES 2001–2004, we also considered a definition of periodontal health newly proposed by the Joint Workshop of the European Federation of Periodontology and the American Academy of Periodontology (EFP/AAP) [30]. Periodontal health was defined as no sites with PPD >3 mm and <10% of sites with BOP in an intact periodontium (CAL <3 mm); the others were set as a reference. Given the small percentage of missing data, a complete case analysis was used in this study. All the analyses were conducted with the R Project for Statistical Computing (version 3.6.0) and SPSS 25 (SPSS Inc., Chicago, IL, USA). A P-value of less than 0.05 was considered statistically significant.

Figure 1. Flow chart indicating the discovery and validation datasets of participants included for the analysis from the National Health and Nutrition Examination Survey 2011–2014 and 2001–2004 dataset.

RESULTS

Characteristics of the Study Sample

As depicted in **Figure 1**, data on 7,081 participants of the NAHENS 2011–2014 were used as a discovery dataset, and data on 5,098 participants of the NHANES 2001–2004 were used as a validation dataset. Table 1 presents the characteristics of participants overall and across the E-DII tertiles in the discovery dataset. On average, participants were 53.3 years of age, with the sample being almost equally divided by gender (50.6% female). The overall percentage of people with moderate/severe periodontitis was 41.8%. The E-DII score ranged from -5.45 to 4.74: the first tertile ($n = 2,360$; E-DII = -5.45 to -0.85), the second tertile ($n = 2,362$; E-DII = -0.85 to 2.81), and the third tertile ($n = 2,359$; E-DII = 2.81 to 4.74). Compared with those in the first tertile of E-DII score (i.e., those who consumed the most anti-inflammatory diet), participants in the third tertile were more likely to be female, less educated, and lower income. They also had a higher prevalence of abdominal adiposity, obesity, hypertension, dyslipidemia, dysglycemia, and cardiovascular disease than those in the first E-DII tertile (all $P < .05$). Additionally, the baseline characteristics of the validation dataset (NHANES 2001–2004) are displayed in **Table S2**.

Table 2. Characteristics of 7,081 adults aged ≥30 years in the discovery dataset (NHANES 2011–2014) overall and by tertile of E-DII

	Energy-adjusted Dietary Inflammatory Index a				
	Overall <i>n</i> = 7,081	Tertile 1 <i>n</i> = 2,360	Tertile 2 <i>n</i> = 2,362	Tertile 3 <i>n</i> = 2,359	<i>P</i> value
Sociodemographic Variables					
Age, year, mean (SD)	53.31 (14.66)	52.51 (14.96)	52.74 (14.57)	54.67 (14.36)	< .001
Age group, <i>n</i> (%)					
<60 years	4,687 (66.2)	1,605 (68.0)	1,506 (63.7)	1,576 (66.9)	.429
≥60 years	2,394 (33.8)	755 (32.0)	860 (36.3)	779 (33.1)	
Gender, <i>n</i> (%)					
Male	3,495 (49.4)	1,289 (54.6)	1,342 (56.7)	864 (36.7)	< .001
Female	3,586 (50.6)	1,071 (45.4)	1,024 (43.3)	1,491 (63.3)	
Race/ethnicity, <i>n</i> (%)					
Non-Hispanic Whites	4,073 (57.5)	987 (41.8)	1,104 (46.7)	917 (38.9)	.046
Others	3,008 (42.5)	1,373 (58.2)	1,262 (53.3)	1,438 (61.1)	
Education, <i>n</i> (%) b					
< high school	3,171 (44.8)	952 (40.4)	1,066 (45.1)	1,153 (48.9)	< .001
college	2,003 (28.3)	637 (27.0)	687 (29.1)	679 (28.8)	
> college	1,904 (26.9)	768 (32.6)	609 (25.8)	527 (22.2)	

Table 1. (Continued)

Annual household income, <i>n</i> (%) <i>b</i>						
<20,000\$	1,456 (21.4)	319 (13.6)	608 (26.3)	529 (24.8)		
20,000-75,000\$	3,399 (50.1)	1,185 (50.4)	1,109 (48.0)	1,105 (52.0)	< .001	
>75,000\$	1,934 (28.5)	846 (36.0)	595 (25.7)	493 (23.2)		
Lifestyle Variables						
Smoking habit, <i>n</i> (%) <i>b</i>						
Non smoker	3,841 (54.3)	1391 (59.0)	1,287 (54.5)	1,163 (49.3)		
Former smoker	1,850 (26.1)	620 (26.3)	621 (26.3)	609 (25.8)	< .001	
Current smoker	1,386 (19.6)	345 (14.6)	454 (19.2)	587 (24.9)		
Smoking intensity, median (IQR) ^c	10 (15)	10 (16)	10 (15)	10 (16)	< .001	
Average alcohol use in past 12 months						
0 drink/week	2,602 (36.8)	969 (41.1)	810 (34.4)	823 (34.9)		
<1 drink/week	1,934 (27.3)	633 (26.9)	723 (30.7)	578 (24.5)	< .001	
1-8 drinks/week	1,719 (24.3)	545 (23.1)	570 (24.2)	604 (25.6)		
>8 drinks/week	817 (11.6)	208 (8.8)	255 (10.8)	354 (15.2)		
Physical activity level, <i>n</i> (%) <i>b</i>						
Low	2,889 (40.8)	968 (41.0)	990 (41.9)	931 (39.5)		
Moderate	2,396 (33.8)	781 (33.1)	789 (33.4)	826 (35.0)	.410	
High	1,796 (25.4)	611 (25.9)	583 (24.7)	602 (25.5)		
Time since the last dental visit, <i>n</i> (%) <i>b</i>						
Less than 1 year	3,961 (56.0)	1,529 (64.8)	1,459 (61.8)	973 (41.3)		
1-3 years	1,368 (19.3)	363 (15.4)	307 (13.0)	698 (29.6)	< .001	
More than 3 years	1,746 (24.7)	467 (19.8)	593 (25.1)	686 (29.1)		
Systemic Disease and Related Factors						
Abdominal adiposity, <i>n</i> (%) <i>b</i>						
Tertile 1st of WHtR	2,290 (33.4)	843 (36.9)	760 (33.6)	687 (29.5)		
Tertile 2nd of WHtR	2,288 (33.3)	763 (33.4)	706 (31.2)	819 (35.2)	< .001	
Tertile 3rd of WHtR	2,288 (33.3)	678 (29.7)	795 (35.2)	815 (35.1)		
Obesity, <i>n</i> (%) <i>b</i>						
Normal	1,921 (27.3)	692 (29.5)	600 (25.6)	629 (26.9)		
Overweight	2,408 (34.3)	771 (32.9)	832 (35.5)	805 (34.4)	.044	
Obese	2,699 (38.4)	881 (37.6)	911 (38.9)	907 (38.7)		
Hypertension, <i>n</i> (%) <i>b</i>						
Normal	2,179 (31.2)	1,100 (47.3)	612 (26.2)	467 (20.1)		
Prehypertension	1,457 (20.8)	388 (16.7)	516 (22.1)	553 (23.7)	< .001	
Hypertension	3,354 (48.0)	837 (36.0)	1,208 (51.7)	1,309 (56.2)		

Table 1. (Continued)

Dyslipidemia, <i>n</i> (%) <i>b</i>						
Normal	2,738 (40.5)	974 (42.9)	881 (39.4)	883 (39.1)		
Intermediate dyslipidemia	1,922 (28.4)	636 (28.0)	671 (30.0)	615 (27.2)	.003	
Dyslipidemia	2,108 (31.1)	661 (29.1)	685 (30.6)	762 (33.7)		
Dysglycemia, <i>n</i> (%) <i>b</i>						
Normal	3,741 (54.3)	1,403 (60.7)	1,419 (62.4)	919 (39.9)		
Intermediate dysglycemia	2,137 (31.0)	582 (25.2)	520 (22.9)	1,035 (44.9)	< .001	
Diagnosed diabetes	1,010 (14.7)	326 (14.1)	334 (14.6)	350 (15.2)		
Cardiovascular disease, <i>n</i> (%) <i>b</i>						
No physician's diagnosis	6,316 (89.4)	2,139 (90.8)	2,125 (90.2)	2,052 (87.3)	< .001	
Physician's diagnosis	747 (10.6)	217 (9.2)	231 (9.8)	299 (12.7)		
Arthritis, <i>n</i> (%) <i>b</i>						
No physician's diagnosis	5,032 (71.2)	1,658 (70.3)	1,676 (71.1)	1,698 (72.1)	.409	
Physician's diagnosis	2,037 (28.8)	699 (29.6)	681 (28.9)	657 (27.9)		
White blood cell count, mean (SD)	7.10 (2.22)	6.99 (2.08)	7.12 (2.20)	7.20 (2.38)	.007	
Total energy intake (Kcal/day), mean (SD)	2,053 (853)	2,077 (873)	2,058 (847)	2,035 (825)	.037	
Total energy intake group, <i>n</i> (%)						
< median	3,541 (50.0)	1,048 (44.4)	1,176 (49.7)	1,317 (55.9)	< .001	
≥ median	3,540 (50.0)	1,312 (55.6)	1,190 (50.3)	1,038 (44.1)		
Periodontal Disease Variables						
Number of the teeth present, median (IQR)	25 (9)	25 (7)	25 (11)	25 (9)	< .001	
CDC/AAP case definition, <i>n</i> (%)						
Non/mild periodontitis	4,124 (58.2)	1,427 (60.5)	1,449 (61.2)	1,248 (53.0)	< .001	
Moderate/severe periodontitis	2,957 (41.8)	933 (39.5)	917 (38.8)	1,107 (47.0)		

^a E-DII ranges for Tertile 1, Tertile 2 and Tertile 3 were -5.45 to -0.85, -0.85 to 2.81 and 2.81 to 4.74.

^b Missing values for total study: education (*n* = 3; 0.1%), income (*n* = 292; 4.1%), smoking status (*n* = 4; 0.1%), Smoking intensity (*n* = 98; 1.4%), alcohol (*n* = 9; 0.1%), dental visit (*n* = 6; 0.1%), abdominal adiposity (*n* = 215; 3%), obesity (*n* = 53; 0.7%), hypertension (*n* = 91; 1.3%), dyslipidemia (*n* = 313; 4.4%), dysglycemia (*n* = 193; 2.7%), cardiovascular disease (*n* = 18; 0.3%), and arthritis (*n* = 12; 0.2%).

^c Average number of cigarettes smoked per day was used as a measure of smoking intensity.

All P-values were calculated with a two-sided significance level of .05.

Abbreviations: NHANES, National Health and Nutrition Examination Survey; E-DII, energy-adjusted dietary inflammatory index; SD, standard deviation; IQR, interquartile range; WHtR, waist-to-height ratio; CDC, Centers for Disease Control and Prevention; AAP, American Academy of Periodontology.

Diet-borne Inflammation and Periodontal Disease

In the discovery dataset, the E-DII score has a non-linear positive relationship with moderate/severe periodontitis ($P_{\text{non-linearity}} < .001$, **Figure 2**). The risk of periodontitis was relatively flat before the E-DII score was around 2 and then increased rapidly

afterward. Based on this, the E-DII score was grouped into tertiles in the further analyses. **Figure 3** shows the results with moderate/severe periodontitis as the outcome for the overall samples in the discovery and validation datasets. After adjustment for potential confounders, participants from the discovery population in the most pro-inflammatory E-DII group (i.e., the third tertile) had a significantly increased risk of periodontitis compared to those in the first tertile (adjusted OR for the third vs. the first tertile of E-DII [$OR_{\text{tertile3vs1}}$]: 1.53, 95% CI: 1.33–1.77). Similar trend and direction of adjusted odds ratios for moderate/severe periodontitis were obtained in the validation dataset (**Figure 3**): $OR_{\text{tertile3vs1}}$: 2.66, 95% CI: 2.17–3.27.

Figure 2. Natural spline curve indicates the non-linear association between the E-DII score and moderate/severe periodontitis in participants aged ≥ 30 years in the discovery dataset (NHANES 2011–2014, $n = 7,081$). The red hollow-circle line and dotted lines represent the estimated values and their corresponding 95% CI. Odds ratios are based on logistic regression models adjusted for age, gender, race/ethnicity, education, income, smoking habit, alcohol consumption, physical activity, dental visit, abdominal adiposity, obesity, hypertension, dyslipidemia, dysglycemia, WBC count, cardiovascular disease, arthritis, total energy intake, and the number of teeth present. Periodontitis was defined by CDC/AAP case definition. Knots are at the 33.3th and 66.7th percentiles for the E-DII score. Abbreviations: NHANES, National Health and Nutrition Examination Survey; E-DII, energy-adjusted dietary inflammatory index; WBC, white blood cell; CI, confidence interval; OR, odds ratio; CDC, Centers for Disease Control and Prevention; AAP, American Academy of Periodontology.

Figure 3. Associations between the tertiles of E-DII and moderate/severe periodontitis in participants aged ≥ 30 years in the discovery dataset (NHANES 2011–2014, $n = 7,081$) and the validation dataset (NHANES 2001–2004, $n = 5,098$). Association is deemed significant if the 95% CI does not include zero. All P values were calculated with a two-sided significance level of .05. A multivariable logistic regression model was adjusted for potential confounders (see legend of Figure 2). Periodontitis was defined by CDC/AAP case definition. Abbreviations: E-DII, energy-adjusted dietary inflammatory index; NHANES, National Health and Nutrition Examination Survey; CI, confidence interval; OR, odds ratio; CDC, Centers for Disease Control and Prevention; AAP, American Academy of Periodontology.

Subgroup Analyses

When stratified by age and gender in the discovery dataset, relatively stronger associations were observed between E-DII tertiles and periodontitis among older adults ($OR_{\text{tertile3vs1}} = 1.84$; 95% CI: 1.45–2.35) and males ($OR_{\text{tertile3vs1}} = 2.69$; 95% CI: 2.17–3.32), with significant interactions (both $P_{\text{interaction}} < .001$, **Table 2**). There was no evidence in the discovery population supporting the modified effect of race/ethnicity on the association between the E-DII tertiles and periodontitis ($P_{\text{interaction}} = .146$, **Table 2**). During the validation analysis in the NHANES 2001–2004, no statistically significant modification effects were observed ($P_{\text{interaction}} = .228$ for age, .243 for gender, and .113 for race/ethnicity, **Table S3**).

Table 2. Subgroup analyses of the associations between the tertiles of E-DII and moderate/severe periodontitis by age, gender, and race/ethnicity in the discovery dataset (NHANES 2011–2014; $n = 7,081$)

Energy-adjusted Dietary Inflammatory Index				P for interaction	
Subgroup	Tertile 1	Tertile 2	Tertile 3		
Age					
<60 years					
Cases/participants	574/1,605	578/1,506	648/1,576		
Odds Ratio (95% CI)	1 [Reference]	1.18 (0.99 to 1.40)	1.36 (1.15 to 1.61)	< .001	
≥60 years					
Cases/participants	359/755	339/860	459/779		
Odds Ratio (95% CI)	1 [Reference]	0.66 (0.52 to 0.83)	1.84 (1.45 to 2.35)		
Gender					
Male					
Cases/participants	581/1,289	543/1,342	589/864		
Odds Ratio (95% CI)	1 [Reference]	0.78 (0.65 to 0.93)	2.69 (2.17 to 3.32)	< .001	
Female					
Cases/participants	352/1,071	374/1,024	518/1,491		
Odds Ratio (95% CI)	1 [Reference]	1.27 (1.02 to 1.56)	1.02 (0.84 to 1.24)		
Race/ethnicity					
Whites					
Cases/participants	285/987	355/1,104	363/917		
Odds Ratio (95% CI)	1 [Reference]	1.09 (0.88 to 1.35)	1.75 (1.40 to 2.18)	.146	
Others					
Cases/participants	648/1,373	562/1,262	744/1,438		
Odds Ratio (95% CI)	1 [Reference]	0.87 (0.72 to 1.04)	1.35 (1.13 to 1.61)		

All logistic regression models were adjusted for potential confounders (see legend of Figure 1) unless the covariate was tested as an effect modifier, in which case it was also entered as an interaction term.
Periodontitis was defined by CDC/AAP case definition.
Abbreviations: E-DII, energy-adjusted dietary inflammatory index; NHANES, National Health and Nutrition Examination Survey; CI, confidence interval; CDC, Centers for Disease Control and Prevention; AAP, American Academy of Periodontology.

Sensitivity Analyses

We conducted a sensitivity analysis in the discovery dataset to determine whether the total energy intake affected the relationship between E-DII tertiles and periodontitis. No significant effect modification by the total energy intake was found for periodontitis ($P_{\text{interaction}} = .240$, **Table S4**). Sensitivity analysis was also performed using an alternate definition of periodontal health in the validation dataset (NHANES 2001–04). The E-DII score had a non-linear

relationship with periodontal health ($P_{\text{non-linearity}} < .001$, **Figure S1**). The odd of periodontal health slowly decreased as E-DII increased until 1.5 and rapidly decreased afterward. Participants who consumed pro-inflammatory diets had worse periodontal health compared with those with anti-inflammatory diets ($OR_{\text{tertile3vs1}}: 0.58$, 95% CI: 0.49–0.69) after adjusting for potential confounders (**Table S5**). Interaction analyses yielded a stronger association between the E-DII tertiles and periodontal health among older adults, although the interaction was not statistically significant ($P_{\text{interaction}} = .159$, **Table S5**). No significant modification effect by gender and race/ethnicity was found ($P_{\text{interaction}} = .482$ for gender and .322 for race/ethnicity, **Table S5**).

DISCUSSION

The consumption of more pro-inflammatory diets was associated with moderate/severe periodontitis among U.S. adults in the cross-sectional study using data from NHANES 2011–2014 and NHANES 2001–2004. This study revealed that the E-DII score has a non-linear positive relationship with periodontitis; the association was more marked when E-DII was higher than approximate 2. The relatively stronger associations of the E-DII tertiles with periodontitis were observed in the elderly and males from the discovery population. However, the modification effects were not replicated in the validation dataset. The primary findings persisted after adjusting for a range of potential confounders and were robust in various validation and sensitivity analysis.

Dietary and nutritional interventions have a favorable effect on periodontal therapy outcomes and have gradually become essential tools for regulating host immunity to prevent periodontitis [5, 31]. In a study on experimental gingivitis, the participants lived under Stone Age conditions (e.g., reduced intake of processed carbohydrates and refined sugars) for 4 weeks [32]. The Stone Age diet significantly decreased gingival bleeding (from 34.8% to 12.6%), although this decrease was accompanied by plaque accumulation. A randomized controlled trial recently indicated that using an anti-inflammatory diet (plant-based whole-foods) –characterized by a higher intake of omega-3, vitamin C, vitamin D, and fiber– as an intervention significantly reduced gingivitis among individuals living on a Western diet, although without changes in plaque [33]. These findings from the small-scale clinical trials were confirmed by the current large-scale observational study that pro-inflammatory diets are associated with periodontal disease in a general population.

The inflammatory potential of different diets could be attributed to different nutritional components. Typically, a pro-inflammatory dietary pattern is characterized by an increased intake of processed and red meat, saturated fats, and simple carbohydrates. A recent prospective study reported that the Western diet (enrich with red meat, processed meat, eggs, butter, and refined grains) was significantly associated with incident periodontitis among obese individuals [12]. In contrast, an anti-inflammatory pattern is characterized by frequent intake of vegetables and fruits, whole grains, legumes, nuts, and fish [34]. Using a data-driven approach in the NHANES population, the dietary pattern (rich in salad, fruit and vegetables, poultry, and seafood) was negatively associated with the extent of periodontitis [13]. These epidemiological studies reported that periodontal status might be affected by inflammatory eating patterns defined using principal components analysis [12] and treelet transformation analysis [13]. Both analyses derive a summary score for each pattern through statistical modelling of dietary data at hand (e.g., food frequency questionnaires or 24-h dietary records) [8]. Thus, principal components analysis and treelet transformation analysis are considered 'a posteriori' diet pattern that is a data-driven approach based on subjective methods and reported dietary intake [35, 36]. In contrast, dietary inflammatory index is 'a priori' diet pattern because the indices are created on the basis of current knowledge and understanding of the diet–disease relationship [8]. Even though the defining methods may vary, the association of pro-inflammatory dietary patterns on periodontitis in the reported studies is consistent with our findings.

Numerous pathways exist through which pro-inflammatory diets can influence periodontal health. The dietary inflammatory index was used to assess overall dietary quality in terms of inflammation. The findings were validated using several different inflammatory markers (e.g., CRP, interleukin [IL]-1, IL-2, IL-6, interferon-gamma, and tumor necrosis factor-alpha) [37, 38]. Periodontal health may be influenced by dietary inflammation via systemic regulation of immunity. The newly proposed definition of periodontal health can accurately reflect a patient's current inflammation level by taking into account gingival bleeding [30]. Recent studies have explored the association between active periodontitis with chronic conditions through systemic inflammatory burden [39, 40]. Since periodontal inflammation might result from a higher intake of a pro-inflammatory diet or the lack of an anti-inflammatory diet, a focus on dental plaque control alone might overlook primary prevention and cause-oriented therapy opportunities [41].

The positive association between the E-DII score and moderate/severe periodontitis was non-linear when E-DII was used as continuous. To be

more specific, when E-DII is above a certain critical threshold, the likelihood of being periodontitis rapidly increases, suggesting some compensatory immunomodulation may exist. Of note, the non-linear relationship was replicated in the NHANES 2001–2004 when the new definition of periodontal health was regarded as an outcome. The J-shaped relationship was consistent with a previous study in which dietary inflammatory index was grouped into quartile groups [20]. Compared to the 1st quartile, the association of dietary inflammatory index and periodontal tooth loss was statistically significant in the 4th quartile ($P = 0.02$) but not in the intermediate quartile groups. This result would have clinical implications in periodontal prevention and treatment that dietary intervention is more important for the target population who consume a more pro-inflammatory diet.

Moreover, we identified a trend towards relatively stronger associations in older people and males through interaction analyses. Previous studies on the association between the E-DII score and the presence of other chronic diseases have obtained inconsistent results concerning age and gender, with the associations being stronger for the elderly [42] and for men [43, 44]. Elderly individuals and males at the upper end of the E-DII score scale may benefit the most from diet and lifestyle interventions if the results concerning causal association presented in this paper can be confirmed in future randomized controlled trials.

Several limitations of this study should be considered. The NHANES 2001–2004 employed a random half-mouth protocol, which underestimates the prevalence and severity of periodontal disease compared to full-mouth examination of six sites on all teeth [45]. It might explain why some results could not be replicated in the validation dataset. Besides, the E-DII score was calculated based on 27 of 45 food parameters. The selection of these parameters may have affected the findings. However, previous study showed no change in the predictive ability of the E-DII food parameters available in NHANES data in terms of assessing inflammation compared with the full list [46]. Similarly, a single 24-hr dietary recall interview is not ideal for estimating long-term habitual intake, given that it may not account for intra-individual (i.e., day-to-day) variability in diet, leading to imprecise estimates [47]. Finally, it is not possible to identify causal relationships between pro-inflammatory diet and periodontitis using cross-sectional designs. Future large-scale randomized controlled trials are needed to elucidate the potential causal association and thus help confirm the beneficial effect of reducing pro-inflammatory foods' consumption or adopting an anti-inflammatory diet on periodontal health.

CONCLUSION

It was found that the consumption of a pro-inflammatory diet may affect periodontal health in a representative population of U.S. adults. The benefits of consuming a less inflammatory diet in terms of periodontal health may be more pronounced for adults ≥ 60 years old and males. In addition to conventional periodontal treatment, dentists could recommend an anti-inflammatory diet (e.g., reduced intake of fats, red meat, and processed foods and accordingly increased consumption of green leafy vegetables, fruits, whole grains, and fish) to their patients.

SUPPLEMENTARY INFORMATION

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CHAPTER 6

White blood cell count mediates the association between periodontal inflammation and cognitive performance measured by digit symbol substitution test among older U.S. adults

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ABSTRACT

Background: Systemic effects of periodontal infection may increase the risk of central neuroinflammation, aggravating impaired cognition. This study aims to examine whether systemic inflammatory factors mediate the possible association between periodontal inflammation and cognitive function.

Methods: We conducted a cross-sectional analysis of 766 participants aged ≥ 60 years and who had complete periodontal and cognitive examinations in the NHANES 2001–2002. We used multivariable linear regression to investigate the overall association between periodontal health and cognitive function as measured by the digit symbol substitution test (DSST). Bleeding on probing (BOP) and periodontal inflamed surface area (PISA) were used to assess the periodontal inflammatory activity and burden, respectively. Mediation analyses were used to test the indirect effects of the BOP/PISA on DSST via C-reactive protein, white blood cell (WBC) count, and fibrinogen.

Results: Participants with superior periodontal health obtained higher DSST scores than those with poorer periodontal health, adjusting for demographic factors and chronic conditions. Concerning the inflammatory activity, WBC count acted as a full mediator in the association between BOP and DSST ($\beta = -0.091$; 95% CI = -0.174 to -0.008) and mediated 27.5% of the total association. Regarding the inflammatory burden, WBC count acted as a partial mediator in the association between PISA and DSST ($\beta = -0.059$; 95% CI = -0.087 to -0.031) and mediated 20.3% of the total association.

Conclusion: Our study indicated the potential role of systemic inflammatory factors as a mediator of associations between periodontal inflammation and cognitive function in the U.S. geriatric population.

INTRODUCTION

Owing to the rapidly aging population, the number of individuals with dementia will more than triple by 2050, compared to 2010. Globally, the number of cases of dementia in people aged over 65 years is predicted to be 70 million [1, 2]. Identifying modifiable factors that can reduce the incidence of dementia should thus become a priority [3]. Numerous studies have indicated the importance of systemic inflammation as a critical determinant of the cognitive impairment associated with dementia progression [4, 5]. Periodontitis is an oral infection affecting tooth-supporting tissues that cause clinical attachment loss (CAL) and alveolar bone loss (ABL), ultimately leading to tooth loss [6]. The prevalence of periodontitis increases with age [7]. A systematic review indicated the association between oral health and cognitive function in old adults [8].

Periodontal health was initially defined as the absence of clinically detected inflammation by the 2018 World Workshop of the European Federation of Periodontology (EFP) and the American Academy of Periodontology (AAP) [9], i.e., no deepening of the gingival sulcus and without the substantial extent of gingival bleeding. Previously, most studies defined a healthy periodontium as the opposite of case definitions of periodontitis [10, 11]. These case definitions are diagnosed with the accumulation of tissue defects, such as radiography findings as well as clinical measurements of CAL and ABL. However, those have limitations for the detection of inflammatory activity, as these clinical signs are often indicators of chronic disease [12]. The pathological progression of periodontitis is a slow continuous process of alveolar bone loss cyclically with periods of exacerbation and quiescence [6]. Periods of exacerbation (activity) result in deeper periodontal pockets and exacerbate gingival bleeding. In contrast, the periods of quiescence (inactivity) are characterized by a reduced inflammatory response and less attachment loss. Thus, it is unclear whether differences exist about associations between cognitive function and different focuses of definitions of periodontal health (active inflammation versus accumulative deficiencies).

Bleeding on probing (BOP) is an essential parameter in the newly proposed EFP/AAP definition of periodontal health to assess the inflammatory activity of periodontium [9]. Notably, the previous studies did not take account of BOP when evaluating the association between periodontal disease and cognitive function [13–16]. On the other hand, periodontal inflamed surface area (PISA) value was recently proposed to reflect the area of bleeding pocket in mm² [17]. It is believed to be an accurate method to quantify inflammatory burden posed

by periodontal disease [18]. PISA is calculated using conventional CAL, probing pocket depth (PPD), and BOP measurements [17]. Periodontitis may contribute to neuroinflammation and may exacerbate Alzheimer’s disease due to the release of inflammatory mediators into the bloodstream [19]. The periodontal infection may increase the risk of neuroinflammation partly via exacerbating the systemic load of pro-inflammatory cytokines and inflammatory factors [20]. Among the markers, C-reactive protein (CRP) [21], white blood cell (WBC) count [22], and fibrinogen [23] are all negatively associated with cognitive function. It is unknown whether these markers mediate possible associations of the periodontal inflammatory activity and inflammatory burden with cognitive function. In this study, we aim to analyze the relationship between periodontal inflammation (assessed by BOP and PISA) with cognitive function; and to examine whether systemic inflammatory markers mediate these processes.

METHODS

Study Design and Population

The data used in this study were retrieved from the National Health and Nutrition Examination Survey (NHANES) 2001–2002 database. NHANES is a national cross-sectional study administered by the National Center for Health Statistics (NCHS) to assess the health and nutritional status of the U.S. population-based on a variety of health-related data. The NCHS Ethics Review Board approved all NHANES protocols. Since this study analyzed public-use data, an additional research ethics review of our analysis was not necessary. The NCHS collected data from a stratified, multistage, clustered probability sample of non-institutionalized civilians. The data were obtained from various sources: the questionnaire, including demographic information, lifestyle, and disease history; physical examination; and laboratory assessments. Details of the NHANES can be obtained at <https://www.cdc.gov/nchs/nhanes/index.htm>. Our study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting cross-sectional studies. For this study, individuals who were below 60 years, edentulous, and/or had no data available on DSST or periodontal measurements were excluded from our dataset. In total, we included 776 respondents in the present study (see **Figure 1**).

Sociodemographic and Health-Related Variables

Sociodemographic variables included age, gender, ethnicity, educational level, and annual household income. Body mass index (BMI) was calculated using height and weight. Lifestyle variables included smoking status, alcohol intake, and the time

since the last dental visit. Systemic biomarkers of inflammation (CRP, WBC count, and fibrinogen) were measured using blood samples taken from the participants. Hyperlipidemia was measured by total cholesterol and high-density lipoprotein (HDL) cholesterol. A doctor-diagnosed of diabetes or glycohemoglobin of 6.5% or higher was used to define diabetes mellitus. The presence of hypertension was identified as a self-report of a doctor’s diagnosis, systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg. Physician-diagnosed myocardial infarction and coronary heart disease were defined as heart disease. Other doctor-diagnosed conditions included arthritis and stroke. All of these variables were identified as potential confounders that might influence both periodontal inflammation and cognitive function [24].

Figure 1. Flowchart indicating the subset of participants included for the analysis from the NHANES 2001–2002 dataset.

Periodontal Variables

Trained and calibrated dentists from the NCHS examined the teeth of each participant. Periodontal status was evaluated by examining two randomly chosen quadrants in one person: one maxillary and one mandibular (random half-mouth protocol, RHMP). The examination included probing assessments for CAL, PPD, and BOP at three sites per tooth (mesiobuccal, midbuccal, and distobuccal). As third molars were excluded, a maximum of 14 teeth and 42 sites per individual could be

examined to assess periodontal health status. Measurements were on the tooth level and after that classified according to the traditional and the newly proposed definitions of periodontal health: (i) the case definition developed by the Centers for Disease Control and Prevention (CDC) in partnership with the AAP (the “CDC/AAP definition”) [25, 26]; (ii) the definition proposed by the world workshop of the EFP and the AAP on the classification of periodontal and peri-implant disease and condition (the “EFP/AAP definition”) [9]. For details concerning the criteria of these classifications, see **Table S1**. In addition, the PISA value reflects the surface area of bleeding pocket epithelium and was used to quantify the total periodontal inflammatory burden in the patient [17].

Cognitive Function Variables

The DSST is a component of the Wechsler Adult Intelligence Test [27]. This test assesses sustained attention, processing speed, and working memory, which is regarded as a cognitive phenotype that reveals the hidden progression of an individual’s dementia or cognitive impairment. The DSST measures cognitive function by asking participants to pair digits with their corresponding symbols within two minutes. Following the standard scoring method, a score is the total number of correct matches. A higher score represents a superior cognitive function. The measurement has been widely used in large-scale epidemiological studies [28, 29].

Statistical Analysis

Normality of distribution of continuous variables was tested by one-sample Kolmogorov-Smirnov test. Continuous variables with normal distribution were reported as mean (standard deviation (SD)); non-normal variables were presented as median (interquartile range (IQR)). Categorical variables were described as number and frequency. Univariable linear regressions were used to evaluate the associations of the covariates with the DSST score. Variables with a significant association ($P < 0.10$) in the univariable analyses were incorporated into the multivariable analyses. Multivariable linear regressions were used to evaluate the overall association between periodontal health and DSST score adjusting for sociodemographic, health-related behaviors, and systemic diseases.

Multivariable linear regressions were used to investigate the potential mediating effect of systemic inflammatory factors (CRP, WBC count, and fibrinogen) on the association between BOP/PISA (exposure) and DSST (outcome) [30]. Three pathways (a, b, and c) and the following criteria were used to establish mediation (**Figure 2**): Step1, regress ‘outcome’ on ‘exposure’ to test if the ‘exposure’ is

significantly associated with ‘outcome’ (total effect). Step2, regress ‘mediator’ on ‘exposure’ to examine if ‘exposure’ is a significant predictor of the ‘mediator’ (path a). If not, then it is unlikely to mediate anything. Step3, regress ‘outcome’ on both ‘exposure’ and ‘mediator’ to test if ‘mediator’ is a significant predictor of ‘outcome’, and to observe whether the association between ‘exposure’ and ‘outcome’ is attenuated when the ‘mediator’ is included (path c, direct effect). The total effect is a sum of a direct effect and a mediation (indirect) effect. The proportion of the mediated effect was calculated using the following formula: $(\beta_{\text{total effect}} - \beta_{\text{direct effect}}) * 100 / \beta_{\text{total effect}}$ [31]. Complete case analysis was used for handling missing data. All statistical analyses were computed in SPSS version 25 (SPSS Inc., Chicago, IL, USA). A value of $P < 0.05$ was considered significant.

Figure 2. Graphic representation of the relationship between periodontal inflammatory activity/burden and cognitive function, and mediated effects ($n = 766$). Total effect: the relationship between BOP/PISA (exposure) and DSST score (outcome). Path a: the relationship between BOP/PISA and systemic inflammatory markers (mediator). Path b: the relationship between systemic inflammatory markers (mediator) and DSST score (outcome). Path c: systemic inflammatory markers mediation models of the relationship between BOP/PISA (exposure) and DSST score (outcome). Abbreviations: DSST, digit symbol substitution test; BOP, bleeding on probing; PISA, periodontal inflamed surface area; X, exposure variable; Y, outcome variable; M, mediator.

RESULTS

Characteristics of the Study Population

The characteristics of the samples are presented in Table 1 ($n = 766$). Participants were on average 70.3 (SD, 7.6) years old; 49% were male, and predominantly non-Hispanic White (61.1%). The mean DSST score was 45.2 (SD, 18.1).

According to the CDC/AAP and EFP/AAP, the prevalence of periodontal health were 56.1% and 59.3%, respectively.

Table 1. Characteristics of the study population (n = 766)

VARIABLES	NHANES 2001–2002 (n = 766)
Continuous variables, mean (SD)/median (IQR)	
Age (year)	70.3 (7.6)
Body mass index (kg/m ²)	28.1 (5.2)
Systolic blood pressure (mmHg)	138.0 (21.3)
Diastolic blood pressure (mmHg)	69.8 (15.0)
Total cholesterol (mg/dL)	210.7 (39.5)
HDL cholesterol (mg/dL)	54.0 (17.0)
Glycohemoglobin (%)	5.9 (1.1)
C-reactive protein (mg/dL) ^a	0.24 (0.37)
White blood cell count (103/μL)	7.2 (2.2)
Fibrinogen (mg/dL)	391.8 (81.3)
DSST	45.2 (18.1)
BOP (%) ^a	2.56 (6.21)
PISA (mm2) ^a	4.89 (18)
Tooth number ^a	22 (12)
Categorical variables, n (%)	
Male	382 (49.9)
Non-Hispanic White	468 (61.1)
Education > college ^b	355 (46.3)
Annual household income >75,000\$ ^b	120 (15.7)
Current smoker ^b	69 (9.0)
Alcohol intake > 12 drinks/year ^b	471 (61.5)
Arthritis ^b	317 (41.4)
Hypertension ^b	360 (47.0)
Diabetes mellitus ^b	124 (16.2)
Stroke ^c	38 (5.0)
Heart disease	97 (12.7)
Time since the last dental visit > 1 year	242 (31.6)
CDC/AAP definition ^c	430 (56.1)
EFP/AAP definition ^d	454 (59.3)

^aNon-normal distribution continuous variable, median (IQR).
^bMissing values for total study: education (n = 1; <1%), income (n = 72; <9.4%), smoking (n = 2; <1%), alcohol (n = 15; 2%), arthritis (n = 2; <1%), hypertension (n = 3; <1%), diabetes (n = 23; 3%), and stroke (n = 2; <1%).
^cThe CDC/AAP case definition identified no/mild periodontitis as indicating periodontal health [26]
^dThe EFP/AAP definition of periodontal health [9]

OP As a Key Indicator of the Association

Univariable linear regression analyses showed that sociodemographic (age, gender, ethnicity, education, and annual household income), time since the last dental visit, the number of teeth, disease history (diabetes mellitus, stroke, hypertension, and heart disease), alcohol intake, total cholesterol, and HDL cholesterol were significantly associated with the DSST score (**Table S2**). These potential confounders were used to adjust the multivariable regression models. Although the current smoking was not associated with DSST scores ($\beta = -0.76$, 95% CI: -4.52 to 2.99), we still included it into the subsequent models to correct for smoking habit's possible confounding effect on periodontal inflammation.

Multivariable linear regressions showed the individuals with periodontal health defined by EFP/AAP performed higher DSST scores, compared to periodontal patients ($\beta = 4.08$, 95% CI: 1.87 to 6.29; **Figure 3**). In contrast, there was no association between periodontal health defined by CDC/AAP and DSST score ($\beta = 1.75$, 95% CI: -0.52 to 4.02). Nevertheless, CDC/AAP case definition was negatively associated with DSST score in the participants with moderate/severe periodontitis and BOP $\geq 10\%$ ($\beta = -6.05$; 95% CI: -9.39 to -2.71) (**Table S3**).

Figure 3. Multivariable linear regression analyses of traditional and new definitions of periodontal health for DSST score (n = 766). Model 1: unadjusted. Model 2: adjusted for sociodemographic variables (age, gender, race, education, income), health behaviors (smoking habit, alcohol consumption, and dental visit), number of teeth present, and systemic diseases (hypertension, HDL cholesterol, total cholesterol, diabetes mellitus, heart disease, and stroke). Association is deemed to significant if the 95% CI does not include zero. All P values were calculated with a two-sided significance level of .05. Abbreviations: CDC, the Centers for Disease Control and Prevention; AAP, the American Academy of Periodontology; EFP, the European Federation of Periodontology; DSST, digit symbol substitution test.

Inflammation As a Potential Mediator

BOP was significantly associated with DSST when controlling for confounders ($\beta = -0.091$, 95% CI = -0.174 to -0.008) (Table 2). When the WBC count was added to an initial model, the association between BOP and DSST did not remain significant ($\beta = -0.066$, 95% CI = -0.148 to 0.016). The proportion mediated through WBC count for the BOP-DSST association was 27.5%. Regarding the burden of periodontal inflammation, PISA was independently associated with DSST score ($\beta = -0.059$, 95% CI = -0.087 to -0.031) in the multivariable linear regression (Table 2). When we introduced the WBC count into an initial model, the association between PISA and DSST remained significant ($\beta = -0.047$, 95% CI = -0.075 to -0.019). WBC count acted as a partial mediator and mediated 20.3% of the total association. There was no evidence that CRP and fibrinogen mediated the association between BOP/ PISA and DSST (Table 2).

Table 2. Mediation analysis of the effects of systemic inflammatory marks on the association of PISA with DSST score (n = 766)				
Coefficient (95% CI)	Path a	Path b	Path c (Direct Effect)	Total Effect
BOP (%)				
CRP (mg/dL)	-0.001 (-0.006 to 0.008)	-0.204 (-1.173 to 0.765)	-.091 (-.174 to -.008) *	-.091 (-.174 to -.008) *
WBC count (103/ μ L)	0.019 (0.006 to 0.032) **	-1.391 (-1.883 to -0.900) ***	-.066 (-.148 to .016)	-.091 (-.174 to -.008) *
fibrinogen (mg/dL)	-0.121 (-0.601 to 0.360)	0.001 (-0.012 to 0.015)	-.090 (-.173 to -.006) *	-.091 (-.174 to -.008) *
PISA (mm ²)				
CRP (mg/dL)	0.000 (-0.002 to 0.002)	-0.204 (-1.173 to 0.765)	-.059 (-.087 to -.031) ***	-.059 (-.087 to -.031) ***
WBC count (103/ μ L)	0.010 (0.005 to 0.014) ***	-1.391 (-1.883 to -0.900) ***	-.047 (-.075 to -.019) **	-.059 (-.087 to -.031) ***
fibrinogen (mg/dL)	0.079 (-0.083 to 0.241)	0.001 (-0.012 to 0.015)	-.059 (-.087 to -.031) ***	-.059 (-.087 to -.031) ***
Proportion Mediated				
				NA
				27.5%
				NA
				NA
				20.3%
				NA

DISCUSSION

The main findings of our study were that individuals considered periodontally healthy based on the EFP/AAP definition exhibited better cognitive performance than those with poorer periodontal health. In the multivariable regression analyses, BOP and PISA as markers of periodontal inflammation were negatively associated with the DSST score. Systemic inflammation (as measured by WBC count) was an explanatory mediator of these associations (27.5% for BOP and 20.3% for PISA). This study shows the role of systemic inflammatory factors in the relationship between periodontal inflammation and cognitive function among the community-dwelling U.S. older adults.

We compared traditional and newly proposed definitions of periodontal health to assess whether inducing gingival bleeding affected the overall association between periodontal health and cognitive function. EFP/AAP definition employed BOP as one of the parameters and remained strongly associated with cognitive performance after controlling all covariables. However, there was no significant association between the CDC/AAP case definition (no/mild vs. moderate/severe periodontitis) and DSST scores. Further, moderate/severe periodontitis individuals with BOP $\geq 10\%$ showed significantly lower DSST scores than no/mild those with BOP $< 10\%$. The active inflammation of periodontium might to be more related to cognitive performance compared to the accumulative deficiencies. Although considering the presence of BOP to predict periodontal disease remains controversial, absence of BOP could be regarded as a valid predictor of a stable periodontium [32, 33]. Based on the inflammatory mechanisms in the pathogenesis of cognitive impairment [4, 5], BOP might act as an informative and precise indicator for outcomes due to infectious exposure. Alternatively, we used PISA, incorporating BOP and PPD/CAL, to quantify the inflammatory burden of periodontitis. Our study found that PISA value, as a continuous variable, showed a notable association with DSST, as expected based on previous evidence [34]. The periodontal burden measured by the PISA has also been associated with other systemic diseases, including diabetes [35], rheumatoid arthritis [36], decreased kidney function [37], and ischemic stroke [38]. In brief, it would be difficult to comprehensively and accurately evaluate the association between periodontitis and cognitive function without assessing an individual's activity and burden of periodontal inflammation.

Mediation analysis suggested that the negative associations between periodontal inflammatory activity/burden and cognitive performance could be explained, at

least in part, by the WBC count (27.5% for BOP and 20.3% for PISA). Our study used a mediation model to explore the process that underlies the association between periodontal inflammation (exposure) and cognitive function (outcome) via the inclusion of the presumed 'mediator' (systemic inflammatory marker). The results well confirm our initial theoretical framework (i.e., inflammatory hypothesis), which expects the decreased cognitive test scores through exposure to systemic inflammatory factors and leads us to explore the possible mechanisms of the association. The neuroinflammation pathogenesis of dementia gives biological plausibility to these mediating effects [39, 40]. The periodontal infection leads to leakage of various pathogenic products (i.e., host inflammatory factors, pathogenic oral bacteria, and its products) through the gingival epithelium into the bloodstream in the active phases of the disease [6]. At the same time, the chronic inflammatory process contributes to activates blood-brain barrier permeability, which results in the entry of the systemic inflammatory products and the pathogen into the brain leading to synaptic and cognitive dysfunction [41].

Notably, the inclusion of the WBC count (mediator) made the association between BOP and DSST be not significant, indicating WBC count might act as a full mediator of the association. That might be because the marker of acute pathogenesis of inflammation (BOP) efficiently translates into systemic inflammatory factors (WBC). PISA, the incorporation of chronic disease parameters (i.e., PPD/CAL), might reflect a historical and long-lasting process of periodontal inflammation compared to acute inflammation [42]. In contrast, we did not detect the effect of CRP and fibrinogen on the relationship between BOP/PISA and DSST scores. It may be due to DSST scores measure psychomotor cognitive performance and reflect the frontal-executive functions. The executive functions are based on the integrity of frontal-subcortical circuits, and all type of vascular lesions results in executive dysfunctions [43]. WBC count is independently associated with vascular and nonvascular mortality in the participants aged 85 years [44]. These results implied that elevated WBC count related to periodontitis could be involved in the process of vascular damage in the brain. Briefly, increased WBC count might support an infection role of periodontal inflammatory activity/burden in the pathogenesis of cognitive impairment.

Several limitations of the current study should be considered. Firstly, NHANES 2001–2002 employed a random half-mouth protocol (RHMP). Compared to full-mouth examination (FME) of 6 sites on all teeth, it might account for underestimating the prevalence and severity of periodontal disease [45, 46]. Smokers have more sites with PPD ≥ 5 mm than non-smoker, especially on the lingual surfaces [47].

To reduce the bias caused by RHMP, we used a half-reduced CDC/AAP case definition [25]. In regard to the extent of BOP, the underestimation was seen in the RHMP with three buccal sites (-11.7%) compared to FME in periodontal patients [48]. PISA could be underestimated using RHMP correspondingly. In addition, amyloid, tumor necrosis factor, and interleukin would likely have been better alternatives, as they are the cognitive-specific inflammatory factors to explore the causal inflammatory mediates [49]. Moreover, we employed a single measure to assess cognition since only the DSST test was available in the NHANES dataset. Although the DSST test was able to describe visuospatial abilities and episodic memory decline well, several other cognitive deficits, including perceptual speed, attention, and executive function, should be comprehensively assessed in future research [50]. Another limitation is that data on oral hygiene behavior (i.e., toothbrushing, interdental cleaning, and use of mouthwash) were not available in NHANES 2001–2002, so the influence of these variables on the associations could not be explored. However, the potential confounding effect of dental services utilization was taken into account by adjusting the regression models for the time since the last dental visit. Finally, the cause-effect relation identified in the current cross-sectional study was ambiguous. When exploring the relationship and mediated effect, we should interpret the association cautiously. Long-term prospective cohort studies and treatment-related randomized control studies are required to reveal the causal association between periodontitis and cognitive disease.

CONCLUSION

The cross-sectional association between periodontal inflammatory activity/burden and cognitive function was found to have a mediated effect by WBC count in the U.S. elder population. The results may provide some valuable insights into the impact of oral infection on cognitive dysfunction via a systemically inflammatory pathway. Further longitudinal cohort studies are warranted to explore the pathogenetic mechanism underlying the neuro-inflammatory disease. From a preventive strategic view, maintaining a healthy periodontium may substantially reduce or delay the onset of cognitive impairment. Also, health workers should be aware of how to make corresponding adjustments to cognition-impaired elderly's dental care patterns to improve their life quality.

SUPPLEMENTARY INFORMATION

<https://academic.oup.com/biomedgerontology/article-abstract/76/7/1309/5901592?redirectedFrom=fulltext>

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CHAPTER 7

Combined association of cognitive impairment and poor oral health on mortality risk in older adults:

Results from the NHANES with 15 years of follow-up

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ABSTRACT

Background: Cognitive impairment and poor oral health are frequently seen among older adults. Both conditions have been identified as risk factors for mortality. However, the combined associations of cognitive impairment and poor oral health with mortality have not been well studied and are therefore the aim of this cohort study.

Methods: We analyzed data from the National Health and Nutrition Examination Survey (1999–2002) linked with mortality data obtained from the 2015 public-use linked mortality file. Cognitive impairment was defined as a digit symbol substitution test score lower than the lowest quartile. Oral health status was assessed based on presence of untreated caries, moderate/severe periodontitis, and edentulism. The combined effects of caries/periodontitis or edentulism and cognitive impairment on all-cause and cardiometabolic mortality were examined using the Cox proportional hazard models after adjusting for potential confounders including demographic characteristics, lifestyle, biomarkers, and comorbidities.

Results: In total, 1,973 participants were enrolled in the prospective study. At a median follow-up of 13.4 years, 978 participants had died (264 deaths due to cardiometabolic disease). Cognitive impairment, periodontitis, and edentulism were each found to be significant predictors of all-cause mortality. Caries, however, was not significantly related to mortality. When analyzing these predictors in combination, a diagnosis of cognitive impairment and periodontitis was associated with an 80.7% increase in all-cause mortality risk and a 90.2% increase in cardiometabolic mortality risk compared with healthy controls. Similarly, the risk for all-cause mortality was highest in cases where impaired cognition and edentulism co-occurred (adjusted hazard ratio = 1.596, 1.235–2.064).

Conclusion: Concomitant presence of cognitive impairment and periodontitis or edentulism can be associated with a higher risk of long-term mortality among older U.S. adults.

INTRODUCTION

Longer life expectancy has been increasing the proportion of older persons in industrialized countries [1] and led to a commensurate increase in the prevalence of Alzheimer's disease (AD) [2]. Cognitive impairment is a common phenomenon in older adults and can be seen as a prodrome of AD [3]. Even at mild levels, cognitive impairment has emerged as a major contributing factor to mortality [4–6]. Also, cognitive impairments are considered the main barriers to maintaining routine dental visits and good oral hygiene care in older adults [7–9]. Oral health problems (such as periodontal inflammation, dental caries, and masticatory dysfunction) are highly prevalent among older adults, giving rise to other health problems [10] and being a risk indicator of mortality [11].

Vascular risk factors and diseases might explain the increased mortality associated with dementia or oral diseases to some extent. Older people with cognitive impairment and systemic vascular comorbidities (e.g., high blood pressure and diabetes mellitus) may have increased mortality risk [12, 13]. In a recent systematic review, poor oral health was found to be associated with mortality [14]. A considerable proportion of such mortality could be attributed to comorbid conditions [15]. Therefore, it is plausible that cognitive impairment or oral diseases may separately increase the risk of cardiometabolic death.

Emerging evidence indicates that cognitive impairment and poor oral health are closely intertwined [16–18], and their relationship could be bidirectional [19, 20]. As a cost-effective method, maintaining oral health conditions seems crucial in reducing complications and deaths, especially in the older populations with cognitive decline. However, studies on the interrelationships between cognitive function, oral health, and mortality are scarce. Hence, we aim to investigate the potential joint effects of cognitive impairment and poor oral health (periodontitis, caries, or edentulism) on all-cause and cardiometabolic mortality among older Americans in a cohort study with a follow-up duration of 15 years.

METHODS

Study Design and Analytical Sample

Data from older adults aged 60 years and older who participated in the U.S. National Health and Nutrition Examination Survey (NHANES, 1999–2000 [21] and 2001–2002 [22]) were linked to public-use mortality files for the period up

to December 2015. The NHANES is a stratified, multistage, clustered probability sampling study focused on U.S. civilians' health and nutritional status; it is administered by the U.S. National Center for Health Statistics (NCHS). The survey consists of an in-home interview followed by physical examinations and biological sample collections at a mobile examination center. The NCHS Ethics Review Board approved all NHANES protocols and testing procedures (including a series of questionnaires, physical and biochemical exams, cognitive function assessment, and a comprehensive dental exam), and all participants provided written informed consent [23]. The prospective cohort study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline [24] (see **Figure S1**).

Covariates

Baseline sociodemographic, behavioral, and clinical variables were used as covariates. Sociodemographic variables included age, gender, race/ethnicity, educational level, and annual household income. Race/ethnicity was categorized into Non-Hispanic white, Non-Hispanic black, and others. Educational level was grouped into high school/less, some college, and higher. Annual household income was grouped into <\$20,000, \$20,000–\$75,000, and >\$75,000. Behavioral variables included smoking status (never, former, and current smoker), alcohol intake (<12 and ≥12 drinks/ year), and the time since last dental visit (<1, 1–3, >3 years). We used the Healthy Eating Index (HEI)-2015 to measure the diet quality [25, 26]. The HEI-2015 contains 13 components that sum to a total maximum score of 100 points (**Table S1**). For details, see Supplemental Methods. A higher score means better adherence to the Dietary Guidelines for Americans.

Clinical variables included cardiovascular disease risk factors (CVD-RF) and medical conditions. CVD-RF included obesity, hypertension, dyslipidemia, and diabetes mellitus, as described in previous study [27]. We calculated the total number of CVD-RF for each individual (range 0–4). The detailed definitions and categories of these risk factors (i.e., obesity, hypertension, dyslipidemia, and diabetes mellitus) are presented in **Table S2**. Medical condition included elevated systemic inflammation (as measured by C-reactive protein [CRP]) level, heart disease, and stroke. **Table S2** also presents the definitions for these medical conditions.

Assessment of Cognitive Function

The digit symbol substitution test (DSST) was administered to assess cognitive function [28]. Participants were asked to draw as many symbols paired with numbers as possible within two minutes. Following the standard scoring method,

a score was given for each correctly drawn symbol (with the maximum score being 133). A higher score represents better cognitive function. Since there are no standard norms for the DSST, we defined scores falling below the lowest quartile (<29 scores) in the study group as indicating cognitive impairment, consistent with the methods previously described [29, 30]; the higher quartiles were considered as the normal cognition.

Oral Health Outcomes

Oral health outcomes were assessed based on periodontal status, dental caries, and edentulism. Trained and calibrated dentists from the NCHS examined each participant's oral health status. The NHANES 1999–2002 used National Institute for Dental Research periodontal probes and the random half-mouth protocol (RHMP). One maxillary quadrant and one mandibular quadrant were randomly chosen, and periodontal status was assessed by probing assessments for clinical attachment loss (CAL) and probing pocket depth (PPD). In 1999–2000, two probing sites per tooth (mesial buccal and mid buccal) were measured, while, for 2001–2002, these assessments were additionally conducted at distal buccal sites. In addition, bleeding on probing was measured at three sites per tooth only in the NHANES 2001–2002. In the present study, mean CAL and mean PPD were calculated using two probing sites for consistency with the NHANES 1999–2000 [31]. As the third molars were excluded, a maximum of 14 teeth and 28 sites per individual could be examined to assess periodontal status.

We used the half-reduced CDC/AAP (Centers for Disease Control & Prevention and American Academy of Periodontology) case definition to define periodontal disease [32]. No/mild periodontitis was defined as no evidence of moderate or severe periodontitis; Moderate: ≥1 inter-proximal site with ≥4 mm CAL, or ≥1 interproximal site with ≥5 mm PPD; Severe: ≥1 interproximal site with ≥6 mm CAL and ≥1 interproximal site with ≥5 mm PPD. The participants were dichotomized as no/mild periodontitis and moderate/severe periodontitis.

Regarding dental caries, the presence of decayed permanent tooth surfaces in an individual was defined as untreated caries; no decay in any tooth surface was set as the reference. Participants with no natural teeth (tooth positions presenting edentulous) were defined as the edentulous population; the others were set as the dentulous population.

Mortality

The primary outcome was mortality from all causes. The secondary outcome was

cardiometabolic (CM) mortality. To increase the statistical power, we combined mortality due to heart disease, cerebrovascular disease, or diabetes mellitus into a single outcome (i.e., CM mortality), as previously reported [33]. Mortality status and cause of death were determined based on publicly accessible mortality files [34]. The follow-up started from the interview date and ended at death or at the end of the study (December 31, 2015), whichever came first, as described before [35].

Statistical Analyses

Descriptive statistics were calculated to describe the characteristics of participants. Continuous variables were reported as mean with standard deviation or median with interquartile range. Categorical variables were described as numbers with frequencies. Characteristics of participants were stratified by cognitive function status and oral health outcomes and compared using one-way ANOVA and Chi-square.

We studied the interrelationship between cognitive impairment, poor oral health, and mortality in two steps. First, we estimated the extent to which the effects of cognitive impairment or oral disease (exposure variables) on all-cause mortality (outcome variable) are attributable to CVD-RF (potential mediator) (see **Figure 1A**). Multinomial log-linear models were conducted to assess the associations between exposure variables and the potential mediator. Then, Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality. In the crude model, estimates were not adjusted. Model 1 was adjusted for sociodemographic variables (age, gender, race/ethnicity, education level, and income level) behavioral variables (smoking, drinking, and dental visit), and medical conditions (elevated systemic inflammation, heart disease, and stroke). Model 2 was further adjusted for CVD-RF. The formula $(HR_1 - HR_2)/(HR_1 - 1) \times 100$ was used to determine the percentage of excess risk (hazard) explained by CVD-RF [36], where HR_1 is the HR of Model 1 and HR_2 is the HR of Model 2. Given no interaction between exposure and mediator on the outcome, the estimation of mediated proportion is based on comparing the total effect and the controlled direct effect [37]; **Figure 1A**).

Second, four mutually exclusive risk groups were created for the joint effect of cognitive performance and oral health status (Figure 1B): Group 1, normal cognition and normal oral health; Group 2, normal cognition and poor oral health; Group 3, cognitive impairment and normal oral health; and Group 4, cognitive impairment and poor oral health. The cumulative mortality curves of the four combined groups were computed using cumulative incidence function. The Cox

Figure 1. Schematic diagrams illustrating the statistical analysis. (A) Mediation models of the separate effects of cognitive impairment or oral disease on all-cause mortality, using cardiometabolic risk as a mediator. (B) The combined effects of cognitive impairment and oral disease on all-cause mortality and cardiometabolic mortality.

model was used to estimate the combined associations of cognitive impairment and oral disease with all-cause mortality, and a cause-specific Cox model was used for CM mortality (**Figure 1B**). All models were adjusted for the aforementioned sociodemographic variables, behavioral variables, medical conditions, and

CVD-RF. Next, interaction analyses were performed to explore the potential interaction between cognitive impairment and oral disease.

Furthermore, we conducted several sensitivity analyses to demonstrate the robustness of the results. Firstly, we defined periodontal health according to the joint workshop of the EFP/AAP (European Federation of Periodontology & American Academy of Periodontology) [38] and repeated the Cox regression analyses of combined effects in the NHANES 2001–2002. Periodontal health was defined as no sites with PPD >3 mm and <10% of sites with bleeding on probing in an intact periodontium (CAL <3 mm); the others were set as a periodontal disease. Secondly, we also repeated the Cox regression analyses in the NHANES 1999–2002 when individuals having eight teeth or fewer were used to define severe tooth loss [39]. Considering the low percentage of the missing data from the covariates analyzed, we conducted complete-case multivariable regression. All data analyses were performed with the R Project for Statistical Computing (version 3.6.0) and SPSS 25 (SPSS Inc., Chicago, IL, USA). A P-value of less than 0.05 was considered statistically significant.

RESULTS

Characteristics of the Study Population at Baseline

Of the 3,706 older American in the NHANES dataset who were eligible to participate in this study, 2,975 adults completed the cognitive assessment. Older participants who did not have data on dental examination (*n* = 1,002) were excluded, resulting in an analytical sample of 1,973 participants. Among those participants, a total of 1,478 older persons were regarded as the dentate subpopulation having periodontal and caries data, as depicted in Figure S2. The mean age was 70.68 + 7.70 years; of the population, 50% were men and 58.2% non-Hispanic (Table 1). By the median follow-up of 13.4 years, 978 participants had died. Among those, 264 deaths (27%) were due to CM disease. Mean DSST score was 41.69 (range: 0–117). In addition, baseline statistics stratified by cognitive function status and oral health outcomes are displayed in Table S3.

Table 1. Characteristics of study participants in NHANES 1999–2002 (*n* = 1,973)

VARIABLES	NHANES 1999–2002
Sociodemographic Variables	
Age (year), mean (SD)	70.68 (7.70)
Male, <i>n</i> (%)	987 (50.0)

Table 1. (Continued)

Race/ethnicity, <i>n</i> (%)	
Non-Hispanic white	1,148 (58.2)
Non-Hispanic black	307 (15.6)
Other race, including multiracial	518 (26.3)
Education level, <i>n</i> (%) *	
<high school	1,287 (65.3)
college	390 (19.8)
>college	293 (14.9)
Annual household income, <i>n</i> (%) *	
<20,000\$	745 (39.3)
20,000–75,000\$	971 (51.2)
>75,000\$	179 (9.4)
Lifestyle Variables	
Smoking habit, <i>n</i> (%) *	
Non smoker	909 (46.2)
Former smoker	805 (40.9)
Current smoker	255 (13.0)
Alcohol intake ≥12 drinks/year, <i>n</i> (%) *	1,183 (61.2)
Time since the last dental visit, <i>n</i> (%) *	
Less than 1 year	1,040 (52.8)
1–3 years	320 (16.3)
More than 3 years	608 (30.9)
Healthy eating index-2015, mean (SD)	54.13 (11.57)
Cardiovascular Disease Risk Factors	
Body mass index (kg/m2), mean (SD)	28.19 (5.28)
Obesity, <i>n</i> (%) *	600 (31.2)
SBP (mmHg), mean (SD)	139.68 (21.88)
DBP (mmHg), mean (SD)	69.73 (15.13)
Hypertension, <i>n</i> (%) *	942 (48.0)
Non-HDL cholesterol (mg/dL), mean (SD)	160.14 (39.77)
Dyslipidemia, <i>n</i> (%) *	945 (49.5)
Glycohemoglobin (%), mean (SD)	5.90 (1.16)
Diabetes mellitus, <i>n</i> (%) *	328 (17.0)
CVD risk factors, <i>n</i> (%)	
0	308 (15.6)
1	782 (39.6)
2	630 (31.9)
3	221 (11.2)
4	32 (1.6)

Table 1. (Continued)

Medical Conditions	
C-reactive protein ‡	0.28 (0.43)
Elevated systemic inflammation, <i>n</i> (%) *	636 (33.8)
Heart disease, <i>n</i> (%) *	306 (15.5)
Stroke, <i>n</i> (%) *	115 (5.8)
Exposure Variables §	
Caries status, <i>n</i> (%)	
Untreated caries	1,150 (58.3)
No untreated caries	328 (16.6)
Periodontal status, <i>n</i> (%)	
No/mild periodontitis	746 (37.8)
Moderate/severe periodontitis	732 (37.1)
Dentate Status, <i>n</i> (%)	
Dentulous population	1,478 (74.9)
Edentulous population	495 (25.1)
Cognitive status, <i>n</i> (%)	
Normal cognition	1,464 (74.2)
Cognitive impairment	509 (25.8)
Outcome Variables ¶ 	
Mortality status, <i>n</i> (%)	
All-cause mortality	978 (49.6)
Cardiometabolic mortality	264 (13.4)

* Missing value for total study: education (*n* = 3; <1%), income (*n* = 78; 4.0%), smoking (*n* = 4; <1%), alcohol (*n* = 40; 2.0%), dental visit (*n* = 5; <1%), hypertension (*n* = 3; <1%), diabetes (*n* = 30; 3%), obesity (*n* = 52; 2.6%), CVD-RF (*n* = 164; 8.3%), elevated systemic inflammation (*n* = 90; 4.6%), dyslipidemia (*n* = 63; 3.2%), heart disease (*n* = 15; <1%), and stroke (*n* = 6; <1%).

‡ The risk factors of cardiovascular disease include obesity, hypertension, dyslipidemia, or diabetes mellitus [27].

¶ Non-normal distribution continuous variable, median (interquartile range).

§ Cognitive impairment defined as DSST score <29 (the lowest quartile of score in population); Moderate/severe periodontitis was defined by the CDC/AAP case definition; Edentulism was defined as the complete loss of all-natural teeth; Untreated caries was defined as having any decayed permanent tooth surfaces.

|| There was no caries and periodontal data in the subgroup of edentulous population (*n* = 495; 25.1%).

¶ The median follow-up period for all-cause mortality was 13.4 years.

Abbreviations: SD, standard deviation; CVD, cardiovascular disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; CRP, C-reactive protein; HDL, high-density lipoprotein; DSST, digit symbol substitution test; AAP, American Academy of Periodontology; CDC, Centers for Disease Control and Prevention.

Separate Associations with All-Cause Mortality

When considered separately, cognitive impairment, periodontal disease, and edentulism were all significantly associated with risk of CVD-RF (Table S4). However, untreated caries was not statistically associated with CVD-RF (Table S4). A similar pattern emerged for all-cause mortality. Cognitive impairment,

moderate/severe periodontitis, or edentulism was significantly associated with all-cause mortality in unadjusted and adjusted models. Specifically, the HR for mortality with cognitive impairment was 1.461 (Model 1) before and 1.385 (Model 2) after adjusting for CVD-RF, a reduction of 16.5% (Table 2). Regarding oral disease, CVD-RF also attenuated the HR of periodontitis for all-cause mortality by 18.5%. Similarly, the estimates of HR were reduced by 16.1% in the edentulous population (Table 2).

Table 2. The separate associations of cognitive impairment or caries/periodontitis/edentulism with all-cause mortality

All-Cause Mortality	Cases/ Participants	Crude Model HR _{unadjusted} (95% CI)	Model 1 * HR1 (95% CI)	Model 2 * HR2 (95% CI)	% excess risk explained †
Cognitive Performance					
normal cognition	647/1464	1 [Reference]	1 [Reference]	1 [Reference]	16.5%
cognitive impairment	331/509	1.760 (1.511 to 2.050)	1.461 (1.235 to 1.728)	1.385 (1.170 to 1.640)	
Caries Status					
No untreated caries	456/1150	1 [Reference]	1 [Reference]	1 [Reference]	5.7%
Untreated caries	165/328	1.366 (1.120 to 1.665)	1.174 (0.951 to 1.450)	1.164 (0.943 to 1.438)	
Periodontal Status					
no/mild periodontitis	249/746	1 [Reference]	1 [Reference]	1 [Reference]	18.5%
moderate/severe periodontitis	372/732	1.758 (1.471 to 2.102)	1.303 (1.094 to 1.552)	1.247 (1.044 to 1.489)	
Dentate Status					
dentulous population	621/1478	1 [Reference]	1 [Reference]	1 [Reference]	16.1%
edentulous population	357/495	2.213 (1.906 to 2.570)	1.361 (1.152 to 1.607)	1.303 (1.103 to 1.540)	

* Model 1 was adjusted for sociodemographic variables (age, gender, race/ethnicity, educational level, and income level), behavioral variables (smoking, drinking, and dental visit), and medical conditions (elevated systemic inflammation, heart disease, and stroke). Model 2 was further adjusted for CVD-RF. The risk factors of cardiovascular disease include obesity, hypertension, dyslipidemia, or diabetes mellitus [27].

† The percentages of excess risk (hazard) explained by CVD-RF were calculated using the formula $(HR_1 - HR_2)/(HR_1 - 1) \times 100$

Bold indicates *P*-value <0.05.

Abbreviations: CVD-RF, cardiovascular disease risk factors; HR, hazard ratio; CI, confidence interval.

Combined Effects on All-Cause and Cardiometabolic Mortality

The results of separate associations showed that CVD-RF partly explained the risk of total mortality. Therefore, we considered CM mortality as the secondary outcome in a biologically plausible way. We found only cognitive impairment or periodontitis was associated with CM mortality separately (Table S5). Figure 2 shows the cumulative mortality curves for the four combined groups. When analyzing the combined effects, participants with cognitive impairment and periodontitis or edentulism (Group 4) tended to have the highest all-cause (Figure 2C, E) and CM mortality (Figure 2D, F). These trends are less marked in the combined group of untreated caries and cognitive impairment (Figure 2A, B).

As shown in Table 3, participants with cognitive impairment and periodontitis had higher all-cause ($HR_{adjusted} = 1.831$, 95% CI: 1.377–2.434) and cardiometabolic ($HR_{adjusted} = 1.877$, 95% CI: 1.102–3.197) mortality than the healthy controls (Group 1). The edentulous population with cognitive impairment was 70.1% more likely to suffer all-cause mortality but was not significantly associated with increased CM mortality (Table 3) compared with those in Group 1. However, when cognition and caries were combined, the progressive and additive trends on mortality were not obvious (Table 3). Furthermore, we did not detect any statistically significant interaction effects of cognitive impairment and caries/periodontitis/ edentulism on all-cause and CM mortality. Sensitivity analyses were consistent with the primary analysis (Table S6 and Table S7).

Figure 2. Cumulative mortality rates among the four combined groups. All-cause mortality for cognitive impairment combined with untreated caries (A), periodontal disease (C), or edentulism (E). Cardiometabolic mortality for cognitive impairment combined untreated caries (B), periodontal disease (D), or edentulism (F). P value denotes the difference between the survival curves.

Table 3. The combined associations of cognitive impairment and caries/periodontitis/edentulism with all-cause and cardiometabolic mortality

All-cause Mortality			Cardiometabolic Mortality §		
Cases/ Participants	Adjusted HR * (95% CI)	P for interaction ‡	Cases/ Participants	Adjusted HR * (95% CI)	P for interaction ‡
Cognitive performance combined with caries status †					
Group 1	343/941	1 [Reference]	76/941	1 [Reference]	
Group 2	96/207	1.223 (0.945–1.583)	28/207	1.508 (0.935–2.432)	
Group 3	113/209	1.526 (1.173–1.984)	33/209	1.711 (0.971–2.878)	.554
Group 4	69/121	1.589 (1.142–2.211)	25/121	1.878 (0.989–3.203)	
Cognitive performance combined with periodontal status †					
Group 1	178/597	1 [Reference]	43/597	1 [Reference]	
Group 2	236/506	1.309 (1.061–1.615)	55/506	1.269 (0.828–1.947)	
Group 3	71/149	1.703 (1.234–2.351)	21/149	1.735 (0.991–3.361)	.203
Group 4	136/226	1.831 (1.377–2.434)	43/226	1.877 (1.102–3.197)	
Cognitive performance combined with dentate status †					
Group 1	439/1148	1 [Reference]	104/1148	1 [Reference]	
Group 2	208/316	1.377 (1.121–1.691)	58/316	1.349 (0.912–1.996)	
Group 3	182/330	1.479 (1.193–1.832)	58/330	1.505 (0.906–2.271)	.329
Group 4	149/179	1.701 (1.338–2.161)	44/179	1.638 (0.947–2.564)	

*Multivariable Cox proportional hazards models were adjusted for sociodemographic variables, behavioral variables, medical conditions, and cardiovascular disease risk factors.
† Four combined groups see the legend of Figure 1.
‡ In the interaction analyses, we included an interaction term (cognitive status * caries/periodontitis/ edentulism).
§ Cardiometabolic mortality combined diseases of heart, cerebrovascular diseases, and diabetes mellitus.
Bold indicates *P*-value <0.05. Abbreviations: HR, hazard ratio; CI, confidence interval.

DISCUSSION

In this prospective cohort study, the association of cognitive impairment and poor oral health with mortality in older people was investigated. Cognitive impairment,

periodontitis, and edentulism were associated with increased all-cause mortality, whereas untreated caries was not related to mortality. Cardiovascular disease risk factors may play an explanatory role in the association of each significant predictor with all-cause mortality. All-cause and cardiometabolic mortality risk significantly increased among older people with coexisting periodontitis and impaired cognition when compared to healthy controls. Similarly, the risk of all-cause death was highest in the participants with coexisting edentulism and impaired cognition.

The strengths of this study include the considerable follow-up duration and event rate. The findings persisted after adjusting for a range of potential confounders and were robust in the sensitivity analysis. Our findings indicated the combined effect of impaired cognition and poor oral health on mortality, an association that has rarely been studied previously. Cognitive impairment and edentulism were found to increase the risk of mortality in a Spanish geriatric population from nursing homes [40]. Marín-Zuluaga et al. demonstrated an association of cognition–oral health with mortality and supports the findings of the current study, although with a different source population.

Plausible biological mechanisms for an increased mortality risk may involve the shared CVD-RF. The separate association of impaired cognition, periodontitis, and edentulism with all-cause mortality was attenuated but still statistically significant in the fully adjusted model. The finding suggests that CVD-RF may partly explain the excess risk of total death, which is consistent with prior studies [14, 41]. Correspondingly, periodontitis combined with cognitive impairment increased cardiometabolic mortality. Periodontal pathogens may increase incident dementia and potentially the risk of AD-associated mortality through a chronic low-grade inflammatory response, oral microbial dysbiosis, and bacterial invasion [42–44]. Edentulism affects masticatory function and nutrition intake and is concomitant with many systemic diseases [45, 46]. The long-term cumulative effects of oral infection or edentulism may contribute to neurological dysfunction [47] and affect a spectrum of cardiometabolic complications [48], thus ultimately increasing death risk in older persons.

In terms of clinical implications, the present study's findings raise awareness of the importance of interdisciplinary efforts between geriatric physicians and dentists. Most phase III clinical trials in AD therapeutics have not been found to change the disease's trajectory [49–52], indicating that no well-studied pharmacotherapy is available. The emphasis has increasingly shifted from pharmacotherapy to

prevention. Delaying the onset and/or progression of AD by only one year would result in a reduction of 9.2 million cases by 2050 [2]. Notably, dental prophylaxis and periodontal treatment had beneficial effects in reducing the occurrence and progression of dementia in a large-scale cohort study [53]. However, physicians often neglect the implications of poor oral health in the vulnerable elderly.

This study highlights the key combinations of oral diseases and cognitive impairments, demonstrating poor periodontal health increases CVD risk, which is also associated with cognitive function. In turn, the comorbidities may increase the mortality risk synergistically. Our findings suggest that great care must be taken in treating oral disease in the elderly, particularly in those with cognitive impairment, to enhance the quality and span of life [54]. From a health economics perspective, providing oral health advice and maintaining periodontal health seems a more cost-effective strategy when compared to intervening in other systemic diseases and lifestyles [54]. Prevention and management of periodontitis and tooth loss are expected to prevent the onset and development of cognitive impairment and improve the quality and span of life. To summarize, maintaining oral health care in older people with cognitive impairment could be a crux of reducing the mortality risk.

Several potential limitations may have affected the interpretation of the findings. First, the RHMP may have underestimated the prevalence and severity of periodontal disease compared to full-mouth examination of six sites on all teeth [55]. The potential bias, however, can be significantly lessened by using the half-reduced CDC/AAP case definition [32] that was used in the present study. In addition, cognitive function cannot be comprehensively evaluated using a single instrument in the present study, the DSST test. Although the DSST is more sensitive to executive function/processing speed than many other measures [56], several other cognitive deficits (e.g., memory, attention, language) should be assessed in future research. In addition, cognitive performance, oral health, and CVD-RF were assessed only at baseline, with no subsequent changes being examined at follow-up period. These changes may potentially affect the relationship between cognitive performance or oral health status and survival over time.

CONCLUSION

In summary, cognitive impairment, periodontitis, and edentulism seem to be significant predictors of all-cause mortality in the U.S. geriatric population, with

CVD-RF partially explaining these associations. The combination of poor cognitive performance and periodontitis or edentulism was found to increase mortality in a progressive and additive manner. Special care should be taken in maintaining a healthy oral environment and functional mouth to prolong life span in older adults, especially for those with concomitant cognitive impairment.

SUPPLEMENTARY INFORMATION

<https://drive.google.com/file/d/1fLts5vi9vLpGAel2ftwyyBpmqWlrUj7j/view?usp=sharing>

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CHAPTER 8

**General discussion,
summary,
and conclusions**

Summary

Periodontal disease is one of the most prevalent oral diseases; severe periodontitis affects 796 million people worldwide [1, 2]. Severe periodontitis can lead to tooth loss, masticatory disturbance, malnutrition, and systemic diseases. Therefore, attaining and maintaining periodontal health have become a global concern for public health [3, 4]. For over a century, epidemiological studies have fueled developments in periodontal science and have made an important contribution to periodontology [5]. Population-level studies enable investigators to discover research questions that cannot be found with clinical trials or individual studies alone. The insufficient number of patients often limits the importance and generalization of findings from randomized clinical trials. Ethical and safety issues also hamper the performance of clinical trials. In contrast, observational studies can better understand the benefits of healthcare and risks of disease among large-scale populations. Population-level research can help identify vulnerable and high-risk populations and provide better information for policymakers and healthcare providers. In turn, the evidence from epidemiological research promotes the development of clinical guidelines and clinical decisions. The contribution mainly consisted of 1) understanding the natural history, 2) estimating the population distribution of periodontitis, 3) identifying risk factors, and 4) planning oral health care services [5]. Epidemiological research can be classified as descriptive epidemiology and analytical epidemiology in light of study type. Descriptive epidemiology aims to answer the basic questions of periodontal disease: what (definition), who (person), where (place), and when (time). Based on the descriptive study results, investigators use analytical epidemiology (quasi-experimental research design) to make inferences about the potential causes and risk factors of periodontal disease, interventional means for preventing disease, and periodontal–systemic associations [6]. Each chapter of this thesis was interpreted and discussed one by one below.

Methodological Challenges

The systematic review presented in **Chapter 2** assessed the definitions of periodontal health. A lack of an explicit and valid definition of periodontal health was observed in the existing literature. The methods of assessing the periodontal status presented significant heterogeneity concerning the full- or partial-mouth periodontal examination protocol, probe used, and number of sites per tooth measured. The measurements were obtained by various combinations of periodontal parameters, including PPD, CAL, gingival bleeding, plaque, and calculus. There were considerable inconsistencies in the different

periodontal parameters and cut-off values used. This reflects a long-standing, yet essentially unresolved, issue in periodontology for decades: lack of a uniform and standard definition of periodontal health. The EFP/AAP workshop defined periodontal health as less than 10% of sites having BOP and PPD <3 mm in an intact periodontium or <4 mm in a reduced periodontium [7]. Loss of periodontal attachment or alveolar bone has not been incorporated, partly because the newly proposed definition focuses on the current status of the periodontium. The new definition of periodontal health offers an opportunity for the field to standardize and unify the methodologies to draw comparisons between different studies. However, future research is needed to validate the cut-off value of definition.

Given that periodontitis is a multifactorial disease, it would be difficult to achieve a healthy periodontium and maintain periodontal stability by exclusively promoting oral hygiene. The few trials available were insufficient to identify the benefit of only relying on personal oral hygiene to prevent chronic periodontitis [8]. Therefore, the monocausal paradigm in periodontology (periodontitis caused by plaque) was gradually deemed unacceptable, in favor of the “complex disease” paradigm of multiple causes and effects [9]. Numerous classification systems for periodontal disease have been proposed over the past decades [10]. Of note, the 2018 classification introduces a multi-dimensional view of periodontitis: the concept of staging and grading [11]. Staging is based on a full-mouth assessment; periodontitis can be subdivided into different severity levels based on clinical phenotypes, tooth loss due to periodontitis, and management and treatment complexity [11]. Grading incorporates biological dimensions of periodontitis, including the rate of progression, interplay of risk factors, predicted response to standard treatments, and potential effect on/interaction with general health [11]. The new classification recognizes that a patient’s disease trajectory is complicated and should be managed and treated deliberately [12].

The reasons for tooth extraction are often not recorded in epidemiological datasets. It is impossible to accurately ascertain the number of missing teeth due to periodontitis and classify patients into severe periodontitis (stage III or IV). A robust analysis of large-scale periodontal data from the general population ($n = 8,978$) was conducted (**Chapter 3**). The study identified a reference indicator to estimate tooth loss due to periodontitis (TLPD). Higher correlation coefficients of PPD and CAL were observed in adjacent teeth than in non-adjacent teeth, and the correlation coefficient increased with increasing periodontitis severity. More importantly, the findings from correlation analyses were validated in the Java Project on Periodontal Disease that provided TLPD data. The teeth adjacent

to teeth lost due to periodontitis presented marked alveolar bone loss (>50%) in the Java study. A plausible indicator can be proposed on the basis of these findings: the presence of moderately-to-severely periodontally compromised teeth adjacent to absent teeth may help estimate the reasons for tooth loss. On the other hand, when teeth adjacent to a lost tooth showed minimal or no periodontal breakdown, it is unlikely that periodontal disease is the cause of that tooth loss. This reference indicator may become a supplemental approach for detecting periodontally susceptible groups. It can be beneficial for detecting more periodontally vulnerable patients by determining whether previous tooth loss was due to periodontal disease instead of using current methods, which focuses on detecting present periodontal disease. Nevertheless, large-scale validation is needed to further verify the reference indicator for TLPD.

Descriptive Epidemiology

Chapter 4 used the repeated cross-sectional data from a series of oral health surveys and performed a trend study in the Dutch population over two decades. Oral hygiene and periodontal status were assessed by the Simplified Oral Hygiene Index and Probing Pocket Depth Index (PDI). Although plaque control significantly improved over time, the age-standardized prevalence of severe periodontitis (PDI = 2) remained (from 6.5% [4.9–8.2%] in 1995 to 5.4% [3.7–7.0%] in 2013). These findings, to some extent, confirm the point of view that the theory of periodontitis being caused by plaque seems outdated [13]. Absolute and relative socioeconomic inequalities in oral hygiene and periodontal health presented in 2013. Even though we did not observe socioeconomic inequalities increased over two decades, the trend in periodontal health has not benefitted both SES groups equally, as the low-SES group has benefitted less than the high-SES group. Oral health workers need to notice that low-SES populations should be provided with more preventive care and dental education. Oral and dental policymakers may need to increasingly target socioeconomic inequality and tailor appropriate policies for different SES groups.

This trend study is a secondary analysis of existing data from different periods in the same region. Secondary research is far more simple and inexpensive than the research conducted from scratch [14]. There are all-so-tiring efforts to conduct the primary research, like recruiting the participants, preparing the measures, and collecting the data. In the secondary research, the investigators need to pay a tiny fee to obtain access to existing data derived from the primary research. Besides, the investigators do not need to assess and reassess the participants over long periods of time if they conduct the secondary research. They still have

an opportunity to deal with longitudinal data to explore the disease trends over time. Despite these advantages, the secondary analysis of existing data has several disadvantages. The secondary data may not be fully appropriate for your own research purposes. For instance, the oral health survey dataset (**Chapter 4**) cannot provide the essential periodontal examination data (i.e., clinical attachment loss). It would not be appropriate to define periodontal health only using probing pocket depth nowadays. Moreover, if the original researchers did not ensure the reliability and validity of the data, this may affect the quality of secondary datasets. Unfortunately, there is little else one can do to in the secondary analysis. Therefore, we should be cautiously optimistic about the secondary analysis of existing data.

Analytical Epidemiology

A population-based study showed that a pro-inflammatory dietary pattern was associated with an increased risk of poor periodontal health (**Chapter 5**). The inflammatory dietary pattern is measured by the energy-adjusted dietary inflammatory index (E-DII). A non-linear positive association with periodontitis was identified for the E-DII score in the general population. More pro-inflammatory diets were associated with an increased risk of periodontitis. Notably, the main results in the validation dataset can be replicated. Relatively stronger associations were observed between E-DII and periodontitis among males and ≥60 years old adults. These findings suggest the possible utility of the modulation of dietary inflammatory potential in strategies intended to prevent and treat periodontal disease.

Emerging evidence of the periodontal–systemic link helps dentists to convince patients to accept extensive dental treatment because gum diseases would increase the risk of morbidity and mortality at the population level [15]. For periodontal researchers, the coming era of periodontal medicine also provides an opportunity to access the larger funds available for research into major public health problems. These tangible benefits of the periodontal medicine drive the development of periodontology. Simultaneously, this phenomenon has come under some criticism: what we need is sound science rather than jubilation that the periodontal health paradigm becomes the savior of dental practice [15].

In **Chapter 6**, the analytical study presented focused on the mediating effect of systemic inflammatory markers on the association between periodontal inflammation (as assessed by BOP and PISA) and cognitive decline. It was observed that individuals with good periodontal health—as the definition by

EFP/AAP—showed superior cognitive performance than periodontal patients. In contrast, there was no association between periodontal health determined by CDC/AAP and cognitive test scores (as measured by Digit Symbol Substitution Test [DSST]). Moderate or severe CDC/AAP periodontitis and BOP $\geq 10\%$ were significantly associated with DSST score, indicating that gingival bleeding is a vital indicator of the association. Moreover, the negative associations between periodontal inflammatory activity/burden and cognitive performance could be explained, at least in part, by the WBC count (27.5% for BOP and 20.3% for PISA). The neuroinflammatory pathogenesis of dementia provides biological plausibility to these mediating effects [16, 17].

A prospective cohort study presented in **Chapter 7** showed that oral health problems and comorbidity increase the death risk in elderly. The oral health status was assessed on the basis of untreated caries, moderate or severe periodontitis, and edentulism. At a median follow-up period of 13.4 years, cognitive impairment, periodontitis, and edentulism were independent predictors of total mortality. Caries, however, was not significantly related to mortality. Cardiometabolic risk factors partly explained the significant associations. Remarkably, the combination of poor cognitive performance and periodontitis or edentulism increased mortality in a progressive and additive manner. Our findings support the importance of interdisciplinary efforts between geriatric physicians and dentists to enhance the quality of life and life span of vulnerable elderly individuals. Physicians often neglect the implications of poor oral health among older people, who are among the most vulnerable members of any community. Therefore, oral hygienists, general dentists, and periodontists could actively liaise with their networks of medical practitioners and provide corresponding oral health guidelines that they can convey to their patients [18].

Strengths and Limitations

This thesis has several strengths and limitations. To our knowledge, the systematic understanding of periodontal health lacks so far. Echoing the 2017 World Workshop, the concept of 'periodontal health' is central to the current thesis. We systematically reviewed the used definitions of periodontal health in the existing literature (**Chapter 2**); we compared the most frequently used parameters and their cut-off values with the definition proposed by the 2017 World Workshop. The stable status of periodontal tissues (i.e., absence of gingival bleeding and pocket deepening) was emphasized when defining a healthy periodontium. In addition, we based the methodological study on a large scope of data (**Chapter 3**). We examined the inter-relationships of periodontal parameters

between natural teeth were in the discovery dataset and replicated these findings well in the validation dataset. The validation analysis suggests that it is unlikely that the strong correlations between adjacent teeth are due to chance alone.

Moreover, we evaluated the trends in socioeconomic inequalities at the absolute and relative levels (**Chapter 4**). Based on the multiple regression model, the confounding effects of covariates were well controlled, and the adjusted prevalence was visualized in different periods. Furthermore, we took into account the probability of non-linearity when the independent variable was a continuous value. Because of this, we detected a threshold effect of the dietary inflammatory index on periodontal disease (**Chapter 5**). The low or medium level of a pro-inflammatory diet seems to be modulated through body compensatory reaction, which was plausible from a biological perspective. In periodontal medicine, the research questions are no longer limited to the oral cavity. We focused on the geriatric population's neurocognitive and oral health problems (**Chapter 6** and **7**). Maintaining periodontal health was expected to be a promising therapeutic target to reduce the risk of comorbidity and mortality for fragile older adults.

Nevertheless, this thesis is not without limitations. Firstly, the small sample size of the JAVA dataset was the main limitation in the methodological study (**Chapter 3**). There is a future need for large-scale studies to validate the periodontally compromised adjacent teeth as reference indicators. Secondly, age-period-cohort effect analysis is subject to the limitations associated with the design of the repeated cross-sectional studies (**Chapter 4**). Thirdly, due to the nature of the cross-sectional study, the causal relationship could not be identified (**Chapter 5** and **6**). Lastly, independent variables were assessed only at baseline, with no subsequent changes being examined at the follow-up period (**Chapter 7**). The dynamic changes should be assessed in further studies.

Conclusions and Future Prospective

This thesis painted an overall picture of periodontal epidemiology in terms of methodological issues, environmental risk factors, and systemic effects. The lack of commonly accepted definitions and the considerable variation in the methods deeply hamper the comparison of the findings across different epidemiological studies involving periodontal health. When tooth extraction reasons are unrecorded or unavailable in the existing database, the periodontal health status of adjacent teeth is a promising reference indicator. Trends of oral hygiene and

periodontal health significantly improved in the Netherlands over two decades, mainly in the high-SES population. This thesis noted the dietary pattern as a modifiable risk factor for poor periodontal health. More pro-inflammatory diets were associated with an increased risk of periodontal disease in the general population, relatively stronger among older adults and males. In contrast, poor periodontal health can also be implicated as a risk factor for aging-associated neurological disorders. Periodontal inflammation could affect cognitive performance via elevated systemic inflammation in the older population. Besides, periodontitis or edentulism and impaired cognition might jointly increase the death risk in the elderly.

The periodontal health definition proposed by the EFP/AAP Workshop offers an opportunity for the field to standardize and achieve uniformity in terms of methodologies. Under a healthy condition in periodontal patients, the inflammatory process enters a programmed resolution cycle activating healing pathways. The concept of healthy periodontal status provides new insights into our understanding of the systemic effects of periodontal inflammation at activation and resolution stages. Through scaling root surfaces, in addition to proper oral hygiene measures by the patients (tooth brush, interdental brushes, mouthwashes) periodontal treatment can effectively eliminate bacterial colonization and prevent pathogenic species growth, ultimately arresting the inflammatory process and periodontal breakdown. However, the conventional treatment methods seem insufficient to halt disease progression in all patients. There remains a need for future studies to develop a 'personalized' treatment method targeting the susceptible individual with uncontrolled risk factors and multiple comorbidities.

The 2018 classification noted the number of periodontitis-caused tooth loss as an indispensable part to assess periodontitis severity. Thus, we suggest that the epidemiological investigators and clinical periodontists/dentists record the reasons for tooth extraction based on the participant recall and clinical profiles. The clinical indicator posed in this thesis facilitates determining whether the tooth loss is due to periodontitis. However, this indicator requires validation in future studies. As epidemiology is an observational science, the findings are more suitable for proposing hypotheses than proving them. Therefore, large-scale and long-term randomized controlled trials are needed to determine whether periodontal treatment benefits patients with systemic diseases, ultimately reducing morbidity and mortality. Epidemiological investigators often use Austin Bradford Hill criteria to assess a potential causal relationship between exposure

and outcome [19]. The causality and direction of periodontitis-systemic link have been controversial. However, one should not ignore the increased risk of systemic diseases associated with poor periodontal health only because all details are not yet understood. In summary, the field of periodontal epidemiology will continue to grow in clinical importance and relevance in terms of the modifiable risk factors and the periodontal-systemic associations.

APPENDICES

LIST OF FREQUENTLY USED ABBREVIATIONS

AAP	American Academy of Periodontology
ABL	alveolar bone loss
AD	Alzheimer's disease
AD-teeth	the adjacent teeth
BMI	Body mass index
BOP	bleeding on probing
CAL	clinical attachment loss
CDC	Centers for Disease Control
CI	confidence interval
CM	cardiometabolic
CO-teeth	the contralateral teeth in the opposite jaw
CPI	community periodontal index
CRP	C-reactive protein
CS-teeth	the contralateral teeth in the same jaw
CVD	cardiovascular disease
CVD-RF	cardiovascular disease risk factors
DSST	digit symbol substitution test
EFP	European Federation of Periodontology
E-DII	energy-adjusted dietary inflammatory index
FDR	false discovery rate
HDL	high-density lipoprotein
HEI	Healthy Eating Index
HIF	Health Insurance Fund
HR	hazard ratio
ICC	Inter-class Correlation Coefficients
IL	interleukin
IO-teeth	the ipsilateral opposing teeth
IQR	interquartile range
MOOSE	Meta-analysis Of Observational Studies in Epidemiology
NCHS	National Center for Health Statistics
NHANES	National Health and Nutrition Examination Survey
OHI-S	Simplified Oral Hygiene Index
OR	odds ratio
PDI	probing pocket depth index
PISA	periodontal inflamed surface area
PPD	probing pocket depth

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RHMP	random half-mouth protocol
SD	standard deviation
SES	socioeconomic status
SP	severe periodontitis
SR	systematic review
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TLPD	tooth loss is related to periodontal disease
TNO	Toegepast Natuurwetenschappelijk Onderzoek
WBC	white blood cell
WHO	World Health Organization

CURRICULUM VITAE

An Li studied a bachelor of science in Clinical Medicine at Anhui Medical University, China. After graduation in 2012, he started a master's degree in Oral Medicine and a doctoral degree in Pathophysiology at Jinan University, China. In 2017, An Li started his PhD trajectory at the University Medical Center Groningen in the Netherlands. He was involved in the Department of Periodontology at the Center for Dentistry and Oral Hygiene (the head of center: Prof. Luc W M van der Sluis [until 2020.8] and Prof. Luc A.M. Marks [2020.9–present]). An Li joined the research group under the supervision of Dr. Geerten-Has Tjakkes. Here he applied epidemiological approaches to do the methodological study and explore the systemic relationships of periodontal health. After defending his thesis, An Li will return to China and continue the clinical research as a postdoc at the Stomatological Hospital of Southern Medical University.

An Li's main research interests reside in:

1) the interaction between dietary patterns, periodontitis, and immune response;

2) the effect of periodontal bacteria and inflammation on the cognitive decline via peripheral pathways.

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