UNIVERSITY of TASMANIA

Risk Factors of Periodontitis in Australian Adults

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BDS, MDSc (Periodontology)

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Doctor of Philosophy

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Declaration of Originality

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Statement of Ethical Conduct

The research associated with this thesis has been approved by Human Research Ethics Committee (HREC) of University of Adelaide (Appendix A) and HREC of the University of Sydney (Appendix B). The prior ethics approval form was filled and submitted to University of Tasmania HREC. The HREC of University of Tasmania notified that no approval is required for the secondarry data analysis of the Nationa Survey of Adult Oral Health 2004-06 since this survey is already has approval from HREC of University of Adelaide,.

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Statement of Co-authorship and list of publications

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This publication is located in Chapter 3 of this dissertation. Candidate was the primary author of this paper who was involved with the conception, design, search, data extraction, construction of table of synthesis and preparation of this manuscript. Co-authors Bettiol, S and Barrington, G were closely involved in this paper and contributed towards critical reviewing of the papers, resolving disagreement in selection of articles and preparation of manuscript. Authors Barnett, T and Crocombe, L contributed to the idea of the project and refinement of the manuscript. This publication has received 17 citations to date.

Paper 2. **Khan, S and Bettiol, S and Kent, K and Barnett, T and Peres, M* and Crocombe, L, "Obesity and periodontitis in Australian adults: A population-based cross-sectional study", International Dental Journal doi:10.1111/idj.12514 ISSN 0020-6539 (2019) [Refereed Article]**

This publication is located in Chapter 4 of this dissertation. Candidate was the primary author of this paper who was involved with the conception, design, data analysis, and preparation of this manuscript. Co-authors Bettiol, S and Kent, K and Barnett, T and Peres, M and Crocombe, L contributed to the idea of the project, formalisation and refinement of the manuscript.

Submitted manuscripts

Paper 3. **Khan, S** and Bettiol, S and Kent, K and Barnett, T and Peres, M and Crocombe, L and Mittinty M. Association between Obesity and Periodontitis in Australian adults: A Single Mediation Analysis

This submitted paper is located in Chapter 5 of this dissertation. Candidate was the primary author of this paper who was involved with the conception, design, data analysis, and preparation of this manuscript. Co-authors Mittinty, M and Peres, M were closely involved in this project by assisting with single mediation analysis, manuscript drafting and preparation. Bettiol, S and Kent, K and Barnett, T and Crocombe, L contributed to the idea of the project, formalisation and refinement of the manuscript.

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Other outputs

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3. Crocombe, LA and Allen, P and **Khan, S** and Godwin, D and Bettiol, S and Barnett, T and Hoang, H and Goldberg, L, "Geographic variation in preventable hospital admissions for dental conditions: an Australia-wide analysis", Australian Journal of Rural Health ISSN 1038-5282 (In Press) (2019) [Refereed Article]

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List of Abbreviations

Acronym	Definition
ABL	Alveolar Bone Loss
ATP	Adenosine tri phosphate
AGHE	Australian Guide for Healthy Eating
ADA	American Diabetes Association
AIHW	Australian Institute of Health and Welfare
ABS	Australian Bureau of Statistics
AHA	American Heart Association
AAP	American Academy of Periodontology
ALT	Alanine aminotransferase;
ARCPOH	Australian Research Centre of Population Oral Health
BOP	Bleeding on probing
BMI	Body Mass index
CDC	Center for Disease Control and Prevention
CEJ	Cemento-enamel junction
CAL	Clinical attachment loss
CPI	Community periodontal index
CIm	Calculus Index mean
CCDRFS	China's 2010 Chronic Disease and Risk Factor Surveillance
CRP	C-reactive protein
DAG	Direct acyclic graph
DMF	Decayed Missing Filled
FFM	Free Fat Mass
GB	Gingival bleeding index
GBm	Gingival bleeding index mean
GCF	Gingival crevicular fluid
GI	Gingival index
GULT-4	Glucose transport protein 4
HaB1c	Glycosylated haemoglobin
HDL	High Density Lipoprotein
HsCRP	Highly sensitive C reactive protein
HOMA-IR	Insulin resistance
IL-6	Interleukin 6
ICD	International Classification of Disease
IOTF	International Obesity Task Force
KNHANES	Korean National Health and Nutrition Examination Survey
LDL	Low Density Lipoprotein
LBM	Lean Body Mass
MeSH	Medical Subject Heading
NHS	National Health Survey
NSAOH	National Survey of Adult Oral Health
NHANES	National Health and Nutrition Examination Survey
NIH	National Institute of Health

NEFA	Non-steroidal fatty acids
PAL	Periodontal attachment loss
PALm	periodontal attachment loss mean
PI	Plaque index
PPD	Periodontal Probing depth
PDm	Pocket depth mean
PCP2	Periodontal condition probe
PPD	Periodontal pocket depth, Probing pocket depth
TNF- α	Tumour Necrosis Factor Alpha
UK	United Kingdom
US	United States of America
USD	American Dollar
VPI	Visible Plaque Index
World Health Organization	WHO

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Abstract

Background: Overweight/obesity and periodontitis are complex health problems, contributing to a high burden of co-morbidities that have a significant economic impact in Australia and worldwide. Although international studies have compared the relationship between these two complex conditions, there is a dearth of research literature reporting their association in the Australian population.

The aims of this PhD were to explore the relationship between overweight/obesity and periodontitis in Australian adults; and to determine if there are mediators of this relationship.

The objective of the first project was to determine the association between overweight/obesity and periodontal disease in young adults and adolescents by a systematic review. Twelve databases were searched using MeSH terms for "overweight or obesity" and "periodontitis". Quality appraisal was conducted using the Newcastle Ottawa scale. Of the 25 eligible studies, 17 showed an association between overweight/obesity and periodontitis (Odds Ratios ranged from 1.1 to 4.5). However, there was a gap in the Australian data on the relationship between obesity and periodontitis.

Hence, an analysis using STATA 15 of the cross-sectional National Survey of Adult Oral Health (NSAOH) 2004-06 was conducted (n = 3715 participants). Body Mass Index (BMI) was calculated using self-reported body height (cm) and body weight (kg). Overweight/obesity was defined as BMI ≥25kg/m^2 [a combined variable of overweight "BMI ≥25-29.9 kg/m^2" and obesity (BMI ≥25kg/m^2)]. Putative confounders included thirteen dietary questions, age, sex, education, annual income, smoking, alcohol intake, oral hygiene behaviours and dental visiting behaviour. The mean number of sites with

probing depth (PPD) $\geqslant$ 4mm, clinical attachment loss (CAL) $\geqslant$ 4mms were used to measure the extent and the CDC/AAP case definition was used to measure the prevalence of periodontitis. Bivariate analysis found a significant association between extent of periodontitis and BMI. Multiple variable analysis indicated that periodontitis (prevalence and extent) was not associated with overweight/obesity when controlled for putative confounders. These results could be false due to the limitation of multiple variable regression analysis that groups putative confounders/mediators as a cluster in determining the effect of exposure on outcome.

Therefore, this dissertation utilised single mediation analysis to determine the relationship between overweight/obesity and periodontitis using all NSAOH participants aged 30 years or older. A Direct Acyclic Graph was constructed. Dental visiting behaviour (a de facto measure of healthy behaviour) was used as a mediator. Confounding variables included age, sex, household income, education, diabetes, alcohol intake and smoking. Overweight/obesity was defined as physical inactivity induced overweight/obesity (BMI $\geqslant$ 25 kg/m^2 and no moderate physical activity). Data was analysed using STATA 15 using the paramed library. Pathway effect analysis using potential outcomes illustrated that the effect of overweight/obesity on periodontitis, which was not mediated by poor dental visiting behaviour, was 10%. The indirect effect of overweight/obesity on periodontitis, mediated through poor dental visiting behaviour, was 3%.

A limitation of the NSAOH 2004-06 was the potential participant under-reporting of chronic health conditions. A cross-sectional pilot study [a trial for measuring feasibility for the future prospective cohort study] was therefore designed, with a healthy cohort of obese people with no co-morbidities, that aimed to determine the relationship between overweight/obesity, diet, prediabetes and periodontitis. This study was part of a larger randomised controlled trial at the University of Sydney. The inclusion criteria were: aged

18 years and older, a body mass index ⩾ 25 kg/m² and pre-diabetic (fasting plasma glucose levels ⩾ 5.6-6.9 mmol/L and/or two-hour post-challenge (oral glucose tolerance test) plasma glucose levels ⩾ 7.8-11.0 mmol/L and/or HbA1c ⩾ 5.7-6.4%), dentate (with at least eight teeth present) and no risk of infective endocarditis. Data was collected from 33 participants for age, sex, smoking, BMI, waist and hip circumference, PPD, CAL, BOP, oral hygiene behaviours, the usual reason for dental visiting, blood levels of highly sensitive C-reactive protein, glycosylated haemoglobin, lipid profile and apolipoprotein. Bivariate analysis using the R statistical package found waist circumference and fasting plasma glucose were significantly associated with periodontitis. No significant association was observed between BMI and periodontitis.

Conclusions: Of the 25 eligible studies in the systematic review, 17 showed an association between obesity and periodontitis. However, there was a gap in the Australian data on the relationship between overweight/obesity and periodontitis. Conventional multivariable analysis of the NSAOH 2004-06 data found no significant association between overweight/obesity and periodontitis. Single mediation analysis to determine the relationship between overweight/obesity and periodontitis using a NSAOH subset of 3715 participants aged 30 years or more found that the effect of overweight/obesity on periodontitis, which was not mediated by poor dental visiting behaviour, was 13%. There was a positive association between waist circumference and periodontitis in the pilot study, which was part of a larger randomised controlled trial at the University of Sydney. To reproduce these outcomes, a prospective cohort study is required.

Chapter 1. Introduction

The global burden of obesity and its co-morbidities including type 2 diabetes mellitus, cardiovascular diseases and various cancers has increased rapidly in recent years [2]. A similar situation is observed in the Australian population with around 28% of the population experiencing obesity [3]. Similarly, the prevalence of periodontitis is also high in Australia and reported to be experienced by one in four individuals [4]. Obesity could be a potential risk factor for periodontitis [5-7].

The association between obesity and periodontitis was first reported by Perlstein et al. [8] in obese Zucker rats. Perlstein et al. demonstrated hyperplasia and hypertrophic vascular changes in the periodontium [8]. Obesity is associated with increased levels of pro-inflammatory cytokines in people with periodontitis as compared to people with a healthy periodontium [9, 10]. Obesity and periodontitis share common modifiable factors including smoking and alcohol intake, consumption of energy-dense and nutrition-deficient food, poor dental visiting behaviour, and poor oral hygiene behaviour[11]. Obesity and periodontitis are also associated with health conditions of cardiovascular diseases and type 2 diabetes, and share common social determinants of health [12, 13].

A positive association between obesity and periodontitis in adults has been found in studies conducted in several countries [5, 14]. However, this relationship remains unexplored in Australia. It is expected that the putative confounders and mediating factors for the obesity and periodontitis relationship may be different in Australia as compared to rest of the world due to the diversity of social, economic, political and environmental factors in Australia. Therefore, it is important to study the relationship between obesity and periodontitis in Australia. A recent literature review by Arboleda et al. [11] reported a positive association between obesity and periodontitis. This paper suggested that there are multiple pathways through which this association could be interpreted. However, the

interpretation of mediating pathways for obesity and periodontitis association should be interpreted cautiously as a result of heterogeneity in periodontitis assessment, obesity measurement, and diet recording. Based on these rationales, this dissertation has the following hypothesis and aims.

The hypothesis of this dissertation is that obesity is associated with periodontitis in Australian adults. The overall aim of this dissertation is to determine the relationship between obesity and periodontitis in the Australian adult population. The objectives of this project have been sub-categorised into four studies, as discussed below.

Specifically, **Study 1** was conceptualised to determine the association between overweight/obesity and periodontitis in adolescent and young adults using the systematic review method. The systematic review was conceptualised based on hypotheses and focused questions using the PICO (Population Intervention Comparator Outcome) tool, a broader search strategy generated using a wide array of search terms, a comprehensive search for evidence using several databases for electronic searching, snowballing technique and hand searching of studies, inclusion of non-English articles, using reproducible inclusion/exclusion, and the rigorous use of the Newcastle Ottawa Scale for appraisal of validity. Despite the rigorous search strategy, more information on this review question may remain embedded in publications focused on other co-morbidities. This review comprised cross-sectional and case-control studies, which are of low level under the hierarchy of evidence [level 4 and level 5] [15]. Future studies should answer this research question using prospective cohort studies. The outcome of this work was published in the *Obesity Review Journal*. Permission was received from the Wiley's Online publishers to reproduce the work of this journal article in this dissertation.

Based on outcomes of Study 1, it was concluded that to the best of author's knowledge, no data existed that explored the relationship between obesity and

periodontitis in the Australian population. This motivated the author to answer this research question in the Studies 2, 3 and 4 of this dissertation.

In **Study 2** the author conducted a secondary analysis of the National Survey of Adult Oral Health (NSAOH 2004-06) dataset to answer the research question, "Is overweight/obesity a risk factor for periodontitis in the Australian adult population?". NSAOH 2004-06 is a cross-sectional observational study of Australian adults conducted by the Australian Research Centre of Population Oral Health (ARCPOH) [4]. Participants in the NSAOH 2004-06 were recruited using a three-stage, clustered randomised sampling technique for selecting the representative samples of dentate Australians aged 15 years and older. The sampling frame of the study was households with listed telephone numbers recorded in an electronic White Pages database. The first stage selected postcodes, the second stage selected households within sampled postcodes, and the third stage selected one person aged 15 years or more from each sampled household. The data collection stage in the NSAOH 2004-06 involved a computer aided telephone interview (CATI) by a trained interviewer, an oral examination by the calibrated dentists, and a baseline mail self-complete questionnaire. The protocol for the data collection was approved by the Human Research Ethics Committee of the University of Adelaide (Appendix A). The variables of interest for the purpose of this study included age, sex, education, annual income, self-reported diabetes, self-reported body heights and self-reported body weights, oral hygiene habits (tooth brushing, mouth rinsing and flossing), dental visiting behaviour, 13 food frequency questions, and measures of Plaque index (PI) and Gingival Index (GI) [16], Probing Depths (PD) and Clinical Attachment Loss (CAL). The questionnaire weights were used for the data analysis of the NSAOH 2004-06 dataset. The limitations of this study include the following: (i) the self-reported body height and weight measures, that introduced a reporting bias. The problems arising due to self-reporting of body composition measures is discussed in the Chapter 2 of this dissertation;

(ii) the cross-sectional study design is another limitation of this study, which makes it difficult to determine the temporal relationship between obesity and periodontitis; (iii) self-reported 13 dietary questions is another important limitation of the NSAOH 2004-06, that resulted in the inability to calculate the absolute intake of sugar and total energy intake, and other macronutrients that constitute the diet; (iv) self-reported type 2 diabetes was another important limitation of this study; (v) the use of conventional regression analysis is another limitation of this study. The outcome of this work has been accepted for publication in the peer-reviewed *International Dental Journal*.

A conventional regression analysis groups confounders and mediators in the same cluster of putative confounders, which is one of the major problems in understanding the causal relationship between exposure and outcome, that could be overcome by using a potential outcome approach. Hence, to develop causal inference using an observational cross-sectional study dataset, mediation analysis is the most suitable technique. It decomposes the exposure effect into the direct effect, which is through the exposure, and the effect of exposure through intermediate variables (mediators) which are on the pathway of the exposure and the outcome. Therefore, **Study 3** utilised counterfactual theory as it allows researchers to deduce causal inference from observational studies [17, 18]. Study 3 had two main objectives: (i) to explore the causal relationship between obesity (physical inactivity related obesity) and periodontitis in Australia using single mediation analysis to answer the question, "Does obesity cause periodontitis?"; and (ii) to determine the indirect effect of obesity through dental visiting behaviour (a de facto measure of health behaviours) on periodontitis using single mediation analysis. Direct acyclic graphs were drawn to determine the best data generation pathway for the obesity and periodontitis relationship. Dental visiting behaviour was considered a mediator between obesity and periodontitis. The confounding variables include demographic factors (age and sex), socioeconomic position (household income and education), and health and

lifestyle factors (diabetes, alcohol intake, smoking status). Obesity was defined as physical inactivity induced obesity (BMI more than 25kg/m^2 and no moderate physical activity). Single mediation analysis was used to decompose the total causal effect of obesity on periodontitis into its direct and indirect effects using the potential outcome approach. This was done in STATA version 15, using single mediation analysis in the statistical package of Paramed Library. Sensitivity analysis was conducted to verify the presence of unmeasured confounding between exposure and outcome using the E-value estimate. The outcome of this work has been submitted to *Oral Diseases*.

Under-reporting of chronic health conditions, self-reporting of body height and body weight measures and limited information on diet were significant limitations of the NSAOH 2004-06 that were addressed through a cross-sectional pilot study (**Study 4** of this dissertation). The study was designed with a healthy cohort of obese people with no co-morbidities based at the Boden Institute of Obesity, Nutrition, Exercise & Eating Disorders, at the Charles Perkins Centre, University of Sydney. The ethics amendment was made for the pilot study project at the University of Sydney to the already approved project of diabetes prevention program led by the team at The Boden Institute (Appendix B). This study aimed to determine the relationship between obesity, diet, prediabetes and periodontitis. It used measurements of body height, body weight, waist circumference and hip circumference, electronic recording of periodontal measures using the Florida Probe System, and a diet diary. The dietary data obtained in this study was analysed using FoodWorks 8. Figure 1.1 shows the flow chart of the project.

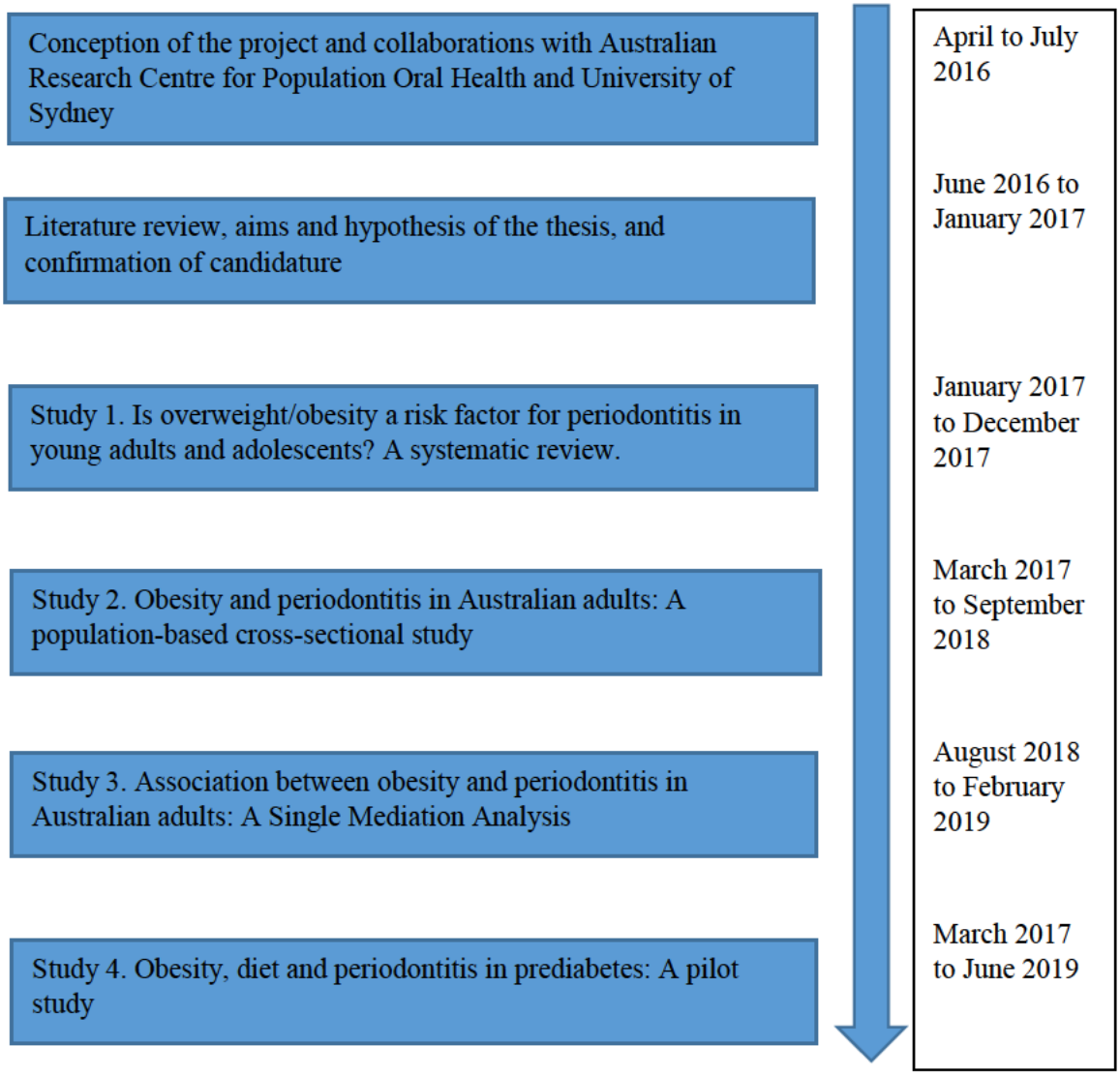

Figure 1.1. Flow chart of the project.

Chapter 2. Literature review

2.1. Periodontitis

2.1.1 Prevalence of periodontitis

i. Worldwide

The Global Burden of Disease Study (GBD, 1990–2010) reported that severe periodontitis was the sixth most prevalent disease globally, affecting 11.2% of the globally ageing population (743 million people), an increase of 57.3% between 1990 and 2010 [19]. The prevalence of periodontitis is expected to rise due to exposure to lifestyle factors (poor oral hygiene, dental visiting behaviour and diet) [20] and risk behaviours (smoking and alcohol) [21, 22]. Factors including ethnicity, geographic location, examination protocols, periodontal probes and case definitions utilised also impact on the reported prevalence of periodontitis [23]. Furthermore, ageing worldwide population is another important factor that may impact by periodontitis rise over time. Periodontitis contributes to a loss of 3.5 million years lived with disability [24]. Periodontitis also contributes to 54 billion USD annually in lost productivity [25]. The worldwide economic impact of periodontitis is 442 billion USD annually [25].

ii. Australia

The prevalence of periodontitis in Australia was 24.5% according to the NSAOH 2004-06 [26]. The experience of moderate/severe periodontitis increased with age beyond 25 years. Men had a higher prevalence of periodontitis than women (26.8% versus 19%) [26]. The proportion of individuals with periodontitis was reported to be lower amongst people with private health insurance compared to those without insurance (19.4% versus 27%) [26]. Individuals with an income of less than 12,000 AUD annually had a higher prevalence of periodontitis than individuals with an income level of 100,000 AUD or more per annum [26].

2.1.2 Definition

Periodontitis (gum disease) is silent or asymptomatic in nature, and characterised by the destruction of supporting periodontal tissues and ultimately loss of teeth [27]. Periodontitis is initiated by plaque accumulation followed by bleeding gums [28], which can be reversed with effective oral hygiene maintenance and periodontal treatment.

The American Academy of Periodontology (AAP) defines periodontal disease as "an inflammatory disease that affects the soft and hard structures that support the teeth". In its early stage, called gingivitis, the gums become swollen and red due to inflammation, which is the body's natural response to the presence of harmful bacteria. In the more serious form of periodontal disease, called periodontitis, bone loss occurs that leads to tooth loss [29]. Periodontal disease is thus divided into two main types: gingivitis and periodontitis.

i. Gingivitis

Gingivitis is the most common gum disease that dental professionals encounter in the dental surgery [30]. It is an age-independent condition, found mostly in children and adolescents. The aetiological factors for gingivitis are classified as (i) local, relating to accumulation of dental plaque and food deposits around teeth and (ii) systemic, where lifestyle (smoking and alcohol), systemic conditions (obesity, type 2 diabetes mellitus and cardiovascular diseases) and hormonal alterations may increase the risk. Gingivitis is characterised by bleeding, redness and swollen gums as a result of inflammation, and the body's natural response to the presence of harmful bacteria [31].

ii. Periodontitis

Periodontitis is commonly seen in adults older than 35 years. It is a major cause of tooth loss in adults [32]. The disease progression is episodic, with relatively short

episodes of exacerbation followed by repair, and prolonged intervening periods of remission [33]. Prolonged episodic bacterial irritation affects the integrity of the dento-gingival junction. The junctional epithelium migrates apically, forming a periodontal pocket. This progressive periodontal attachment loss leads to exposure of the root cementum to the sub-gingival and/or oral environment [34], with a mean yearly attachment loss of 0.05 to 0.5 mm [28].

The clinical features of periodontitis include increase in Clinical Attachment Loss (CAL), Periodontal Pocket depth (PPD), loss of alveolar bone, and inflammation of the gingiva [35]. In addition, it may include receding of gingival margin, Bleeding on Probing (BOP) and increased mobility of the affected teeth [35].

Histologically, periodontitis is marked by an apical movement of the junctional epithelium in relation to the cemento-enamel junction [36]. The loss of collagen fibres is predominant, with polymorphonuclear leukocyte infiltration and predominance of plasma cells, B-cells, lymphocytes, and macrophages in the connective tissue adjacent to the junctional and pocket epithelium [37], leading to the development of a periodontal pocket. Alveolar bone loss is the main feature of periodontitis. Furthermore, breakdown of connective tissue leads to apical migration of the junctional epithelium, forming a periodontal pocket. Migration of polymorphonuclear neutrophils (PMNs) occurs into the pocket lining epithelium and the periodontal pocket, forming a barrier between the tissues and plaque biofilm. Ulceration and increase in permeability of the pocket epithelium promotes further ingress of microbial products, production of inflammatory cytokines, including tumour necrosis factor-alpha (TNFα), interleukin1 (IL1) and prostaglandin E2 (PGE2) [38], and continuum of the pro-inflammatory processes, inducing destruction of both connective tissue and alveolar bone [39, 40].

Periodontitis has a distinct appearance on a radiograph. Radiographic changes observed in periodontitis include interruption in lamina dura, crestal irregularities,

triangulations and interseptal bone changes [41]. The earliest detectable sign on radiographs is finger-like projections extending from the crestal bone to the interdental alveolar bone [42]. The later changes are associated with more severe bone loss [41].

2.1.3 Classification of periodontal disease

Substantial knowledge has been developed from population-based surveillances, animal-based studies, randomised controlled trials and basic science studies in the area of periodontal research, that triggered the need for an update of the AAP 1999 classification of periodontal disease. Therefore, a new classification of periodontal diseases was introduced in 2018 [43] to assist in clinical decision making using clear criteria that may aid accurate diagnosis, prevention and early management of risk factors for periodontitis. This classification is also used for the identification of aetiology and understanding of the pathology of periodontal conditions, diagnosis and treatment planing, and the facilitation of communication between clinicians, researchers, educators, students, epidemiologists and public health workers.

The 2018 classification of periodontal disease defines specific criteria for the diagnosis of the following: (i) periodontal health [44]; (ii) gingivitis [45]; (iii) reduced but healthy periodontium (successfully treated periodontitis) [46]; (iv) gingival inflammation in a periodontitis patient (treated periodontitis with persistent inflammation) [46]; (v) periodontitis [47, 48] (vi) periodontitis as a manifestation of systemic diseases [49, 50]; and (vii) necrotising periodontal disease [51].

Historically, the first classification of periodontal disease was proposed by the AAP in 1977. It has evolved over time, from being a simple classification system with two types of periodontal disease (juvenile periodontitis and chronic marginal periodontitis) to three updated versions published in 1986, 1989 and 1999. Table 2.1 shows the AAP 1989 and 1999 classifications of periodontal disease [52]. For the purpose of this dissertation,

the author has discussed the changes that occurred to the 1999 classification of periodontal disease, because this was the classification adhered to when this dissertation was conceptualised and developed.

Table 2.1 The AAP 1989 and 1999 classification of periodontal disease [52].

AAP 1989 classification	AAP 1999 classification
I. Early Onset Periodontitis a. Pre-pubertal periodontitis 1. Localised 2. Generalised b. Juvenile periodontitis 1. Localised 2. Generalised c. Rapidly progressing periodontitis II. Adult Periodontitis III. Necrotising Ulcerative Periodontitis IV. Refractory Periodontitis V. Periodontitis Associated with Systemic Disease	I. Gingivitis o Plaque induced gingival diseases o Non-plaque induced gingival diseases II. Chronic Periodontitis III. Aggressive periodontitis IV. Periodontitis as a manifestation of systemic diseases V. Necrotising ulcerative gingivitis/ periodontitis VI. Abscesses of the periodontium (gingival, periodontal, pericoronal) VII. Combined periodontic-endodontic lesions VIII. Developmental or acquired deformities and conditions.

i. Addition of Gingival Disease Component

Gingivitis is categorised into two different categories; i.e., dental plaque-induced gingivitis and non-plaque induced gingivitis. Dental plaque is a condensed bacterial

biofilm layer that forms on the surface of teeth, which, if left undisturbed, leads to gingival inflammation and periodontal disease [53].

Dental plaque-induced gingivitis is further classified depending on the presence of systemic diseases, endocrine problems, medications, and malnutrition, whereas non-plaque induced gingival conditions represented diseases coming from non-plaque microorganisms (*Neisseria gonorrhoea*, viral infections and fungal infections), immune mediated disorders (e.g. lichen planus and pemphigoid allergic reactions), restorative materials, toothpastes, gingival trauma (chemical, physical or thermal) and from disorders of genetic origin (hereditary gingival fibromatosis) [52].

ii. Replacement of "Adult Periodontitis" with "Chronic Periodontitis"

One of the drawbacks of the 1989 classification of periodontal disease was the grading of diseases on the basis of age. In a 1999 consensus, the term "adult periodontitis" was replaced with "chronic periodontitis" [52] due to adult periodontitis being considered an arbitrary term typically referring to a specific age of 35+ years. However, similar bone loss patterns were observed even in slightly younger age groups. Hence, chronic periodontitis is characterised to occur mostly in adults, but can be observed in younger individuals [52].

iii. Elimination of Refractory Periodontitis

Refractory periodontitis referred to continuing progressive periodontitis in spite of oral hygiene care and the provision of periodontal therapy. Several factors were found to be associated with the continuing progressive nature of refractory periodontitis. These factors included the severity of periodontal disease before the periodontal therapy, tooth type and furcation involvement, species and strains of microflora, degree of host response (particularly the immune response) and smoking status. It was observed that refractory periodontitis was not a separate disease but the recurrence of the disease, therefore it was discontinued in the 1999 classification[54].

iv. Replacement of "Early-Onset Periodontitis" with "Aggressive Periodontitis"

Early onset periodontitis was a term used to describe periodontitis exhibited in individuals <35 years of age, with significant attachment loss in the presence of local factors (plaque and calculus). It was assumed that this condition was early onset because it affected younger people. It was grouped into three subcategories which included prepubertal, juvenile and rapidly progressive periodontitis. It was concluded that early onset periodontitis was a term which limited the disease domain due to its occurrence below 35 years of age and therefore it was replaced by aggressive periodontitis. Diagnosis of aggressive periodontitis is carried out on the basis of clinical, radiographic and historical findings which show rapid attachment loss [54].

v. Subclassified "Periodontitis as a Manifestation of Systemic Disease"

The 1999 classification was an expanded version of the 1989 classification of periodontal disease [55], which lacked systemic disease as a risk factor for periodontitis [52]. The subclass of periodontitis as a manifestation of systemic disease was included in the 1999 classification. Periodontitis as a manifestation of systemic disease included subcategories for haematological disorders (acquired neutropenia and leukaemia), genetic disorders (familial and cyclic neutropenia, Down syndrome, leukocyte adhesion deficiency syndromes, Papillon-Lefèvre syndrome, Chediak-Higashi syndrome, histiocytosis syndromes, glycogen storage disease, infantile genetic agranulocytosis, Cohen syndrome, Ehlers-Danlos syndrome types IV and VIII, hypophosphatasia and other) and other disorders [54].

vi. Other Changes

In the 1999 classification, "Necrotising Ulcerative Periodontitis" was replaced with "Necrotising Periodontal Diseases". It included necrotising ulcerative gingivitis (NUG) and necrotising ulcerative periodontitis (NUP). New categories of "Periodontal

Abscess" and "Periodontic-Endodontic Lesion" were added to the classification. The addition of a category for "Developmental or Acquired Deformities and Conditions" included local factors associated with teeth and restorations, mucogingival deformities around teeth and on edentulous ridges, as well as occlusal trauma [52].

2.1.4 Case Definition of Periodontitis

A case definition of periodontitis is used in defining the prevalence, incidence and extent of periodontitis in population-based surveillances. The Center of Disease Control and the American Academy of Periodontology (CDC-AAP) have proposed a case definition of periodontitis for population-based surveillance [56] and epidemiological studies [57].

Numerous case definitions have been used for the diagnosis and treatment planning of periodontitis in research and clinical practice. Previous definitions lacked uniformity in the criteria to define a case for periodontitis [58]. They were commonly based on the measurement of disease extent and severity [58]. Also, previous definitions had wide variations in measures indicating the "threshold" of "disease" and "health" status, causing difficulty in the calculations of odds ratio or relative risk and making data interpretation difficult. Hence, the prevalence of periodontitis differed depending on which definition was used [59].

In a clinical setting, differences in the case definition of periodontitis used to identify disease and its severity may not have a huge impact on the actual clinical management. This is because treatment provided is based on the clinical manifestation of the disease signs and symptoms, and patient-centred risk assessment and treatment needs. However, in clinical research investigating the effectiveness of various interventions (non-surgical periodontal treatment and surgical periodontal treatment), it is necessary that the case definitions be clearly defined and standardised. Hence, a strategic case definition was proposed by CDC-AAP towards standardised measurement and

surveillance of disease extent and severity in population-based studies [56]. However, it lacked the definition of mild periodontitis. Thus, an updated version (Table 2.2) of case definition for diagnosis and surveillance of periodontitis was introduced in 2012 by CDC-AAP [60].

Table 2.2 Case Definition Proposed for Population-Based Surveillances of Periodontitis

Case	Definition
No periodontitis	No evidence of mild, moderate or severe periodontitis
Mild periodontitis	⩾ 2 interproximal sites with CAL ⩾ 3 mm, and ⩾ 2 interproximal sites with PPD ⩾4 mm (not on same tooth) or one site with PPD ⩾5 mm
Moderate periodontitis	⩾ 2 interproximal sites with CAL ⩾ 4 mm, and ⩾ 2 interproximal sites with PPD ⩾4 mm (not on same tooth) or one site with PPD ⩾5 mm
Severe periodontitis	⩾2 interproximal sites with CAL ⩾6 mm (not on same tooth) and ⩾1 interproximal site with PPD ⩾5 mm

2.1.5 Aetiology and Pathogenesis of Periodontitis

Periodontitis is caused by pathogenic microorganisms residing in the dental plaque biofilm [61]. The pathogenesis of periodontitis is caused by the host response to the bacterial insult [35] that induces cytokines and chemokines production in the gingival epithelium, which results in adhesion molecules expression, increase in capillary permeability and transport of PMNs to the gingival sulcus from the junctional epithelium [62]. Continuum of this process leads to the extension of inflammation into the connective

tissues. This ultimately results in loss of connective tissue support, loss of alveolar bone and the development of a periodontal pocket. Maintenance of oral hygiene could reverse this process, preventing progression of gingivitis to periodontitis.

Loe et al. [61] studied the effect of easing tooth brushing and oral hygiene on gingival inflammation. Participants were examined at regular intervals for gingival inflammation and oral hygiene, using a gingival index and a plaque index respectively. They found that ceasing oral hygiene leads to increased dental plaque accumulation and marginal gingivitis [61]. The time required for gingivitis to appear clinically was 10 to 12 days. The onset of gingivitis was associated with changes in the microbial flora. When oral hygiene maintenance was reinstated, the signs and symptoms of gingivitis were reversed and the gingiva was healthy [61]. It was concluded that dental plaque biofilm is the aetiological factor in gingivitis and periodontal disease and that host hygiene behaviour is the factor in the progression of gingivitis [61].

2.1.6 Microbiology of Periodontitis

The human body is composed of 10^{14} cells [63, 64]. Approximately 90% of these cells are microorganisms found on the environmentally exposed surfaces of the body [64]. In humans, all environmentally exposed surfaces have different characteristic patterns of microbial colonisation. The microflora of the skin, mouth, digestive and reproductive tracts are distinct, based on the biological and physical properties of each site [63]. The mouth has a distinct environment and ecology suitable for the interplay between dental plaque biofilm and host immune response [65, 66].

Dental plaque biofilm is a complex and diverse environment, with more than 700 different microbial species living in a community which maintains its nutrition from the extracellular matrix [67]. Macromolecules of the extracellular matrix, including exopolysaccharides and protein, hold the microbial biofilm intact [68]. Factors including

age, natural acquisition, smoking, immuno-competence, stress, geographic location, use of antibiotics, and supra-gingival plaque levels contribute to the variation in composition of dental plaque biofilm [69]. Additional factors, including plaque retentive factors, microbial factors and physical factors (e.g. mechanical stress from the action of the tongue or cheeks against the tooth surface) influence dental plaque accumulation and build-up [70].

The microbial communities that cause periodontitis are diverse and complex and constitute up to 500 different bacterial species residing in a biofilm [71]. Dental plaque occurs either on exposed surfaces, such as supragingival plaque, or on subgingival plaque. Dental plaque is found in three areas: (i) on the tooth surface; (ii) in pocket gaps; and (iii) on the soft walls of the pocket [72]. Diagrammatically, these microbial species can be designated into colour zones (Figure 2.1) There are five clusters of identified microbial species designated by colour (red, yellow, green, purple and orange) [73]. The species of orange and red clusters are mostly isolated from deep pockets. In contrast, species of yellow, green and purple clusters are isolated from the healthy sites (Figure 1). Of all these microorganisms, gram negative anaerobic bacteria are the most common bacteria found in subgingival dental plaque. Gram negative anaerobic bacteria are virulent organisms, and include *Porphyromonas gingivalis*, *Provetella intermedia*, *Tannerella forsythia* and *Actinobacillus actinomycetemcomitans* [74].

Porphyromonas gingivalis (a gram negative anaerobe) is a key bacterial species that damages periodontal tissues, leading to periodontitis [75]. It produces virulence factors and extracellular proteases, including fimbria, lipopolysaccharide and gingipain, that result in destruction of periodontal tissues [76]. Other bacteria that are significantly associated with periodontitis are *Treponema denticola*, *Tannerella forsythia* and *Fusobacterium nucleatum*. Oral infection models of these species have suggested that polymicrobial infection enhances virulence of the microorganisms, inducing acceleration

and aggravation of alveolar bone loss, as compared to that caused by one bacterium alone [77].

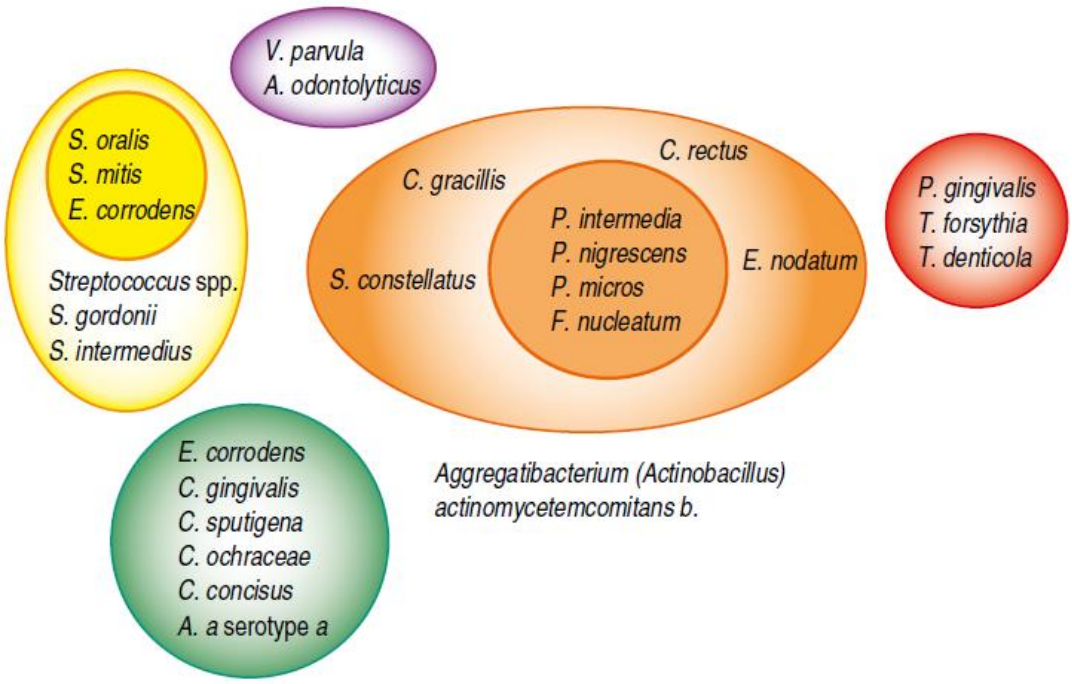

Figure 2.1 Five clusters of oral microbial species [73, 78].

2.1.7 Risk Factors for Periodontitis

Periodontitis has various risk factors that include non-modifiable risk factors and modifiable factors. These are elucidated in the following paragraphs.

i. Non-modifiable Risk Factors

The non-modifiable risk factors for periodontitis include age, gender and ethnicity. These factors are further discussed in a later section (2.3) of the literature review.

ii. Modifiable factors

a. Smoking

Smoking is a health risk behaviour significantly associated with increased risk of cardiovascular diseases, lung diseases and oral diseases, including periodontitis, tooth

decay and oral cancers. People who smoke have high incidence and prevalence of periodontitis and increased alveolar bone loss [21, 79, 80]. Epidemiological studies have found that smoking is associated with periodontitis [81]. The third edition of the US-based National Health and Nutrition Examination Survey (NHANES) reported that people who are current smokers had 41.9% attributable risk of periodontitis, as compared to former smokers who had 10.9% attributable risk of periodontitis [81]. The Australian NSAOH (2004-06) survey suggested that almost 700,000 cases of moderate to severe periodontitis are attributed to smoking [82]. Despite the fact that many smokers have inferior levels of oral hygiene, the relationship between smoking and periodontitis has been found to be independent of plaque exposure [83].

Smoking has the potential to affect the host response at the cellular, vascular and tissue repair level, including alteration in neutrophil function, antibody production, fibroblast activities, vascular factors and inflammatory mediator production [84]. Neutrophils are the body's primary defence against periodontal pathogens [85]. The periodontal manifestations of genetic neutrophil defects have been well characterised [86]. Smoking is associated with altering neutrophil function [87]. Nicotine from cigarette smoking produces vascular changes that interfere with tissue metabolism and leads to a vasoconstrictive response. This is followed by a decrease in gingival blood flow and impaired healing ability of periodontal tissues [88].

b. Type 2 Diabetes

Type 2 diabetes is a highly prevalent public health problem that is estimated to affect 451 million people worldwide and is projected to affect more than 693 million people within the next 20 years [89]. In Australia, the prevalence of periodontitis based on the CDC-AAP case definition was 26.7% compared to 23.9% in non-diabetics. Dental plaque accumulation was the strongest factor associated with type 2 diabetes

[90]. The two-way relationship between type 2 diabetes and periodontitis has been recognised for a long time [91-94]. For people with diabetes the risk of periodontitis is three times higher risk than for non-diabetics [95]. Thorstensson et al. [96] found that people with type 2 diabetes had fewer teeth, more plaque, deeper PPD and a higher degree of bone loss than people who were non-diabetic. It was apparent that the level of glycemic control was the risk indicator for periodontitis among the type 2 diabetics [96]. Katagiri et al. [97] found that, even in type 2 diabetes patients without periodontal therapy, a reduction in BOP was observed by improving glycaemic control.

Systemic inflammation is a result of the crossing of periodontal bacteria and their virulence factors into the micro-circulation [98]. This leads to elevated levels of serum C-reactive protein, other acute-phase reactants, and biomarkers of oxidative stress [98]. Biologically plausible evidence suggest that non-resolving chronic inflammation derived from periodontal disease impacts on diabetes control [elevated glycosylated haemoglobin - HbA1C] [98] by impacting on HbAlc levels, beta-cell function and insulin resistance [98].In the reverse direction, there is a growing body of evidence that suggests that periodontitis has a negative effect on glycaemic control in people with type 2 diabetes [99]. A recent systematic review has suggested that non-surgical periodontal therapy reduces HbA1c by 0.5% after three months [100]. Winning et al. [101] conducted a prospective study with bi-annual follow-up. It was found that people with untreated moderate to severe periodontitis had a 69% increased risk of developing type 2 diabetes [101]. A recent 12-month follow-up randomised controlled trial indicated that people who underwent intensive periodontal therapy (non-surgical periodontal therapy and surgical periodontal therapy) experienced reduced HbA1c levels in type 2 diabetes patients with moderate to severe periodontitis. These outcomes suggest that routine oral health checks and management of periodontitis could be an effective method to prevent and manage type 2 diabetes [102].

2.2 Obesity

Obesity is a priority public health issue due to its adverse effects on health and quality of life [103]. The following section provides an outline and definition of obesity, and discusses the prevalence, risk factors and the association between obesity and various chronic diseases.

2.2.1 Definition of Obesity

Obesity is a state of abnormal or excessive fat accumulation that may impair health [104]. Obesity increases the risk of chronic diseases, including cardiovascular diseases, type 2 diabetes and stroke [103]. It is the second highest contributor towards the burden of disease in Australia and a growing public health issue [103].

2.2.2 Measurement of obesity

Obesity is measured using body composition tools of Body Mass Index (BMI) or Quetelet index, waist circumference (WC), hip circumference (HC), waist-hip ratio (WHR) and waist to height ratio (WHtR) [105, 106].

i. BMI

Overweight and obesity are defined using the cut-off points of BMI, where a BMI equal to or greater than 25 kg/m^2 is classified as overweight and a BMI equal to or greater than 30 kg/m^2 is classified as obese [107]. BMI is calculated by dividing the body weight in kilograms (kg) by the body height in squared metres (m^2).

$$\text{BMI} = \text{Body weight (kg)} / \text{Height}^2 \text{ (m}^2\text{)}$$

BMI is the most commonly used measure to determine the weight status of an individual [108]. The World Health Organization (WHO) categorises BMI into two main classes: International and Asian. Table 2.3 shows the International and Asian classification of BMI into four subcategories (underweight, normal weight, overweight,

and obesity) [107, 109]. The International classification BMI cut-off point for obesity is 30 kg/m^2 [110]. However, this cut-off point is not applied to Asian populations. The explanation for this is that Asians are typically smaller in stature compared with their international counterparts [111]. Asians are also at higher risk of cardiovascular disease at a BMI score of less than 30 kg/m^2 [111]. Thus, the recommended cut-off point of BMI for obesity amongst Asians is 27.5 kg/m^2 [112].

Table 2.3. WHO Classification for BMI [107, 109]

	BMI (kg/m^2)	
Classification	International	Asian
Underweight	<18.50	<18.50
Normal range	18.50 - 24.99	18.50 - 22.99
Overweight	≥25.00	≥23.00
Pre-obese	25.00 - 29.99	23.00 - 27.49
Obese	≥30.00	≥27.50
Obese class I	30.00 - 34.99	27.50-34.99
Obese class II	35.00 - 39.99	35.00 – 39.99
Obese class III	≥40.00	≥40.00

The BMI is a basic screening tool, with several strengths, that include its cost-effectiveness, ease of use and non-invasiveness [113]. BMI measurement does not require specialised equipment and presents no potential hazard [113]. A study on specificity and sensitivity of BMI in capturing obesity and its associated risk for metabolic syndrome reported 100% specificity and 50% sensitivity of BMI [114]. Accurate measurement of BMI

requires precise measurement of body height to the nearest centimetre and body weight in kilograms [114].

BMI has certain limitations as a measure. It is unable to distinguish between free fat mass and lean body mass [115]. In addition, it cannot discriminate between gender-specific differences in adiposity due to varying health risks in gender and ethnic groups at lower BMI thresholds [116]. The follow-up of people from the 1989 Framingham Heart Study until 2004 reported that WC and WHR are more rigorous predictive indicators of congestive heart disease, cardiovascular disease risk and mortality than BMI [117].

ii. Waist Circumference (WC)

The International Diabetic Federation (IDF) recommends WC as a diagnostic risk indicator for abdominal obesity, cardiovascular diseases and metabolic syndrome [118]. The WHO consultation recommended International WC cut-off point for obesity as 102 cm in men and 88 cm in women [119]. Similar to BMI, ethnic-specific differences have been observed with WC measurements. This is due to differences in total mass, composition of skeletal muscles, subcutaneous and intra-abdominal adipose tissues and bone density in different ethnic groups [120]. Table 2.4 illustrates the WHO recommendations for WC cut-off points for overweight and obesity. Studies have reported that there is an increased health risk in Asian societies at WC levels below the international recommended WC cut-off points [121-123]. Hence, the WC cut-off point for obesity in Asian populations should be 90 cm for men and 80 cm for women [124].

Table 2.4. Recommendations of waist circumference cut-off points made for overweight or obesity, and association with disease risk. Source: Adapted from Zimmet and Alberti (2006)

Ethnic origin	Waist circumference (cm)	
	Men (cm)	Women (cm)
International	>102	>88
Europid	>94	>80
South Asian	>90	>80
Chinese	>90	>80
Japanese	>90	>80

One of the major strengths of WC is its ability to predict obesity-related health risks more reliably than BMI [125]. The plausibility of WC being a preferable measure instead of BMI is because the abdominal cavity is a harbinger of high metabolic and inflammatory activity in comparison to the subcutaneous regions like the gluteal-femoral region [126]. WC is also a better predictor of cardiovascular and metabolic health risk than BMI, as it measures abdominal fat distribution [12, 127]. Thus, it is recommended that WC should be measured as an adjunct to BMI when assessing obesity-related health risks [128].

Additional strengths of WC include ease of use, reliability and cost-effectiveness. It is an efficient tool to differentiate between gender and ethnic-specific health risks in a population-wide perspective through its developed cut-off points for International and Asian populations amongst males and females [124].

iii. Waist-to-Hip Ratio

Waist-to-hip ratio (WHR) is a measure of the abdominal fat distribution [129]. A multi-centred study conducted across 52 countries has suggested that WHR is a more appropriate tool for prediction of risk of health conditions [127] including periodontitis [130, 131]. The strengths of the WHR measurement are similar to that of BMI and WC in terms of ease of use, sensitivity and cost-effectiveness. WHR is less dependent on body height

and body size than WC. WHR ⩾1.00 in men and WHR ⩾0.85 in women is classified as obesity [132].

iv. Waist to Height Ratio (WHtR)

A systematic review of 78 studies of adults and children reported WHtR as a better predictor of cardio-metabolic outcomes than WC and BMI [133]. A meta-analysis of 10 studies reported that WHtR (an abdominal obesity measure) is a better discriminator of risk of cardiovascular disease, diabetes, hypertension and dyslipidaemia than BMI [134].

WHtR is a universally acceptable and widely applicable tool across all countries towards assessment of obesity and its associated health risks [135]. The application of WHtR, as an adjunct measure for central obesity and shape can be used in population-based surveillances and public health practice amongst adults, children and all ethnic groups, with a recommended cut-off point of 0.5 [136]. WHtR below this value is recommended to reduce the risk of cardiovascular diseases [136].

2.3 Underestimation of Bodyweight: Evidence, Reasons and Challenges towards Better Health

Obesity is a widespread societal issue. It often goes unnoticed and undetected, based on how a person perceives their weight status, or how an individual regards their body weight and size. Studies have suggested a significant difference in self-reported weight status and the measured weight status based on BMI [137-139]. Underestimation of weight status tends to be more common in individuals who are overweight (BMI of 25-29.9) than with individuals of normal weight (BMI of 18.5-24.9) [137-139]. The inability of overweight individuals to recognise themselves as “overweight” is of concern because it may adversely influence healthy behaviours, such as exercise, diet and weight management [140]. Underestimation of body weight may also increase the risk of chronic diseases, including type 2 diabetes, cardiovascular diseases and metabolic syndrome [140].

A study of a representative samples in Spain from 1987 to 2006/2007 confirmed a rising trend of overweight and obesity, accompanied by an increase in the percentage of women who were overweight failing to recognise their body weight was a higher than normal body weight. Overall, 34% of overweight men and 20% of overweight women in the Spanish study perceived themselves as being normal weight when their actual body weight was overweight [139]. Similarly, the US-based NHANES 2003-2008 survey of more than 16,000 participants reported that 48% of men and 23% of women tended to underestimate their body weight [141].

The underestimation of self-reported weight status among obese people is driven by social determinants, such as education level [142], gender [137] and ethnicity [143]. A high education level was found to be associated with knowledge about current guidelines of overweight and obesity, which lead to a more accurate interpretation of body weight and greater percipience and motivation towards weight control [142].

Gender-specific differences have also been reported in studies on the underestimation of self-reported body weight. Men tend to underestimate their body weight more than women. In women, increased mis-reporting of body weight may be due to societal pressures, advertisements, mass media, and cultural norms [137]. A study comparing body image and weight control in young adults from 22 countries reported that people of Asian background had higher perceptions of being overweight and more frequent attempts to lose weight than people of Mediterranean background, suggesting that local cultural attitudes may moderate the individual's attitude towards their weight [143].

Perceived weight status, rather than measured weight status, may be an important determinant of motivation to lose weight. In the US-based NHANES 2003-2008 study, individuals who perceived themselves to be overweight and were overweight based on a

health care professional assessment were more likely to make dietary changes, be physically active or both [141]. Health care professionals (HCPs) may increase the motivation of a patient by correcting a mistaken perception of their weight and by providing supportive counselling [141].

2.2.4 Epidemiology of Obesity

Epidemiology is the study of the distribution and determinants of health-related states or events (including disease) and its application to the control of diseases and other health problems [144]. Epidemiology forms the cornerstone of public health and shapes policy decisions and evidence-based practice by identifying risk factors for disease and targets for preventive healthcare. The current epidemiological distribution of obesity worldwide is presented below.

i. Worldwide

Obesity is a global epidemic. In 2016, more than 1.9 billion adults aged 18 years and older were overweight and over 650 million adults were obese [145]. Obesity is associated with higher mortality than being underweight/malnourished. Global prevalence of obesity outstrips that of underweight/malnourished in all areas of the world, with the exception of sub-Saharan Africa and Asia. The overall prevalence of overweight and obese adults worldwide is 13% and 39% respectively, with more women being obese or overweight than men. The incidence of overweight or obesity was reported to be 340 million in children and adolescents aged 5-19 [145].

In the US, English and German adult populations, the prevalence of obesity was reported to be 36%, 25.6% and 23% respectively [146-148]. Obesity has not been limited to high-income nations; it also affects people in middle/low-income countries. Table 2.5 summarises the global and regional distribution of obesity. Figure 2.2 illustrates the trends of obesity in various countries around the world (2015 or nearest years) [149].

Table 2.5 Global and Regional – Overall and gender-specific prevalence of obesity [150]

			BMI >= 30 (age-standardised estimate)	BMI >= 30 (age-standardised estimate)	BMI >= 30 (age-standardised estimate)
WHO region	Year		Both sexes	Female	Male
Africa	2014		10.4 [9.2-11.5]	15.2 [13.3-17.3]	5.5 [4.3-6.8]
	2010		9.0 [8.1-9.8]	13.3 [12-14.7]	4.6 [3.8-5.5]
Americas	2014		26.8 [24.5-29.2]	29.6 [26.4-33]	24.0 [20.9-27.2]
	2010		24.6 [23-26.2]	27.4 [25.2-29.8]	21.7 [19.5-23.9]
South-East Asia	2014		5.0 [3.9-6.1]	6.8 [5.1-9.1]	3.2 [2.1-4.7]
	2010		4.0 [3.3-4.7]	5.6 [4.5-7]	2.5 [1.8-3.3]
Europe	2014		23.0 [20.7-25.2]	24.5 [21.5-27.7]	21.5 [18.7-24.3]
	2010		21.2 [19.6-22.7]	23.0 [20.7-25.2]	19.3 [17.3-21.3]
Eastern Mediterranean	2014		19.0 [17-21]	23.6 [20.4-26.9]	14.6 [12-17.5]
	2010		17.1 [15.6-18.5]	21.6 [19.4-24]	12.8 [11-14.7]
Western Pacific	2014		6.9 [4.9-8.7]	7.9 [5.4-11.2]	5.9 [3.7-8.6]
	2010		5.4 [4.2-6.4]	6.3 [4.7-8.3]	4.4 [3.2-6]
Global	2014		12.9 [12-13.9]	15.2 [13.8-16.8]	10.7 [9.4-12]
	2010		11.5 [10.8-12.1]	13.7 [12.7-14.7]	9.3 [8.5-10.2]

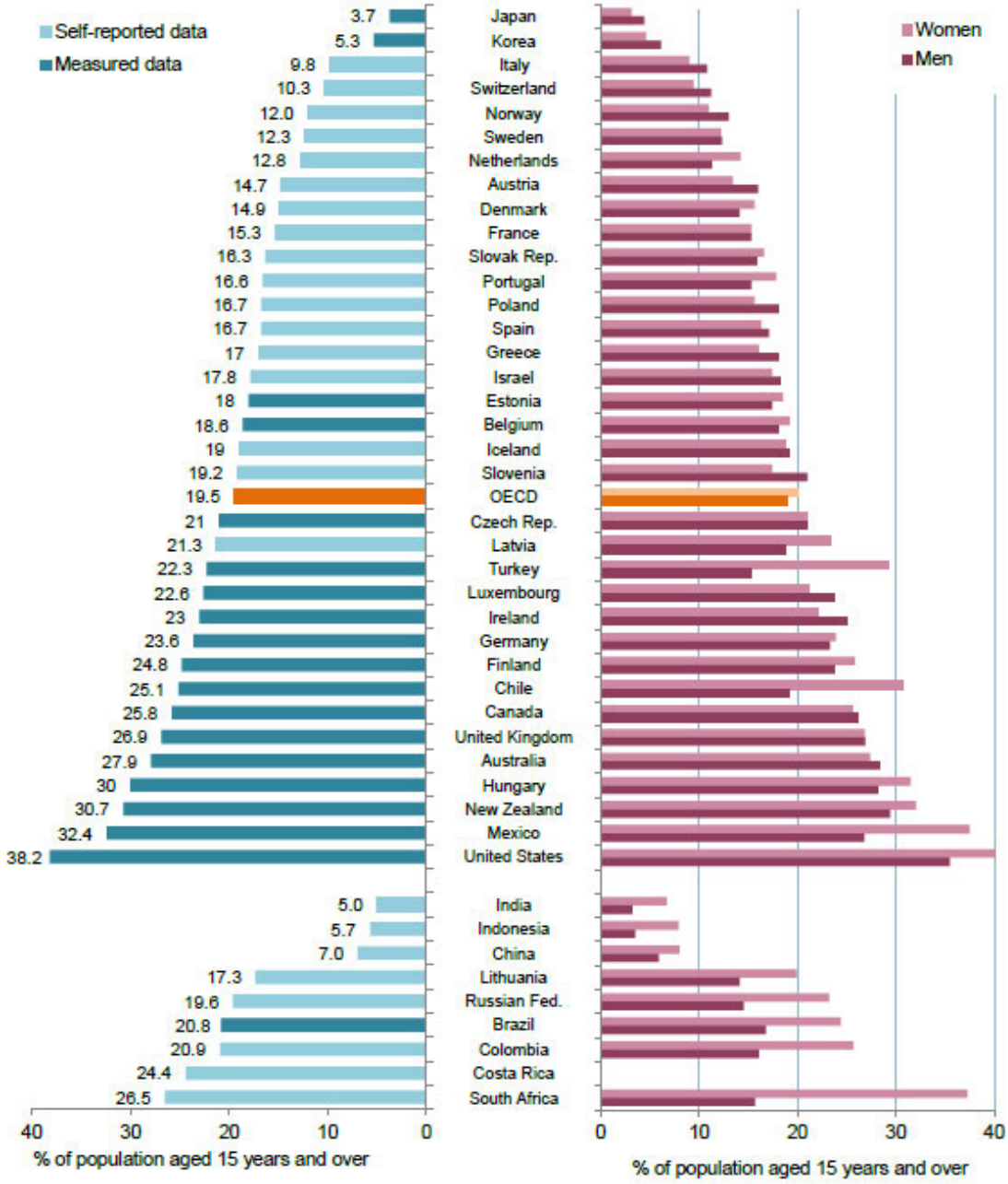

Figure 2.2 Obesity among adults, 2015 or nearest year [149].

ii. Asia Pacific Region. Obesity Rise, Predisposing/Modifying Factors and Prevalence.

The Asia Pacific countries include the countries of Southeast Asia, South Asia, East Asia, and Oceania. The burden of overweight and obesity has been significantly lower in Asia Pacific nations than the rest of the world. However, it has been on the rise at an alarming rate in recent years. Figure 2.3 shows the prevalence of obesity across Asia Pacific countries according to the WHO Global Health Observatory (2014) [151]. The trend of obesity was noted to be higher in Middle Eastern nations as compared to the far Asia Pacific. Malaysia (14%) has the highest prevalence of obesity, followed by Thailand (8.8%) in Southeast Asian nations. These figures were lower than in Oceanic countries, where 27% of people in Australia and 28.3% of people in New Zealand experienced obesity (Figure 2.4) [152].

The driving factors for the rising trend of overweight and obesity in Asia Pacific nations are the economic boom and socio-cultural factors. The Asia Pacific is transforming rapidly with increased industrialisation and Westernisation. Increased access to and availability of complex carbohydrates and refined food products, overconsumption of dietary sugar, sedentary behaviour, physical inactivity, ethnic cultural shift and lack of health education programmes are all factors that contribute to the escalation of obesity in Asia Pacific nations [132]. Consequently, there has also been a rise in the risk of chronic conditions, including type 2 diabetes and cardiovascular diseases [153, 154].

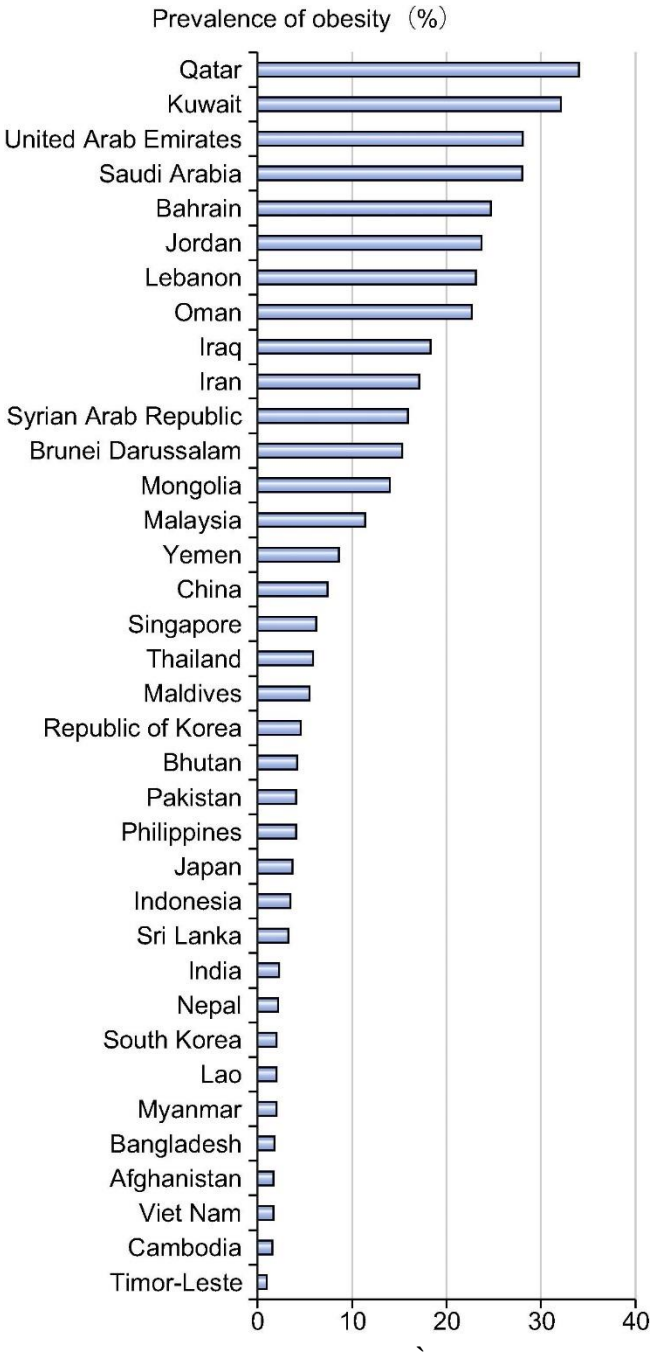

Figure 2.3 Prevalence of obesity across Asian countries according to the WHO Global Health Observatory in 2014 [151].

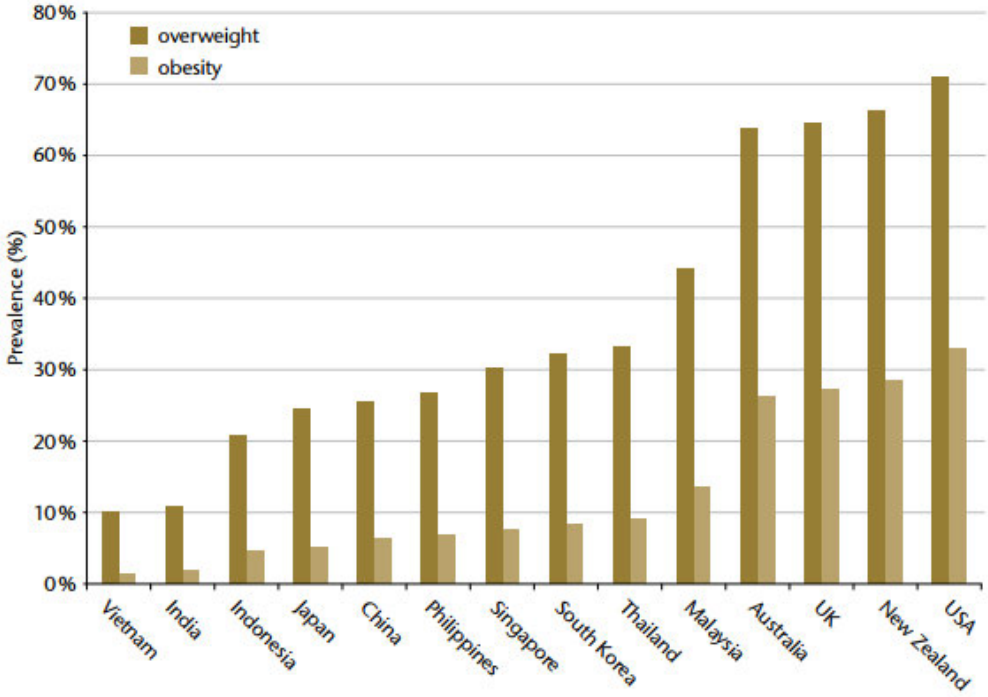

Figure 2.4 Prevalence rates of overweight and obesity in Asia Pacific countries compared to non-Asia pacific nations of Australia, UK, New Zealand and USA [152].

iii. Australia

Two out of three (63%) Australian adults are either overweight or obese [3]. The prevalence of overweight or obesity has been rising constantly; i.e., from 56.3% in 1995 to 63% in 2014-15, with a 50% rise in obesity (18.7% versus 28%) during the same period [3]. The prevalence of obesity in males is higher than in females (69.7% versus 55.7%) [3]. Diet is the leading risk factor for chronic diseases, followed by obesity. Obesity is associated with high risk for cardiovascular diseases, type 2 diabetes, arthritis, and cancer. It poses a significant burden on the Australian healthcare system [155]. It is projected that the direct and indirect costs of obesity will rise up to 87.7 billion AUD over the next decade [3].

One quarter of Australian children are overweight and obese [3]. The Australian birth cohort analysis (1990-1993) reported that the prevalence of overweight and obesity increased significantly from 19.9% at age 2-5 years to 28% at age 14-17 years [3].

Aboriginal and Torres Strait Islanders (28%) had higher prevalence of obesity than non-Indigenous people (16%). Rurality was associated with increased prevalence of overweight and obesity. Individuals living in rural and remote areas had a higher prevalence of overweight and obesity as compared to urban and sub-urban regions (72.8% versus 61.6%) [3].

2.2.5 Risk Factors for Obesity

Obesity is a result of genetics and environmental influences. Adoption of a Westernised lifestyle, industrialisation, economic growth, physical inactivity, social disparities, high-caloric low-energy food, and stress are the major contributors to obesity [156]. Genetics and environmental predispositions are discussed below.

i. Genetics.

The concept of inheritance of obesity was discovered in the early 1920s by Davenport. In his study, entitled "Body Build and Inheritance", it was suggested that there are at least two or more genetic factors involved in the development of body build [157]. In 1994, the discovery of the ob *gene* and the leptin receptor *gene* improved the knowledge and understanding of the genetic component of obesity [158]. Studies on twins have suggested that genetics could be responsible for 50-80% of variation in BMI [159]. Research has identified more than 50 genetic *loci* involved in the regulation of body mass and the development of obesity including the *leptin receptor gene* (*LEP gene*) and the melanocortin 4 receptor *gene* [160]. Genetic variation contributes to two main types of obesity: monogenic obesity and polygenic obesity [161, 162].

Monogenic obesity is a single *gene* polymorphism that accounts for about 5% of obesity cases. This genetic polymorphism variation affects appetite regulation and satiety. About 11 *genes* have been discovered to be associated with this type of obesity. Among these *genes,* the *LEP, leptin receptor gene (LEPR), pro-opiomelanocortin (POMC),*

melanocortin 4 receptor (MC4R) and proprotein convertase subtilisin/kexin-type 1 (PCSK1) genes were the most important indicators of severe obesity among children [161].

Polygenic obesity is an obesity *gene* variation seen with simultaneous presence of DNA variations in multiple *genes*. There are two main strategic approaches used to identify polygenic variance in obesity: candidate *gene* studies and Genome-Wide Association Studies (GWAS) [162]. The candidate obesity *gene* approach has found a strong association between obesity and several genetic variants [162].

ii. Environmental Factors.

Environmental factors are the driving influences on behaviour and physiological state. Physical inactivity is an important environmental factor that contributes towards energy expenditure and it is found to play a major role in the development of overweight and obesity [163]. Physical inactivity increases the risk of an individual having a fatal cardiovascular accident by 1.5 to 2 times [164]. It is associated with increased risk of obesity, cardiovascular diseases, type 2 diabetes and mortality [165]. Sedentary behaviours (e.g. time spent watching television) are a significant contributor to cardio-metabolic disorders [166].

Snacking habits, diets rich in refined carbohydrates, increased portion size, and dining out have been found to modulate different levels of overweight and obesity respectively [167]. Dietary habits along with a modern lifestyle, such as a contemporary transport system and new informative technology, may increase the occurrence of obesity [168]. Diet and its influence on obesity are discussed in greater detail in the later section (Section 2.3).

2.2.6 Obesity-related Diseases

Obesity is a metabolic risk factor for various non-communicable diseases, including type 2 diabetes, cardiovascular disease, hypertension, Alzheimer's disease, osteoarthritis, chronic asthma, and periodontal disease [169-172].

i. Type 2 diabetes

Type 2 diabetes is a progressive condition in which the body becomes resistant to insulin and/or gradually loses the capacity to produce sufficient insulin in the pancreas [173]. Such a deficiency results in increased concentrations of glucose in the blood, which in turn damage many of the body's systems, in particular the blood vessels and nerves, resulting in serious complications and reduced life expectancy of 8-10 years [174]. Beta-cell damage reduces insulin resistance, resulting in alteration in glucose transportation into the liver, muscle cells, and fat cells, marked by an increase in the breakdown of fat with resultant hyperglycaemia [175]. As a consequence of beta-cell dysfunction, there is a rise in glucagon and hepatic glucose levels, leading towards a greater hyperglycaemia as a result of insulin insufficiency [173].

The liver is a regulator of glucose metabolism, where insulin functions as an inhibitor of gluconeogenesis and glycogen breakdown. Insulin induces GLUT-4 (a glucose transport protein) increasing the cellular glucose uptake and its metabolism to Adenosine tri phosphate (ATP) or glycogen [176]. Adipose tissues regulate lipogenesis by conversion of glucose into glycerol-3-phosphate, which is synthesised with non-steroidal fatty acids (NEFA) to triglycerides.

The global prevalence of type 2 diabetes has quadrupled since the 1980s, with an increasing prevalence in lower and middle-income countries [177]. Type 2 diabetes is the most common form of diabetes, contributing 90% of all diabetes cases worldwide. The global estimate of type 2 diabetes is approximately 422 million adults, with an annual

mortality of 1.5 million, a number that is expected to double by 2025 [174]. In 2016, type 2 diabetes was associated with more than 1 million hospitalisations in Australia [178]. The risk of type 2 diabetes is three times higher in Indigenous Australians than non-Indigenous Australians [179]. The aetiology of type 2 diabetes is complex; however, overweight/obesity and lack of physical activity are major drivers towards its occurrence [180]. The increase in the diabetes prevalence is a result of lifestyle factors, including an unhealthy diet, obesity, physical inactivity, sedentary behaviour, cigarette smoking and alcohol consumption [181, 182].

Obesity is an important risk factor for type 2 diabetes, contributing to 55% of cases [183]. The risk particularly increases with excess distribution of adipose tissue in the intra-abdominal region. Numerous studies have demonstrated a positive correlation between obesity and type 2 diabetes, where insulin resistance and inflammation increase the risk of hypertension, stroke and cardiovascular disease [183].

Glycaemic control is a major focus of the treatment of type 2 diabetes patients [184]. It works together with comprehensive cardiovascular risk factor control programmes, smoking cessation and the adoption of healthy lifestyle habits (physical activity and healthy diet), blood pressure control and lipid management [184]. Reducing hyperglycaemia decreases the onset and progression of microvascular complications [185]. Diabetes Australia stated that prevention and early management of type 2 diabetes is an important goal towards healthy living. Prevention includes promotion of lifestyle modifications that focus on increased physical activity, dietary change and weight loss, and the application of structured diabetes prevention program [186]. People with a high risk of type 2 diabetes and the severe form of obesity are advised to carry out bariatric surgery [186].

A pooled cross-sectional analysis of 900,000 individuals from seven Asian countries has suggested a strong association between increased body mass index and the

prevalence of type 2 diabetes [187]. Complementing these outcomes, a cohort study of nurses suggested that a 20-fold increase in type 2 diabetes is experienced in women with obesity, compared to women with BMI lower than 23 kg/m^2 [188]. A multi-centre study from China (2,800 individuals), Japan (6,300 individuals) and India (3,300 individuals) has suggested high age-adjusted prevalence of diabetes across BMI categories >30kg/m^2 in comparison to 15 kg/m^2 (a 2-fold higher risk in China and a 4-fold higher risk in Japan and India respectively) [189]. A clinical trial on the effects of dietary modification and exercise in type 2 diabetes patients suggested a reduced risk of type 2 diabetes with moderate changes in lifestyle, incorporation of healthy diet, physical activity and weight management [190].

ii. Cardiovascular Diseases

Cardiovascular diseases (CVDs) are disorders of the heart and its associated structures. CVDs includes coronary artery disease, rheumatic heart disease, cerebrovascular diseases and other conditions. Over 17 million people die from CVDs annually, which constitutes 31% of all deaths worldwide [191]. In 2014-15, one in five Australian adults (4.2 million adults) experienced a CVD. Of those, 0.5 million adults were either overweight or obese [192].

Obesity is a risk factor for CVD [154, 193] ; other associated factors are ageing, an unhealthy diet, a sedentary lifestyle, tobacco smoking and excessive alcohol use [154]. These factors contributed towards chronic fat accumulation in the visceral tissues, increases in inflammatory adipokines or cytokines, insulin resistance and, ultimately, CVD [193].

In addition to cardiovascular risk, obesity is also associated with promoting intermediate risk factors, such as dyslipidaemia, hypertension, glucose intolerance, inflammation and obstructive sleep apnoea [194]. The longitudinal Framingham Heart Study,

the Manitoba Study and the Harvard School of Public Health Nurses Study reported obese individuals were associated with a higher risk of CVD compared to non-obese individuals [13, 195, 196]. It is expected that the existing growth rate of obesity (7% annually in men and 10% annually in women by 2020) will lead to an increase in the proportion of CVD events (predicted to be 14% in 2035) [191].

iii. Cancer

After smoking, overweight/obesity is a second most avoidable risk factor for cancer [197]. The incidence of cancer increases with age, with 23% of all cancers occurring after the age of 65 [198]. Obesity is a risk factor for several types of cancer, including breast, colon, renal, uterine, gall bladder, prostate and pancreatic [198]. A meta-analysis evaluating the association between breast cancer and BMI among post-menopausal women suggested that women with a BMI >28 kg/m^2 have a higher risk for breast cancer than those with the recommended BMI [199].

2.2.6 Obesity and Healthcare Costs

Health problems associated with obesity have a substantial economic impact on Australian society [200]. The global economic impact of obesity is approximately 2.0 trillion USD per annum [201]. In Australia, the annual total direct cost and annual indirect cost associated with overweight and obesity in adults has been estimated at 21 billion AUD (6.5 billion AUD for overweight and 14.5 billion AUD for obesity) and 56.6 billion AUD respectively [202].

A systematic review of 34 studies comparing BMI and healthcare costs suggested that obesity (36%) was associated with significantly higher total annual healthcare costs than overweight (12%) due to increased risk of type 2 diabetes and CVD amongst people with obesity [200]. Factors contributing to the increased healthcare costs were medications (18% for overweight and 68% for obese), inpatient care (12% and 34%) and ambulatory

care (4% and 26%) [200]. Based on these outcomes, it could be deduced that obesity has a significant economic impact. Policy updates are required that may help to reduce this economic impact and its related social, biological, cultural and environmental outcomes.

2.2.7 Obesity, Physical Inactivity and Sedentary Behaviour

Physical activity and healthy eating are essential for maintaining a healthy weight and overall general health [165]. Physical activity is an important factor in the prevention and management of chronic disease, including type 2 diabetes and cardiovascular diseases [165]. There are various forms of physical activity, including playing tennis, bushwalking, going to the gym and swimming [165]. Moderate to vigorous physical activity is useful in the maintenance of health and it is recommended in physical activity guidelines [165].

Prolonged periods of physical inactivity are associated with high attributable risk of becoming overweight or obese, having cardiovascular disease, diabetes, and cancer [203]. The 45 and Up Study conducted in New South Wales, Australia, between 2006 and 2010, linked prospective questionnaire data of 222,497 individuals (45+ years) with their mortality data obtained from the New South Wales Registry of Births, Deaths, and Marriages [204]. All-cause mortality hazard ratios increased significantly with the increase in the total number of hours per day of sedentary behaviour [204]. People who spend 11 or more hours per day sitting had 1.40 times higher risk of all-cause mortality as compared to people who had a sedentary behaviour for 4 to 8 hours per day [204]. The study concluded that prolonged sitting was significantly associated with all-cause mortality, independent of physical activity. It was recommended that public health programmes should focus on reducing sitting time and increasing physical activity [204].

2.2.8 Obesity and Periodontitis

i. Animal Studies

The association between obesity and periodontitis was first reported by Perlstein et al. [8] in Zucker rats, who demonstrated histopathological changes such as hyperplasia and hypertrophic vascular changes of the periodontium.

This was supported by Amar et al. who found that *Porphyromonas gingivalis* infected obese mice developed a higher degree of alveolar bone loss than *Porphyromonas gingivalis* infected non-obese mice [205]. In addition, obesity was associated with a greater burden of inflammation and an increased host immune response [205]. The Cavangi et al. study reported similar results by showing that alveolar bone loss was associated with increased body weight [206]. Virto et al. [207] and Zuza et al. [208] evaluated the systemic effects of obesity and periodontitis in a validated experimental model of Wistar rats fed on high fat diet. They showed that rats fed on a high-fat diet had more severe periodontitis, increased PPD, lipid profile, adipocytokines and glucose levels.

ii. Human Studies

Epidemiological studies and randomised controlled trials based systematic reviews and meta-analyses have studied the association between obesity and periodontitis [5, 14]. Higher BMI, WC, subcutaneous body fat, and blood lipids are suggested risk factors for periodontitis compared to people with normal-weight [5, 14]. These results do advocate for a positive association between obesity and periodontitis; however, the causal relationship and the mediating factor in this association remains elusive [7, 209-213]. Furthermore, the studies utilised in these reviews had no information on how obesity interacts with periodontitis in Australia. Based on the outcome of these studies, it is reasonable to hypothesise that an obesity and periodontitis relationship would also exist in Australia due to the high burden of obesity and periodontitis, and their risk factors.

However, to date there is no published work on the relationship between obesity and periodontitis in the Australian population.

iii. Obesity, Periodontitis and Inflammation

Obesity and periodontitis are inflammatory conditions that may share a similar pathophysiological pathway [214, 215]. Adipose tissue secrete factors including TNF-α, interleukin-6 (IL-6), leptin, adiponectin, complement components, plasminogen activator inhibitor-1, proteins of the renin-angiotensin system, and resistin [216], which are often referred to as adipokines. These adipokines contribute to a pro-inflammatory state associated with obesity [9] and modulate the hormonal and metabolic changes that lead to abnormal host response and increased systemic inflammation [214, 217-219]. These adipokines also function in the regulation of blood pressure, angiogenesis, inflammation and the acute phase response, energy regulation and insulin sensitivity, and play a role in lipid metabolism [220].

TNF-α and IL-6 are cytokines/adipokines that are associated with inflammation in periodontitis, and are mainly released by monocytes and macrophages in the junctional epithelium circumscribed around the gingival sulcus [221]. They function in the destruction of alveolar bone in periodontal tissues [222] and trigger leucocytosis and the synthesis of highly sensitive C-reactive protein (HsCRP) and amyloid A [223]. TNF-α and IL-6 derived from adipose tissues are triggered by lipopolysaccharide (LPS). TNF-α and IL-6 interact with gram negative bacteria in periodontal tissues, promoting hepatic dyslipidaemia and decreasing insulin sensitivity, leading to increased risk of type 2 diabetes [130, 224]. A decrease in insulin sensitivity produces advanced glycation end-products (AGE), which promote the production of pro-inflammatory cytokines, such as leptin, TNF-α and IL-6, which act in the predisposition to periodontal inflammation [224, 225].

A study in non-diabetic obese individuals showed high circulating levels of TNF-α were found to be associated with periodontitis [225]. An *in-vivo* study, among obese mice

and non-obese mice infected with an oral or systemic induction of *Porphyromonas gingivalis* showed that the obese mice displayed higher immune responses (increased levels of TNF-α and IL-6) and alveolar bone resorption than the controls [205]. Dietary free fatty acids have also been proposed as the mechanism that links inflammation to obesity and periodontal infection, that in turn modulates production of advanced glycation end-products and insulin resistance. Insulin resistance may be caused by (1) apoptosis of the beta-cells of the pancreas, and (2) adipocytes producing cytokines like TNF-α, which interrupt insulin signalling, resulting in insulin resistance. Insulin resistance in turn contributes to the development of type 2 diabetes, which further deteriorates the hyper-inflammatory state resulting in abundant macrophage and cytokine production. Hence, type 2 diabetes induced inflammation may induce inflammation in periodontal tissues, resulting in periodontitis [225].

2.3 Putative Confounders

2.3.1 Social Determinants of Health

Social determinants of health are defined as conditions in which people are born, grow, live, work and age [226]. Social determinants are an important public health issue under advocacy in Australia [227] and a common risk factor for various chronic conditions; e.g., obesity, diabetes, CVD and rheumatoid arthritis [228-232]. The social determinants of health such as age, sex, education level, Indigenous identity, living in rural areas, access to oral health services and dental insurance are important risk factors for periodontitis [233].

2.3.2 Income

i. Income and Obesity

Pampel et al. evaluated data from 67 countries and examined the relationship between economic development, socio-economic status and obesity [234]. The study concluded that obesity rose with a nation's economic development; however, with socio-economic status the index of the people with obesity varied. Low-income countries were found to have obesity among high-income groups, while high-income countries had obesity among low-income groups [234]. It has been observed that high-income groups in low-income countries had an increased utilisation of energy dense food [234].

ii. Income and Periodontitis

The NSAOH 2004-06 reported that people in household income quartiles of less than AUD 20,000 per year had a significantly higher prevalence of periodontitis than those with an income greater than the AUD 80,000 income quartile (43% versus 15%) [26].

A study of 2,248 people aged 45-54 years among the randomly sampled population from the metropolitan areas of Adelaide, South Australia, reported a significant increase in the prevalence, severity and extent of periodontitis in people with

incomes of less than AUD 80,000 per year than in people with incomes over AUD 80,000 annually [235]. Income is associated with behaviours that are significantly associated with periodontal disease, including dental visiting behaviour, utilisation of health services, health-related behaviours and smoking [236, 237].

2.3.3 Education

i. Education and Obesity

Education is associated with chronic conditions such as obesity, diabetes, dementia, cardiovascular disease and chronic renal disease. Having a lower education level is a key factor associated with income, socio-economic status and an overall poor social gradient [103]. Education improves health literacy and the understanding of the health consequences of a person's lifestyle [238].

Education is associated with obesity in the Australian population [238]. A social gradient exists between obesity and education, where people with low education levels (year 11 or lower) were more frequently overweight or obese (69%) than people with education levels higher than year 12 or equivalent (54%) [3, 238]. Likewise, people who had Certificate I to IV level of education were likely to be more overweight or obese than people with a, diploma, degree or higher education. This has been consistently supported by various reports published between from 2007-08 to 2018 by the Australian Bureau of Statistics [3, 238].

ii. Education and Periodontal Disease

The NSAOH 2004-06 reports that people with better education levels had less periodontitis than people with lower education levels [237]. This finding was supported by a report by Brennan et al. amongst people aged 45-54 years living in metropolitan areas of Adelaide, South Australia [237, 239]. The study reported that people with a diploma or

degree had a lower risk of periodontitis and dental caries than people with a lower education level (primary, secondary or certificate) [235, 239].

2.3.4 Dental Visiting Behaviour

Access to dental care is an integral part of a dental health care system that works on providing high quality and equitable oral healthcare. According to the National Oral Health Promotion Clearinghouse report, every individual has different oral health needs and risk levels which should be reflected in the frequency of dental assessment. Hence, it is advised that patients talk to their oral health professional about their risk level and how frequently they need to visit for a dental check [240].

Inequalities in oral health have been found to be associated with delayed dental attendance [235, 241], which is subsequently associated with periodontitis [242] and dental caries [243]. A New Zealand birth cohort study on dental visiting trajectory patterns amongst people of 18 to 32 years found that low socio-economic status and dental anxiety were strong predictors of poor dental visiting behaviour [244]. Similar findings were reported in studies from Turkey and Hong Kong, where low socio-economic status and dental anxiety were significantly related to poor dental visiting behaviour [245, 246].

Other factors that were significantly associated with delayed or poor dental visiting behaviour included cost of care, lack of transport, increased waiting time and having a medical disability, as reported by studies in United Kingdom, Jordan and Saudi Arabia.[247, 248].

Social inequality, followed by dental anxiety, is the major driver in delayed dental visits. It is advised that healthcare systems should work towards reducing inequalities in oral healthcare in relation to social determinants of health. Therefore, it is necessary to

desensitise people in early childhood to dental settings and encourage them to maintain good oral hygiene with regular dental attendance [244].

Figure 2.7 illustrates the factors influencing dental visiting behaviour developed by the author of the dissertation. It illustrates that poor dental visiting behaviour is associated with poor oral health outcomes. It also shows that dental anxiety, cost of treatment, having no insurance and social demographic factors (young adults, females, lower education level, marital status) are important determinants of poor dental visiting trajectory.

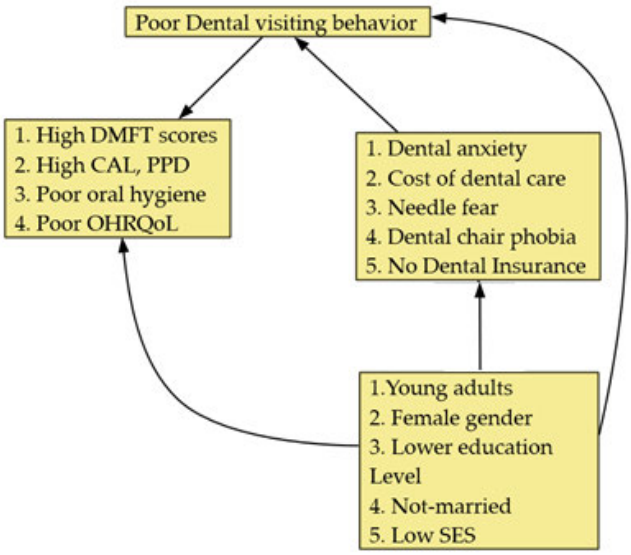

Figure 2.7 Factors influencing dental visiting behaviour

i. Dental Visiting Behaviour in Australia

The Australian Dental Association (ADA) recommends that an adult should see a dentist at least once every six months [249]. This is in line with the American Dental Association guideline and focuses on reducing the burden of dental conditions and on the maintenance of oral hygiene [249]. In Australia, two-thirds of dentate adults report that they have visited a dentist in the last 12 months; over 80% of adults report that they have visited their dentist in the last two years [249]. Based on the Australian system of private

dental care, cost of treatment is the main reported barrier to determine the individual's dental visiting pattern [249].

Private health insurance is critical for addressing inequality in dental visiting behaviour. Having private dental insurance has been associated with higher levels of dental visiting and visiting for a check-up [244]. A systematic review of dental insurance and dental services use in Australia reported a positive association between dental insurance and dental visiting [250]. However, private health insurance is expensive and not all people can afford it. Therefore, a universal Medicare-based dental insurance is required to improve the dental visiting behaviour and dental health of Australian adults.

2.3.5 Age

i. Age and Obesity

Age is an independent, non-modifiable risk factor for obesity [251]. The improved healthcare system, better access to health care, healthier food choices, reduction in smoking rates, clean water supply and sanitation have resulted in significant improvements in health and survival of the human population [252]. However, with a greater degree of survival, the world encounters threats to the economy from chronic diseases associated with ageing [252].

In Australia, obesity (including overweight) has increased from 56% to 63% in adults and from 21% to 27% for children over the span of two decades [3]. The AIHW reports suggests that age is an independent risk factor for overweight and obesity in Australian adults [3]. Overweight and obesity peaks in men and women at the age of 55 and 60 years respectively [194]. The Australian birth cohort analysis (1995 to 2014-15) reported a significant increase in the percentage of overweight and obesity from 19.9% in 2-5 years to 28% in 14-17 years old. In adults born between 1974–1977, the prevalence of overweight and obesity has more than doubled with age, from 27.8% at age 18–21 to 64.3% at age 38–41 [3].

ii. Age and Periodontitis

Age is suggested to be an independent, non-modifiable risk factor for periodontitis. Periodontitis is an age-dependent disease, with more than 10% of the global population aged 35-44 years affected by severe periodontitis [253-256]. In Australia, a significant age-dependant trajectory in prevalence of periodontitis was observed, with 12% of periodontitis cases reported in patients aged 15-34 years, 23.5% in patients aged 55-74 years and 25.9% in patients aged 75 years and older [26].

Although the prevalence of periodontitis increases with age, it is unlikely that ageing in itself predisposes an individual to periodontitis. Rather, there are several factors associated with increasing age that may predispose an individual to a pro-inflammatory state that may induce periodontitis in response to bacterial insult [257].

2.3.6 Sex

i. Sex and Obesity

Sex is a characteristic feature which refers to socially constructed roles, behaviour, attitudes and activities that are related to men and women, respectively. The mechanisms of obesity in men and women are different as a result of biological factors, environment and genetics [258]. Men and women have specific differences in adipose tissue storage and metabolism, with women having a higher risk of being obese than men [258]. In Australia (1995 and 2014-15), the proportion of men and women who were obese advanced from 18.9% to 27.9% and 19.1% to 27.0% respectively [259]. Men have a higher cumulative prevalence of overweight and obesity than women (70.8% versus 56.3%) [259].

ii. Sex and Periodontitis

Sex-specific differences in periodontitis have been observed in epidemiological studies based on national survey results [260]. Shaiu et al. [260] conducted a systematic review based on 12 population-based surveys which found that men have a higher risk of periodontitis as compared to women (37.4% versus 28.1%, respectively). It was suggested that men have a higher risk of periodontitis than women because of high-risk health behaviours; e.g., smoking, poor oral hygiene habits, and poor dental visiting behaviour are more common in men compared to women [260].

In Australia, the prevalence of periodontitis was higher in men (26.8%) compared to women (19%). Men experienced more sites with PPD >4 mm, CAL >4 mm as compared to women [26]. This aligns with the US-based NHANES (2009-2012) which

found that men (13.3%) experienced severe periodontitis more often than women (4.7%) [261]. Similarly, the UK-based Adult Dental Health Survey 2009-10 reported men were more likely to have bleeding gums and more sites with PD >4 mm and PD >6 mm compared to women [262].

2.3.7 Ethnicity

i. Ethnicity and Obesity

The ethnic composition of Australia is diverse [263]. The most significant ethnic groups in Australia are of European descent, which constitute more than 90% of Australia's population. Other ethnic groups are Indigenous peoples (Aboriginals and Torres islanders), and migrants from Asian, Middle Eastern and American countries [263]. Ethnic-specific differences are observed in the prevalence and incidence of obesity in Australia. Obesity is higher in people of Indigenous identity than Non-Indigenous people [3]. This is attributed to lifestyle habits (dietary patterns, physical inactivity and smoking), poor access to care, low education levels, high unemployment and a genetic predisposition to obesity [264].

ii. Ethnicity and Periodontitis

Ethnic-specific differences have been reported in the prevalence of periodontitis in various populations [265]. In Australia, the NSAOH 2004-06 reported that 29% of people with an Indigenous identity and 22.9% of people with a non-Indigenous identity experienced periodontitis [26, 266]. This disparity existed across all periodontal parameters (PPD >4 mm, CAL >4 mm, PI, and BOP) [26].

Similar disparities have been reported in the US and New Zealand. The 2009-2012 US-based NHANES survey found significant differences in prevalence of periodontitis across Hispanics (13.4%), non-Hispanic blacks (10.7%), non-Hispanic whites (68.8%)

and other (7.1%) ethnic groups. The risk of severe periodontitis was 2.3 times higher in non-Hispanic blacks compared to Hispanics, non-Hispanic whites or other ethnic groups [261].

The prevalence of moderate periodontal pocketing (5 mm or more) in New Zealand in 2009 was 20.9% in people with Pacific origin (20.9%), followed by 19.5% in people of Asian origin, 16.4% in people with Māori origin and 8.4% in people with European origin. The prevalence of CAL >4 mm was highest among Māori (53.9%), followed by people of Pacific origin (51.9%), European origin (49.1%) and Asian origin (46.6%) [267].

2.3.8 Alcohol

i. Alcohol and Obesity

Alcohol is the commonly used recreational drug in Australia [259]. Around 17.4% of adults in Australia consume more than two standard drinks per day [259]. One in six Australians consume alcohol at levels that place them with a lifetime risk of an alcohol-related health problem [259]. Overconsumption of alcohol is a major health problem, which is associated with increased risk of chronic conditions, such as obesity, cardiovascular diseases and oral health problems [268]. Alcohol consumption contributes $1.7 billion to the burden of the health economy in Australia [268]. A systematic review of 18 studies suggested that alcohol consumption is higher in rural and remote regions of Australia than in the metropolitan areas. Nearly a quarter (24.7%) of preventable hospitalisations in rural and remote areas are due to alcohol intake, whereas 17.6% of hospitalisations in metropolitan areas are due to alcohol intake [269].

ii. Alcohol and Periodontitis

A systematic review of 11 cross-sectional and five longitudinal studies on the relationship between alcohol dependence or alcohol consumption with periodontitis

reported a positive association [22]. A systematic review including 31 studies reported that overconsumption of alcohol could lead to weight gain [270]. The association between alcohol intake and periodontitis remains unclear. Analysis of the US-based NHANES (2009-10 and 2011-12) data has suggested that people who consumed more than eight alcoholic drinks per week experienced a 1.9 times higher risk of having severe periodontitis as compared to people who consumed one or less drink per week. People who consume more than eight drinks per week had higher mean PDs, a higher percentage of sites with PD $\geqslant$ 4 mm, mean CAL, and percentage of sites with CAL $\geqslant$ 3 mm than people who consumed one or less drink per week [271]. A study in Brazil of 1,115 adults, aged 18–65 years found that women who drank more than one glass/day of alcohol were more likely to experience periodontitis (OR = 3.8, 95% CI = 1.4–10.1), as compared to women who consumed up to one glass/day [272].

2.3.8 Smoking

i. Smoking and Obesity

Tobacco smoking is a threat to global health, affecting over 1.1 billion people [273]. Although the prevalence of smoking in Australia has declined from 22.4 % smokers in 2001 and 16.1% in 2011-2012 to 15% in 2014-15 [259], smoking still remains one of the greatest contributors to mortality amongst Australians. Tobacco smoking is associated with chronic conditions such as type 2 diabetes, cardiovascular disease and periodontitis [274-276]. Nicotine, a constituent of tobacco, is associated with increased energy expenditure and reduced appetite in smokers, leading to reduced body weight. A systematic review and meta-analysis of 35 cohort studies suggested that quitting smoking was associated with 2.61 kg gain in body weight and 1.14 kg/m^2 gain in BMI [277].

ii. Smoking and Periodontitis

Smoking increases the risk of periodontitis by 85% [278]. A meta-analysis of 14 studies suggested that quitting smoking may reduce risk of periodontitis by 14% [278]. Similar results were presented in the Australian NSAOH (2004-06which suggested that almost 700,000 cases of moderate to severe periodontitis could be prevented if the risk behaviour of smoking were eliminated [82].

2.3.9 Diet

Diet is influenced by various risk factors and modifiable factors, including the socio-economics of an individual (income and education), food prices, an individual's beliefs and preferences, cultural attributes and geographical location. These factors interact in a complex manner to shape dietary patterns [279]. The WHO recommends that a healthy diet is protective against malnutrition and non-communicable diseases such as type 2 diabetes, obesity, cardiovascular diseases and stroke. Therefore, consumption of a healthy diet throughout the lifespan is helpful in reducing heath risk [279].

i. Diet and Obesity

The global transition towards urbanisation and adoption of a Westernised lifestyle has resulted in greater utilisation of refined and processed foods, and a shift in dietary patterns [279]. Energy dense food (rich in fat, free and added sugars, salt and other products) increases the risk to global health and economy [279].

A low carbohydrate diet helps in reducing body weight, maintaining cardiovascular and metabolic health, and lowering blood pressure, triglycerides and cholesterol levels [280]. A systematic review found that a diet low in carbohydrate was associated with a significant reduction in body weight and improvement in psychological and social outcomes in overweight and obese individuals [280]. The short- and long-term

improvements in psychosocial outcomes seen in patients undergoing weight-loss treatment were independent of the macronutrient composition of their diet [280].

A randomised control trial with one year follow-up of 63 obese men and women randomly allocated to two diets — i.e., (i) low carbohydrate, high protein, high fat; or (ii) low calorie, high carbohydrate, low fat (conventional) diet showed that a low carbohydrate diet was associated with greater reduction in body weight than a conventional diet for the initial six months [281]. A study of differential weight loss of low carbohydrate versus low fat diet on insulin resistance level in adults with BMI ranging from 20-24 kg/m^2 suggested that a low carbohydrate or low fat diet significantly reduces the body weight and insulin resistance/sensitivity levels [282]. An experiment using a Stone Age diet (high fibre, high anti-oxidants and fish oil and low refined carbohydrate) suggested that people who followed such a diet experienced a reduction in gingival bleeding (35% to 13%) [283]. A pilot study conducted at the University of Freiburg, Germany, showed that a diet low in carbohydrate and rich in Omega-3 PUFA, vitamins C and D and fibre, can significantly reduce periodontal inflammation [284]. Consumption of added sugars (i.e. high-fructose products obtained from cane and beet sugar) may induce a hyper-inflammatory state or meta-inflammation. This state leads to abdominal obesity, dyslipidaemia and insulin resistance. It also leads to periodontitis and type 2 diabetes [284].

Studies have reported that a diet rich in milk and dairy products has a protective effect on periodontal health. A Korean survey (2007-2010) on dietary sources of milk and dairy products and their relationship with periodontal disease suggested an inverse relationship between the consumption of dairy products and the risk for periodontitis [285]. Likewise, the Hisayama Study of 942 participants aged 40-79 years reported that daily intake of dairy products or lactic acid-rich food products had a beneficial effect on periodontal disease [286]. A study of the relationship between intake of dairy products and

periodontitis suggested that calcium in dairy products has a prophylactic effect against periodontal disease [287]. A cross-sectional study among Japanese cohorts of the Kyushu Okinawa Maternal and Child Health Study reported a low prevalence of periodontal disease associated with increased calcium intake among young Japanese women [288]. Evidence-based studies have reported that calcium and vitamin D at optimal levels have considerable health benefits [289]. Deficient levels of calcium and vitamin D are risk factors for bone loss and inflammation, both of which occur in periodontal disease. The recommendation for calcium intake is 1,200 mg/day for people aged 50 years and older [289, 290]. In addition to calcium, certain other elements of dairy products are protective towards periodontal health; these may include whey, casein and lactoferin. A Copenhagen Oral Health Senior Study (COHSS) 2004-05 examined the effect of dairy products on periodontal outcomes and reported that the intake of dairy products (milk and yoghurt) rich in calcium and lactic acid products was beneficial and protective to periodontal health and inversely related to periodontal disease [291].

2.3.10 High Sensitivity C-reactive Protein (HsCRP)

HsCRP is a hepatic acute phase protein, regulated by IL-6. HsCRP is a marker that is used to predict the risk of coronary artery disease and the severity of atherosclerosis [292]. The Center for Disease Control and Prevention and the American Heart Association recommended the use of HsCRP as a measure towards prevention and early diagnosis of cardiovascular diseases in public health and clinical practice [293].

Epidemiological studies found increased plasma levels of HsCRP in people with obesity as compared to people of normal weight [294, 295]. A systematic review and meta-analysis suggested a strong association between obesity and elevated levels of HsCRP [295]. A study on the effect of periodontitis on the levels of adiponectin, HsCRP, Immunoglobulin-G (IgG) and *Porphyromonas gingivalis* reported low levels of

adiponectin and high levels of CRP and IgG to be associated with *Porphyromonas gingivalis* in patients with severe periodontitis, independent of overweight and obesity levels [296]. A systematic review and meta-analysis of randomised control trials on effect of anti-infective periodontal therapy on HsCRP outcomes suggested that non-surgical periodontal treatment helps in the reduction of HsCRP levels by 0.4 mg/L (short-term outcome) [297].

2.4 Summary

Both being overweight/obese and periodontitis are health problems with a growing incidence and economic burden in Australia and internationally [3, 29]. It has been proposed that obesity is associated with periodontitis; however, only limited data are available in Australia. An explanatory factor between obesity and periodontitis is yet to be discovered.

To answer the question, "Is overweight/obesity a risk factor for periodontitis?", a systematic review was undertaken. Following the systematic review, this dissertation proposed that diet could be a link between obesity and periodontitis and conducted a secondary analysis of the National Survey of Adult Oral Health (NSAOH 2004-06) to determine the association between obesity and periodontitis in Australian adults. Furthermore, it utilised the cutting-edge research method of single mediation analysis to determine the direct and indirect causal relationship between obesity and periodontitis in Australian adults. In addition to the secondary analysis of NSAOH 2004-06 dataset, the researcher planned and conducted an investigation to find association between obesity, diet and periodontitis, using clinical periodontal and anthropometric measures, and blood markers from a sub-sample of 33 participants who were enrolled in a pilot study [a feasibility project for future prospective study] in Sydney, New South Wales.

Chapter 3. Is overweight/obesity a risk factor for periodontitis in young adults and adolescents? a systematic review.

Khan S, Barrington G, Bettiol S, Barnett T, Crocombe L. Is overweight/obesity a risk factor for periodontitis in young adults and adolescents? a systematic review. Obesity reviews. 2018 Jun;19(6):852-83. https://doi.org/10.1111/obr.12668 (Clarivate Analytics Journal Impact factor: 8.48; Number of citations = 17)

This research paper was submitted to the journal, Obesity Reviews in October 2017, and accepted on 1st December 2017.

3.1 Abstract

Background: Overweight/obesity in young adults and adolescents is associated with chronic co-morbidities. This project investigated whether being overweight or obese is a risk factor for periodontitis in adolescents (13-17 years) and young adults (18-34 years).

Methods: A search of 12 databases was conducted using MeSH/Index and Emtree terms. Based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses, articles published between 2003-2016 were screened that reported periodontal and anthropometric measures. The Newcastle Ottawa scale was used to appraise the quality of studies.

Results: Of 25 eligible studies from 12 countries, 17 showed an association between overweight/obesity and periodontitis (Odds Ratios ranged from 1.1 to 4.5). The overweight/obesity indicators of body mass index, waist circumference, waist-hip ratio and body fat percentage were significantly associated with measures of periodontitis of bleeding on probing, plaque index, probing depths, clinical attachment loss, calculus, oral hygiene index and community periodontal index. Two prospective cohort studies in the review showed no significant association between overweight/obesity and periodontitis,

but these studies had limitations of study design and used inappropriate epidemiological diagnostic measures of periodontitis.

Conclusion: There was evidence to suggest that overweight/obesity is associated with periodontitis in adolescents and young adults.

Systematic Review Registration: PROSPERO Registration Number: CRD42016046507

3.2 Introduction

The overweight/obesity epidemic is on the rise in adolescents (13-17 years) and young adults (18-30 years) [2, 298, 299], categorizing them as a "vulnerable group" [300]. Lifestyle transitional changes among these age groups increases their susceptibility to energy imbalance often leading to weight gain and health consequences in later life [301]. Non-communicable diseases and co-morbidities, such as cardiovascular disease, type 2 diabetes and some forms of cancers are associated with obesity [301-304] as well as oral diseases such as tooth decay [305] and periodontitis [14]. Obesity has been reported to be associated with periodontitis in adults compared to non-obese individuals [14, 306-308] due to increased levels and proportions of periodontal pathogens [309] and pro-inflammatory cytokines [10, 310].

Periodontitis (gum disease) is a silent condition, resulting in periodontal tissue destruction and tooth loss [311]. It is associated with non-modifiable risk factors (age, gender, ethnicity and genetics) and modifying factors (diabetes mellitus, cardiovascular diseases and obesity) [312]. The global burden of periodontitis is as high as 30-35% [311]. with prevalence of periodontitis in adolescents and young adults reported in national surveys as high as 24% in the USA [313] and 7% in Australia [4].

To further understand and tackle the health burden of communities as populations' age, it is important to determine the association of obesity and periodontal disease in young adults and adolescents. Based on the hypotheses that: (i) systemic inflammation is

associated with obesity in young adults/adolescents that may affect susceptibility to chronic co-morbidities; and (ii) periodontitis is a result of exposure to risk factors that can affect any age group; the aim of this review is to determine if overweight/obesity is associated with periodontitis in adolescents and young adults.

3.3 Methodology

The review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The PICO (Population Intervention Comparator Outcome) criteria were used to devise the review question.

Scope of review

A systematic electronic search was conducted on PubMed/MEDLINE (National Library of Medicine, Bethesda, MD), EMBASE, COCHRANE, LILACS, DARE, BIOSIS, TRIP, PROQUEST, CINAHL, Google Scholar and WOS databases. PROSPERO portals of systematic review registration was searched for any registered protocol on this topic. The systematic review was registered as a protocol with PROSPERO (2016: CRD42016046507).

Search terms

The search terms used in the systematic review aligned with the National Library of Medicine (NLM) Medical Subject Headings (MeSH), Emtree terms and free text terms. Table 3.1 shows the search terms employed to generate the search syntax.

Table 3.1 Population Intervention/Exposure Comparator Outcome – Search Terms	
PICO	**Search Terms**
Population	Young adults, adolescent, teenager, youngsters
Intervention/Exposure	Overweight, obesity, morbid obesity, abdominal obesity, central obesity, adiposity, adipose, BMI, body mass index, weight gain, body weight, waist circumference, waist hip ratio
Comparator	Non-obese, normal weight
Outcome	Periodontal disease, periodontitis, adult periodontitis, chronic periodontitis, dental, oral, gum disease, gingival disease, mouth

Inclusion and Exclusion criteria

Studies considered eligible were: (i) original studies on the association of periodontitis and overweight/obesity in young adults and adolescents; (ii) studies reporting periodontitis as a primary outcome; (iii) cross-sectional studies, cohort studies and case-control studies; (iv) studies conducted between January 1990 until August 2016. This time period was chosen because the 1990's was a period when systemic diseases became a focus of research in terms of oral health. Exclusion criteria were: previous systematic reviews, literature reviews, mini reviews, dissertations, short commentaries, letters to the editor, *in vitro* studies and randomised controlled trials. Studies on middle age and older adults were also excluded. A PRISMA flow diagram was constructed showing the identification, screening, eligibility and included studies (Figure 3.1). Obesity was defined using body mass index (BMI), waist circumference (WC), waist to hip ratio (WHR) or waist to height ratio (WhtR) in the included studies. The definition of

periodontitis was based on case definition adopted by the individual studies. Age distribution was defined for adolescents as 13-17 years and young adults as 18-34 years.

Covidence ™ – Cochrane review production tool

The results of all searches were entered into the web-based reviewing platform Covidence ™ following removal of duplicated search items. Titles and abstracts of all research papers were independently reviewed by two researchers (SK and GB). After screening of titles and abstracts, the selected studies were extracted and were critically reviewed by reading the full text papers based on the inclusion and exclusion criteria. Any conflicts were mutually addressed via discussion with the third researcher (SB).

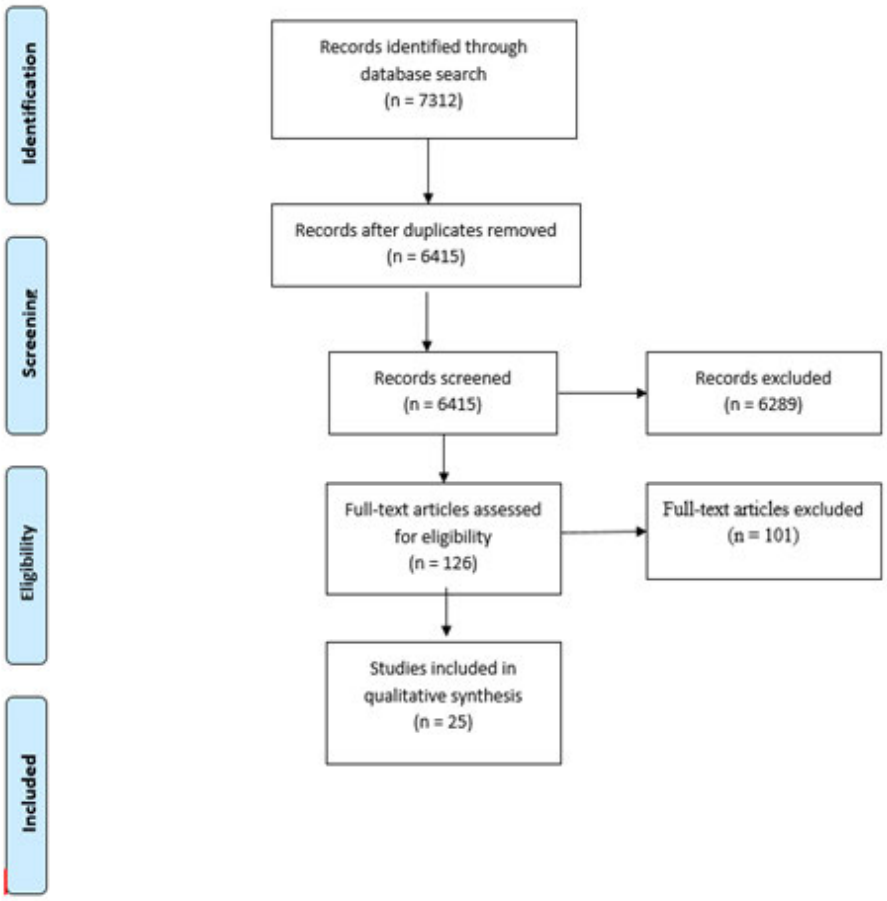

Figure 3.1 Prisma flow diagram of literature review and paper selection process

Missing data and contacting the authors

A full text review of the included studies was carried out and a table of synthesis was constructed. Authors of 32 studies that did not report the age distribution of participants were contacted via email and age distribution data was requested in relation to body composition measures, covariates and periodontal outcomes. All authors responded to the data request query, however none of them was able to provide the requested data.

Quality appraisal

The Newcastle Ottawa Quality Assessment Scale (NOS) was used for quality appraisal of included studies by two independent reviewers (SK and GB) (Table 3.2), a validated tool for quality assessment of observational and nonrandomized studies. The results of NOS is a star based (☆) system of assessment with three domains i.e. Selection (Maximum 5 stars), Comparability (Maximum 2 stars) and Outcome (Maximum 3 stars).

Table 3.2 Quality assessment of included studies using Newcastle Ottawa scale (N=25)

Author, Year	Selection	Comparability	Outcome	Score
Wood et al. 2003	☆☆☆☆	☆	☆☆☆	8
AL-Zahrani et al. 2003	☆☆☆	☆	☆☆☆	7
Lundin et al. 2004	☆☆	☆	☆☆	5
Lalla et al. 2006	☆☆☆	☆	☆☆☆	7
Reeves et al. 2006	☆☆☆☆☆	☆	☆☆☆	9
Lalla et al. 2007	☆☆	☆	☆☆☆	6
Ekuni et al. 2008	☆☆		☆☆☆	5
Sarlati et al. 2008	☆☆☆	☆	☆☆	6
Amin et al. 2010	☆☆		☆☆	4
Furuta et al. 2010	☆☆	☆	☆☆☆	6
Franchini et al. 2011	☆☆☆☆☆	☆	☆☆☆	9
Modeer et al. 2011	☆☆	☆	☆☆☆	6
Merchant et al. 2011	☆	☆	☆☆☆	5
Tomofuji et al. 2011	☆☆☆	☆	☆☆☆	7
de Castilhos et al. 2012	☆☆☆☆	☆☆	☆☆☆	9
Zeilger et al. 2012	☆☆☆☆	☆	☆☆☆	8
Irigoyen-Camacho et al.2013	☆☆☆☆☆	☆	☆☆	8
Fadel et al. 2014	☆☆☆☆	☆	☆☆☆	8
Lula et al. 2014	☆☆☆	☆	☆☆☆	7
Markovic et al. 2014	☆☆☆☆	☆	☆☆☆	8
Galkina et al. 2015	☆☆	☆	☆☆	5
Lee et al. 2015	☆☆☆☆☆	☆	☆☆☆	9
Zeilger et al. 2015	☆☆☆☆	☆	☆☆☆	8

Kawabata et al. 2016	☆☆☆☆	☆	☆☆☆	8
Kesim et al. 2016	☆☆☆	☆	☆☆☆	7

3.4 Results

Search results

The search produced 7312 studies. Of these, 6415 studies were available after duplicates were removed and when screened using title and abstract. A total of 126 studies were found to be eligible for full text review. Full text reviews resulted in 57 studies for data extraction. Of these, 32 studies were considered ineligible due to inadequate classification of age distribution for adolescents and young adults. This resulted in a yield of 25 studies for the review.

Characteristics of studies

The review included 18 cross-sectional, five case-control and two prospective cohort studies (Table 3.3). The studies, published between 2003 and 2016, were from 12 countries: The United States, Sweden, Japan, and one study from each of Egypt [314], Brazil [315], Turkey [316], South Korea [317], Mexico [318], Iran [319], Italy [320], Serbia [321] and Russia [322]. Thirteen studies reported on only adolescents [316, 317, 320-330], eight studies were based on young adults [211, 314, 315, 319, 331-334] and four studies included a combination of adolescents and young adults [335-338]. Four studies were based on national surveys, i.e. three US studies [255, 337, 338] and one South Korean study [317].

Table 3.3 Characteristics of included studies (N=25)			
Author, Year, Country	Study design Statistical power calculation	Number of participant Age range, gender	Examiner Calibration
Wood et al. 2003 United States	Cross-sectional NHANES 1988 to 1994 N/A	N=17660 18-34 years 35-49 years 50-64 years 65 years and above	Yes

AL-Zahrani et al. 2003 United States	Cross-sectional NHANES 1988-1994 N/A	N=13665 Young adults, 18-34 years, n= 5608 Middle-aged 35-59 years, n= 5092 Older adults 60-90 years, adults n= 2965 6466 male, 7199 female	Yes
Lundin et al. 2004 Sweden	Case-control N/A	N=33 adolescents and young adults, 13-24 years 11 male, 22 female	N/A
Lalla et al. 2006 United States	Case-control N/A	N=342 182 cases 99 male, 83 female Participants with diabetes 6-18 years 160 controls no diabetes 6-18 years 80 male, 80 female 6-11 years n=177 79 cases, 98 controls 12-18 years n= 155 94 cases, 61 controls	Yes
Reeves et al. 2006 United States	Case-control NHANES 1988-1994 Yes	N=2452 self-reported non-smokers 13-16 years n=1022 17-21 years n=1430 111 cases with periodontitis 2341 healthy controls Participants non-smokers	Yes

Table 3. *Continue*

Lalla et al. 2007 United States	Cross-sectional N/A	N=700 350 diabetic (cases) 350 non-diabetic (controls) 6-11 years n=183 98 male, 85 female 12-18 years n=167 99 male, 68 female Participants diabetic children	Yes
Ekuni et al. 2008 Japan	Cross-sectional N/A	N= 618 18-24 years (Mean age 21.6 years) 296 male, 322 female	Yes
Sarlati et al. 2008 Iran	Case-control N/A	N=80 18-34 years 40 overweight/obese cases 5 male, 35 female 40 normal weight controls 5 male, 35 female	Yes

Amin et al. 2010 Egypt	Cross-sectional N/A	N=380 20-26 years 170 male, 210 female (55.2%)	Yes
Furuta et al. 2010 Japan	Cross-sectional No sampling procedure was performed.	N=2225 18-19 years 1264 male, 961 female Participants with hepatic abnormalities	Yes
Franchini et al. 2011 Italy	Cross-Sectional/Observational comparative study Yes	N=98 10-17 years 48 male, 50 female 66 overweight/obese, 32 normal weight	Yes
Modeer et al. 2011 Sweden	Cross-sectional N/A	N=104 11-17.9 years 52 Obese Cases 29 male, 23 female 52 Normal weight controls 29 male, 23 controls	Yes

Table 3.3 Continue			
Merchant et al. 2011 United States	Cross-Sectional N/A	N=155 <20 years 126 Type 1 diabetic 64 male, 62 female 29 Type 2 diabetic 15 male, 14 female	Yes
Tomofuji et al. 2011 Japan	Cross-sectional N/A	N= 801 18-25years 413 male, 388 female Participants University students	Yes
de Castilhos et al. 2012 Brazil	Prospective Cohort N/A	N=720 23-24 years 379 male, 339 female	Yes
Zeilger et al. 2012 Sweden	Cross-sectional N/A	N=87 Mean age 14.7years 29 obese cases 18 male, 11 female 58 normal weight 36 male, 22 female	N/A
Irigoyen-Camacho et al, 2013 Mexico	Cross-sectional Yes	N= 257 15 years 137 male, 120 female Participants n=161 public school, n=96 private school	Yes
Fadel et al. 2014 Sweden	Case-control N No	N=55 13-18 years 27 obese cases 15 male, 12 female 28 normal weight controls 14 male, 14 female	Yes

Lula et al. 2014 United States	Cross-sectional NHANES 1988-1994 Yes	N=2437 18-25 years 1249 male, 1385 female	Yes

Table 3.3 *Continue*

Markovic et al. 2014 Serbia	Cross-sectional Yes	N=422 187 male, 235 female 6-11 years 12-18 years	Yes
Galkina et al. 2015 Russia	Cross-sectional N/A	N=168 12-17 years 104 male, 64 female	N/A
Lee et al. 2015 South Korea	Cross-sectional 4th KNHANES 2007 Yes	N=941 12-18 years 512 male, 429 female 12-14 years n=467 15-18 years n=465	N/A
Zeilger et al. 2015 Sweden	Cross-sectional N/A	N=75 12-18 years 42 male, 33 female Participants obese	N/A
Kawabata et al. 2016 Japan	Prospective cohort N/A	N=2588 18-27 years 1278 male, 1310 female	Yes
Kesim et al. 2016 Turkey	Cross-sectional Yes	N= 4,534 6-17 years 2,018 male, 2,516 female 6-11 years 278 male, 322 female 12-17 years 518 male, 879 female	Yes

NHANES – National Health and Nutrition Examination Survey; KNHANES – Korean National Health and Nutrition Examination Survey

Case definition of periodontitis

The case definition of periodontitis varied among the studies included in this systematic review. Seven studies used the Community Periodontal Index (CPI) [211, 316, 317, 322, 325, 332, 333], two studies used a combination of probing depths and clinical attachment loss [255, 338], two studies used a combination of probing depths and bleeding on probing [333], two studies used clinical attachment loss [323, 324, 326, 337], two studies used radiographic bone loss [326, 329] to measure periodontitis. Five studies provided no information on their case definition of periodontitis [314, 319-321, 328].

Protocol used for periodontal examination

Ten studies used a partial-mouth protocol [211, 255, 316, 323, 324, 329, 331, 334, 337, 338], seven studies used a full-mouth protocol [314, 315, 319, 327, 328, 330, 335] and one study employed full mouth radiographic assessment to define periodontitis [326]. Other studies used different protocols for the periodontal examination. Kawabata *et al.* used 10 selected teeth (two molars in each posterior sextant, upper right and lower left central incisor) [333], Franchini *et al.* used first upper and lower molars, central and lateral incisors teeth [320], Tomofuji *et al.* used two molars in each posterior segment and upper right and lower left central incisors [332], Irigoyen-Camacho *et al.* used right upper central and right lower central incisors [325], and Lee *et al.* used six permanent index teeth (first molars in each posterior sextant and the upper right and lower left central incisors) [317]. Two studies did not describe their periodontal examination protocol [321, 322].

Anthropometric measures and obesity definitions

Anthropometric measures of BMI, waist circumference, hip circumference and waist-hip ratio were frequently used as indicators of obesity in the included studies. Obesity was defined using the Cole criteria, ⩾ 95th percentile, adjusted for age and gender (BMI-SDS, BMI-standard deviation score) and the International Obesity Task Force definition (BMI⩾30kg/m^2) [339]. The BMI was calculated using one or more of the following classifications; Quetelet's index of obesity [340]; the Center of Disease Control and Prevention (CDC) age and sex specific growth charts [341]; four categories from the National Institute of Health (1998) [342]; standard definition by Cole et al. (2000) [339] and WHO (1997) [343]; growth references for children and adolescents percentiles (WHO 2007) [344]; International Classification of Disease (ICD) - overweight, obesity and other hyperalimentation E66 ICD-10; WHO expert consultation paper on appropriate BMI for Asian populations [345].

Examiner calibration and statistical power calculation

Twenty studies out of 25 studies reported that examiner calibration was conducted [211, 255, 314-316, 319-321, 323-328, 331-334, 337, 338]. Three studies out of 25 studies reported on statistical power calculation [314, 320, 335].

Covariates

The covariates of age, gender, smoking habits, ethnicity, diabetes type, glycosylated haemoglobin (HbA1c) levels and lipid profiles and the frequency of dental visits were frequently reported in the studies. Some studies included parent education and country, use of antibiotics and other medications, consumption of sugary food, sugar sweetened soft drinks, physical activity, watching television or computer use, socioeconomic status, and frequency of tooth brushing.

The association between obesity and periodontitis

Seventeen (68%) studies showed a significant association between obesity and periodontitis (Table 4) [255, 314, 316, 318-321, 323, 324, 327-329, 331, 332, 334, 338, 346]. Eight studies showed no association between obesity and periodontitis (five cross-sectional, two prospective cohort and one case-control study) [218, 315, 317, 322, 326, 330, 333, 335].

Of these 17 studies that suggested an association between obesity and periodontitis, seven were on young adults [211, 255, 314, 319, 331, 332, 334] and nine on adolescents [314, 315, 317, 320, 321, 323, 324, 327, 328] and one study included both adolescents and young adults. The indicators of BMI, WC, WHR and body fat percentage were significantly associated with periodontal measures (bleeding on probing, plaque index, probing depths, clinical attachment loss, calculus, oral hygiene index and CPI index).

The multiple variable analysis within the studies showed odds ratios of 1.1. to 4.5 for association between obesity and periodontitis. Not all studies provided a statistically significant evidence of an association between overweight/obesity and periodontitis.

There were two prospective cohort studies included in the review. Of these studies, Kawabata et al. did not provide sufficient information on the obesity and periodontitis association and was focused on relationship between prehypertension/hypertension and periodontal disease [333]. deCastilhos et al. study showed no significant association between obesity and periodontitis, however the association was observed in gingivitis and obesity in regards to calculus and gingival bleeding [315].

In addition to poor periodontal health, individuals with obesity had poor compliance towards oral hygiene [320, 327, 329]; consumed a fat-rich diet frequently and vegetables infrequently [332]; had high added sugar [334]; increased oral microbial counts [329]; decreased salivary flow rates [328, 345]; low pH [323] and high IgA levels [317]. In one study, no significant association was observed between radiographic alveolar bone loss and obesity [326].

Table 3.4 Case definitions, protocol, anthropometrics, covariates and outcome of studies							
Author	Case definition	Protocol, Probe	Periodontal outcomes	Anthropometric measures and obesity definition	Covariates	Results	Sig
Wood et al. 2003 [337]	Extent scores of PAL based on Carlos et al. 1986 definition was used to categorise participants in to three groups [347]. 1. Normal subjects had 0–33% of sites with PAL ⩾ 3 mm. 2. Early periodontitis had 33–66% of sites with PAL ⩾ 3 mm. 3. Severe periodontitis had 67–100% of sites with PAL ⩾ 3 mm.	Partial mouth protocol.	PALm, PDm, GBm indices, CIm.	Body weight (kg), Height (cm),BMI kg/m^2 WC (cm), WHR, HC (cm), FFM. Bioelectric impedance analysis (LBM, FFM, Skin fold thickness) was carried out using RJL system, Detroit, MI, USA. Obesity was measured using Quetelet Index of obesity [343].	Age, gender, smoking status (current smoker), a history of diabetes (self-reported) and socioeconomic status (poverty income ratio i.e. un-imputed income).	No significant association was observed in PAL and body composition measures in 18-34 years. In individuals 35 years and older: • An increasing percentage of PAL was significantly associated with WHR ($p<0.05$) and BMI ($p<0.01$), and FFM ($p<0.05$). • Adjusted PD significantly correlated with WHR, BMI and skin fold thickness at $p<0.01$ but not FFM. • Adjusted GB significantly associated with WHR, FFM and BMI at $p<0.005$, but not skin fold thickness. • Adjusted CI significantly associated with WHR, BMI and skin fold thickness at $p<0.01$ and FFM at $p<0.05$.	No

Al-Zahrani et al. 2003 [255]	⩾1 site with attachment loss (AL) of ⩾3 mm and probing depth (PD) of ⩾4 mm.	Partial-mouth protocol. Randomly assigned one upper and one lower quadrant. Third molars, partially erupted teeth, and retained roots were excluded. N/A	PD, CAL.	Weight (kg), Height (m), BMI (kg/m^2), WC (cm) BMI: Four categories: 1. Underweight (BMI < 18.5 kg/m^2). 2. Normal weight (BMI 18.5–24.9 kg/m^2). Overweight (BMI 25–29.9 kg/m^2). 3. Obesity (BMI ≥30 kg/m^2). 4. (NIH, 1998) [342]. WC was defined according to WHO 1998 criteria as obesity i.e. WC ⩾102cm men and WC ⩾88cm women [343].	Age, race, gender, education, poverty index, smoking, diabetes, and time elapsed since last dental visit.	Prevalence of periodontitis = 14% in the total population. Age-specific prevalence of periodontitis in obese individuals (BMI ≥30 kg/m^2). • Young adults (12.49%). • Middle age adults (19.45%). • Older adults (21.76%). Age stratified analysis showed a significant association between obesity (BMI) and periodontal disease in young adults in crude analysis as compared to other age groups. • Young adults (OR 1.85, CI 1.31-2.60. p<0.01). • Middle age (OR 1.28, CI 0.97-1.68). • Older adults (OR 1.85, CI 0.99-1.62). Age stratified analysis showed a significant association between high WC and periodontal disease in young adults in crude analysis. • Young adults (OR 2.14, CI 1.52-3.01. p<0.001). • Middle age (OR 1.13, CI 0.88-1.44). • Older adults (OR 1.01, CI 0.77-1.31). Association of periodontal disease and BMI in young adults attenuated when controlling for covariates of gender, race,	Yes

						smoking, poverty index, education, diabetes and time since last dental visit (OR 1.85 – 1.75 p<0.01), while association of PD and WC increased after controlling for covariates (OR 2.14 – 2.27 p<0.001).	
Lundin et al. 2004 [335]	Pathological periodontal pocket was defined as depth ≥4mm. Alveolar bone loss was defined as 2mm or more distance of CEJ to the alveolar crest.	Full mouth protocol. 2 or 4 Bitewing radiographs or 2 periapical radiographs. Graded Periodontal probe (Type LM Instruments)	GBI% and PD were measured at 6 sites per tooth excluding 3rd molars. 2 or 4 Bitewing radiographs or 2 periapical radiographs were taken to detect alveolar bone loss. Gingival crevicular fluid samples were collected at six sites using paper strips to measure TNFα and IL-8 levels.	Body weight (kg), Height (cm), BMI (kg/m^2). Age-specific index was used to define range of obesity (Cole et al. 2000) [339].	Age, gender, smoking habit (number of cigarettes per day and years of smoking).	In univariate model no statistical correlation of BMI was found with age, number of periodontal pockets (⩾4mm), smoking, TNFα and IL-8. When grouped, subjects with BMI>40 and BMI<40 had no significant differences in age, gender, smoking, pathological periodontal pocket and levels of the biochemical variables (TNFα and IL-6). TNFα in GCF and BMI>40 were positively correlated (p<0.01) in individuals without pathological periodontal pockets. When comparing groups with and without pathological periodontal pockets (≥4 mm) a positive correlation was found between BMI and TNFα. TNFα in GCF may be affected by the obese condition through a systemic effect.	No
Lalla et al. 2006 [324]	At least one site with attachment loss >2 mm on	Partial mouth protocol (one randomly	Missing teeth, Dental caries, and dental restoration.	BMI (kg/m^2). BMI for age and percentile rank calculated based	Diabetes history and its type, age, sex, ethnicity, frequency of	A positive and statistically significant association between number of affected teeth (at least one site with >2mm of attachment loss) and BMI was reported (r = 0.12 p<0.03).	Yes

	at least two teeth.	assigned maxillary and the diagonally opposite mandibular quadrant). Periodontal probe.	PI and GI was recorded 4sites per tooth for primary and permanent dentition (Loe and Silness 1963) [348, 349]. For permanent dentition measures of probing depths and location of gingival margin were measured. Attachment loss were computed from probing depths and location of gingival margin scores.	on Center for Disease Control and Prevention age- and sex-specific growth charts [341].	dental visits, dental examiner, insulin regimen, oral hypoglycemic medications, other medications, hbA1c and lipid profiles.	BMI-for-age percentiles were similar in both age groups, with actual BMI significantly higher in older children 25.0 +- 7.5 kg/ m^2 compared with 19.2 +-4.4 kg/m^2 at $p<0.001$. Children with diabetes had more dental plaque, gingival inflammation, bleeding on examination, clinical attachment loss than non-diabetics ($p<0.001$). Number of teeth with attachment loss $\geqslant$ 2mm were found significantly higher in diabetic children from both age groups (6-11 years & 8-12 years).	
Reeves et al. 2006 [338]	Presence of 1 or more periodontal sites with both a loss of tissue attachment of	Partial mouth protocol (randomly selected one upper and	Probing depths, Loss of tissue attachment were recorded from mesio-	Weight (kg), Height (cm), BMI (kg/m^2) Skinfold thickness and WC (cm).	Age, sex, race/ethnicity, poverty index ratio, last dental visit, self-reported	No significant relationship was found between BMI and periodontitis. Skinfold thickness was not associated with periodontitis.	Yes

	3 mm or more and a probing depth of 3 mm or more subjects not meeting the criteria based on the case definition provided above were classified as controls.	one lower quadrant).	facial and mid-facial sites of 28 teeth excluding third molar.	Adiposity was assessed by triceps, subscapular, supra-iliac, thigh, and sum of skinfold thickness (triceps subscapular) measures.	calcium intake. Additional confounders included were insulin use, non-fasting serum glucose level, self-reported vitamin C intake.	Weighted prevalence of periodontitis was 3.3% in individuals with periodontitis were 7kg heavier, with WC of 8cm larger than the control of same age. Adjusted models for adolescents aged 17-21years showed 6% increased risk of periodontitis for every 1kg increase in body weight and 5% increased risk of periodontitis for every 1cm increase in WC. Crude and adjusted models for adolescents aged 13-16 years showed no association between periodontitis in relation to body weight (OR 1.00, CI 0.98 – 1.0) and WC (OR 1.00, CI 0.98 – 1.02). .	
Lalla et al. 2007 [323]	3 definitions used to define periodontitis. 1. One site with CAL≥2mm and GI≥2 at the same site. 2. At least two teeth with one site having GI≥2.	Partial mouth protocol, one randomly assigned maxillary and the diagonally opposite mandibular quadrant. Manual periodontal probe.	Following were evaluated four sites or all fully erupted teeth except third molars PI [348], GI (bleeding) [349], Probing depths, Location of the gingival margin.	BMI kg/m^2, BMI percentiles for age.	Age, gender, ethnicity, dental visits, plaque index and dental examiners, type and duration of diabetes, insulin regimen, HbA1c over two year period and Lipid profiles.	BMI indexed for age was similar between age groups 6-11 years and 12-18 years, actual BMI was higher in the age group 12-18 years. A strong association was observed between HbA1c and periodontitis using the combined case definition of CAL and GI. Logistic regression showed clinical attachment loss was found weakly associated with BMI, but significant. No significant relationship was observed in diabetes duration or BMI-for-age and	Yes

	3. At least two teeth with one site with CAL≥2mm.		CAL were calculated by computing probing depths with location of the gingival margin.			measures of gingival/periodontal disease in this cohort. Periodontitis and BMI indexed for age were associated in the whole population (OR 1.02, p=0.006) and in the older subgroup aged 12-18 years (OR 1.06, p=0.007).	
Ekuni et al. 2008 [211]	CPI score 3 and 4 was defined as periodontitis group. CPI score 0-2 was defined as control group.	Partial mouth using CPI method.	CPI (WHO community periodontal index) [350]. Total number of teeth Decayed, missing and filled teeth.	BMI ⩾ 30kg/m^2 is obesity. Body fat was measured using the bio-impedance method and a Body Fat Analyzer (TBF-202; Tanita Co. Tokyo, Japan).	Age, sex	The overall prevalence of periodontitis in this study was estimated as 7.9%. The average BMI of participants in periodontitis group (21.8, SD 2.4, p<0.009) was significantly higher than the control group (BMI 20.9, SD 2.6). Age was also found to be significantly higher in periodontitis group (21.8, SD 1.4, p<0.002) as compared to the control group (21.1, SD 1.6). Risk of periodontitis increased by 16% with each unit increase in BMI. Subjects with periodontitis had 16% increased risk of periodontitis with 1kg/m^2 increase in BMI (adjusted OR 1.16 – CI 1.03 -1.31). No significant association was observed between Body fat and periodontitis.	Yes
Sarlati et al. 2008 [319]	No case definition was used to define periodontitis.	Full mouth protocol (four sites per tooth).	Following measures with used four sites per tooth	BMI, WC. BMI: Four categories:	Age, gender, education, time elapsed since the	PPD (p<0.002) was significantly associated with BMI showing higher PPD in overweight/obese (2.82, SD 0.40) as	Yes

	Measures of PPD and CAL were used as mean values to compare in relation to BMI and WC.	Williams Probe.	PPD, CAL, PI [351].	1. Underweight (BMI < 18.5 kg/m^2). 2. Normal weight (BMI 18.5–24.9 kg/m^2). Overweight (BMI 25–29.9 kg/m^2). 3. Obesity (BMI ≥30 kg/m^2). WC ⩾102cm for men and ⩾88cm for women were considered obesity. BMI and WC were defined using WHO criteria [343]	previous dental visit, smoking and diabetes. Women who reported that they had diabetes during pregnancy were considered non-diabetics.	compared to normal weight (2.56, SD 0.36). CAL (p<0.000) was significantly associated with BMI showing higher CAL in overweight/obese (1.98, SD 0.5) as compared to normal weight (1.63, SD 0.33). PI was not shown to be significantly different between overweight/obese and normal weight. Increased WC was associated with significantly higher CAL in overweight/obese group as compared to normal weight (2.02, SD 0.49 versus 1.61, SD 0.33, p<0.000). PPD was significantly higher in the high WC group compared to normal WC group (2.58, SD 0.32 versus 2.55, SD 0.37, p<0.000). PI was higher in high WC as compared to normal WC, but did not reach statistical significance (75.6, SD 22.3, p=0.054).	
Amin et al. 2010 [314]	N/A.	Full mouth protocol. Periodontal probe.	GI was recorded for all permanent teeth except third molars (Loe, 1967) [16].	BMI, WC BMI and WC were defined for obesity based on WHO criteria [343]. BMI: Four categories	Smokers, pregnant women, diabetics, and individuals with endocrine disorders excluded from	Obese females (2.1 mm) had significantly higher CAL as compared to normal and overweight females (0.2 mm, 1.5 mm), with a statistically significant correlation between CAL and BMI (r = 0.9, p < 0.01). High WC was significantly associated with CAL in females with mean CAL of 1.9	Yes

			CAL on six sites per tooth for all fully erupted permanent teeth using the Ramfjord method and only the highest measurement was recorded [352]. CPI on index teeth [350].	1. Underweight (BMI < 18.5 kg/m^2). 2. Normal weight (BMI 18.5–24.9 kg/m^2). 3. Overweight (BMI 25–29.9 kg/m^2). 4. Obesity (BMI ≥30 kg/m^2) [343]. WC⩾ 102cm in men and 88cm in women is obesity.	study. Non-regular tooth rushing, periodontal treatment and antibiotic use also excluded.	mm and a statistically significant correlation (r = 0.8, p = 0.003). Obese females had a mean GI of 1.8 as compared to normal weight (GI 0.3) and overweight (GI 0.8) females, with a statistically significant correlation between GI and BMI (r = 0.9, p < 0.01). Periodontitis prevalence, measured as CPI score 3-4, by weight category in men was; Obese (56.4%), Overweight (53.5%), Normal (45.5%). In Women; Obese (63.9%), Overweight (56.7%), Normal (25.0%). Males with high WC had significantly higher GI (0.8) as compared to normal WC (0.4) individuals; the correlation was statistically significant (r = 0.6, p = 0.01). Females with high WC had a mean GI 1.5 as compared to normal WC (0.5), with statistically significant correlation between GI and WC (r = 0.7, p = 0.003). BMI and WC were significantly associated with periodontitis in young adult females. WC was significantly associated with periodontitis in young adult males.	
Furuta et al. 2010 [331]	One or more teeth with PPD ≥ 4 mm.	Partial mouth protocol (randomly selected one	PPD, Percentage of sites with BOP,	BMI (kg/m^2). Two BMI categories were defined using WHO criteria [353].	Serum ALT, total cholesterol and	Periodontitis was present in 5.8% in males, 3.2% in females.	Yes

		maxillary and one mandibular quadrant at two sites per tooth).	Number of teeth present Decayed teeth.	: 1. Normal weight (BMI<25 kg/m^2). 2. Overweight/obese (BMI⩾25 kg/m^2). Following were measured using venous blood samples serum ALT, total cholesterol, serum level of hemoglobin. Urinalysis, blood pressure and pulse rate were also measured.	hemoglobin levels. Urinalysis, blood pressure. smoking, dental flossing, visit to dentist, interdental cleaning, flossing, regular dental clinic attendance.	Overweight/Obese individuals with periodontitis was 13% in males and 11% in females. BMI and serum level of ALT were associated significantly with periodontitis in males. Adjusted logistic regression showed overweight and obese females had higher levels of periodontitis than normal weight females (OR 4.5, 95% CI 1.8-10.7). Adjusted logistic regression showed males with high levels of serum ALT were significantly more likely to have periodontitis as compared to males with low ALT (OR 2.3, 95% CI 1.0-5.2). BMI was significantly associated with periodontitis in both males and females. Serum ALT was significantly associated with periodontitis in males only.	
Franchini et al. 2011 [320]	PI and GI was defined based on Loe and Silness, (1963) [348]. No definition of periodontitis provided	First upper and lower molar and central and lateral incisors were the examined teeth. No deciduous	PI, GI (Loe and Silness, 1963) [348].	Weight (Kg), Height (cm). BMI percentile for corresponding to BMI ⩾25kg/^{2} and BMI⩾ 30kg/m^2 were used as cut-off for overweight and obesity (Cole et al. 2000) [339].	Age, weight, height, blood pressure, psychological profile (multi-dimensional self-concept scale), insulin resistance (HOMA-IR), oral hygiene habits,	Overweight and obese subjects showed a poor attitude towards oral hygiene as compared to normal weight individuals. Plaque index and gingival index scores were significantly higher in overweight/obese as compared to normal weight individuals. Most of the normal weight subjects were free of gingival inflammation (65.6%),	Yes

		tooth sites were recorded to exclude the effect of exfoliation or immature status of the gingival complex on plaque accumulation and inflammation.		WC (cm) and HC were recorded. .	preventive attitudes. Subjects affected by major chromosomal pathologies and major medical conditions excluded.	however only 29% of overweight/obese individuals had healthy gingiva. Two way Anova analysis showed PI scores were found significantly less in normal weight females as compared to normal weight males ($p<0.01$). In logistic regressions, GI showed a strong positive correlation with PI and male gender. Overweight and obesity, HOMA index and age were found to be not predictive of gingival inflammation.	
Modeer et al. 2011 [327]	1 or more site with pocket depth > 4mm.	Full mouth protocol, six sites per tooth, third molars excluded. Graded Periodontal Probe (LM Instruments OY, Finland).	VPI%, BOP%, pathological periodontal pocket. Supra and sub-gingival calculus was recorded. Incipient alveolar bone loss was measured using two bitewing radiographs.	Body weight (kg), Height (m). Individuals with obesity had BMI⩾30); Patients with Normal weight i.e. controls (BMI<25) [339]. Body mass was expressed as BMI (kg/m^2), as well as by BMI adjusted for age and sex (BMI-SDS) [354].	Age, medication, dietary habits, oral hygiene habits, parental educational level and country of birth.	Obese subjects had significantly lower frequency of tooth brushing ($p<0.006$), use of dental floss ($p<0.040$) and less use of electric toothbrush ($p<0.041$) as compared to the control group. Higher frequency of BOP% (25%) and pathological periodontal pockets, IL-8 and IL-1β were observed in obese subjects compared with controls ($p< 0.001$). No significant difference was observed in supra-gingival calculus and sub-gingival calculus in obese and controls. BMI-SDS was significantly ($p< 0.030$) associated with the pathological periodontal pockets (>4 mm) even after	Yes

			GCF was collected from tooth number 16 and 41 and volume of GCF calculated using Periotron 8000. GCF samples were analysed in relation to inflammatory markers (TNFα, adiponectin, IL-1β, IL-6, IL-8 and PAI-1).			adjusting for the variables BOP (>25%), and sub-gingival calculus (OR 1.87 of adjusted BMI-SDS). Age and sex adjusted BMI was significantly associated with periodontal pocket.	
Merchant et al. 2011 [326]	≥3mm alveolar bone loss at one or more permanent teeth was classified as periodontal damage on radiograph.	Full mouth radiographic assessment. Williams-marking periodontal probe (Hu-Friedy, Chicago, IL, USA).	Bitewing radiographs to measure alveolar bone loss. Measurement of alveolar bone loss was conducted on mesial and distal sites of all permanent	BMI (kg/m^2), WC (cm). BMI was calculated by dividing weight in kg by squared height in meters, and age and sex specific z-scores were obtained by using the Centers for Disease Control and Prevention growth curves [341].	Covariance analysis was conducted for age, sex, race, education level, family income, duration of diabetes, diabetes control, time between study visit and date of radiograph,	WC was reported to be higher in individuals with periodontal damage as compared to periodontal healthy individuals in both type 1 and type 2 diabetes, but did not reach statistical significance. Periodontal damage was significantly associated with high triglycerides level and lower c-peptide levels in type 2 diabetics ($p<0.01$).	No

			teeth except third molars.		treatment history, tooth brushing and date of dental visit. Other measured covariates were blood pressure, hypertensive medications, frequency of Flossing, brushing and dental visits. A1c, Total cholesterol, HDL-C and triglycerides were measured. LDL-C was also measured.	Periodontal damage was higher in type 2 diabetes as compared to type 1 diabetics (55% versus 29%, p<0.02). Increasing age and males were associated with type 2 diabetes and periodontal damage. HDL was lower and LDL was higher in type 2 diabetics than in type 1 diabetes, but did not reach statistical significance.	
Tomofuji et al. 2011 [332]	CPI score 3 or 4 was referred as periodontitis. CPI 0 to 2 were referred as controls.	CPI index on index teeth. Simplified oral hygiene index for dental plaque and calculus index	CPI [350] Simplified oral hygiene index and calculus index [355].	Patients were classified as 1. Underweight (BMI<18.5 kg/m^2). 2. Normal weight (BMI of 18.5 to 22.9 kg/m^2). 3. Overweight (BMI >23	Sex, age, eating habits based on eight questions, oral health behavior and exercise status.	Overweight individuals had higher risk of periodontitis with higher oral hygiene index scores (OR 15.4, 95% CI 3.3-72.2, p<0.001) and debris index (OR 1.8, 95% CI 0.6-5.7, p<0.28). The risk of periodontitis was higher in individuals who consumed fatty diet (p = 0.021).	Yes

		measured on index teeth; two molars in each posterior segment and upper right and lower left central incisors, six sites per tooth. CPI Probe.		kg/m^2). Using Appropriate body-mass index for Asian populations [340].	Blood pressure was measured in right upper arm.	The risk of periodontitis reduced in overweight with frequent consumption of vegetables (OR 2.8, 95% CI 1.2-6.6, p<0.008). In periodontitis group, overweight students were significantly associated with frequent consumption of fatty diet (56.5%) and lower consumption of vegetables (10.9%) as compared to the control group.	
de Castilhos et al. 2012 [315]	Gingivitis: all sites were probed, waiting 10 s to verify the presence or absence of gingival bleeding. Periodontal pocket: all sites were probed, pocket should have probing depth ⩾4 mm in at least one site. Calculus: all sites were probed for	Full mouth protocol.	Gingival bleeding Calculus, Periodontal pocket.	Weight (kg), Height (cm), BMI, WC. At 15 years: the following cut-off were used to categorize BMI eutrophic (BMI in z score for age and sex 1 SD), overweight (BMI > 1 and <2 SD) or obesity (BMI ⩾2 SD) [344]. At age 18 to 23 year, the BMI were categorised as given below:	Sex, skin color, smoking, schooling, family income, asset index, use of dental floss, brushing frequency percentage dietary intake from carbohydrate, C-reactive protein.	Prevalence of dental outcomes reported were: • Gingivitis = 37.5% • Calculus = 87.4% • Periodontal pocket = 3.3% Obese individuals were more likely to have two or more teeth with gingival bleeding. However, after adjusting for mediators the effect was shown to be significant. Odds of gingival bleeding were reduced as WC increased from level 1 to level 2. Dental calculus was associated with obesity, this association was not mediated by diet, oral hygiene or inflammation. WC was associated with calculus at level 2 with high risk.	No

	detection of calculus. The variable was dichotomized in absence or presence of dental calculus.			Overweight (BMI 25 and _29.9 kg/m2) and Obesity (BMI 30 kg/m^2) [342]. 1998). WC were categorized according to sex in normal (men < 94 cm, women < 80 cm), Level 1 (men >94 and <102cm women >80 and <88cm Level 2 (men ≥102 cm; women ≥88 cm [343].		Periodontal pockets and risk for bleeding gums were not associated with obesity or WC. Gingivitis was significantly associated with obesity, this association was mediated by oral hygiene behaviour and systemic inflammation markers. No significant association was observed between obesity and periodontitis.	
Zeilger et al. 2012 [329]	Incipient marginal bone loss was classified as positive if the distance between CEJ to alveolar bone crest was ≥2mm.	Partial mouth protocol, consisting of first molars, right upper central and right lower central incisors.	VPI [356], Bleeding on probing [356] were measured at six sites per tooth. Probing depths, supra-gingival calculus. Supra-gingival calculus was recorded on	BMI In children, age specific BMI ranges were used to define obesity according to Coles criteria (ISO-BMI>30)I (kg/m^2) [339]. Obesity was defined in adolescent using age and gender adjusted BMI (BMI-SDS) [354].	Medical condition, medication, meal frequency and oral hygiene habits, smoking habits, as well as their parent's education and country of birth.	Obese samples were associated with low frequency of tooth brushing ($p<0.002$) and higher visible plaque index scores ($p<0.005$) compared to normal weight controls. None of the subjects showed signs of alveolar bone loss. Microbiological analysis showed threefold higher amounts of bacterial cells in the obese individual's plaque samples as compared with normal weight controls. Out of six bacterial phyla's determined, five were found at higher counts in the obese subjects. All families in these	Yes

			all teeth as present or absent; sub-gingival calculus was recorded as present or absent on proximal surface of first molar and premolar on the radiograph taken as well as clinically probing the gingival sulcus. Incipient alveolar bone loss was recorded by two bitewing radiograph. Stimulated saliva was collected by asking patient to chew on 1g of paraffin wax for 5min. Saliva secretion rate			phyla's were significantly higher ($p<0.001$) in the obese samples. Out of the totally 40 different bacterial species, 32 species were present in significantly higher amount ($p<0.01$) in the obese subjects compared to normal weight controls. In bivariate logistic regression the measures of VPI, chronic disease, medication, lack of daily tooth brushing in the evening or morning, salivary flow rate, bacterial count and type were significantly associated with obesity ($p<0.005$). Multivariate logistic regression analysis showed a significant association of obesity with bacterial count ($p<0.006$) after adjusting for all the potential confounders.	

			and amount of saliva collected were determined in milliliters per minute. Plaque samples were collected for microbiological processing using paper points and were stored at -70 degree Celsius. Checkerboard DNA-DNA hybridization was used for analyses of the plaque samples.				
Irigoyen-Camacho et al. 2013 [325]	CPI 3 or 4 [350].	Using WHO criteria, the teeth examined in 15 year old were right upper central and right lower central incisors.	CPI [350] Periodontal loss of attachment index was only applied if CEJ was clearly visible.	Anthropometry was performed by a qualified dietitian for weight (kg) and heights (m) and age- and sex-specific Z-score for anthropometric data were obtained.	Smoking habit, number of cigarettes per week and duration of smoking, sex and school type.	About one third (32.7%) of the students had DI-S >1. High DI-S was detected in 31.3% and in 41.0% of non-smokers and smokers (p = 0.230). CPI⩾3 was found in 3.1% individuals and CPI⩾2 was found in 26.9% individuals. No students had deep periodontal pockets (CPI score 4).	Yes

		WHO periodontal probe.	Plaque score were determined by Simplified Debris index (DI-S) [355].	IOTF ISO-BMI age- and sex-specific cut-off points were used to identify normal weight, overweight (OW) and obese (OB). IOTF proposed that the adult cut-off points (25 kg/m^2 for overweight and 30 kg/m^2 for obesity) be linked to body. mass index percentiles for children and adolescents aged 2–18 years old [339]. BMI cut off points for 15.6years [339]: Overweight: • Males 23.6kg/m^2 • Females 24.17kg/m^2. Obese: • Males 28.6kg/m^2 Females 29.96kg/m^2 BF% was recorded using Tetra-polar leg–		The results of the multinomial logistical regression model fitting CPI⩾2 identified an association with BF% (OR = 1.06), having poor oral hygiene (OR = 20.09) and smoking (OR = 2.49). Overweight/obesity was associated with CPI⩾2 (OR = 1.78) adjusting for school attended (public school OR = 0.35), oral hygiene (DI-S >1, OR = 23.92) and tobacco consumption (smoker OR = 1.81).	

				leg bioelectrical impedance analysis.			
Fadel et al. 2014 [328]	Not available.	Full mouth technique for pocket depth and bleeding on probing. Marginal gingival bleeding and modified plaque control was recorded from two crossed upper and lower quadrants. DMFT. Oral bitewing radiographs for assessment of approximal caries and alveolar	Probing pocket depth and bleeding on probing was measured on 4 sites per tooth. Marginal gingival bleeding [356] and modified plaque control record [351] was recorded from two crossed upper and lower quadrants. the numbers of decayed and filled teeth and tooth surfaces were registered in modification to the World Health Organization	BMI (kg/m^2), WC, WHR. Obesity was defined based on definition of IOTF for 13 to 18 years old [339]. Hbalc, hsCRP.	Smoking, age, gender, medication. Dietary assessment score was generated based on information on meal frequency and amount of 33 specific sugary and snack products commonly consumed in Sweden. Questionnaire on general health, oral hygiene, fluoride use and smoking habit. HbA1c and HsCRP levels	hsCRP levels were high among obese group = 4.3 (SD 3.8) mg/L. Obese individuals had lower salivary secretion rate ($p<0.001$), pronounced pH drop after the glucose rinse ($p<0.05$) and higher IgA levels ($p<0.001$) as compared to controls. Individuals with obesity had significantly more decayed tooth surfaces ($p<0.02$) and gingival bleeding ($p<0.001$) than controls even after controlling for confounders (smoking, age, gender and medication). There was no significant difference between microbial profiles of obese and controls. All plaque samples showed high proportions of *Streptococcus oralis, Porphyromonas gingivalis and Fusobacterium nucleatum.*	Yes

		bone levels in relation to CEJ in posterior region. Plaque sampling from the periodontal pockets.	(WHO) criteria [350]. Four bitewing radiographs for assessment of approximal caries and alveolar bone levels in relation to CEJ in posterior region Unstimulated salivary samples collected for estimating salivary secretion rate and IgA concentration was measured using ELISA. Plaque pH was determined using pH strips insertion in interproximal areas between the teeth at 7		were also measured Assessment of plaque pH, collection and measurement of cytokine in GCF, sub-gingival plaque sampling and microbial profiling.		

			intervals after rinsing with 10ml of 10% glucose solution for 1 minute. GCF was collected, stored and analyzed for concentration of nine inflammatory cytokines. Sub-gingival plaque samples were collected for microbial profiling of 18 microbial species using checkerboard DNA-DNA hybridization technique.				
Lula et al. 2014 [334]	PD≥3mm and BOP at one or more site.	Partial-mouth protocol, Randomly assigned one upper and	BOP, PD at the mesio-buccal and mid-buccal sites of all teeth, excluding	BMI (kg/m^2) data were used to classify Participants. 1. Normal weight (<25).	Age, race-ethnicity, education, poverty-income ratio, serum cotinine as an indicator	Prevalence rate (PR) of periodontitis in whole population was 18.8%. The periodontitis prevalence in individuals with obesity was 31.9%.	Yes

		one lower quadrant.	third molars, partially erupted teeth and residual roots. .	2. Overweight (BMI25–29.99). 3. Obese (BMI≥30) [343].	of smoking status and self-reported diabetes record. Dietary added sugar intake and frequency and carbohydrate	Crude and adjusted analysis showed a significant association of periodontitis with obesity (OR 2.63, OR 2.22), added sugar (OR 1.54, OR 1.42) and high education level (OR 0.48, OR 0.79) ($p<0.001$)	
Markovic et al. 2014 [321]	No case definition provided for periodontitis. GI and DI-S used to measure gingival index and plaque scores respectively. DMF/dmf was code 0 for no decayed, missing filled teeth and code 1 for at least 1 decayed, missing and filled teeth.	Standard dental examination. Dental probe and mirror.	Simplified Debris index (DI-S) [355] Gingival index (Loe and Silness, 1963) [348] DMF/dmf indexThe oral hygiene was	Weight (kg), Height (cm), BMI and Percentile for Age adjusted BMI (kg/m^2). BMI aligned with WHO growth references for children and adolescents, 5th and 85th percentile is categorized as 'normal weight,' children and adolescents with a BMI between the 85th and 95th percentile are classed as 'at risk of overweight,' and those with BMI greater than the 95th percentile as 'overweight' [344].	Age, sex, daily consumption of sugary food, sugar sweetened soft drinks, physical activity, watching television or computer use, socioeconomic status, frequency of tooth brushing.	Overweight/obese children and adolescents (12-18 years) had higher gingival index score as compared to normal weight individuals ($p<0.001$). Normal weight children and adolescents had higher DMFT scores as compared to overweight/obese individuals ($p<0.01$). Spearman correlation showed BMI was significantly associated to gingival index ($p<0.001$), no correlation was observed between plaque index and nutritional status. Logistic regression showed overweight/obese had two times higher risk of having high plaque index score as compared to normal weight individuals. Multiple variable analysis adjusted for all confounders showed tooth brushing and being at risk of overweight remained associated with plaque index (OR2.5, 95%CI 1.2-4.7, $p<0.01$).	Yes

Galkina et al. 2015 [322]	CPI scores based on WHO criteria [350].	N/A	CPI [350] Tartar/Calculus index, Dental caries, Periodontal disease, fluorosis was also measured. Simplified oral hygiene index OHI-S [355].	BMI Obesity of varying severity (E66 ICD-10) was measured using WHO criteria.	N/A	It was established that the prevalence of caries in children diagnosed with exogenous-constitutional obesity was 75 ± 0.03%. 79% of participants had signs of periodontal disease. Chronic catarrhal gingivitis: localized form (from 3 to 7 teeth) and generalized. The CPI index was 3.43 ± 0.05 segments, with bleeding spread to 1.7 ± 0.2 sextants. • Tartar - by 1.5 ± 0.16. • Pathological pockets - by 0.23 ± 0.3.	No
Lee et al. 2015 [317]	CPI score =1.	Six permanent index teeth, first molars in each posterior sextant and the upper right and lower left central incisors, were selected for the periodontal examination.	CPI [350].	Weight (kg), Height (cm), WC. Abdominal obesity was defined as WC (cm) ⩾ sex and age-specific 90th percentiles according to 2007 Korean Children and Adolescent Growth Standard (Korea Centers for Disease Control and Prevention 2007) [357]. Metabolic syndrome was defined based on National Cholesterol	Age, gender, income, brushing frequency, dental visits in last year, frequency of eating between meals blood pressure, serum triglyceride, HDL cholesterol, fasting blood sugar, physical activity time per week.	Individuals with higher CPI scores were significantly associated with male gender, older age and low HDL levels (<40mg/dl). Among 216 participants with gingivitis, 7.7% participants had high risk of metabolic syndrome, 32% participants had HDL levels below 40mg/dl and 8.8% had abdominal obesity. There was no significant difference observed between the WC in individuals with or without gingivitis (70.85, 71.40). In multiple variable analysis, abdominal obesity was found to have increased odds of gingivitis (OR 1.33, 95% CI 0.59-2.99) when adjusted for confounders of age, gender, income, dental check-up,	No

				Education Program Adult Treatment Panel III (NCEP ATP III) guidelines for adolescents [358]. Participant had metabolic syndrome if they had three or more conditions. • Abdominal obesity; • Fasting glucose level ⩾110 mg/dl; • Elevated blood pressure • Hypertriglyceridemia: serum triglyceride level ⩾110 mg/dl; and low HDL cholesterol: serum HDL cholesterol ⩽40 mg/dl.		frequency of brushing, frequency of eating between meals, and physical activity.	
Zeilger et al. 2015 [330]	PD ≥4mm at one or more site was considered as occurrence of pathological periodontal pocket.	Full mouth protocol,6 sites per tooth. Graded periodontal probe (LM-instruments,	VPI [356], BOP [356] were measured at six sites per tooth. PD, supra-gingival calculus were	Height (cm), Weight (kg), BMI. BMI-SDS adjusted for age and gender [354].	Medical conditions, medications, meal frequency, oral hygiene habit, smoking habit, parent education and	No significant difference was observed between adolescents with and without PD ⩾4mm in regard to age, gender, BMI-SDS, tooth brushing habits, social demographics, medical history or VPI%. Adolescents with PD⩾4 mm had significantly higher BOP> 25%, diastolic blood pressure (P = 0.008) and IL-6 (P <	No

		Parainen, Finland).	recorded on all teeth as present or absent; sub-gingival calculus was recorded as present or absent on proximal surface of first molar and premolar on the radiograph taken as well as clinically probing the gingival sulcus.		country of birth, blood pressure. Serum HDL, TSH, hsCRP, IL-1β, IL-6, IL-8, MCP-1, TNF-α and leptin levels were also measured.	0.001), Leptin (P = 0.018), MCP-1 (P = 0.049) and TSH (P = 0.004).	
Kawabata et al. 2016 [333]	Periodontal disease was defined using two criteria. • PPD ≥4mm (CPI 3 or 4) [211]. • PPD ≥4mm and BOP>30 % [359].	10 teeth selected for examination two molars in each posterior sextant, upper right and lower left central incisor. CPI probe (YDM, Tokyo, Japan).	CPI [350] was measured at six sites per tooth BOP% , plaque and calculus was assessed using simplified oral hygiene index. PPD was measured in	Height (cm), Weight (kg) Categories of BMI were the following [353] 1. Underweight (BMI < 18.5 kg/m^2). 2. Normal weight (BMI 18.5–24.9 kg/m^2). 3. Overweight (25–29.9 kg/m^2). 4. Obesity (≥30 kg/m^2).	Age, gender, blood pressure, oral health behaviour, general health condition, diet, soft-drinks, habitual physical activity, daily alcohol consumption, smoking, frequency of	No association was reported between obesity and periodontitis in the study. The study focused on relationship between hypertension, prehypertension and periodontitis controlling for covariates, of which obesity was one.	No

			10 teeth used for CPI.	For the analysis overweight and obesity were combined together due to lower number of participants.	tooth brushing, use of dental floss, regular dental check-up.		
Kesim et al. 2016 [316]	CPI = 0 (healthy), CPI > 0 (unhealthy).	Partial mouth: six sextants six sites per tooth. WHO 621 Trinity periodontal probe (Campo Mourao; PR Brazil).	CPI [350]. DMFT (adolescent) and measured in the permanent dentition. dmft (6-11 years) measured in primary dentition.	BMI (kg/m^2), WC (cm), body fat percentage. Body fat percentage was measured by bioelectrical impedance analysis (BIA).	Inhabitation, socio-economic status, parents level of education and employment status, Media consumption, sleep duration and nutritional habits. Individuals with growth disorders or using medications were excluded.	BMI and WC was found significantly associated with CPI>0 scores in boys. In Univariate analysis, • DMFT scores were significantly associated with BMI and WC in both genders. • CPI scores were significant for these indices only among boys. • DMFT scores were significantly associated with fat percentage only among girls. In multiple binary logistic regression models, • BMI significantly predicted CPI scores only in boys. • BMI significantly predicted DMFT scores in both genders. According to CPI, there were significant differences between the frequencies of the BMI groups at the age of 16 (boys only) and 17 (girls only) ($p<0.05$).	Yes

PAL – periodontal attachment loss; PALm – periodontal attachment loss mean; PDm – mean pocket depth; GB – gingival bleeding index; GBm – mean gingival bleeding index; Clm – mean calculus index; BMI – body mass index; WC – waist circumference; WHR – waist hip ratio; HC – hip circumference; FFM – free fat mass; LBM – lean body mass; PD – Probing depth; CAL – Clinical attachment loss; PPD – probing pocket depth; TNF- α – Tumour necrosis factor alpha; IL-6 – Interleukin 6; GCF – gingival crevicular fluid; PI – plaque index; GI – gingival index; GR – gingival recession; HbA1c – glycosylated hemoglobin; CPI – community periodontal index; DMFT – decayed missing filled teeth; NIH – National institute of health; ALT – Alanine aminotransferase; HOMA-IR – insulin resistance; VPI% –visible plaque index percentage; BoP – bleeding on probing; BMI-SDS – age and sex adjusted body mass index; IL-8 – interleukin 8; IL-1 β – interleukin 1 beta; HDL – High density lipoprotein; LDL – Low density lipoprotein; CRP – C reactive protein; ABL – Alveolar bone loss; CEJ – Cemento-enamel junction; hsCRP –High sensitivity C-reactive protein; IgA – Immuno-globulin A; WHO – World Health Organisation; ICD – International classification of disease codes; TSH –Thyroid Stimulating Hormones; MCP - Monocyte chemotactic protein; dmft – deciduous (decayed, missing, filled tooth); GBI% - gingival bleeding index percentage; PLI – O'Leary Plaque index; ALT - alanine aminotransferase; PAI-1 – Plasminogen activator inhibitor 1; HbA1c – glycosylated hemoglobin; A1c – glycosylated hemoglobin; BF% - Body fat percentage; DI-S – Simplified Debris Index; IOTF – International Obesity Task Force; Sig – Significant

3.5 Discussion

This review indicated that being overweight or obese, having a high body weight, high BMI and a large waist circumference may be risk factors for periodontal disease as assessed by plaque index, bleeding on probing, probing depth, clinical attachment loss and alveolar bone loss in adolescents and young adults. Seventeen of 25 studies showed a positive association between being overweight/obese and periodontitis [218, 255, 314, 316, 318-321, 323, 324, 327-329, 331, 332, 334, 338, 346].

Of the two prospective cohort studies in the review, DeCastilhos *et al.* suggested a statistically significant association between obesity and gingival index and calculus, which are pre-cursors of periodontal disease [315]. However, no significant association was observed between obesity and periodontitis. Kawabata *et al.* study focused on pre-hypertension/hypertension and periodontitis and did not report on the association between obesity and periodontitis, but included obesity as a covariate [333]. The outcomes of these two prospective cohort studies are inconclusive. Prospective cohort studies are advised to determine the temporal relationship between obesity and periodontitis in younger cohorts.

In the studies which utilized multiple anthropometric measures, waist circumference was strongly associated with periodontitis compared to BMI [255, 314, 317, 319, 326], suggesting that accumulation of visceral fat could be better predictor of periodontitis than BMI.

Several mechanisms were proposed to explain the association of obesity and periodontitis. First, adipose tissues secrete cytokines such as tumour necrosis factor alpha (TNF-α) and interleukin 6 (IL-6) [310]. TNF-α is associated with inflammation in the periodontium, mainly released by monocytes and macrophages in the junctional epithelium circumscribed around the gingival sulcus [360], functions in the destruction of alveolar bone and cartilage in periodontal tissues [361]. It also triggers leucocytosis and synthesis of C-reactive protein (CRP) and amyloid A [362]. Secondly, lipopolysaccharide

(LPS) from gram-negative bacteria harboured in periodontal tissues triggers the secretion of TNF-α and IL-6 via adipose tissues. LPS can promote hepatic dyslipidaemia and decrease insulin sensitivity, leading to increased obesity and diabetes risk [130, 363]. Thirdly, insulin resistance induced by apoptosis of the beta-cells of the pancreas, and cytokines produced by adipose tissues interrupts insulin signalling resulting in insulin resistance [364]. Advanced glycation end products (AGE) promote the production of pro-inflammatory cytokines leptin, TNF-α and IL-6 leading to periodontal inflammation [363, 364]. Finally, dietary free fatty acids have been proposed as a component of the mechanism that links inflammation to obesity, diabetes, and periodontal infection, which in turn modulates production of advanced glycation end-products and insulin resistance.

Lula *et al.* reported consumption of added sugar and sugar-rich diet as an associative factor for obesity and periodontitis [334]. The glucose content of added sugars contributes to postprandial hyperglycaemia and pro-inflammatory cascade that may persist for 16 hours. These postprandial peaks exert oxidative stress and modulate a hyper-inflammatory state, which has been associated with periodontal disease and obesity [334]. Furthermore, Baumgartner et al. study suggested that diet low in refined carbohydrate is associated with reduced gingival bleeding from 35% to 13% [283]. Consumption of added sugars i.e. high fructose products obtained from cane and beet sugar, may induce a hyper-inflammatory state or meta-inflammation. This state leads to abdominal obesity, dyslipidaemia, insulin resistance and periodontal disease. Woelber et al. pilot study on oral health optimized diet and its effect on periodontal inflammation has suggested that diet low in carbohydrate, rich in omega-3 PUFA, Vitamin C and D and fibres can significantly reduce periodontal inflammation [284].

Studies among adults have reported that a diet rich in milk and dairy products has a protective effect on periodontal health. The South Korean survey (2007-2010) on dietary sources of milk and dairy products and their relationship with periodontal disease

in a sample of 1690 adults underwent periodontal assessment (PPD) and nutritional assessment using 24-hour dietary recall. Multiple logistic regression analysis showed an inverse relationship between consumption of dairy products and risk for periodontitis, following adjustment for age, BMI, energy intake, income, smoking/alcohol intake [285]. A study in 942 Japenese adult participants, who underwent a periodontal examination and a diet survey (food frequency questionnaire) reported that daily intake of dairy products or lactic acid rich food products had a beneficial effect on periodontal disease [286].

Heterogeneity of studies

There was a high level of heterogeneity observed in the studies included in the systematic review that limits our ability to conduct a meta-analysis. We identified methodological problems with the study design such as the lack of power calculation in most of the studies. Other variations included the report of body composition thresholds and periodontitis case definitions which might affected the association between obesity and periodontitis. Numerous variations were centered around the sampling frame, inclusion/exclusion criteria, study design, clinical examination protocols and periodontal probes used, examiner reliability and social determinants such as age, gender, education, ethnicity and other covariates which may have affected the association. Despite this, a consistent pattern emerged to suggest that risk of periodontitis is associated with obesity at young age. Hence, heterogeneity may have affected the magnitude of the risk, rather than precluding the risk.

Due to the differences between studies when comparing measures of body composition, periodontal outcome, sampling methds, protocol and probes used, an attempt by the reviewers to quantify the relationship between obesity and periodontitis through meta-analysis or other statistical methods would most likely produce an effect size estimate that is at best spurious if not misleading and unhelpful for future research.

Rather, the reviewers have focussed on limiting the subjectivity of this narrative review by employing robust methodology for the formulation of the review question (PRISMA, PICO), thorough and reproducible literature searches and objective reporting of study results.

Recommendations for future research

From this study, we determined that obesity and periodontitis are chronic conditions with multiple influences. The recommendation for future researchers for obesity and periodontitis studies in adolescents and young adults are presented in the Table 3.5 according to the structure suggested by Brown et al. for formulating research recommendations in systematic reviews [1].

The association between obesity and periodontitis may not be a product of single influencing factor, but the result of a synergy of multiple factors. Hence, prospective studies should consider the inclusion of multiple measures to better identify those factors that may link obesity and periodontitis and to develop an ecological framework to examine this relationship. Particularly in reference to dietary habits, oral health behavior (tooth brushing, flossing, interdental cleaning or using a fluoride rinse), water fluoridation, and other factors.

Additional factors recommended in future studies are; (1) multiple measures of body composition; (2) use of a full-mouth protocol with universal periodontal probe or Florida probe to measure the periodontal measures of pocket depth, clinical attachment loss, bleeding on probing and plaque index; (3) adopting a universal case definition of periodontitis [365]; (4) using an appropriate definition for obesity such as International Obesity Task Force and Cole's criteria for young adults and adolescents [339].

Table 3.5 Research Recommendations (based on format from *Brown et al.* 2006)	
Core elements	**Recommendation for future research**
(E) Evidence (current)	Systematic review identified predominantly cross-sectional, case control and few cohort studies Future studies should focus on understanding the role of fat in obesity and periodontitis association.
(P) Population	Adolescents and young adults WHO specific age distribution for adolescents and young adults
(I) Intervention/Exposure	WHO defined BMI and BMI categories for adolescents and young adults Use of multiple body composition measures such as waist circumference, waist-hip ratio, waist to height ratio and body fat percentages.
(C) Comparison	Normal weight individuals (BMI<25kg/m^2)
(T) Time stamp	August 2017
(O) Outcomes	Periodontal disease according to Eke et al. 2012 case definition of periodontitis. Full mouth periodontal assessment using calibrated Florida probe system. Periodontal measures of clinical attachment loss, probing depth, plaque index and bleeding on probing on six sites per tooth. Include age, gender, smoking, diet diary and blood markers (CRP, Lipid profile and apolipoprotein B) as covariates in analyses.
(d) Disease burden	Around 1.9 billion adults aged 18 years and older were overweight and over 600 million adults were obese (WHO, 2014) The worldwide prevalence of periodontitis is 35% in adults
(t) Timeliness	Cohort follow-up of young adults over a period of years, Clinical trials on dietary intervention and its effect on obesity and periodontitis with 6-month follow-up
(s) Study type	Prospective cohort studies or clinical trials

There is a need for studies to clearly illustrate the age distribution according to the WHO criteria to define adolescents [366]. Hence, a consensus is needed to clearly define the age range for people who are young adults. More importantly high evidence based studies (e.g. prospective cohort) in large population representative samples with long term follow-ups, devised using a pre-specified hypothesis are essential to truly understand the temporal relationship between body composition and the onset or extent and severity of periodontitis in young adults and adolescents.

Strengths and limitations

The strengths of this systematic review include the development of hypotheses and focused review question on obesity and periodontitis association in young adults and adolescents using the PICO strategy. Other potential strengths lie in the generation of broader search strategy using a wide array of search terms (Mesh terms, Emtree terms and Free text terms), a comprehensive search for evidence using several databases for electronic searching; snowballing technique and hand searching of studies. Our criteria also included non-English articles. The use of explicit and reproducible inclusion/exclusion criterion-based selection of relevant evidence using PICO, the rigorous use of NOS for appraisal of validity and the summary table of synthesis reporting study characteristics and outcomes are other important strengths of this review.

Despite the rigorous search strategy, it is expected that more information on this review question may lie embedded in publications focusing on studies of comorbidities such as cardiovascular disease, metabolic syndrome or diabetes and periodontitis. The results and value of these collateral data existing as part of previously conducted investigations remains unknown. Additional researchers might have investigated the association between obesity and periodontitis in young adults and adolescent, however not reported it due to a lack of positive findings, therefore resulting in a publication bias.

A limitation of this review was that it comprised mainly of cross-sectional and case-control studies, which are low quality study design according to hierarchy of evidence.

Chapter 4. Overweight/obesity and periodontitis in Australian adults: A population-based cross-sectional study

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4.1 Abstract

Background: Overweight/obesity and periodontitis are public health issues in Australia. This study aimed to determine the association between overweight/obesity and periodontitis in Australian adults.

Methods: The cross-sectional National Survey of Adult Oral Health 2004-06 data was analysed. Body mass index was calculated, and a self-reported questionnaire was used to measure the estimated daily intake of added sugar. Mean number of sites with probing depth (PD)⩾4mm and clinical attachment loss (CAL)⩾4mms, prevalence and extent of periodontitis were used as outcome measures. CDC/AAP periodontitis case definition was adopted. Bivariate analyses and multiple variable regression models were constructed.

Results: The study sample was 4170 participants. The proportion of people that were overweight/obese were 51.9% (95%CI 48.1%,54.1%). Overall 21.3% (95%CI 19.3%, 23.5%) people experienced periodontitis. Mean number of sites with PD⩾4mm and CAL ⩾4mm were recorded as 0.7 [95%CI, 0.5, 0.9] and 2.4 [95%CI, 2.1, 2.6] respectively. Multiple variable analysis suggested that periodontal parameters (sites with PD⩾4mm

[0.13, 95%CI -0.86, 0.35] and sites with CAL⩾4mm [0.11, 95%CI-0.58, 0.35],presence of periodontitis [1.23, 95%CI 0.96, 1.57] and extent of periodontitis [measured using CAL⩾4mm were not associated with overweight/obesity when controlled for putative confounders.

Conclusion: No association was observed between overweight/obesity and periodontitis in this study.

Keywords: Periodontal disease, Obesity, Oral health, Public health, Chronic disease, BMI

4.2 Introduction

Overweight/obesity is a global epidemic. The prevalence of being overweight or obese in Australian adults is 63% and 28% respectively [259]. Overweight/obesity is a result of a complex system that includes multiple influences (contextual, cultural, psychological, metabolic, and genetic risk factors), often referred to as the socio-ecological framework of obesity [2]. Obesity is defined as *"imbalanced levels of energy intake and energy expenditure,"* that is impacted, compounded and driven by these multiple influences [367]. Chronic co-morbidities, including type 2 diabetes and cardiovascular diseases are significant health outcomes associated with obesity [368].

Periodontitis occurs as a pro-inflammatory state that affects the supporting periodontal tissues of the teeth. The aetiopathogenesis of periodontitis occurs as a result of the ecological interaction of dental plaque biofilm [61] and the host immune-system response leading to metabolic changes in the bone and localisation of pro-inflammatory cytokines [369], under the influenced by lifestyle factors [370] and chronic co-morbidities [371]. The prevalence of periodontitis in Australia is reported to be 24.5% [26]. Socio-economic factors e.g., low income, low education and unemployment; lifestyle habits including dental visiting behaviour and oral hygiene behaviour; and risk behaviors such as smoking

and alcohol consumption are factors significantly associated with periodontitis in Australian adults [26].

The relationships between obesity and periodontitis have been reported in previous studies.[14, 371] Obesity contributes to increased complexity of periodontal pathogens [309] and raised levels of pro-inflammatory cytokines [9]. Lifestyle changes, including higher added sugar intake increases the susceptibility to energy imbalance often leading to weight gain [372] and other long-term health consequences including periodontitis [371].

Obesity and periodontitis are significant health problems in Australia, with common contributing factors including socio-economic, diet and chronic co-morbidities. This leads to the hypothesis that obesity or being overweight is associated with periodontitis in Australian adults and the research question "*Is obesity or being overweight a risk factor for periodontitis in Australian adults*?". Hence, this study aimed to determine the association of overweight/obesity and periodontitis in Australian adults.

4.3 Methods

4.3.1 Study design

This study was a secondary analysis design using data from the cross-sectional survey, National Survey of Adult Oral Health 2004-06 (NSAOH 2004-06). This survey was conducted by the Australian Research Centre for Population Oral Health (ARCPOH) and recruited the representative sample of dentate Australians aged 15 years and older using a clustered randomised sampling technique. The NSAOH had three stages that included computer aided telephone interview (CATI), oral examination and mailed questionnaire. The details of the NSAOH 2004-06 data are described elsewhere [4]. STROBE statement guidelines, essential for good reporting of cross-sectional studies, were followed.

4.3.2 Computer-aided telephone interview

The CATI was undertaken using Windows-based WinCati 4.2 software. Approximately ten days prior to the CATI, a primary approach letter was sent to the participants outlining the purpose of the survey. A toll-free telephone number was provided to participants, in the event of any queries raised regarding the survey. The telephone number of participants who made contact to withdraw from the survey were removed from the interview sample list. The CATI consisted of 79 questions regarding social demographics (age, gender, rural location, indigenous identity, remoteness, country of birth, and language spoken at home), perceived need for treatment, subjective periodontal outcome measures, questions about gum treatment, medical history (self-reported diabetes), dental visiting behaviour, oral hygiene behaviour, risk behaviour, income and education, height and weight.

4.3.3 Oral epidemiological examination

The oral epidemiological examination of participants was carried out following a standardised dental examination procedure. Clinical appointments were scheduled at the nearest public dental clinic within or near the postcode of the participant. Informed consent and a medical history was obtained prior to the dental examination. Participants were asked to complete a medical history form about conditions which, if present, would preclude a periodontal examination as follows: (i) a doctor or dentist told that the participant must take antibiotics before to get a dental check-up or care; (ii) a doctor told the participant they had a congenital heart murmur, heart valve problem, congenital heart disease or bacterial endocarditis; (iii) rheumatic fever; (iv) kidney disease requiring dialysis; (v) haemophilia; (vi) a pacemaker or automatic defibrillator; other artificial material in the participant's heart, veins, or arteries (this was a contraindication in 2004-06 when the NSAOH 2004-06 was conducted, hence it has been retained as a contraindication for periodontal examination in this paper); (viii) a hipbone or joint

replacement that has been inserted in the last 3 months; (ix) transplanted organs. People who answered yes to at least one of these questions were excluded from the periodontal examination. Individuals with no contraindication underwent full-mouth periodontal charting (three sites per tooth – mesio-buccal, mid-buccal and disto-buccal) of probing depths (PD) and clinical attachment loss (CAL) using a periodontal condition probe (PCP2, Hu - Friedy, Chicago, USA). Third molars were excluded from the oral examination.

4.3.4 Mailed questionnaire

The questionnaire included 13 food frequency questions on dietary sugar intake. These questions asked about the intake of fruits, sweetened fruit drinks and soft drinks, plain and flavored milk, sweetened dairy products, breakfast cereals, biscuits and cakes, table sugar, chocolate and confectionery, syrups and jams, and muesli bars. For each food item, the total number of servings consumed on a usual day and in the last hour before bed was requested. The AUSNUT 2011-2013 food composition database [373], that enables food, dietary supplement and nutrient intake estimates to be made from dietary data and was used to generate grams per day intake of added sugar in FoodWorks version 8 dietary analysis package (a nutritional analysis software) [374]. A qualified nutritionist (KK) carried out the dietary analysis. Questionnaire and data base foods were matched using the most similar generic food item. Serving sizes were initially generated by consulting the NSAOH questionnaire; where these were unclear, a serving size for the selected food or beverage was obtained through the standard portion sizes, as outlined in the Australian Guide to Healthy Eating (AGHE). Where foods were not available from the AGHE (e.g. discretionary foods), a value of ~600kj was attributed.

4.3.5 Data analysis

The STATA version 15 was used for statistical analysis [StataCorp.2017] [375] The complex survey design of the NSAOH was accounted for; data were stratified by metropolitan and rural regions, clustered by post code and weighted for the probability of participants being selected for inclusion in the questionnaire. Categorisations used were: age (15-44 years; 45-59 years; and ⩾ 60 years); sex (male; female); education (degree/teaching and nursing; trade/diploma/certificate; and high school or less); total household income in Australian dollars (<$30 thousand; $30 thousand to <$60 thousand; and ⩾$60 thousand); alcohol intake (2 drinks per day; ⩾2 drinks per day); smoking (current; former; and never); self-reported diabetes (yes or no); tooth brushing (<2times per day; and ⩾2times per day); flossing (yes; and no); mouth rinsing (yes; and no); usual reason for dental visiting (problem based dental visits or r egular checkup); and BMI (underweight/normal weight "<25kg/m^2"; and overweight/obese " ⩾ 25kg/m^2"). Periodontitis was defined according to the Center for Diseases Control and Prevention and the American Academy of Periodontology case definition of periodontitis (no periodontitis or periodontitis) [376], where no or mild periodontitis were grouped as "no periodontitis" and moderate or severe periodontitis were grouped as "periodontitis".

The extent of periodontitis is defined as a measure of the percentage of teeth that have periodontitis, calculated using variables of PD⩾4mm and CAL⩾4mm respectively [377]. Extent scores calculation is important for comparing study participants with varying numbers of teeth [378]. The extent of periodontitis was calculated for PD⩾4mm and CAL ⩾4mm and reported as percentages. Extent of periodontitis was calculated by dividing the number of periodontal sites with PD⩾4mm or CAL⩾4mm with the total number of the periodontal sites. Bivariate analysis was undertaken for the extent of periodontitis.

Multiple variate linear regression analysis was performed for the adjusted odds ratios of the extent of periodontitis (using CAL $\geqslant$ 4mm measure) in relation to independent variable of overweight/obesity and the confounders (age, sex, income, education, smoking, flossing, type 2 diabetes, added sugar, and the usual reason for dental visit)..

National guidelines for alcohol consumption was used as a recommendation for daily alcohol intake, which defined a standard alcohol beverage contains 10 grams of alcohol is an established metric for estimating alcohol consumption across drink types [379]. The American Heart Association recommendation that added sugar intake should be limited to 36 grams per day for men and 25 grams per day for women [380] was adopted for the analysis.

The variables were analysed using frequency distribution for categorical variables and mean (standard deviations) for the continuous variables. Bivariate analysis (using Rao-Scott chi-square test and Independent sample t-test) were conducted for overweight/obesity and its putative confounders; and for periodontitis, extent of periodontitis and its putative confounders. The Independent sample t-test was used to analyse periodontal parameters (sites with PD $\geqslant$ 4mm and sites with CAL $\geqslant$ 4mm) in relation to putative confounders. The Center for Disease Control and Prevention and American Academy of Periodontology criteria was used to allow comparisons with previous studies. Multiple variable models (linear and logistic regression models) were generated to analyse the association of overweight/obesity with periodontitis and extent of periodontitis when controlled for the confounders.

The ethics approval for NSAOH 2004-06 was obtained from University of Adelaide Human Research Ethics Committee and the study was conducted according to the World Medical Association Declaration of Helsinki (version, 2008). All examined subjects provided a signed, informed consent to participate in the study. For participants

under the age of 18years, a written inform consent was taken from the parents/guardians, approved by the University of Adelaide Human Research Ethics Committee.

4.4 Results

A total of 4170 participants completed the mailed questionnaire and were included in the data analysis. The prevalence of overweight and obesity in the NSAOH was found as 32.7% and 16.6% respectively. Characteristics of participants were described in Table 1. More than half of the participants were overweight/obese, aged 15-44 years, had high school or lower education level, were non-smokers, consumed less than two drinks of alcohol per day, rinsed their mouth daily, brushed their teeth twice daily and visited their dentist for regular check-ups (Table 4.1). Around 48% of the participants flossed daily. Nearly 47% of participants had an annual income more than $60,000 per annum. Males and females were equally distributed in the sample. Less than five percent participants had self-reported diabetes. The proportion of participants with periodontitis was 22.7%. Approximately 17% of the participants had added sugar intake above the American Heart Association recommended level of added sugar intake. Individuals 15-19 years and 20-30 years were distributed as 3.5% and 8.4% respectively in the sample population. Only one participant in the 15-19 years had periodontitis and 21 participants aged 20-30 years had periodontitis. This sample size was not considered large enough for further analysis.

Table 4 1 Characteristics of participants

Characteristic	Level	n	weighted percentage %	95% CI (Lower)	95% CI (Upper)
Age	15-44	1591	56.7	54.2	59 3
	45-59	1333	25.2	23.3	27 1
	60+	1246	18.1	16.4	19.7
Sex	Male	1604	50.0	47.4	52.6
	Female	2566	50.0	47.4	52.6
Income	<30k	1253	24.1	21.7	26.6
	30k-<60k	567	29.4	26.9	31 9
	60k+	2093	46.5	43.3	49.8
Education	High school or less	1349	56.4	52.7	60.0
	Trade/Dip/cert	1351	38.6	35.2	42.0
	Degree/Teaching/nursing	1372	5.0	3.9	6.3
Diabetes	Yes	213	4.3	3.2	5.5
	No	3956	95.7	94.5	96.8

Smoking	Current	578	15.2	13.2	17 1
	Previous	1315	27.3	25.1	29 5
	Never	2277	57.5	55.0	60 1
Alcohol	⩽2 drinks	2191	57.7	54.5	60.8
	>2 drinks	1152	42.3	39.2	45 5
Usual Reason for Dental Visit	Check-up	1712	58.5	52.6	58.8
	Problem	1602	41.5	41.2	47.4
Mouth Rinsing	No	2821	41.9	39.3	44.6
	Yes	1347	58.1	55.4	60.7
Tooth Brushing	<2 day	1612	44.5	41.8	47 2
	⩾2 day	2535	55.5	52.8	58 2
Flossing	No	1952	51.5	48.6	54 3
	Yes	2217	48.5	45.7	51.4
BMI	Underweight/Normal	1685	48.1	45.9	51 9
	Overweight/Obese	2060	51.9	48.1	54 1
		Mean	SE		
Added sugar	rams/day	19.1	0.5	18.1	20 1

Bivariate analysis found that the factors significantly associated with overweight/obesity included age (45-59 years) ($p<0.001$); male ($p<0.001$); no university level of education ($p<0.05$); former smoking habit ($p<0.001$); and problem based dental visits ($p<0.001$) (Table 4.2). No association was observed between added sugar intake and overweight/obesity in the bivariate analysis. It was found that the factors that were significantly associated with periodontitis (Table 4.3) included being age ≥60 years ($p<0.05$); male ($p<0.05$), and having an annual income less than $30000 ($p<0.05$), less than secondary education ($p<0.05$), a current smoking habit ($p<0.05$), problem-based dental visiting behaviour ($p<0.05$) and being overweight/obese ($p<0.05$). Added sugar intake was inversely associated periodontitis ($p<0.05$).

Table 4.2 Bivariate analysis of BMI (Underweight/Normal BMI ⩽25 kg/m^2, Overweight/Obese BMI as >25 kg/m^2), and putative confounders. Chi-squared test for significance used for categorical predictors, t-test for continuous predictors. Significance at $p<0.05$.

Characteristic	Level	Underweight/ Normal %	95%CI (Lower)	95%CI (Upper)	Overweight/ Obese %	95%CI (Lower)	95%CI (Upper)	p-value
Age	15-44	57.5	52.7	62.3	42.5	37.7	47.3	
	45-59	37.8	33.9	41.6	62.2	58.4	66.1	
	60+	37.1	33.3	40.9	62.9	59.1	**66.7**	**<0.001**
Sex	Male	43.2	38.1	48.2	56.8	51.8	61.9	
	Female	54.9	51.7	58.1	45.1	41.9	**48.3**	**<0.001**
Income	<30k	44.0	37.9	50.2	56.0	49.8	62.1	
	30k-<60k	47.1	42.7	51.5	52.9	48.5	57.3	
	60k+	49.4	44.3	54.5	50.6	45.5	55.7	0.366

Education	High school or less	50.7	42.2	52.7	49.3	47.3	57.8	
	Trade	41.1	36.4	47.3	58.9	52.7	63.6	
	Degree	39.6	46.0	56.8	60.4	43.2	**54.0**	**0.027**
Diabetes	Yes	47.4	42.2	52.7	52.6	46.0	56.8	
	No	41.9	36.4	47.3	58.1	47.3	57.8	0.1222
Smoking	Current	50.2	43.0	57.5	49.8	42.5	57.0	
	Previous	37.1	32.3	41.8	62.9	58.2	67.7	
	Never	54.1	50.2	57.9	45.9	42.1	**49.8**	**<0.001**
Alcohol	<=2drinks	45.0	42.0	49.8	55.0	50.2	58.0	
	>2 drinks	47.8	42.7	54.3	52.2	45.7	57.3	0.401
Usual Reason for Dental Visit	Check-up	54.3	50.1	58.5	45.7	41.5	49.9	
	Problem	40.9	36.4	45.4	59.1	54.6	**63.6**	**<0.001**
Mouth Rinsing	No	47.6	42.9	52.2	52.4	47.8	57.1	
	Yes	49.9	46.1	53.6	50.1	46.4	53.9	0.498
Tooth brushing	<2times/day	45.0	39.7	50.4	55.0	49.6	60.3	0.08
	>=2 times/day	50.6	47.1	54.1	49.4	45.9	52.9	
Flossing	No	46.5	41.8	51.3	53.5	48.7	58.2	0.24
	Yes	49.9	46.3	53.5	50.1	48.7	54.9	
		Underweight/ Normal mean	**95%CI (Lower)**	**95%CI (Upper)**	**Overweight/ Obese mean**	**95%CI (Lower)**	**95%CI (Upper)**	**t-test p-value**
Added Sugar (mean)	gram/day	19.7	17.7	21.7	18.8	17.5	19.8	0.455

Table 4.3 Bivariate analysis of periodontitis and putative confounders. Chi-squared test for significance used for categorical predictors, t-test for continuous predictors. Significance at p<0.05

Characteristic	No periodontitis	95%CI (Lower)	95%CI (Upper)	Periodontitis	95%CI (Lower)	95%CI (Upper)
Age						
15-44	89.1	86.7	91.1	10.9	8.9	13.3
45-59	68.4	64.5	72.1	31.6	27.9	35.5
60+	52.4	48.3	56.4	**47.6***	43.6	51.7
Sex						
Male	72.4	69	75.6	**27.6***	24.4	31.0
Female	81.9	79.9	83.7	18.1	16.3	20.1
Income						
⩽30K	63.4	59	67.6	**36.6***	32.4	41.0
>30k-<60K	75.3	71.4	78.8	24.7	21.2	28.6
60K+	83	79.9	85.7	17	14.3	20.1
Education						
University/teaching/nursing	79	75.9	81.8	21	18.2	24.1
Trade certificate/Dip/Cert	75.9	72.3	79.3	24.1	20.7	27.7
No post-secondary education	64.1	52.2	74.6	**35.9***	25.4	47.8
Diabetes - Self-reported						
Yes	62.2	51.9	71.6	37.8	28.4	48.1
No	77.9	75.9	79.8	22.1	20.2	24.1
Smoking						
Current	70.5	64.8	75.6	29.5*	24.4	35.2
Former	71.1	67.3	74.7	28.9	25.3	32.7
Never	82.1	79.7	84.3	17.9	15.7	20.3
Alcohol						
⩽2 drinks	76.3	73.5	78.8	23.7	21.2	26.5
> 2 drinks	77.1	73.3	80.4	22.9	19.6	26.7
Mouth-rinsing						
No	79.2	76.5	81.7	20.8	18.3	23.5
Yes	75.9	73.2	78.5	24.1	21.5	26.8
Tooth brushing						
<2times/day	79.2	75.8	82.2	20.8	17.7	24.2
⩾ 2 times/day	78.1	75.4	80.5	21.9	19.4	24.6
Flossing						
No	77.1	73.9	80.0	22.9	20.0	26.1
Yes	80.2	77.6	82.6	19.8	17.4	22.4
Usual reason for dental visit						
Check-up	81.3	79.1	83.4	18.7	16.6	20.9
Problem	71.6	68.5	74.5	**28.4***	25.5	31.5
BMI						
Underweight/Normal	83.9	80.4	85.3	16.1	14.7	19.6
Overweight/Obesity	74.7	70	76.2	**25.3***	23.8	30.0
Variables	No periodontitis	95%CI (Lower)	95%CI (Upper)	Periodontitis	95%CI (Lower)	95%CI (Upper)
Added sugar	19.2	18.0	20.2	**17.2***	16.2	18.1

In bivariate analysis, periodontal parameters of sites with PD≥4mm ($p<0.05$) and sites with CAL≥4mm ($p<0.001$) were significantly associated with obesity. The putative confounders that were significantly associated with mean number of sites with PD≥4mm included sex ($p<0.01$), smoking ($p<0.001$), alcohol ($p<0.05$), usual reason for dental visiting ($p<0.001$), BMI ($p<0.05$), mouth rinsing ($p<0.001$), tooth brushing ($p<0.01$) and flossing ($p<0.03$) (Table 4.4). The putative confounders that were significantly associated with mean number of sites with CAL≥4mm included age ($p<0.001$), sex ($p<0.001$), education ($p<0.001$), income ($p<0.001$), self-reported diabetes ($p<0.05$), smoking ($p<0.001$), usual reason for dental visiting ($p<0.001$), BMI ($p<0.001$) and added sugar intake ($p<0.001$).

The multiple variable analysis indicated that periodontal parameters: sites with PD≥4mm [Odds ratio (OR) 0.13, 95% CI -0.86, 0.35] and sites with CAL≥4mm [OR -0.11, 95% CI -0.56, 0.35] (Table 4.5) and presence of periodontitis [OR 1.23, 95% CI 0.96, 1.57] (Table 4.6) was not associated with overweight/obesity when controlled for putative confounders that were significant in the respective bivariate analysis. As mean estimates can be skewed, the bivariate and multiple variable analyses were recalculated using proportions for CAL≥4mm and PD≥4mm and the results were very similar to that found using means (Table S1 and Table S2).

Table 4 4 Bivariate analysis of periodontal parameters (Chi-squared test for significance used for categorical predictors, t-test for continuous predictors) Significance at p<0 05

Characteristic		PD⩾4mm (mean)	95%CI (Lower)	95%CI (Upper)	P value	CAL⩾4mm	95%CI (Lower)	95% CI (Upper)	P value
Age	15-44	*0.6*	**0.4**	**0.9**	0.33	**0.9**	**0.7**	**1.1**	**<0.001**
	45-59	*0.9*	0 6	1 1		3 4	3 0	3 9	
	60+	*0.7*	0 6	0 9		6 1	5 4	6 9	
Sex	Male	*0.9*	0 6	1 2	0.01	2 8	2 4	3 2	**<0.001**
	Female	*0.5*	0 4	0 6		1 9	1 7	2 1	
Income	<30K	*1.1*	0 6	1 6	0 06	4 3	3 6	5 0	**<0.001**
	>30k - <60K	*0.7*	0 5	0 9		2 6	2 1	3 1	
	60K+	*0.6*	0 4	0 8		1 6	1 3	1 9	
Education	University/teaching/nursing	*0.5*	0 6	0 7	0 15	2 1	1 8	2 5	**<0.001**
	Trade certificate/Dip/Cert	*0.8*	0 6	1 0		2 7	2 3	3 2	
	No post-secondary education	*2.0*	-0 8	4 8		4 8	2 8	6 9	
Diabetes - Self-reported	Yes	*0.8*	0 4	1 3	0 64	3 8	2 2	5 3	**0.03**
	No	*0.7*	0 5	0 9		2 3	2 1	2 6	
Smoking	Current	*1.9*	1 0	2 7	**<0.001**	3 6	2 8	4 5	**<0.001**
	Former	*0.6*	0 5	0 8		3 1	2 7	3 6	
	Never	*0.4*	0 3	0 5		1 7	1 4	1 9	
Alcohol	⩽2 drinks	*0.6*	0 4	0 7	**0.02**	2 4	2 1	2 7	0 669
	> 2 drinks	*1.0*	0 6	1 4		2 5	2 0	2 9	
Usual reason for dental visit	Check-up	*0.4*	0 3	0 5	**<0.001**	1 9	1 7	2 2	**<0.001**
	Problem	*1.1*	0 8	1 5		3 0	2 6	3 4	
BMI	Underweight/Normal weight	*0.5*	0 4	0 7	**0.05**	1 9	1 5	2 2	**<0.001**
	Overweight/Obese	*0.8*	0 6	0 9		2 8	2 4	3 2	
Mouth-rinsing	No	*0.5*	0 4	0 6	**<0.001**	2 3	1 9	2 6	
	Yes	*0.9*	0 6	1 1		2 4	2 1	2 7	0 52
Tooth brushing	<2times/day	0 9	0 6	1 3	**<0.01**	2 2	1 8	2 6	0 15
	⩾2 times/day	0 5	0 4	0 6		2 5	2 2	2 8	
Flossing	No	*0.9*	0 6	1 2	**0.03**	2 5	2 1	2 9	0 20
	Yes	*0.5*	0 4	0 7		2 2	2 0	2 5	
Added sugar	grams/day	*19.2*	18 2	20 3	0 66	19 2	18 2	20 3	0 009

Table 4 5 Multiple variable linear regression models for periodontal parameters (mean number of sites CAL >= 4mm and mean number of sites with PD >=4mm in relation to potential confounding variables.

Characteristic	Level	Coefficient CAL ⩾ 4mm	95%CI (Lower)	95%CI (Upper)	*P values*	Coefficient PD ⩾ 4mm	95%CI (Lower)	95%CI (Upper)	*P values*
BMI	Overweight/Obese	-0.1	-0.6	0.4	0.61	0.1	-0.9	0.3	0.23
Age	60+	2.8	2.4	3.3	<0.001				
Sex	Female	-0.6	-1.1	-0.1	0.01	-0.1	-0.3	0.1	0.17
Education	Degree/Teaching/nursing	0.3	-0.3	0.8	0.29				
Smoking	Never	-0.6	-1.00	-0.2	0.002	-0.4	-0.6	0.2	**<0.001**
Usual reason for dental visit	Check-up	0.7	0.2	1.2	0.007	0.4	0.2	0.6	**<0.001**

Table 4.6 Multiple variate binary logistic regression analysis – Adjusted model for periodontitis, overweight/obesity and confounding factors (age, sex, smoking and usual reason for dental visit

Characteristic	Levels	Odds Ratio	95%CI (Upper)	95%CI (Lower)	P value
BMI	Normal weight	1 (Reference)			
	Overweight/Obese	1.2	0.9	1.5	0.09
Age	15-44	1 (Reference)			
	45-59	1.2	0.9	1.4	<0.001
	60+	2.5	1.7	3.6	<0.001
Sex	Female	1 (Reference)			
	Male	1.7	1.3	2 1	<0.01
Smoking	Never	1 (Reference)			
	Current	1.8	1.2	2.6	<0.001
	Former	1.3	1.0	1.7	<0.05
Usual reason for dental visit	Check-up	1 (Reference)	-	-	-
	Problem	1.6	1.2	2.0	<0.05

Appendix E reports report extent of periodontitis. No association was found between overweight/obesity and extent of PD⩾4mm variable. Hence, no multiple variable analysis was done for PD⩾4mm. Age, sex, income, smoking, flossing, usual reason for dental visiting, tooth brushing and frequency of mouth rinsing were significantly associated with PD ⩾4mm.

The extent of CAL⩾4mm was significantly associated with BMI, age, sex, income, education, smoking, flossing, type 2 diabetes, added sugar intake, and the usual reason for dental visiting. In the multiple variable analysis, there was not a significant association between overweight/obesity and CAL⩾4mm (appendix F). The confounders of age ($p<0.001$), income ($p<0.001$) and smoking ($p<0.001$) were significantly associated with higher CAL⩾4mm.

4.5 Discussion

After adjusting for the putative confounders in the four multiple variable regression models, no association was found with overweight/obesity with prevalence and extent of periodontitis [when measured by CAL≥4mm]. This could be a result of complexity in the relationship between overweight/obesity, periodontitis and putative confounders including smoking, diabetes and dental visiting behaviour.

The finding is supported by studies on prevalence and extent of periodontitis. The prevalence study by Castilhos et al. study that suggested there was no association between obesity and periodontitis in young adults [315]. Similar results were found in the fourth Korean National Health and Nutrition Examination Survey (KNHANES) and Health 2000 Health Examination Survey of Finland, where obesity was not associated with periodontitis in adults after adjusting for putative confounders [212, 381]. Contrary to this finding, numerous systematic reviews report a significant association between obesity and periodontitis [14, 371]. Extent of periodontitis studies reported similar results. The Khader et al., and Sarlati et al., studies found a significant relationship between extent of periodontitis (whether measured by CAL≥4mm and PD≥4mm) and overweight/obesity [131,319].

Periodontitis occurs as a result of interaction between dental plaque biofilm and the host-immune response from modifiable factors including obesity. People with obesity have a pro-inflammatory state, due to the deposition of visceral adipose tissues that secretes immune-modulatory factors such as leptin, adiponectin, complement components, plasminogen activator inhibitor-1, proteins of the renin-angiotensin system, and resistin [214]. These bioactive molecules modulate angiogenesis, hormonal and metabolic changes, that lead to increased systemic inflammation and acute phase reactions [214]. These events appear to be related to periodontal disease and may injure periodontal tissue.

This study found that overweight/obesity was significantly associated with the periodontal parameters of sites with PD⩾4mm in the bivariate analysis. This result accorded with the Hisayama study that found that obesity was significantly associated with deep pockets (sites with PD ⩾4mm) [382]. Similar results were found in Japanese adults where, with each 1kg/m^2 increase in BMI, there was 16% increased risk of periodontitis (sites with PD ⩾4mm) [346]. Deep pocket is a measure of active or existing periodontal disease, therefore it could be said that obesity was associated with primary stage of periodontal disease.

In this study, no association was found between overweight/obesity and sites with CAL ⩾4mm. The results of our study are similar to those reported by Saito et al. where it was found that obesity was not associated with CAL [382]. CAL is a measure of alveolar bone loss and is an indicator of history of periodontal disease. It occurs as a result of inflammation that leads to periodontal tissue destruction [382].

Periodontal disease prevalence experience among the NSAOH 2004-06 sample was significantly associated with increasing age, being male, a current or former smoking habit and problem-based dental visiting behaviour's. These findings are in line with previous studies [84, 138, 243, 248, 255, 257, 383]. Periodontal disease extent as measured by CAL≥4mm as well as associated with variables immediately above, it was also significantly associated with low income and lower education level.

Periodontitis is an age-dependent disease with increasing prevalence and severity of periodontitis among adults 30 years and older [255]. The results of this study reflects similar population based study amongst 30-39 year and 50-59 year old Thai adults, suggesting a significant increase in periodontal outcome measures (PD and CAL) among the older age group as compared to the younger counterpart [383]. The concept of ageing as a potential marker for periodontitis has evolved with research, from being an inevitable consequence of ageing to the

current concept of periodontitis as a cumulative effect of long-term exposure to its true risk factors [257].

This study found that people who floss daily had significantly higher extent of CAL≥4mm. A Cochrane systematic review found a weak and unreliable evidence from 10 studies that flossing may be associated with reduction in periodontitis [384]. Regardless of research, it is a usual dental practice to recommend the use of dental floss (as a de facto healthy oral hygiene behaviour) in daily care. As NSAOH was a cross-sectional survey it cannot be used to determine causal effect. It may be people with periodontitis are advised to floss as a result of their disease. Alternatively, it may be people haven't got periodontal disease because they regularly flossed in the past.

In this study, added sugar intake was significantly associated with the extent of CAL≥4mm. A longitudinal study by University of Freiburg showed that a diet low in added sugar can significantly reduce periodontal inflammation [284]. On the other hand, consumption of added sugars (i.e. high-fructose products obtained from cane and beet sugar) induced a pro-inflammatory state that leads to metabolic syndrome and periodontitis [284]. It has been recommended by the World Health Organisation that added sugar intake should be limited to less than 10 grams daily [385].

The current study found that type 2 diabetes was significantly associated with the extent of CAL≥4mm. Kapellas et al., and Thorstensson et al., found a significant association between the extent of CAL≥4mm and type 2 diabetes [96, 378]. In 2015-16, type 2 diabetes was experienced by more than 451 million people worldwide and was projected to affect more than 693 million people by the following 20 years [89]. The two-way relationship between type 2 diabetes and periodontitis has been recognised for a long time [91-94]. For people with diabetes the risk of periodontitis is three times higher risk than for non-diabetics [95].

The limitations of this study include the following: (i) the self-reported body height and weight measures, that introduced a reporting bias. Obesity is a widespread societal issue. Individuals with overweight/obesity tends to underestimate their weight status as compared to people of normal weight [138]; (ii) the cross-sectional study design is another limitation of this study, which makes it difficult to determine the temporal relationship between obesity and periodontitis. It is advised that, in future studies should incorporate a prospective cohort study design, to investigate the causality between overweight/obesity and periodontitis; (iii) self-reported 13 dietary questions, that resulted in inability to calculate the absolute intake of sugar and total energy intake, and other macronutrient that constitutes the diet. The ecology of nutrition is based on combination of dietary intake factors, rather than single factor or caloric intake; (iv) type 2 diabetes was self-reported and no objective measure of type 2 diabetes was used. Hence it hindered the ability to determine the severity of type 2 diabetes in relation to risk and progression of periodontitis; (v) the use of conventional regression analysis is another limitation of this study. In regression analysis, the confounders and mediators of exposure (overweight/obesity) and outcome (periodontitis) are grouped together as putative confounders/mediators, which limits the ability to truly understand the effect of exposure on outcome, (vi) NSAOH did not provide information to enable the measurement of the severity and extent of periodontitis. A major strength of this study was that NSAOH is only the second nationwide survey on oral health in Australia; it had a large sample size; and a small degree of non-participation bias.

Future research needs to be undertaken with recording of complete 24-hour food-recall diaries of participants and with utilisation of robust statistical methods such as mediation analysis or marginal structural modelling to truly understand the causal relationship between overweight/obesity and periodontitis. In addition, future studies should not combine

"overweight" and "obesity", and that four rather than two BMI categories be used in the analysis.

4.5.1 Conclusion

Within the limitation of this study, no association was observed between overweight/obesity and periodontitis. Future studies should adopt objective measures of overweight/obesity and diet diaries for food record. The risk factors of age, sex, smoking and dental visiting behaviour were found to be associated with periodontitis.

4.5.2 Public Health Implications

Risk behaviours such as poor dental visiting behaviour and smoking, and age are significantly associated with periodontitis as compared to obesity or being overweight. Actions are required towards promotion of healthy behaviours including regular visit to a dentist, maintenance of oral hygiene and avoiding smoking habit to reduce periodontitis burden in Australians.

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Contribution of authors: SK, SB, TB, and LC conceived and designed the study. SK, SB and LC acquired the data. SK KK SB LC analysed and interpreted the data. SK drafted the report. SK, SB, KK, TB, MP and LC critically revised the report for important intellectual content. SK did the statistical analysis.

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Table S1. Bivariate analysis of proportion of sites with PD ⩾ 4mm and proportion of sites with CAL ⩾ 4mm in relation to putative confounders.

Characteristics	Level	Healthy sites PD<4mm (%)	Sites with PD ⩾4mm (%)	p-value	Healthy sites PD<4mm (%)	Sites with CAL ⩾4mm (%)	*P value*
Age	15-44	84.6	15.4	<0.005	76.6	23.4	<0.001
	45-59	77.1	22.8		39.5	60.5	
	60+	77.1	22.9		25.9	74.0	
Sex	Male	78.4	21.6	<0.0004	55.4	44.5	0.005
	Female	84.7	15.2%		63.3	36.7	
Income	<30k	78.8	21.2	0.61	44.3	55.7	<0.001
	30k-<60k	80.1	19.9		55.3	44.7	
	60k+	81.3	18.7		64.5	35.5	
Education	High school or less	82.5	17.4	0.06	59.5	40.5	0.14
	Trade	76.5	23.5		54.8	45.2	
	Degree	76.7	23.3		46.5	53.4	
Diabetes	Yes	81.9	18.1	0.94	49.4	50.6	0.18
	No	81.5	18.5		59.7	40.3	
Smoking	Current	71.0	29.0	<0.001	49.7	50.3	<0.001
	Former	77.7	22.3		50.5	49.5	
	Never	86.2	13.7		66.0	34.0	
Alcohol	<=2 drinks	83.0	17.0	0.03	57.5	42.5	0.73
	>2 drinks	78.1	21.9		58.6	41.4	
		80.9	19.1				
Usual Reason for Dental Visit	Check-up	85.8	14.2	<0.001	64.9	35.1	<0.001
	Problem	75.7	24.3		51.3	48.7	
Mouth Rinsing	No	83.9	16.1	<0.05	60.0	40.0	0.67
	Yes	79.8	20.2		58.9	41.1	
Tooth brushing	<2times/day	79.4	20.6	0.06	64.7	35.3	<0.001
	>=2 times/day	83.3	16.7		54.9	45.1	
Flossing	No	80.8	19.2	0.46	59.3	40.7	0.95
	Yes	82.4	17.6		53.4	40.6	
Added Sugar (mean)	g/day	19.1 (0.5)	19.7 (2.0)	0.77	20.1 (0.6)	17.9 (0.9)	0.07
BMI							
Underweight/ Normal weight	<25kg/m^2	83.6	16.4	0.06	64.6	35.4	0.0004
Overweight/ Obesity	⩾25kg/m^2	79.3	20.6		53.6	46.4	

Table S2. Multiple variable logistic regression model of proportion of sites with CAL≥4mm adjusted for BMI, age, sex, smoking and usual reason for dental visit.

Characteristic	Levels	Odds ratio	95% CI (Lower)	95% CI (Upper)	*P values*
BMI	Underweight/Normal weight	1 (Reference)	-	-	-
	Overweight/obesity	1.0	0.8	1.3	0.85
Age	15-44	1 (Reference)	-	-	-
	45-59	2.7	2.2	3.5	
	60+	3.7	3.2	4.4	<0.001
Sex	Male	1 (Reference)	-	-	-
	Female	0.7	0.5	0.9	0.01
Smoker	Current/Former	1 (Reference)	-	-	-
	Never	0.7	0.5	0.8	<0.001
Usual reason for dental visit	Check-up	1 (Reference)	-	-	-
	Problem	1.7	1.3	2.2	<0.001

Chapter 5. Association between Overweight/Obesity and Periodontitis in Australian adults: A Single Mediation Analysis

Khan, S and Bettiol, S and Kent, K and Barnett, T and Peres, M and Crocombe, L and Mittinty, M. Association between Overweight/obesity and Periodontitis in Australian adults: A Single Mediation Analysis.

This research paper is currently under revision with Journal of Periodontology.

5.1 Abstract

Aim: To investigate whether overweight/obesity causes periodontitis using effect decomposition analysis in Australian National Survey of Adult Oral Health 2004-06 dataset.

Methods: A secondary analysis was constructed for subset of 3715participants, ⩾30years. A direct acyclic graph was constructed to display overweight/obesity and periodontitis relationship. Dental visiting behaviour (a de facto measure of healthy behaviours) was considered as mediator. Confounding variables include age, sex, household income, education, diabetes, alcohol-intake and smoking. Overweight/obesity was defined as physical inactivity induced obesity (BMI ⩾ 25kg/m^2 and no moderate physical activity). Single-mediation analysis was used to decompose the total causal effect of overweight/obesity on periodontitis into its (in) direct effects using potential outcome approach. Data was analysed using STATA 15 using paramed library. Sensitivity analysis was conducted to detect unmeasured confounding using the E-value estimate.

Results: Total causal effect of overweight/obesity to periodontitis was 14%. Pathway effect analysis using potential outcomes illustrate that the effect of overweight/obesity on periodontitis which was not mediated through poor dental visiting behaviour was 10%. Indirect

effect of overweight/obesity-mediated through poor dental visiting behaviour on periodontitis, was 3%.

Conclusion: The direct effect of overweight/obesity on periodontitis was higher than the indirect effect of overweight/obesity on periodontitis through poor dental visiting behaviour.

Keywords: Obesity, Periodontitis, Epidemiology, National Survey, Public Health, Oral Health

Clinical Relevance

Scientific rationale of the study: This study is one of the few studies that has utilised mediation analysis to define the causal relationship between overweight/obesity and periodontitis. Single mediation analysis decomposes the exposure effect into the direct effect "which is through the exposure" and the indirect effect of exposure through intermediate variables (mediator) which are on the pathway of the exposure and the outcome.

Principal findings: The direct effect of overweight/obesity on periodontitis was 14%.

5.2 Introduction

Obesity (including overweight) is an emerging epidemic (that has reached to unprecedented proportions) of developing and developed nations including Australia [145]. It is the second highest contributor to burden of disease in Australia, with a prevalence of 63% [3]. Obesity is associated with risk of pre-mature death, disability and chronic co-morbidities including type 2 diabetes [183] and cardiovascular diseases [154] that are also intermediate factors for periodontitis [50]. Systematic reviews and meta-analysis suggest the existence of association between obesity and periodontitis [14, 371].

Periodontitis is a chronic inflammatory condition that affects the supporting periodontal tissues and alveolar bone associated with the teeth [27]. The aetiological factor for periodontitis is dental plaque biofilm [61], that evolves in complexity through ecological interaction with host immune-system response [386], leading to metabolic changes in the bone and localisation of pro-inflammatory cytokines [369], under an influence of lifestyle factors [370, 387] and chronic co-morbidities [388].

Obesity potentially results in a persistent pro-inflammatory state [225] that alters the micro-environment of the periodontal sites, favouring the growth and complexity of oral microflora [214]. Lipopolysaccharide from the gram negative bacteria (in the periodontal sites) triggers the production of pro-inflammatory cytokines (TNF-α, IL-6) by adipose tissues, promoting hepatic dyslipidaemia and decreased insulin sensitivity, that may contribute towards obesity and type 2 diabetes [224]. Reduced insulin sensitivity triggers production of advanced glycation end products (AGE) that promotes the production of pro-inflammatory cytokines

including leptin, TNF-α and IL-6 which acts in predisposition of periodontal inflammation [224, 225].

The association of obesity and periodontitis have been reported by studies using the conventional regression methods [14]. These methods are appropriate when the intention is to do predictive analysis. However, when one is interested in studying the causal relations these techniques have limitations [389]. Moreover, when one has a prior understanding of the causal relations and has a prior knowledge on how the data is generated it can be noticed that the relation between overweight/obesity and periodontitis may look similar to the one in the Figure-1. It is from here we learn that between the path of overweight/obesity and periodontitis there are several other paths. Conventional regression methods in these situations yield incorrect results [18, 389-391]. Limitations to determining causality lead recent studies to utilise sophisticated statistical methods including marginal structural modelling and G formula to estimate the relationship between overweight/obesity and periodontitis [7, 392]. The outcomes of those studies developed data generation models that were relevant to a developing nation using prospective cohort study datasets.

To develop causal inference using observational cross-sectional study dataset, mediation analysis is the suitable technique. It decomposes the exposure effect into the direct effect which is through the exposure and the effect of exposure through intermediate variables (mediator) which are on the pathway of the exposure and the outcome. Using the developed country context, it was expected that the outcomes in Australia would be different to other countries based on counterfactual thinking, via appropriate handling of the data generating

mechanism. This study used counterfactual theory as it allows to deduce causal inference from observational studies [17, 18].

Hence, this study aimed to explore the causal relationship between overweight/obesity (physical inactivity related obesity) and periodontitis in Australia (a developed nation, with cultural and behavioural diversity) using single mediation analysis to answer this question "*Does overweight/obesity cause periodontitis"*? Furthermore, we also study the, indirect, effect of overweight/obesity through dental visiting behaviour (a defacto measure of health behaviours) on periodontitis.

5.3 Methods

5.3.1 The National Survey of Adult Oral Health (NSAOH) 2004-06

Data from the NSAOH 2004-06 was used to determine the causal relationship between overweight/obesity and periodontitis using single mediation analysis. NSAOH 2004-06 used a three-stage, stratified, clustered sampling design to draw a representative sample of the Australian population aged 15 years and older [4]. Full details of sampling, examination protocol and survey participation have been described previously [4]. Ethics approval for the survey was obtained by the University of Adelaide's Human Research Ethics Committee. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed for rigorous reporting of this research dataset.

The NSAOH recruited 14,123 people, who interviewed with a computer assisted telephone interview (CATI). Of these, 5,507 underwent clinical examination and 4,170 completed the mailed questionnaire (4). This study is the secondary analysis of the NSAOH 2004-06 dataset, where the analysis was limited to people 30 years and older.

5.3.2 Outcome

A standard examination of teeth was carried out for the measurement of periodontal parameters that included gingival recession and probing pocket, measured at three sites per tooth (mesio-buccal, mid-buccal and disto-buccal), on all fully erupted teeth except third molars. Clinical attachment loss was calculated by computation of the measured variables through summation of gingival recession and probing pocket depth of each individual sites for all the participants. The presence of periodontitis was categorised into two categories, (i) periodontitis; and (ii) no periodontitis; following the Center for Disease Control and Prevention and Prevention and American Academy of Periodontology case definition for periodontitis [56].

5.3.3 Nutritional status assessment

Following the oral health assessment, survey participants reported on their self-reported body weight (kg) and self-reported height (cm) by filling out the questionnaire. These measures were computed to calculate the body mass index (BMI) of the participants, using the World Health Organisation (WHO) definition for body mass index [393]. The BMI were classified into two categories: (i) underweight/normal BMI as <25 kg/m^2, and (ii) overweight/obese $\geqslant$25 kg/m^2.

This study questions, "Does overweight/obesity causes periodontitis?". This question is inadequate, when we try to interpret the meaning of contrafactual outcome $Y^{a=1}$, which is the occurrence of periodontitis, when a person is exposed to overweight/obesity. It results in ill-defined contrafactual outcome, which could mean too many different things and therefore the causal effect is also ill-defined. Thus, a well-defined intervention based on unambiguous definition is required for the interpretation of counterfactual contrasts, where a=1 and a=0. The WHO definition of BMI defines overweight/obesity status as a snapshot in time for the cross-sectional study, and it doesn't provide information on how the person reached that level of BMI, for this scenario BMI<25 kg/m^2 and BMI $\geqslant$25 kg/m^2. BMI is not an intervention at all, but

rather a result of many different types of interventions, which could be physical inactivity, diet or both. Using these concepts, we defined overweight/obesity (based on BMI) using variables of added sugar and physical inactivity (at least one time of moderate physical activity in the last week). This study tested the assumptions of consistency, exchangeability and positivity and chose physical inactivity as a strongest intervening confounder for overweight/obesity (Figure 5.1). Hence, we use overweight/obesity in this study interchangeably to physical inactivity induced obesity i.e. "BMI more than 25kg/m^2 (overweight/obese) as a result of no moderate physical activity". This definition led to computation of two groups i.e. (i) physical inactivity induced obesity group and (ii) recommended physical activity induced normal weight group.

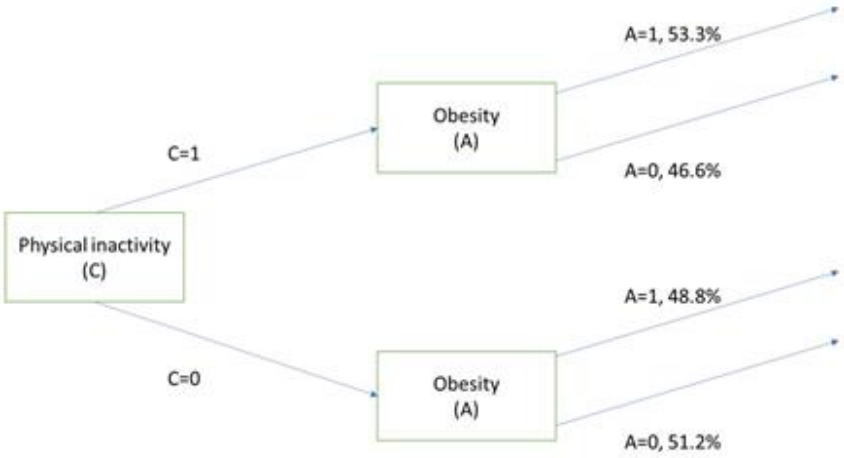

Figure 5.1 Nesting map of A (Obesity) and C (Physical inactivity)

5.3.4 Mediators

Dental visiting behaviour (a de facto measure of healthy behaviours) was considered as an intermediate factor between exposure (overweight/obesity) and outcome (periodontitis). Dental visiting behaviour was categorised as problem-based dental visiting behaviour; and regular check-up based dental visiting behaviour.

5.3.5 Confounding variables

The potential confounders reported in the NSAOH 2004-06 selected for the mediation analysis included: demographic factors (age and sex), socioeconomic position (household income and education), and health and lifestyle factors; (diabetes, alcohol intake, smoking status). Categorical variables were designated for sex (male, female), diabetes (yes, no), alcohol consumption ($\leqslant$2, >2 standard drinks per day), age (15-44, 45-59, $\geqslant$60 years), income (<$30k, $30k-$60k, $\geqslant$$60k), education (high school or less, trade certificate/diploma, and degree or higher) and smoking (current, previous, never). Physical inactivity was calculated using responses to the question "*Have you performed any moderate physical activity in the last one week"*. Other measured variables that were calculated but not included in the mediation analysis included tooth brushing (>=2times per day, <2times per day) and mouth rinsing (yes, no).

5.3.6 Direct Acyclic Graph (DAG)

To answer the research question "*Does overweight/obesity causes periodontitis*?", a DAG was drawn, defining exposure *A*, outcome *Y*, mediator's *M* and confounders *C*. Figure 5.2 represents the DAG of this study, where exposure *A* was overweight/obesity, outcome *Y* was periodontitis, mediators was dental visiting behaviour (*M*), *and* confounders *C* were age (C_1), smoking (C_2), alcohol (C_3) and income (C_4). Figure 5.2 represents various pathways that represents the direct and indirect relationship of *A* and *Y*, under the influence of mediators (*M*). We came to this data generation mechanism after testing of pathways and other possible mechanisms based on evidences from previous studies. Assumptions of consistency, exchangeability, positivity and faithfulness were verified to determine that the intervention was well defined. Following the testing of these assumptions mediation modelling was conducted.

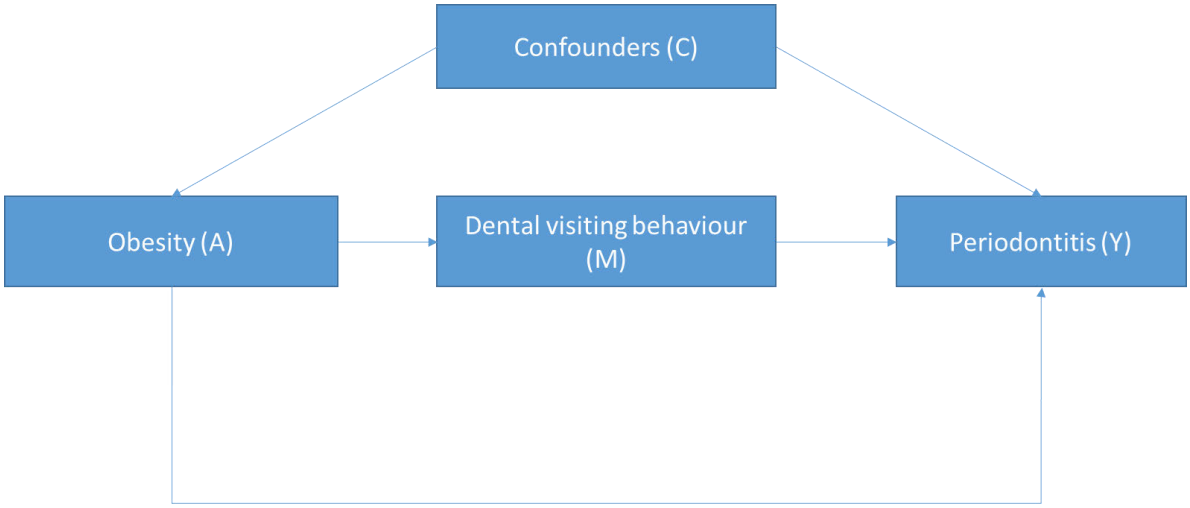

Figure 5.2. Direct Acyclic Graph of Overweight/obesity (A), Periodontitis (O), Dental visiting behaviour (M) and Confounders (age, smoking, alcohol, income) (C)

5.3.7 Mediation assumptions and modelling

A single mediation analysis was used to decompose the total causal effect of *A* on *Y* into natural direct and indirect effects. Direct and indirect effects were estimated using the counterfactual theory. The direct effect (A→Y) is defined as the effect of overweight/obesity (A) on periodontitis (Y) that is not mediated by dental visiting behaviour (M) [394]. The indirect effect is defined as the effect of overweight/obesity (A) that is mediated through dental visiting behaviour (M) [394]. A scenario using counterfactual theory was constructed to estimate the changes in the outcome (Appendix A). To estimate the direct and indirect effects, below defined four assumptions are required to be satisfied.

1. The effect exposure *A* on outcome *Y* is un-confounded conditional on *C*
2. The effect of mediator (*M*) on outcome *Y* is un-confounded conditional on exposure *A* and confounder *C*.
3. The effect of exposure *A* on mediators (*M*) is un-confounded conditional on *C*.

4. None of the mediator–outcome confounders are affected by the exposure.

5.3.8 Weighing of the NSAOH dataset

The NSAOH used questionnaire weights to generate population estimates with 95% confidence intervals (CI) that allowed for the complex sampling design to be used in this survey. To do this, data was stratified by metropolitan and rural regions, clustered by post code and weighted for the probability of participants being selected for inclusion in the questionnaire. To reflect this in this study, the inverse probability treatment weight was multiplied by questionnaire weights to avoid any further selection bias.

5.3.9 Sensitivity analysis

Unmeasured confounders or uncontrolled confounders are the factors that might be associated with both exposure and outcome, and it might explain the association between the exposure and the outcome. In observational studies, it is difficult to achieve certainty of controlling the common factors associated with exposure and outcome. To resolve this problem, sensitivity analysis (or "bias analysis") is constructed using the E-value estimate. The E-value represents the minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need to have with both the exposure and outcome to fully explain away a specific exposure–outcome association, conditional on the measured covariates.

5.4 Results

The NSAOH 2004-06 survey recruited 14,123 people, who were interviewed with a computer assisted telephone interview (CATI). Of these, 5,507 underwent clinical examination and 4,170 completed the questionnaire. For the purpose of this study 3715 participants, 30 years and older were included in the analysis.

This study included participants 30 years and older, with mean age 50.1 years [CI 49.3-50.9]. Sexes were equally distributed post application of population weighting. The characteristics related to the studied population are reported in Table 5.1. Around 43% of participants had an annual income $60,000 or more and almost 55% of the people in the NSAOH 2004-06 had high school or less level of education. Five percent of people reported to being told by a doctor that they had diabetes. Risk behaviours including current smoking habit and drinking two or more standard alcoholic drinks per day was reported by 14.5% and 34.7% of participants respectively. Sixty percent were estimated to be overweight/obese. Fifty-nine percent reported brushing their teeth twice or more daily. Mouth rinsing was a common oral hygiene behaviour among 55% participants. Thirteen percent reported their daily intake of added sugar was >=30g/day. Almost 77% of people reported that they didn't perform any form of moderate physical activity within the last week.

Table 5.1 Characteristics of participants

Characteristic		Mean	95% CI
Age	Years	50.15	[49.3 – 50.9]
	Level	**weighted percentage %**	**95% CI**
Sex	Male	50.0	[47.4 – 52.4]
	Female	50.0	[47.4 – 52.5]
Income	<30k	26.4	[24.1 – 28.9]
	30k-<60k	30.6	[28.2 – 33.2]
	60k+	42.8	[39.7 – 46.0]
Education	High school or less	54.9	[51.5 – 58.2]
	Trade/Dip/cert	39.6	[36.4 – 42.9]
	Degree/Teaching/nursing	5.4	[4.4 – 6.7]
Diabetes	Yes	4.8	[3.9 – 6.0]
	No	95.1	[93.9 – 96.0]
Smoking	current	14.5	[12.7 – 16.3]
	previous	31.8	[29.6 – 33.9]
	never	53.7	[51.3 – 56.1]
Alcohol	⩽2 drinks	65.3	[62.2 – 68.2]
	>2 drinks	34.7	[31.7 – 37.7]
Usual Reason for Dental Visit	Problem	55.7	[53.0 – 58.4]
	Check-up	44.2	[41.6 – 47.0]
Mouth Rinsing	No	45.1	[42.5 – 47.6]
	Yes	54.9	[52.3 – 57.4]
Tooth Brushing	<2 day	40.9	[38.2 – 43.5]
	⩾2 day	59.1	[56.4 – 61.7]
BMI	Underweight/Normal	40.3	[37.6 – 43.0]
	Overweight/Obese	59.7	[56.9 – 62.3]
Added sugar	Recommended (<=36g/day for men and <=25g/day for women)	86.7	[84.7– 88.5]
	High sugar (>=36g/day for men and >=25g/day for women)	13.2	[11.5 – 15.3]
Physical inactivity	Yes	76.9	[74.4 – 79.3]
	No	23.1	[20.7 – 25.5]

Table 5.2 illustrates the results of single mediation analysis. The results suggest that the total causal effect of overweight/obesity (A) to periodontitis (O) was 14%. The direct effect of overweight/obesity (A) on periodontitis (O) was 14% and the indirect effect of overweight/obesity to periodontitis was 3% when the effect of overweight/obesity (O) was decomposed through dental visiting behaviour (M) on periodontitis.

Table 5.2 Single mediation analysis result

Effect	Interpretation	Risk ratio Mean (SD)	95% CI (Upper, Lower)
$E(Y_{1M1}/Y_{0M0})$	Total causal effect	1.14	0.88, 1.52
$E(Y_{1M1}/Y_{0M1})$	Direct effect not through M (dental visiting behaviour)	1.10	0.82, 1.47
$E(Y_{1M1}/Y_{1M1})$	Indirect effect through M (dental visiting behaviour))	1.03	1.01, 1.07

Figure 5.3 shows the results of the sensitivity analysis in context of overweight/obesity and periodontitis relationship. The sensitivity analysis suggested an E-value of 1.58 that indicated the effect of unmeasured confounder in the relationship between overweight/obesity and periodontitis was low.

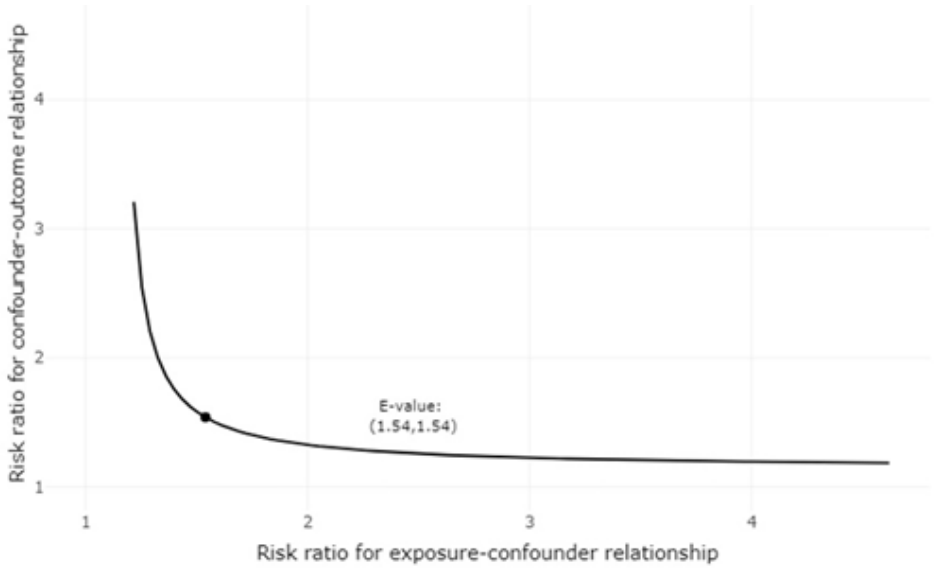

Figure 5.3 E-Value of the joint minimum strength of association on the risk ratio scale that an unmeasured confounder must have with the overweight/obesity and periodontitis to fully explain away an observed treatment–outcome risk ratio of RR = 1.14

5.5 Discussion

To our knowledge, this study is the first to investigate the influence of overweight/obesity on periodontitis among the Australian adults nationwide oral health data set using cutting edge research method of single mediation analysis. The findings of the study suggested that the direct effect of overweight/obesity (A) to periodontitis (O) was 14% when the exposure of the population was set to be obese people with no moderate physical activity. The indirect effect of overweight/obesity through dental visiting behaviour on periodontitis was 3%. The finding is supported by Castilhos et al. study that suggested there was no association between overweight/obesity and periodontitis in adults [315] Similar results were found in the fourth Korean National Health and Nutrition Examination Survey (KNHANES) and Health 2000 Health Examination Survey of Finland, where overweight/obesity was not associated with periodontitis in adults after adjusting for putative confounders [212, 381].

Contrary to the findings of this study, systematic reviews and meta-analysis has reported significant association between obesity and periodontitis [14, 371, 395]. Similarly, a longitudinal study in the Brazilian population have reported a dose-response relationship between obesity and periodontitis using adjustment for time-varying covariates [392].

Adipose tissues secrete cytokines such as tumour necrosis factor alpha (TNF-α) and interleukin 6 (IL-6) [310]. TNF-α is associated with inflammation in the periodontium, mainly released by monocytes and macrophages in the junctional epithelium circumscribed around the gingival sulcus [360] and functions in the destruction of alveolar bone and cartilage in periodontal tissues [361] and triggers the leucocytosis and synthesis of C-reactive protein (CRP) and amyloid A [362]. Lipopolysaccharide (LPS) from gram-negative bacteria harboured in periodontal tissues triggers the secretion of TNF-α and IL-6 by adipose tissues. LPS functions in promoting hepatic dyslipidaemia and decreases insulin sensitivity, leading to increased obesity and diabetes risk [224]. Insulin resistance induced by apoptosis of the beta-cells of the pancreas, and cytokines produced by adipose tissues, interrupts insulin signalling resulting in insulin resistance [225] and production of advanced glycation end products (AGE) which promotes the production of pro-inflammatory cytokines leptin, TNF-α and IL-6 leading to periodontal inflammation [224]. Dietary free fatty acids have been proposed as a component of the mechanism that links inflammation to obesity, diabetes, and periodontal infection, and in turn modulates production of advanced glycation end-products and insulin resistance.

The limitations of this study include the following: (i) reporting bias from the self-reported body height and weight measures. People with obesity have been reported to underestimate their weight status as compared to people of normal weight [138]; (ii) the cross-sectional study design, makes it difficult to determine the temporal relationship between obesity and periodontitis. Future studies are advised to incorporate a prospective cohort study design, to investigate the causality between overweight/obesity and

periodontitis; (iii) no reports on objective multiple measures of body composition (waist circumference, waist hip ratio and waist to height ratio); (iv) self-reported 13 dietary questions, resulted in inability to estimate the absolute sugar intake and total energy intake, and other macronutrient that constitutes the diet.

Regardless of the limitations, the strength of this study were: the NSAOH is only the second nationwide survey on oral health in Australia; it had a large sample size; and a small degree of non-participation bias. This study used a single mediation analysis that differentiate between confounders and mediators and recognise the unmeasured confounders that may affect the overweight/obesity and periodontitis relationship, which is better than regression analysis, in which the confounders and mediators of exposure (overweight/obesity) and outcome (periodontitis) are grouped together as putative confounders/mediators, limiting the ability to truly understand the effect of exposure on outcome. Although mediation analysis shows some potential to help determine cause and effect using cross-sectional surveys, it is too early to be specific with cause and effect at this stage.

Conclusion

This study reported that the causal effect of overweight/obesity on periodontitis was 14%, while the causal effect of overweight/obesity through oral hygiene to periodontitis is only 3%. Thus, indicating a small indirect effect. Further research is required to estimate the causal relationship between overweight/obesity and periodontitis through prospective cohort studies in the Australian population.

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Government Department of Health and Aging, Population Health Division, the Australian Institute of Health and Welfare, Colgate Oral Care, the Australian Dental Association, and the US Centers for Disease Control and Prevention.

Conflict of Interest: The author declare no competing interests.

Appendix 5.A Single mediation analysis. Counterfactual theory allows estimation of the marginal effect as compared to the simple regressions that only compute the conditional estimates. Before moving further, following terms are defined below:

1. Total effect: captures the relationship of *A* and *Y* across all possible pathways. Its effect measures the interventions that targets the exposure of interest in the studied population. It decomposes in to natural direct effect and natural indirect effect.

$$Total\ effect = E\ (Y_x - Y_{x*}\ |C)$$

It could also be written as below:

$$Total\ effect = E\ (Y_x - Y_{x*}\ |C) = E\ (Yx_{Mx} - Y_{x*Mx*}\ |C) = E\ (Y_{xMx} - Y_{x*Mx}\ |C) + E\ (Y_{x*Mx} - Y_{x*Mx*}\ |C)$$

$$E\Big[\sum_{m_1}\sum_{m_2} E(Y_{am_1m_2}\ |\ c)\{P(M_{1a} = m_1\ |\ c) - P(M_{1a^*} = m_1\ |\ c)\} P(M_{2a^*} = m_2\ |\ c)\Big].$$

To estimate the interventional (in) direct effect, four conditions needs to be satisfied that includes the following.

2. The effect exposure *X* on outcome *Y* is un-confounded conditional on *C*

$$Y_{xm} \perp\!\!\!\perp X|C$$

3. The effect of mediator (*M*,) on outcome *Y* is un-confounded conditional on exposure *A* and confounder *C*. $Y_{xm1} \perp\!\!\!\perp M\ |\ [X, C]$

4. The effect of exposure *X* on mediators (*M*). is un-confounded conditional on *C*.

$$M_x \perp\!\!\!\perp X|C$$

5. None of the mediator–outcome confounders are affected by the exposure. Also referred to as cross world assumption

6. $Y_{xMx} \perp\!\!\!\perp M_{x*}|C$

Chapter 6. Obesity, diet and periodontitis in prediabetes: A pilot study

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Target journal: Clinical obesity (Wiley's Online Library)

6.1 Abstract

Aim: To trial a pilot study for planning a large prospective study, using robust anthropometric tools, dietary measures and periodontal outcome measures designed to determine the association between obesity, diet and periodontitis

The aim of the pilot study was to trial to plan a bigger study. In the bigger study we will include robust measures (aims, method, analysis and conclusion)

Methods: A cross-sectional pilot study (testing the feasibility of a future prospective cohort study) was constructed as part of a large randomised controlled trial at the University of Sydney. A convenience sampling method was utilised for recruitment of participants. The participants included were: 18 years and older, with a body mass index $\geqslant$ 25 kg/m^2 and pre-diabetic (fasting plasma glucose level $\geqslant$ 5.6-6.9 mmol/L and/or 2hour post-challenge (oral glucose tolerance test) plasma glucose $\geqslant$ 7.8-11.0 mmol/L and/or HbA1c $\geqslant$ 5.7-6.4%), dentate (with at least eight teeth present) and had no risk of infective endocarditis. Data was collected for age, sex, smoking habit, anthropometric measures of body mass index, waist circumference and hip circumference. Periodontal examination was conducted using a specialised Florida probe system for recording probing depths, clinical attachment loss and bleeding on probing scores. Comprehensive three-day diet diary record was taken from the participants that was converted to grams per day intake of macronutrients. The participants were asked how many times they

"brushed their teeth", "used a mouth rinse", "chew a sugar free gum" or "used interdental cleaning devices" during the last week. Participants were also asked questions on their usual reason for dental visiting, with options that included "checkup" or "dental pain/problem". Blood levels of highly sensitive C-reactive protein (HsCRP), glycosylated hemoglobin (HBA1c), lipid profile and apolipoprotein were measured. Statistical analysis was undertaken using R statistical software version 3.4.1.

Results: A total of 33 participants were enrolled in the study. In the bivariate analysis, waist circumference and fasting glucose were significantly associated with periodontitis. Waist circumference ($p<0.05$) and fasting plasma glucose (p,0.05) were significantly associated with periodontitis in the bivariate analysis. No association was found between BMI and periodontitis. Being obese (BMI ≥ 30) was significantly associated with interdental cleaning ($p <0.02$). People who experienced obesity had less intake of dietary fibre as compared to overweight people ($p<0.01$). No significant association was observed between diet and periodontitis. The total energy intake, grams intake and number of teaspoons of added sugar per day was higher in people experiencing obesity (10%, 134 grams, 18 teaspoons) as compared to people who were overweight (6%, 112 grams, 8 teaspoons). The total energy intake, grams per day intake and number of teaspoons of added sugar per day was higher in people with periodontitis (12%, 164 grams, 22 teaspoons) as compared to people with no periodontitis (6%, 97 grams, 9 teaspoons). People with periodontitis had significantly higher number of problem based dental visits to a dentist as compared to people without periodontitis ($p<0.007$).

Conclusion: Waist circumference and fasting plasma glucose were significantly associated with periodontitis. It is recommended that future studies should employ a prospective cohort study design, with robust anthropometric tools, dietary measures and periodontal outcome measures, and a larger sample size to better understand the relationship between diet, obesity and periodontitis.

6.2 Introduction

Overweight and obesity are in epidemic proportions, affecting more than 65% of the worldwide population [145], which represents a major public health challenge. The Australian population is also experiencing a high burden of overweight (63%) and obesity (28%) [3]. Diet is a significant contributing factor for obesity, through excessive energy intake from foods and beverages, particularly the consumption of energy dense (but nutrient poor) foods [396]. Diet-induced obesity is associated with adverse health outcomes including cardiovascular diseases, prediabetes and type 2 diabetes, sleep apnoea and cancers [3, 397]. People with obesity have poor oral hygiene behaviour and poor dental visiting behaviour and have poor periodontal health [398].

Periodontitis progression is episodic, with relatively short episodes of exacerbation with the advent of clinical signs (gingival recession, drifting of teeth, mobility/loss of tooth) followed by repair and prolonged intervening periods of remission [33, 399]. The aetiopathogenesis of periodontitis occurs due to ecological interaction of a dental plaque biofilm [61] and the host immune response [369]. The prevalence of periodontitis is reported to be 30-35% worldwide [27] and 24.5% in the Australian population [4]. Periodontitis has a global economic impact of 54 billion USD per annum [25]. A positive association between obesity and periodontitis have been proposed by multiple studies [11, 371, 400]. However, the mechanism that links obesity and periodontitis remains poorly understood. Poor diet, pre-diabetes and type 2 diabetes are common factors associated with obesity and periodontitis, that are expected to be linking factor between obesity and periodontitis relationship.

A diet rich in fish oils [401], dietary fibre and antioxidants, and low in refined carbohydrate has been associated with reduced gingival bleeding from 35% to 13% [283] and periodontal inflammation [284]. Dietary sugar restriction has been associated with a

reduction the extent of gingivitis [283]. Milk and dairy products rich in calcium and lactic acid products have a protective effect on periodontal health [285, 286, 291]. Regardless of these positive reports, the relationship of diet and periodontitis remains inconclusive as a result of lack of clarity in the assessment of dietary intake record, non-compliance of participants, use of self-reported measures [402]. Dietary sugar consumption induces a pro-inflammatory state that may lead to the development of periodontitis [334]. It is expected that the burden of this pro-inflammatory state may increases in people with obesity, dyslipidaemia, insulin resistance and prediabetes [403]. However, the association is not well understood due to the complexity in relationship between obesity, diet, periodontitis, prediabetes and type 2 diabetes.

People with type 2 diabetes are associated with three times higher risk of periodontitis as compared to people who are non-diabetic [95]. Dental plaque accumulation, deeper periodontal pocket and greater degree of bone loss are higher amongst people with type 2 diabetes as compared to people who are non-diabetic [96]. It is established that type 2 diabetes and periodontitis have a bi-directional relationship [404]. Management of glycaemic levels have been shown to reduce gingival bleeding in people experiencing type 2 diabetes [97]. In the reverse direction, non-surgical periodontal therapy have shown to improve glycaemic control in people with type 2 diabetes [99]. A recent systematic review has suggested that non-surgical periodontal therapy reduces glycosylated haemoglobin A1c (HbA1c) by 0.5% after three months [100].

It is expected that people with a poor diet, type 2 diabetes and obesity will have high degree of periodontitis, and the risk of periodontitis would be higher than in people in a pre-diabetic state [402]. People with prediabetes have significantly higher plaque index scores, bleeding on probing, probing depth, clinical attachment loss, missing teeth and marginal bone loss levels as compared to nondiabetics [405]. They have significantly higher number of sites with pocket depth ≥5 mm as compared to normoglycaemic individuals

[406]. Impaired fasting glucose in prediabetes is strongly associated with gingival bleeding, a marker of chronic gingival/periodontal inflammation [402].

The risk of prediabetes is higher in people with obesity and poor diet [407]. People with obesity, poor diet and prediabetes have a higher burden of inflammation as a result of clustered effect, that may result in higher risk of periodontitis [402] and type 2 diabetes [407]. No ample evidence exists to supporting association between people with obesity experiencing prediabetes (but no co-morbidities) in relation to periodontitis. Findings obtained from a study that incorporates the clustered effect of obesity (with no co-morbidity), prediabetes and diet on periodontitis would be useful in defining strategies to prevent and manage both periodontitis and type 2 diabetes amongst high risk populations. It would also be helpful in determining the true pathway of obesity and periodontitis relationship, via multiple factors. To plan a larger prospective cohort study that incorporates innovative, exhaustive and robust tools for measuring diet, obesity and periodontitis this cross-sectional pilot study was trialled. It used the same analyses that would be used in later prospective cohort study to determine the association between obesity, diet, and periodontitis in people with prediabetes residing in New South Wales, Australia.

6.3 Methods

This cross-sectional pilot study was nested in an ongoing randomised controlled parallel-arm study on two different dietary supplements [FBCx (a formula based on α-cyclodextrin) and Ginst15 (a ginseng extract formula based on Compound K)] [408]. This study used a convenience sampling technique for the recruitment of participants. The channels of recruitment of participants included the existing Boden Institute database, the Sydney Local Health District (SLHD) intranet, the University of Sydney website, the SFI Research Study website, social media, and advertising in local newspapers and radio stations. Participants were also recruited through editorial pieces, health awareness stands, education sessions, primary care, pharmacies and advertising on the Australian Clinical Trials website. Interested participants were provided with the Patient Information Sheet (PIS) for the study. Ethics approval was obtained from the Sydney Local Health District (Royal Prince Alfred Zone) Ethics Review Committee (HREC/14/RPAH/440 and SSA/14/RPAH/441, Appendix B).

Inclusion and exclusion criteria

The inclusion criteria were: 18 years and older, with a BMI ≥ 25 kg/m² and pre-diabetic (determined by blood test results at the Screening visit or 6 months prior to Screening). Pre-diabetes status was determined using American Diabetes Association (ADA) guidelines as a fasting plasma glucose level ≥ 5.6-6.9 mmol/L and/or 2 hour post-challenge (oral glucose tolerance test) plasma glucose ≥ 7.8-11.0 mmol/L and/or HbA1c ≥ 5.7-6.4%.

The periodontal examination of participants was conducted if they were dentate (with at least eight teeth present) and had no risk for endocarditis for periodontal examination. Prior to oral health assessments participants were instructed to fast for 12 hours and to not brush their teeth the night before and morning of assessment.

A fasting plasma glucose ≥ 7.0 mmol/L and/or 2-hour post-challenge (oral glucose tolerance test) plasma glucose ≥11.1mmol/L and/or HbA1c ≥ 6.5% were considered as type 2 diabetes. Participants were also excluded (i) if they were on medications (anti-lipidaemia for cholesterol control, anti-diabetic for pre-diabetes, weight loss medications and other drugs that may affect body weight e.g. anti-psychotics, anti-depressants, or corticosteroids), (ii) had type 1 diabetes, (iii) unstable angina pectoris or recent onset of cardiovascular disease (within 1 month of screening), (iv) bariatric surgery, (v) a history of significant liver, kidney or gastrointestinal disease and/or ALT or AST > 2.5 times upper limit of normal, serum creatinine > 1.5 times upper limit of normal or eGFR < 60ml/min/1.73m² or presence of microalbuminuria, (vi) chronic diarrhoea, bowel motility problems, or other conditions that could affect intestinal fat absorption, (vii) untreated thyroid disease, (viii) greater than 10% change in body weight over the past 3 months (ix) alcohol or illicit drug abuse, (x) pregnancy or breastfeeding women, and women who might be planning pregnancy during the duration of the study, (xi) taking the following medications which may show reduced absorption of the antibiotics, anticoagulants, anticonvulsants, antiarrhythmic, immunosuppressant's, or any other drug that is necessary to take with a meal, (xii) commencement of a new prescription medication within 3 months of screening or change in dose regimen of a prescription medication within 1 month of screening, (xiii) a history or presence of malignancy [completely resected basal or squamous cell carcinoma of the skin if treatment completed > 6 months prior to enrolment and participants in remission for > 5 years prior to screening remain eligible, (xiv) inability to read and write English, (xv) a history of frequently changed smoking habits, in addition to smoking cessation within 6 months prior to screening, (xvi) individuals who were part of another clinical trial in the last month and (xvii) individuals who couldn't commit to the scheduled appointments. Exclusion of the participants was also made if the study investigators has an opinion that they have some other condition

or disorder that may adversely affect the outcome of the study or the safety of the participant.

Data collection

Data collection involved three phases (i) telephone screening of participants; (ii) onsite screening; (iii) baseline assessment of participant.

i. Telephone screening of participants

The telephone interview involved screening of the participant for the Australian Type 2 Diabetes Risk Assessment Tool. It also involved screening the participant's most recent pathology results to determine pre-diabetic eligibility for the study. The participants not excluded were asked to attend the screening visit with one of the interviewers. The potential participants who didn't had blood reports on pre-diabetes eligibility within the last 6 months were asked to attend post-fasting screening visit, where a blood sample was collected.

ii. Onsite screening

An informed consent was obtained from the participant at the onsite screening visit and the samples were obtained for evaluation of fasting blood glucose, glycated haemoglobin (HbA1c in percentages) and full lipid profile (total cholesterol, HDL-cholesterol, LDL-cholesterol, total cholesterol: HDL ratio, triglycerides) in mmol/L. The pro-inflammatory cytokines of apolipoprotein B, high-sensitivity C-reactive protein (hs-CRP) were also measured using the blood samples.

iii. Baseline visit

The body height was measured using a scale (in nearest centimetre) and body weight was measured using a weighing scale in kilograms (kg). Waist circumference was measured to the nearest 0.5 cm at the midpoint between the top of the iliac crest and lower edge of the costal margin in the mid-axillary line, using a flexible tape measure.

All Participants were required to keep 3-day diet diaries record (2 working days and 1 week-end day) at baseline as a measure of daily dietary intake record. The participants entered the amount of food or drinks consumed each day. The food intake was recorded on factors such as number, weight and volume. Participants were asked to measure the intake using household measures such as hand, dimensions and takeaway container size and shape. Checklist of commonly forgotten foods was also provided.

The oral assessment was carried out by a registered dentist (SK) using a hospital bed and a light source. The case report form was used to collect the following information (Appendix C).

a. *Plaque score* were measured using Loe & Silness Plaque Index (PI) [16].
b. *Periodontal examination:* The periodontal examination was completed by a registered dentist (SK) utilising an electronically-calibrated Florida Probe® system (Florida Probe Corp; USA). Prior to the periodontal examination, an examiner calibration was conducted to ensure the correct pressure was used with the electronic Florida probe. A calibration exercise was done on a pad before examining each participant. If the pressure was too great or too low the electronic probe system gave an error message on the computer. The same occured when the participant was examined. The electronic probe did not generate a score. So kappa scores could not be made.

   A full-mouth periodontal examination (except for 3rd molars) protocol was followed. The Florida Probe® was pre-calibrated to deliver 15g of force for measuring periodontal pockets depths (PD), clinical attachment loss (CAL) and bleeding upon probing (BOP) on six sites per tooth i.e. mesio-buccal, buccal and disto-buccal, mesial-oral, oral and disto-oral surfaces. These three measurements were immediately recorded on the Florida Probe software (FP-32; by Florida

Probe Corp) through the attached laptop (Dell Latitude E7270). Appendix D shows the preparation of hospital bed prior to periodontal examination.

c. *Post-examination questionnaire*: A questionnaire was given to the participant on their oral health and dental visiting behavior. The participants were asked how many times they "brushed their teeth", "used a mouth rinse", "chew a sugar free gum" or "used interdental cleaning devices" during the last week. Participants were also asked questions on their usual reason for dental visit, with options that included "check-up" or "dental pain/problem".

Data analysis

Statistical analysis was undertaken using R statistical software version 3.4.1 [409] within R Studio Version 1.0.153 [410]. The data was operationalised for variables of sex (men and women), BMI (BMI 25-29.99 "overweight" and BMI 30 and above "obese"). The mean values of age and PI were calculated. The dental visiting behaviour was operationalised in to binary variables of "problem" and "check-up". The blood profile (HsCRP, cholesterol, triglycerides, HDL, LDL, Apolipoprotein B) were also recorded as mean values. The Florida probe data was operationalised to obtain the mean PD, mean CAL and mean BOP. The total percentage of sites with CAL $\geqslant$4mm, PD$\geqslant$4mm, CAL $\geqslant$6mm, PD$\geqslant$6mm were also recorded. The percentage of sites with BOP was coded into two categories i.e. (i) 0-25% and (ii) >25%. Diet diary record of the participants was analysed by a registered nutritionist (KK) who calculated grams per day intake and total energy intake of calculated intake of protein, total fat, saturated fat, polyunsaturated fat, monounsaturated fat, cholesterol, carbohydrate, sugar and dietary fibre using the FoodWorks version 8 dietary analysis package [374] using the Australian Food, Supplement and Nutrient Database (AUSNUT) 2011-2013 food composition database [373].

Descriptive analysis was carried out to understand the overall distribution of participants and their social demographic factors (age, sex, level of education and income), medical history, lifestyle factors (dental health and oral hygiene behaviour) and risk behaviors. Bivariate and multivariate analysis was carried out to assess relationship between diet, obesity, periodontitis and other putative confounders. Pearson's Chi-square test and independent sample t-tests were utilised to determine the differences in levels of categorical variables and continuous variables. The Centre of Disease Control (CDC) and the American Academy of Periodontology (AAP) case definition for periodontitis was used to identify cases of periodontitis [411]. The participants were divided into two groups based on the case definition for periodontitis: (i) no periodontitis; (ii) periodontitis [411].

6.4 Results

A total of 33 participants were enrolled in the study. The mean age of participants was 55.20 years for people who were overweight and 52.43 years for people with obesity. Over 68% of participants enrolled in the study were females. More than 60% of the participants had tertiary level of education (degree/teaching/nursing). Table 6.1 illustrates the characteristics of participants with BMI $\geq 25 kg/m^2$.

Table 6.1 Characteristics of participants

Variables	level	BMI≥25kg/m²
n		33
Age (mean (sd))		53.81 (8.09)
Sex n (%)	Male	12 (31.17)
	Female	21 (68.25)
BMI kg/m²		32.80 (0.80)
Waist circumference (mean) cm		104.59 (7.74)
Periodontitis (%)	No	9.0 (27.27)
	Yes	24.0 (72.73)
DMFT (mean (sd))		8.81 (0.73)
PIMean (mean (sd))		1.12 (0.13)
Usual reason for dental visit (%)	Check-up	24 (72.73)
	Problem	9 (27.27)
Tooth brushing (mean (sd))		12.36 (0.63)
Mouthwash (mean (sd))		0.27 (0.14)
Chewing gum (mean (sd))		0.42 (0.20)
Dental flossing (mean (sd))		1 (0.13)
Interdental cleaning (mean (sd))		2.84 (0.54)
Missing teeth (mean (sd))		1.21 (0.28)
CAL (mean (sd))		1.58 (0.40)
PD (mean (sd))		1.47 (0.44)
BOP % (mean (sd))		13.30 (8.30)
CRP (mean (sd)) mg/L		3.67 (0.64)
Glucose Fasting (mean (sd)) mmol/L		5.28 (0.49)
Cholestrol (mean (sd)) mmol/L		5.76 (0.17)
Triglycerides (mean (sd)) mmol/L		1.33 (0.09)
HDL (mean (sd)) mmol/L		1.41 (0.04)
LDL (mean (sd)) mmol/L		3.73 (0.16)
HbA1c (mean (sd)) %		1.12 (0.04)
Apolipoprotein B (mean (sd)) g/l		1.11 (0.04)

The bivariate analysis of BMI, periodontitis and their respective putative confounders are reported in Table 6.2. The results found no significant association between BMI and periodontitis. Being obese (BMI ≥30) was significantly associated with having high waist circumferences ($p<0.05$) and interdental cleaning ($p<0.02$). No significant difference was found between people with overweight or obesity for variables of dental visiting behaviour, oral hygiene habits (tooth brushing, mouthwash use, chewing gum and dental flossing), missing teeth, periodontal parameters of PD, CAL and BOP. The HsCRP, fasting glucose, Cholesterol, Triglycerides, HDL, LDL, HbA1c and Apolipoprotein B levels had no statistically significant difference between people with overweight or people with obesity. People with periodontitis had problem based dental visiting behaviour ($p<0.007$) as compared to people with no periodontits. People with periodontitis had significantly higher waist circumference ($p<0.05$) and fasting plasma glucose levels ($p<0.05$) as compared to people with no periodontitis.

Table 6.2 Bivariate analysis (i) overweight, obesity and its putative confounders; (ii) periodontitis and its putative confounders. *p<0.05

Variables	Level	Overweight (BMI 25-29.99)	Obesity (BMI ≥30)	No Periodontitis	Periodontitis
Age (mean (sd))		55.20 (4.69)	52.43 (11.50)	54.61 (8.45)	51.67 (11.57)
Sex (%)	Male	2 (20.0)	10 (43.5)	4 (22.2)	8 (53.3)
	Female	8 (80.0)	13 (56.5)	14 (77.8)	7 (46.7)
Periodontitis_severity (%)	none	7 (70.0)	11 (47.8)	18 (100.0)	0 (0.0)
	mild	0 (0.0)	1 (4.3)	0 (0.0)	1 (6.7)
	moderate	3 (30.0)	10 (43.5)	0 (0.0)	13 (86.7)
	Severe	0 (0.0)	1 (4.3)	0 (0.0)	1 (6.7)
Education (%)	Trade/Dip/cert	4 (40.0)	6 (27.3)	4 (22.2)	6 (42.9)
	Degree/Teaching/nursing	6 (60.0)	16 (72.7)	14 (77.8)	8 (57.1)
BMI (mean (sd))	kg/m^2			31.66 (4.14)	34.19 (5.11)
WC (mean (sd))	cm	92.65 (5.41)	**109.78 (8.84)***	100.47 (9.97)	**109.53 (10.91)***
DMFT (mean (sd))		9.70 (3.77)	8.43 (4.42)	7.78 (3.39)	10.07 (4.86)
PIMean (mean (sd))		1.08 (0.53)	1.16 (0.75)	1.00 (0.66)	1.29 (0.70)
Usual reason for dental visit (%)	Check-up	7 (70.0)	17 (73.9)	17 (94.4)	7 (46.7)
	Problem	3 (30.0)	6 (26.1)	1 (5.6)	8 (53.3)*
Tooth brushing (mean (sd))		12.10 (2.96)	12.48 (3.93)	13.06 (3.30)	11.53 (3.93)
Mouthwash (mean (sd))		0.00 (0.00)	0.39 (0.99)	0.22 (0.94)	0.33 (0.72)
Chewing gum (mean (sd))		0.10 (0.32)	0.57 (1.41)	0.28 (1.18)	0.60 (1.24)
Dental flossing (mean (sd))		1.20 (0.79)	0.91 (0.79)	1.17 (0.79)	0.80 (0.77)
Interdental cleaning (mean (sd))		4.70 (4.37)	**2.04 (1.99)***	3.50 (3.54)	2.07 (2.37)
Missing teeth (mean (sd))		0.90 (1.37)	1.22 (1.70)	0.72 (1.32)	1.60 (1.80)
CAL (mean (sd))		1.56 (0.47)	1.59 (0.41)	1.35 (0.31)	**1.85 (0.38)***
PD (mean (sd))		1.46 (0.43)	1.48 (0.40)	1.29 (0.28)	**1.70 (0.40)***
BOP % (mean (sd))		13.72 (8.39)	12.29 (8.60)	11.02 (8.76)	14.77 (7.81)
CRP (mean (sd))	mg/L	2.20 (1.84)	4.30 (4.15)	3.63 (2.14)	3.70 (5.09)
Glucose Fasting (mean (sd))	mmol/L	5.18 (0.48)	5.34 (0.50)	5.13 (0.42)	**5.49 (0.52)***
Cholesterol (mean (sd))	mmol/L	5.92 (0.88)	5.60 (1.18)	5.92 (1.11)	5.43 (1.05)
Triglycerides (mean (sd))	mmol/L	1.12 (0.54)	1.42 (0.53)	1.32 (0.54)	1.34 (0.55)
HDL (mean (sd))	mmol/L	1.48 (0.21)	1.37 (0.24)	1.41 (0.21)	1.40 (0.26)
LDL (mean (sd))	mmol/L	3.92 (0.84)	3.57 (1.06)	3.90 (1.05)	3.41 (0.89)
HbA1c (mean (sd))	%	5.46 (0.18)	5.49 (0.27)	5.46 (0.25)	5.51 (0.24)
Apolipoprotein B (mean (sd))	g/L	1.17 (0.23)	1.09 (0.26)	1.16 (0.26)	1.06 (0.24)

Table 6.3 illustrates the bivariate analysis of the relationship between obesity, periodontitis and dietary variables respectively. None of the other variables were found significantly associated with periodontitis. The total energy intake, grams per day intake and number of teaspoons of added sugar per day was higher in people with periodontitis (12%, 164 grams, 22 teaspoons) as compared to people with no periodontitis (6%, 97 grams, 9 teaspoons). No significant difference of total energy intake from saturated fat was observed in people with periodontitis (13.8%) and in people with no periodontitis (14.2%). Regardless of a diagnosis of periodontitis, all participants exceeded recommended guideline for the intake of saturated fat i.e. less than 10% of the total energy intake.

Table 6 3 Bivariate analysis of the dietary variables in grams and kilojoule intake in relation to BMI, overweight and obesity, periodontitis *p<0 05						
	BMI ≥25Kg/m^2	Overweight (BMI 25-29 99)	Obesity (BMI ≥30)	Periodontitis		AMDR
Variables				No	Yes	
Protein_g (mean (sd))	103 87 (20 56)	101 39 (14 72)	106 35 (26 41)	103 17 (21 69)	106 86 (25 86)	
Total_fat_g (mean (sd))	97 44 (31 43)	98 33 (30 43)	96 55 (32 43)	94 53 (24 18)	100 16 (39 00)	
Saturated_fat_g (mean (sd))	38 015 (14 85)	36 85 (13 11)	39 18 (16 59)	37 10 (10 10)	40 13 (20 41)	
Trans_Fatty_Acids_g (mean (sd))	1 75 (0 62)	1 78 (0 58)	1 73 (0 66)	1 79 (0 58)	1 69 (0 70)	
Polyunsaturated_fat_g (mean (sd))	14 48 (5 01)	16 10 (5 26)	12 87 (4 76)	13 73 (4 50)	13 98 (5 83)	
Monounsaturated_fat_g (mean (sd))	36 97 (12 60)	37 35 (12 43)	36 60 (12 78)	35 59 (9 99)	38 31 (15 19)	
Cholesterol_mg (mean (sd))	375 71 (160 93)	348 40 (139 23)	403 02 (182 64)	418 16 (147 17)	348 43 (192 92)	
Carbohydrate_available_g (mean (sd))	245 74 (99 53)	232 46 (62 81)	259 02 (136 25)	224 03 (45 66)	283 31 (165 76)	
Sugars_g (mean (sd))	123 4 (86 81)	112 67 (55 36)	134 13 (118 26)	97 01 (24 41)	164 37 (144 22)	
Dietary_fibre_g (mean (sd))	26 33 (8 23)	29 18 (9 28)	23 48 (7 18)	25 37 (7 96)	25 00 (8 69)	On average, most Australians consume 20–25 g of fibre daily The Heart Foundation recommends that adults should aim to consume approximately 25–30 g daily
Kj_from_protein_percent (mean (sd))	18 24 (3 66)	18 24 (3 28)	18 24 (4 04)	18 55 (3 33)	17 86 (4 35)	protein (10%-35% of energy)
Kj_from_fat_percent (mean (sd))	36 01 (6 33)	36 94 (6 93)	35 09 (5 73)	36 40 (5 24)	34 76 (7 01)	total fat (20%-35%)
Kj_from_saturated_fat_percent (mean (sd))	13 94 (3 32)	13 67 (3 44)	14 22 (3 20)	14 25 (2 31)	13 83 (4 16)	Max 10% of total energy
Kj_from_trans_fat_percent (mean (sd))	0 65 (0 18)	0 67 (0 15)	0 64 (0 21)	0 69 (0 17)	0 60 (0 22)	-
Kj_from_carbohydrate_percent (mean (sd))	40 10 (7 80)	39 77 (6 62)	40 44 (8 99)	38 79 (5 63)	41 97 (10 53)	CHO 45-65% of energy
Kj_from_fibre_percent (mean (sd))	2 17 (0 63)	2 45 (0 80)	**1.89 (0.46)***	2 17 (0 73)	1 93 (0 47)	
Added_sugars_tsp (mean (sd))	13 49 (15 80)	8 71 (3 43)	18 27 (28 18)	9 04 (4 33)	22 98 (34 13)	
Energy_from_added_sugar (mean (sd))	906 71 (1062 04)	585 58 (230 32)	1227 85 (1893 76)	607 60 (290 77)	1543 97 (2293 49)	
Energy_from_added_sugar_percent (mean (sd))	8 02 (6 20)	6 11 (2 62)	9 92 (9 79)	6 29 (2 86)	11 73 (11 62)	The WHO recommends that no more than 10% of our total daily energy intake come from added sugars

AMDR - acceptable macronutrient distribution ranges are an estimate of the range of intake for each macronutrient for individuals (expressed as per cent contribution to energy), which would allow for an adequate intake of all the other nutrients whilst maximising general health outcomes. AMDRs are established for macronutrients (carbohydrate (45%-65% of energy), protein (10%-35% of energy), and fat (20%-35% of energy; limit saturated and trans fats) to reduce chronic disease risk whilst still ensuring adequate micronutrient status.

The highlight of this analysis was that people with obesity had significantly less consumption of dietary fibre as compared to overweight people ($p<0.01$). In this study the energy intake of carbohydrate was higher in overweight and obese people in comparison to the Australian Dietary Guidelines, that recommends the average intake of carbohydrates should be 45-65% of the total energy intake. The total energy intake, grams per day intake and number of teaspoons of added sugar per day was higher in people experiencing obesity (10%, 134 grams, 18 teaspoons) as compared to people who were overweight (6%, 112 grams, 8 teaspoons). No significant difference of total energy intake from saturated fat was observed in overweight (13.6%) and obese people (14.2%). Regardless of significance, both overweight and obese people exceeded recommended guideline for the intake of saturated fat i.e. less than 10% of the total energy intake. The carbohydrate intake was found to be lower in people in both overweight (39.7%) and obese people (40.4%). The carbohydrate intake was lower than the recommended total energy intake ranges of 45-65%. The protein intake in overweight (18%) and obese people (18%) was in the optimal range based on recommended guidelines (10-35%).

6.5 Discussion

This study found a significant association between waist circumference and periodontitis in the bivariate analysis. This finding is supported by a systematic review that reported that increased waist circumference may be a risk factor for periodontitis development and progression [14]. The US-based NHANES (1988-1994) in people 18+years found that having high waist circumference (above the cut-off value of obesity) was associated with 2.27-time higher risk of periodontitis [255]. Similarly, Beguingui et al. found that having high waist circumference was associated with significantly higher risk of moderate/severe periodontitis [412].

This study found no significant association between BMI and periodontitis in the bivariate analysis. This finding aligns with results from the Malaysian pilot study, the fourth Korean National Health and Nutrition Examination Survey (KNHANES) and Health 2000 Health Examination Survey of Finland that found no association of BMI with periodontitis in adults after adjusting for putative confounders [212, 381, 413].

People experiencing obesity have unhealthy diet which is of low nutrition and high sugar and fat content, leading to production of advanced glycation end products and induction of insulin resistance by apoptosis of the beta-cells of the pancreas or by adipocytes produces cytokines including TNF-α, which interrupts insulin signalling. Insulin resistance in turn contributes to development of prediabetes and type 2 diabetes state, which further deteriorates the pro-inflammatory state resulting in abundant macrophage and cytokine production that may induce inflammation in periodontal tissues resulting in periodontitis [225].

Another important finding of this study was that people with periodontitis had higher fasting glucose level as compared to people with no periodontitis. It was noted that people with periodontitis had impaired fasting plasma glucose level as compared to

people with no periodontitis. Fasting plasma glucose is an indicator of diabetes risk. The American Diabetic Association guidelines states that fasting plasma glucose level more than 5.6-6.9 mmol/L is pre-diabetes and fasting plasma glucose level greater than 7 mmol/L is type 2 diabetes [414]. A 12-month follow-up randomised controlled trial indicated that people who underwent intensive periodontal therapy (non-surgical periodontal therapy and surgical periodontal therapy) experienced improvement in fasting plasma glucose levels in type 2 diabetic patients with moderate-to-severe periodontitis [102].

Type 2 diabetes is a highly prevalent public health problem, that is estimated to affect 451 million people worldwide and is projected to affect more than 693 million people over the next 20 years [89] Type 2 diabetes mellitus is a fast growing epidemic and one of the leading cause of death in Australia [415]. The healthcare costs associated with type 2 diabetes is estimated to be 14.6 billion AUD annually [416]. More than 3.2 million Australians are estimated to be experiencing pre-diabetes and type 2 diabetes [415]. Interventions towards prevention of pre-diabetes and type 2 diabetes and its associated complications are a priority of the Australian Healthcare System [415, 416]. The interpretation of the findings of high fasting plasma glucose level in this study, and evidence of fasting plasma glucose levels in the randomised controlled trials by D'Auito et al. (2018) suggests that periodontal care improves metabolic control and diabetes outcomes via reducing fasting plasma glucose and HbA1c levels in people at risk with prediabetes or with pre-existing type 2 diabetes [102].

This study found that people with BMI <30kg/m^2 had significantly better interdental cleaning behaviour as compared to people with BMI ≥30kg/m^2. This finding aligns with Reichert et al. (2015) study that found that people with lower BMI had better interdental cleaning behaviour as compared to people with higher BMI [417]. Better oral hygiene practices among people with BMI<30kg/m^2 could be speculated as a measure of good oral health and good general health. Poor oral hygiene practices are associated with

an increase in deposition of dental plaque and development of periodontitis, that may contribute to systemic inflammation associated with obesity.

In this study low dietary fibre intake was significantly associated with obesity. On average, the daily intake of dietary fibre amongst Australians is 20-25 grams per day [418]. In the current study people with obesity had reduced intake of dietary fibre (23.48 grams per day) when compared to the recommendations from the Heart Foundation. The Heart Foundation recommends that adults should aim to consume approximately 25-30 grams per day of dietary fibre [418]. Dietary fibre functions by binding with the dietary fat thus reducing its absorption throughout the gastrointestinal tract. It prevents absorption of fat in the small intestine and reduces fermentation activity by the gut microflora [419]. Reduced intake of dietary fibre is associated with an increase in absorption of dietary fat and cholesterol into the bloodstream, thus increasing the risk of dyslipidaemia, type 2 diabetes, cardiovascular diseases and obesity [419].

The following are limitations of this pilot study that will be addressed when a future prospective cohort study is conducted. Firstly, this study had a low sample size of 33 participants that limited the ability to come up with meaningful conclusion. Furthermore, the factors of patient compliance, obesity-related stigma, limited funding and limited clinical sessions hindered the recruitment process. Secondly, this study utilised a convenience sampling technique for recruitment of participants. Although, this method is convenient, cost effective, and easy, the samples recruited using this method are not representative to the population. Thus, the result of these finding cannot be generalized to the population. Thirdly in this study there was an absence of a non-obese control group, which if include would have benefitted in better understanding the association of obesity and periodontitis. Future studies are recommended to non-obese control groups. If a randomised controlled trial is conducted it should be randomised for

treatments i.e. group 1 receiving non-surgical periodontal therapy and oral hygiene instruction, and control group 2 receive oral hygiene instructions only.

This was the first study among pre-diabetics that compared obesity/overweight, diet and periodontitis. Other strengths of this study included: (i) using a definite case definition for periodontitis which is universally acceptable (Eke et al. 2012); (ii) conducting comprehensive full mouth periodontal examination using Florida probe system that calibrated the examiner with the system and reduced the margin of errors in probing. Future studies should employ a prospective cohort study design to better understand the relationship between diet, obesity and periodontitis.

Conclusion

Lessons learned from this pilot study will be addressed in a larger prospective study by addressing the limitations mentioned in the previous section of this chapter. Waist circumference and higher fasting blood glucose levels were significantly higher in participants with periodontitis compared to participants without periodontitis. The level of obesity and being overweight are a public health challenge, affecting more than 65% of the worldwide population [145]. The Australian population is also experiencing a high burden of overweight (63%) and obesity (28%) [3]. Being obese or overweight adversely affects health and is associated with chronic diseases such as cardiovascular diseases, pre-diabetes and type 2 diabetes, sleep apnoea and cancers [3, 397]. Overweight and obesity are also associated with poor oral hygiene behaviour and poor dental visiting behaviour in Australian adults [398]. Lifestyle factors (physical activity, alcohol intake and diet), insufficient sleep as well as, medical problems, certain medications and social-demographics are associated with weight gain [420]. Energy dense food and high fat diet are important determinants of obesity/overweight [396]. In conclusion, the association between obesity and periodontitis may be clustered effect of multiple factors rather than single

influencing factor. Prospective cohort studies are required in people with obesity that should incorporate multiple rigorous measures to better understand the mediating factor in obesity and periodontitis relationship.

Chapter 7. Discussion

This chapter is a discussion of the key results, the credibility and implications of the results and future directions that were deduced from this dissertation (systematic review, the secondary data analysis of the NSAOH 2004-06 and a study conducted in the University of Sydney, herein referred to as a pilot study).

7.1 Key Results

7.1.1 Primary Findings

i. In this PhD dissertation, the systematic review found that being overweight/obese (having a high body weight, high BMI and a large waist circumference) may be risk factors for periodontal disease as assessed by the plaque index, bleeding on probing, probing depth, clinical attachment loss and alveolar bone loss in adolescents and young adults. Seventeen of 25 studies showed a positive association between being overweight/obese and periodontitis [218, 255, 314, 316, 318-321, 323, 324, 327-329, 331, 332, 334, 338, 346].

ii. The second objective of this dissertation was to study the relationship between overweight/obesity and periodontitis in Australian adults using the NSAOH 2004-06 dataset. The conventional multiple variable regression analysis was utilised. The result of this aim suggested no association between overweight/obesity and periodontitis in Australian adults. These results align with findings from studies conducted in national surveys from Canada, South Korea and Finland that also found no significant association between obesity and periodontitis [212, 381, 421]. Contrary to these findings, multiple systematic reviews and meta-analyses have suggested a significant association between obesity and periodontitis in children, adolescents and adults [5, 14, 371]. The factors of age, sex, smoking, and dental visiting behaviour were the significantly associated putative confounders for

periodontitis in the multiple variable regression models. These findings are consistent with results of a Canadian population-based study, in which obesity was not associated with periodontitis, and the variables of age, sex, smoking, and dental visiting behaviour were strongly associated with periodontitis [422].

iii. The third objective of this dissertation employed a single mediation analysis to determine the association between overweight/obesity and periodontitis in the Australian NSAOH 2004-06 dataset. The result of this analysis indicated no causal relationship between overweight/obesity and periodontitis. The direct and indirect effect of dental visiting behaviour (a de facto measure of healthy behaviours) and of overweight/obesity on periodontitis was 14% and 3% respectively. However, it was recognised that there were multiple unmeasured mediators that may have influenced the relationship between overweight/obesity and periodontitis. These may include pro-inflammatory mediators, associated co-morbidities and diet.

iv. The fourth objective of this dissertation analysed a subpopulation contained within a pilot study, administered as part of a registered trial obesity prevention study. The results of this study found waist circumference and fasting plasma glucose were significantly associated with periodontitis in the bivariate analysis. BMI and dietary variables were not associated with periodontitis in the bivariate analysis.

7.2 Credibility of the results

7.2.1 Strengths

- To the best of researcher's knowledge, this dissertation is the first project exploring the association between overweight/obesity and periodontitis in Australian adults.

- The NSAOH 2004-06 provided the best available representative oral health/periodontal data of the Australian population.
- The researcher utilised the NSAOH 2004-06 dataset to determine the relationship between overweight/obesity and periodontitis, using bivariate and multiple variable conventional regression analyses, and a single mediation analysis. This dissertation also established a pilot study to understand the relationship between overweight/obesity and periodontitis amongst people with pre-diabetes (with no co-morbidities) in New South Wales, Australia.
- In Chapter 5 of this dissertation, a DAG was developed to understand the complex relationship between overweight/obesity and periodontitis in Australian adults. A single mediation analysis was applied to answer the research question "*Does overweight/obesity cause periodontitis?*" using the cross-sectional NSAOH 2004-06 dataset. This analysis assisted in differentiation between confounders and mediators. Further, it helped in acknowledging the unmeasured confounders that may affect the relationship between overweight/obesity and periodontitis. Single mediation analysis is a robust and cutting-edge research tool as compared to conventional regression analysis (in which the confounders and mediators of exposure [overweight/obesity] and outcome [periodontitis] are grouped together as putative confounders/mediators, limiting the ability to truly understand the effect of exposure on the outcomes).
- The NSAOH 2004-06 used a rigorous, clustered stratified random sampling technique for the recruitment of participants. Participants in the study were recruited using a three-stage clustered randomised sampling technique for selecting a representative sample of dentate Australians aged 15 years and older. The sampling frame of the study was households with listed telephone numbers recorded in an electronic White Pages database. The first stage selected postcodes,

the second stage selected households within sampled postcodes, and the third stage selected one person aged 15 years or more from each sampled household.

- This project utilised a full-mouth periodontal examination protocol for the measurement of periodontal outcome (PPD, CAL, BoP). The stability of the examination protocol is important in determining the true periodontal disease status of an individual [423]. In population-based surveillance, a variety of partial-mouth periodontal examination protocols have been used historically, due to time and cost constraints, lack of workforce and funding, patient and/or examiner fatigue, large measurement errors, and dropout rates experienced in full-mouth periodontal examination protocol [424, 425]. Previous evidence-based research supports the finding that partial-mouth periodontal examination protocols underestimates the true prevalence of periodontitis due to the site-specific nature of periodontal disease [424, 425]. Partial-mouth periodontal examination protocols also result in extensive misclassification bias due to low-sensitivity to elicit the accurate periodontal state. As a result, negative implications occur, which affect the outcomes of research questions on relationships between periodontitis and its risk factors [426].
- Regardless of the time constraints associated with the full-mouth periodontal examination protocol, it is the most reliable and sensitive tool for determining the true prevalence, extent and severity of periodontitis. The Center of Disease Control and Prevention, Division of Oral Health and the National Institute of Dental and Craniofacial Research support the proposition that the full-mouth periodontal examination protocol is the "gold standard tool" for measurement of accurate periodontitis levels [427].
- The Center for Disease Control and Prevention and American Academy of Periodontology's universally-accepted case definitions of periodontitis were

adopted in this dissertation [376, 411]. The case definitions assisted in relating the findings to other studies [376, 411]. It is recommended that future studies should adopt the Center for Disease Control and Prevention and American Academy of Periodontology's case definition of periodontitis for maintaining consistency and reliability, which would aid in relating these research findings to other studies [411].

- One of the major strengths of the pilot study was the utilisation of electronically calibrated Florida Probe® system (Florida Probe Corp; USA). The Florida Probe® system is a specialised tool used in modern periodontics, making periodontal examination recordings reliable and reproducible. It is pre-calibrated and delivers 15g of force when measuring PD, CAL and BOP. It immediately records these readings through a wired-transfer to an attached laptop (Dell Latitude E7270). The advantages of this system are: (i) the delivery of constant probing force; (ii) precise electronic measurement to 0.1 mm; (iii) a non-invasive and light-weight instrument; and (iv) automated computer storage of the collected data [428]. Electronic data recording via pressing the foot switch eliminates errors and record bias that had previously resulted from reading probe-tip markings aloud to an assistant, who transferred the data to a sheet of paper'[428]. Furthermore, it has been an effective tool in prospective cohort studies and randomised controlled trials, facilitating a comparison of changes in PPD and CAL across patients' dental appointments [428].
- As reported in Chapter 2, overweight/obesity is a complex condition associated with multiple risk and modifiable factors. Therefore, to reduce the confounding effect of these factors, the pilot study included obese people with no co-morbidity to truly understand the relationship between overweight/obesity, diet and periodontitis.

- In the pilot study, the body composition measures of body height, body weight, and waist circumference were measured objectively. The recordings of the body composition measures are preferable to self-reported measures, as supported by previous studies discussed in the Chapter 2.
- Recording of the three-day dietary record through administration of a diet diary was one of the important strengths of the pilot study. Comprehensive recordings made in the diet diary are essential for understanding the accurate intake of macronutrients and micronutrients by an individual. In addition, it aids in measuring the total energy intake of nutrients, which is not possible with the questionnaire-based dietary record.

7.2.2 Limitations

The NSAOH 2004-06 and the pilot study were cross-sectional studies in which the exposure and outcomes were measured at the same time point. The cross-sectional study design allows exposure and outcome variables to be measured simultaneously in a given population [429]. Cross-sectional studies are conducted to estimate the prevalence of outcomes of interest and associations between risk factors and disease outcomes in a given population for public health planning. Cross-sectional studies are limited in that, they only provide a snapshot of one-time point and give no indication of whether the exposure occurred pre, post or during the onset of the disease outcome. Therefore, cross-sectional studies are a poor indicator to infer causality. Hence, it is advised that future studies should use a prospective cohort study design, as it is considered a "gold standard" study design to answer causal relationship hypotheses in research.

The NSAOH 2004-06 study recorded self-reported body height and body weight. These measures were used to determine the BMI of participants. Self-reported body composition measures are associated with reporting bias. People who are overweight and

obese tend to underestimate their body weight status as compared to people of normal weight [137-139]. The underestimation of self-reported body weight status among obese people is influenced by social determinants such as education [142], sex [137] and ethnicity [143]. Sex-specific differences have also been reported in previous studies on the underestimation of self-reported body weight. Men tend to underestimate their body weight more than women; however, this reporting is towards the higher end in men as compared to women [141]. In women, increased mis-reporting of body weight is suggested as a result of societal pressures, advertisement, mass media, and cultural norms [137]. Based on the above evidence, it is advised that studies should involve clinically objective measurements of body height and body weight to calculate the accurate BMI, rather than an estimated BMI based of self-reported data. Measuring both the self-reported and machine-measured measures could be used for the purpose of validating self-reported BMI in prospective studies. However, objective measurement of BMI was not cost-effective in Australian context, due to limited financial resources. . It is recommended that where feasible, clinically objective measurements of body height and body weight should be used to calculate an accurate BMI

For calculating BMI, the NSAOH 2004-06 recorded self-reported body height and body weight, whilst the pilot study involved objective measurements of body height and body weight. BMI is a cost-effective, simple tool and does not require specialised equipment [430]. The limitations of BMI are outlined in Chapter 1.

The NSAOH 2004-06 did not report on body composition measures of waist circumference, hip circumference and waist to hip ratio. The advantages of using multiple body composition measures have been discussed in the Chapter 1 of this dissertation. It is advised that future studies at the national level should report on multiple body composition measures [128]. It would help towards better understanding the relationship

between body composition measures and periodontal disease. Hence, the pilot study involved the recording of multiple body composition measures.

The NSAOH 2004-06 utilised a 13-item food frequency questionnaire that provided information on the participants' daily intake of the 13 food items during the whole day and before bed. The limitations associated with this questionnaire involved the incomprehensive nature of the questionnaire to estimate the true daily intake and portion of sugar in diet by the participant. It is advised that future studies should use food recall record diaries to better predict the dietary sugar intake and other macronutrient intake of participants. This would be helpful in predicting the true relationship between diet and periodontitis. Acknowledging the challenges in determining the relationship between obesity, dietary sugar and periodontitis in the NSAOH 2004-06 data, a three-day food diary record was undertaken in the pilot study.

This dissertation utilised the 1999 classification of periodontal disease because this was the classification adhered to when this research project was conceptualised and developed. The new classification of periodontal disease was introduced in 2018. It is recommended that future studies should adopt periodontitis-based surveillances using the 2018 classification of periodontal disease [43].

The NSAOH 2004-06 was unable to identify whether participants were of Asian background. This would have been useful for applying the correct obesity definition for Asian populations in this study, and for secluding the confounding factor of ethnic background.

In the pilot study of Chapter 6 of this dissertation, there were two important limitations associated with HbA1c marker. First, the mean and standard deviations of the HbA1c were very low in the pilot study. Low sample size of the study could be a potential reason for this value. Second, the HbA1c scores were analysed in percentage HbA1c

levels in the pilot study. This was one of the important limitations because percentage HbA1c levels is not a preferred measure. For future studies, it is recommended using mmol/mol values of HbA1c in accordance to the International Federation of Clinical Chemistry recommendations [431].

7.2.3 Sources of Bias

i. Response bias: A response bias was recognised in this project. First, from the self-reporting of body heights and body weights in the NSAOH 2004-06 and, second, due to the responses of participants to the oral hygiene questions and dental visiting behaviour questions in both NSAOH 2004-06 and the pilot study. A third source of response bias was evident in the recording of the diet diaries in the pilot study. People tend to distort their responses to reduce embarrassment and to create a positive impression [432]. They also alter their responses due to increased fear of consequences and a feeling of breach of their confidentiality that a true response might have had [432]. Researchers have found several ways to reduce reporting bias, either by pre-testing the questionnaire or rewording the questionnaire. Response bias is influenced by how questions are worded, ordered, or presented to the respondent. Hence, addressing this might help in reducing the potential for response bias [433].

   The NSAOH 2004-06 employed two methods for assessment of non-participation bias. Firstly, a "population benchmark" approach was used to compare the estimates of the NSAOH samples in relation to the selected demographic variables distribution in the Australian adults using census data [90]. However, the census data lack information on characteristics that were part of the NSAOH 2004-06 e.g. socio-economic status, a prominent determinant of population oral health status and an important factor that is associated with survey response rates. To encounter this issue, the NSAOH 2004-06 used "small area socioeconomic characteristic

approach for non-participation bias evaluation [90]. The details of the bias are provided in the Australian Dental Generations report [90].

ii. Non-response bias: In monitoring and mapping risk factors in a given population, understanding the selective non-response bias estimate is paramount for understanding how it may impact on the prevalence estimates. A *"non-response bias refers to the mistake one expects to make in estimating a population characteristic based on a sample of survey data in which, due to non-response, certain types of survey respondents are under-represented"*. Non-response bias was observed in NSAOH 2004-06 survey during the CATI [90]. The most common reasons for non-response bias in the NSAOH were: (i) the participant's phone was disconnected; (ii) researchers' inability to contact a participant in spite of multiple, repeated phone calls; (iii) a selected participant opted not to respond to questions; and/or (iv) the unwillingness or inability of participants to attend for an oral health assessment [90]. The NSAOH 2004-06 interviewed 49% of sampled population that were recruited. Of these, 44% underwent the oral examination [90]. The demographic factor of non-English speakers was underrepresented in this survey and participation rates varied by socioeconomic status. This was a problem because several oral health measures and indicators were associated with non-English speakers and with socio-economic status. As a result, the estimate observations produced in this survey found that participants in the survey were "healthier" as compared to the population. An overestimation was reported for favourable dental visiting "frequency" and an underestimation for oral diseases. Yet, non-participation bias was small. For most indicators of the oral health weighted adjustment resulted in estimates differing by <3% [in absolute terms]. Adjusted estimates of disease severity measures differed by < 10% in relative terms. The magnitude difference was similar to variability magnitude, that was

attributable to random error. There was a low magnitude of bias in majority of the estimates, suggesting that NSAOH data represented the Australian adult population [90].

iii. Organisational issues: In the pilot study of obesity and periodontitis, a high level of non-participation was observed in participants recruited in the clinical trial. Factors such as non-response bias influenced the recruitment process. However, there were other factors that were associated with loss of participants. First, the pilot study was part of a larger RCT which had its own recruitment staff. The recruitment staff were non-dental professionals, who lacked knowledge and understanding that better oral health is related to better general health. They were less motivated and untrained to explain the aim and objectives, potential benefits and adverse effects associated with this study. Second, time constraints and lengthy appointments in the trial resulted in participant fatigue, that also influenced attrition of participants to undergo oral health assessment. To overcome this, participants were offered the opportunity to attend an oral health assessment the next day, which was mostly refused due to the reason that participants lived long distances away, had an estimated travel time of one hour or more, and had no monetary incentive to participate in the pilot study.

iv. Measurement error: In this dissertation, oral hygiene behaviours were measured with open-ended questions; e.g., "In the last week, how many times did you; brush your teeth or use a mouth wash or chew a sugar-free gum or clean between the teeth?" These questions are sensitive to measurement errors due to under-reporting of risk behaviour.

7.3 Measurement of Periodontitis

Diagnosis of periodontitis was made using the updated Center for Disease Control and Prevention and American Academy of Periodontology case definition of periodontitis

in the pilot study [411] and CDC-AAP 2007 definition for the NSAOH 2004-06 study [376]. The definition used in the NSAOH 2004-06 categorised periodontitis into three categories: (i) no periodontitis ("healthy periodontium or mild periodontitis"); (ii) moderate periodontitis; and (iii) severe periodontitis [376]. The definition of periodontitis used in the pilot study categorised periodontitis into four categories: (i) no periodontitis; (ii) mild periodontitis; (iii) moderate periodontitis; and (iv) severe periodontitis [411]. These both definitions are different because the 2007 definition had moderate/severe periodontitis were a combined category, whereas in the 2012 updated definition the moderate and severe periodontitis categories were separated. The CDC-AAP case definitions of periodontitis are widely used to estimate the prevalence of periodontitis in the population-based surveillances. The details on the case definition of periodontitis are provided in the methods section of this dissertation.

A new "joint" case definition of periodontitis was proposed in 2018 that defines periodontitis into three main forms (i) "necrotising periodontitis"; (ii) periodontitis as a manifestation of systemic disease; and (iii) "periodontitis – combination of aggressive and chronic form". Aligning with the aims of this dissertation the author focused on category three "periodontitis". This classification uses a grading and staging system that has different levels based on the severity and progression of the periodontitis. The grading system includes three levels based on the progression of periodontitis (A- low risk; B-moderate risk; C-high risk) and includes information related to general health status and exposures including tobacco smoking and type 2 diabetes. Staging is categorised into four stages and is determined using CAL, the percentage and amount of bone loss, PD, angular bone defect, and furcation involvement. However, this definition of periodontitis could not be used in this thesis, because the data were not available in NSAOH 2004-06 or the pilot study. In any future research, the new classification of periodontitis should be used.

The NSAOH 2004-06 and pilot study data were also analysed to measure the extent of periodontitis. The extent of periodontitis is defined as the number or proportion of sites with periodontitis based on the measures of PD ⩾4mm and CAL ⩾4mm. The prevalence, extent and severity of periodontitis are important risk indicators that help in: determining the distribution and pattern of periodontitis; establishing treatment plans; and prevention programmes.

7.4 Prevalence and Extent of Periodontitis in the Overweight/Obese versus Normal Weight Individuals

The secondary analysis of the NSAOH 2004-06 found the prevalence of periodontitis in the overweight/obese Australians was 25.3%. This finding is lower than the US National Health and Nutrition Examination Survey 2009-12 and the fifth Korean National Health and Nutrition Examination Survey which found the prevalence of periodontitis in adults experiencing overweight/obesity was 73.5% and 46% respectively [434, 435].

The secondary analysis of the NSAOH 2004-06 found that the extent of CAL⩾ 4mm was significantly associated with BMI, age, sex, income, education, smoking, flossing, type 2 diabetes, added sugar intake, and the usual reason for dental visiting in the bivariate analysis. No association was found between the extent of PD⩾4mm and BMI. CAL is a more accurate measure of the loss of alveolar bone than PD. The detailed discussion of the findings of the extent of periodontitis have been reported in Chapter 4 [4.5 Discussion].

The lower prevalence of periodontitis in overweight/obese individuals in Australia could be due to better oral hygiene behaviour and regular dental visiting behaviour in Australia as compared to US, South Korea and the UK, as suggested in a comparison report of adult oral health in Australia, the USA, Germany and the UK [436].

Regardless of the lower prevalence of periodontitis in Australia as compared to other countries, the burden of periodontitis is high enough to: influence the risk of co-morbidities; increase waiting times at public hospitals and private dental clinics; increase absences from work and school; and increase the cost of care. There is a need for intervention programmes and the implementation of a universal public dental health benefit scheme in Australia that may encourage people to improve oral health. In addition, an Australian government priority is to reduce the burden of non-communicable diseases, including obesity and periodontitis in Australia. This is reflected in the proposal to implement a sugar-sweetened beverages tax of 20% that may result in reducing the burden of disease and creating health care cost saving of AUD 666 million over a decade [437].

7.5 Periodontitis and the Putative Confounders: Results from the NSAOH 2004-06 Secondary Data Analysis

7.5.1 Association between Age and Periodontitis

The results of this study found that people 34-59 years and 60+ years had a higher risk of periodontitis as compared to people aged 15-34 years. This finding aligns with the US-based NHANES 2009-2014, which reported that 46% of adults 30 years and older had periodontitis [438]. Periodontitis is an age-dependent disease with increasing prevalence and severity amongst people 30+ years [255]. However, the concept of periodontitis as an inevitable result of ageing has evolved over time to the current concept that periodontitis is a cumulative effect of long-term exposure to its true risk factors [257].

7.5.2 Association between Sex and Periodontitis

In Chapter 4, the secondary data analysis of the NSAOH 2004-06 showed that males had a higher prevalence of periodontitis as compared to females, at 27.6% and 18.1% respectively [237]. This aligns with the US-based NHANES, which found that males

had a higher prevalence of periodontitis as compared to females [439]. This could be attributable to better oral hygiene practices and increased utilisation of dental health services by females as compared to males [440]. Sexual dimorphism has been reported in relation to various chronic diseases. Strong linkages have been proposed between sex and periodontitis as compared to any other putative confounder [441].

7.5.3 Association between Socio-economic Status and Periodontitis

In Chapter 4 of the thesis, the socio-economic measures (income <20,000 AUD/year and no secondary education) were significantly associated with periodontitis [400]. According to the income thresholds, the household income quartiles of 20,000 AUD/year were associated with a higher prevalence of periodontitis as compared to the quartile with <80,000 AUD per year income (43% versus 15%) [442].

The finding of this dissertation aligns with a South Australian study where a high prevalence of periodontitis was found in people with incomes <$80,000 AUD/year as compared to people with incomes >80,000 AUD/year. Individuals with high incomes have better education levels and better access to dental services, that significantly impacts on having better oral hygiene practices and better periodontal outcomes (income and Health Care Card) [235].

7.5.4 Dental Visiting Behaviour and Periodontitis

In the current study, the problem-based dental visiting behaviour was significantly associated with periodontitis. Dental visiting behaviour is defined as the visiting pattern/reason of an individual to see a dentist. It comprises the factors of potential barriers to dental care, which might be the result of poor health literacy, dental fear or anxiety, poor attitudes to dental care and cost of treatment [248]. Studies have reported that regular dental visiting is a de facto measure for healthy behaviours and it is associated with better oral health/periodontal outcomes.[243]

7.5.5 Added Sugar Intake and Periodontitis

In Chapter 4, added sugar intake was not associated with periodontitis in the bivariate analysis. This finding is in disagreement with the US-based NHANES III (1988-1994), which found a significant association between added sugar intake and periodontitis in young adults in the US [334]. Added sugar intake is associated with a pro-inflammatory state, insulin resistance and chronic co-morbidities, including abdominal obesity and type 2 diabetes [283], which are also significant risk factors for periodontitis. Added sugar intake contributes to dental plaque formation [283] and leads to pH reduction in the mouth and to an increase in bacterial diversity [443].

7.6 Overweight/obesity and the Putative Confounders: Results from the NSAOH 2004-06 Secondary Data Analysis

7.6.1 Association between Age and Overweight/obesity

The results of this dissertation found that people age 45 to 59 years and people aged 60+ years had a higher prevalence of smoking as compared to people of 15-44 years. This finding aligns with a US-based study (2005-2014) [146] that found that increased age was associated with higher odds of being obese. The overall trend was found to be rising from young adult to middle age. Age is an independent, non-modifiable risk factor for chronic diseases including obesity [251].

7.6.2 Association between Gender and Overweight/obesity

This dissertation showed being male was associated with a higher risk of being overweight/obese. This is contrary to previous studies, which have reported an increased risk of obesity among women as compared to men. The National Health Survey of Australia 2015 reports that the prevalence of being overweight or obese is higher in men as compared to women throughout the life span [259]. The OECD countries including Australia have a high prevalence of overweight and obesity in men as compared to women

[444]. In contrast, the US, Middle East and North Africa have a higher prevalence of obesity in women as compared to men [444, 445]. The WHO defines sex as "*biological and physiological characteristics that define men and women*," whereas gender "*refers to the socially constructed roles, behaviours, activities, and attributes that a given society considers appropriate for men and women"*[446]. Both the biological and social factors influence obesity-related outcomes of men and women [446].

7.6.3 Association between Socio-economic Status and Overweight/obesity

In this dissertation, having no secondary education was found to be significantly associated with overweight/obesity. In Australia, according to the Australian National Preventive Health Agency (ANPHA), the prevalence of obesity is higher among people: who have lower education levels; lower incomes; live in rural location; have refugee status; and Indigenous identity [447]. This finding matches with other OECD countries where obesity/overweight was significantly higher in people with lower education levels [448]. Epidemiologists and public health practitioners use education as a measure of the socio-economic status of an individual. It is often used in conjunction with chronic conditions, quality of life assessments, and psychological evaluations. In addition to obesity, a lower education level is a risk factor for various other chronic disease (type 2 diabetes, dementia, cardiovascular disease and chronic renal disease), low income, low socio-economic status and an overall poor social gradient [103].

7.6.4 Association between Smoking and Overweight/obesity

In this dissertation, being a former smoker or non-smoker was significantly associated with being overweight or obese. Similar findings were reported by a systematic review of 35 cohort studies, which reported that quitting smoking was associated with a 4.10 kg (95% confidence interval [CI]: 2.69, 5.51) increase in body weight and a

1.14 kg/m^2 (95% CI: 0.50, 1.79) increase in BMI as compared to continuing smokers [277]. Smoking and obesity together have a negative impact on the health of an individual. Nicotine, a constituent of tobacco, leads to an increase in energy expenditure, resulting in reduced appetite and lower body weight in smokers as compared to non-smokers. In contrast, individuals who smoke heavily tend to gain more weight than do light smokers/non-smokers, which reflects a clustering of risky behaviours (e.g., low physical activity, poor diet, and smoking) that is conducive to weight gain [277]. Smoking is an established risk factor for various other chronic conditions associated with obesity, including type 2 diabetes, cardiovascular disease and periodontitis [274-276].

7.6.5 Association between Dental Visiting Behaviour and Overweight/obesity

Overweight/obesity was deemed to be significantly associated with poor dental visiting behaviour. This finding aligns with a study by Khader et al. which found that people experiencing obesity had poor dental visiting behaviour [131]. This could be a result of dental fear or anxiety, being embarrassed about their body weight, lack of knowledge, differing beliefs, poor attitudes to dental care or the cost of treatment.

7.6.6 Added Sugar and Overweight/obesity

In the NSAOH 2004-06 and the pilot study, no association was found between overweight/obesity and sugar intake. This result could be due to the limitations of 13-item food frequency questionnaire in the NSAOH 2004-06, and the lower sample size in the pilot study.

The Australian National Health Survey reported that more than half of Australians exceed the WHO's recommendation of limiting added sugar to 10% of daily energy intake [259, 385]. Also, additional health benefits could be obtained with a reduction below 5% of total energy intake [385]. The 2013 ADGs advises Australians to limit their intake of added

sugar (food and beverages), especially all SSB, sports drinks, confectionery, biscuits and cakes, as these contribute to the major added sugars burden in Australia (74%) [449].

7.7 Relationship between Overweight/obesity and Periodontitis using Single Mediation Analysis on the NSAOH 2004-06 dataset

To validate the results of the conventional regression analysis that are reported in the Chapter 4 of this dissertation, the author utilised a cutting-edge and robust method of single mediation analysis to truly understand the relationship between overweight/obesity and periodontitis in the NSAOH 2004-06 survey. A DAG was drawn to answer the research question "*Does overweight/obesity cause periodontitis*?", defining exposure *A*, outcome *Y*, mediators *M* and confounders *C*. The DAG of this study was represented by exposure *A* as overweight/obesity, outcome *Y* as periodontitis, mediator as dental visiting behaviour *M and* confounders *C* as age (C_1), smoking (C_2), alcohol (C_3) and income (C_4). Various pathways that represent the direct and indirect relationship of *A* and *Y*, under the influence of mediators (*M*) were generated. The author came to a final data generation mechanism after testing of pathways and other possible mechanisms based on evidence from previous studies, as discussed in Chapter 4 of this dissertation. Assumptions of consistency, exchangeability, positivity and faithfulness were verified to determine that the intervention was well defined. Following the testing of these assumptions, mediation modelling was conducted.

The findings of the current study suggested that the direct effect of overweight/obesity (A) on periodontitis (O) was 14% when the exposure of the population was set to be obese people with no moderate physical activity. The indirect effect of overweight/obesity through dental visiting behaviour on periodontitis was 3%. The finding is supported by a study by Castilhos et al. that suggested there was no association between obesity and periodontitis in adults [315]. Similar results were found in

the fourth Korean National Health and Nutrition Examination Survey (KNHANES) and Health 2000 Health Examination Survey of Finland, where obesity was not associated with periodontitis in adults after adjusting for putative confounders [212, 381]. Contrary to the findings of this study, systematic reviews and meta-analyses have reported significant association between obesity and periodontitis [14, 371, 395]. Similarly, a prospective cohort study in the Brazilian population has reported a dose-response relationship between obesity and periodontitis using adjustment for time-varying covariates [392].

7.8 Obesity and Periodontitis: A Pilot Study in Pre-diabetics

The pilot study was a feasibility study for a future prospective cohort study to determine the true relationship between obesity, diet and periodontitis. The methodological errors encountered in the pilot study will be addressed in the future prospective cohort study. The key methodological errors that will be addressed include: (i) low sample size; (ii) random sampling; (iii) having no control group [non-obese group]. This will be carried out through sample size estimation, proper planning and use of exhaustive recruitment strategies and using the public health concepts for establishing an observational study.

The pilot study found a significant association between BMI and periodontitis in the bivariate analysis. A study by Castilhos et al. study found similar results that suggested there was no association between obesity and periodontitis in young adults [315]. Likewise, the fourth Korean National Health and Nutrition Examination Survey and Health 2000 Health Examination Survey of Finland found no association of obesity with periodontitis in adults after adjusting for putative confounders.[212, 381].

The US-based NHANES (1988-1994) in people 18+years found that having high WC (above the cut-off value of obesity) was associated with a 2.27-time higher risk of

periodontitis [255]. Similarly, Beguingui et al. found that having high WC was associated with a significantly higher risk of moderate/severe periodontitis [412].

Another important finding of the pilot study of this dissertation was that people with periodontitis had impaired fasting plasma glucose level as compared to those with no periodontitis. Fasting plasma glucose is an indicator of diabetes risk. The American Diabetic Association guidelines state that a fasting plasma glucose level of more than 5.6-6.9 mmol/L is pre-diabetes and a fasting plasma glucose level greater than 7 mmol/L is type 2 diabetes [414]. A 12-month follow-up randomised controlled trial indicated that people who underwent intensive periodontal therapy (non-surgical periodontal therapy and surgical periodontal therapy) experienced an improvement in fasting plasma glucose levels in type 2 diabetic patients with moderate-to-severe periodontitis [102].

In this study, no dietary variable was found to be significantly associated with periodontitis. This could be a result of low sample size of the studied population. Low dietary fibre intake was significantly associated with obesity. Dietary fibres reduce dietary fat and cholesterol absorption into the bloodstream, thus reducing dyslipidaemia, type 2 diabetes, cardiovascular diseases and obesity [419]. Dietary fibre functions by binding with dietary fat, thus reducing its absorption throughout the gastrointestinal tract. It prevents absorption of fat in the small intestine and reduces fermentation activity by the gut microflora [419].

Chapter 8. Conclusions

From the available data this dissertation found no association between overweight/obesity and periodontitis. This could be a result of the complex nature of overweight/obesity and periodontitis interaction and the effect of unmeasured confounders and unmeasured mediators. Hence, further studies are required to understand the true relationship between overweight/obesity and periodontitis by using more robust prospective cohort study design and objective recording of overweight/obesity, inflammation, periodontitis and diet.

The author of this dissertation also conducted a systematic review of 25 studies, which found that 17 out of these 25 studies showed a positive association between overweight/obesity and periodontitis in adolescents and young adults. This finding was meaningful in understanding that both overweight/obesity and periodontitis are conditions that develop along the life-course under the influence of poor health behaviours.

Methodological limitations of cross-sectional study design and conventional regression analysis were also highlighted in this dissertation. To overcome these limitations, an advanced statistical model of single mediation analysis was applied to understand the causal relationship between overweight/obesity and periodontitis. In **Study 3** of this dissertation, the author used a single mediation analysis that aided in differentiating between confounders and mediators, and recognised the unmeasured confounders that may affect the overweight/obesity and periodontitis relationship. This statistical method is better than conventional regression analysis, where the confounders and mediators of exposure (overweight/obesity) are grouped together as putative confounders/mediators, limiting our ability to truly understand the effect of exposure on outcome. This study reported that the causal effect of overweight/obesity on periodontitis

was 14%, while the causal effect of overweight/obesity through dental visiting behaviour to periodontitis is 3%, thus indicating a small indirect effect through dental visiting behaviour. Further research is required to estimate the causal relationship between overweight/obesity and periodontitis through prospective cohort studies in the Australian population.

8.1 Implications for Research

This dissertation found no relationship between overweight/obesity and periodontitis. Based on the limitations of the NSAOH 2004-06 and the pilot study, however, it cannot be concluded that this result is true. There is a need for future studies to replicate the current findings in population and its subsets. This would assist in better understanding the role of putative confounders including age, gender, ethnicity, education, income, dental visiting behaviour, oral hygiene behaviour, diabetes and diet on the relationship between overweight/obesity and periodontitis. Lessons learned from this dissertation and review of previous studies pave the way towards developing future studies with the adoption of standardised and universally acceptable Center of Disease Control and American Academy of Periodontology definitions of onset, presence and progression of disease, and recording of precise phenotype measures of body composition and fat distribution, to truly infer the causal effect of overweight/obesity on periodontitis.

Either prospective cohort studies or longitudinal randomised controlled trials are needed to ascertain the long-term relationship between overweight/obesity and periodontitis, and other oral health problems.

8.2 Implications for Practice

Regardless of the results of this dissertation, Risk assessment should be part of routine periodontal care. This is based on the concept that periodontitis is a complex condition, with multiple modifiable factors and pre-disposing factors, which varies from

one person to another. Therefore, patient-specific treatment strategies should be targeted based on an estimation for risk of each patient to risk behaviours and pre-existing health conditions. Although it is still the area of debate, the assessment of markers for obesity in the dental surgery may be a powerful tool for diagnosing overweight/obesity related health complications.

Overweight/obesity as a risk factor for periodontitis that remains unresolved based on the variation in results of the studies in the systematic reviews, meta-analysis and in this dissertation. To the best of the researcher's knowledge, there is minimal evidence on the effect of weight management in reducing the effect of overweight/obesity on periodontal outcomes. Therefore, it is difficult to define periodontal treatment strategies for obese patients with periodontitis. However, in the context of overweight and obesity, recording of body height, body weight and waist circumference should be routine practice as a part of risk assessment in dental care. This could help in raising awareness among patients visiting the dental practice in regards to weight reduction and weight management.

Randomised controlled trials on the effect of periodontal therapy in the reduction of overweight/obesity related markers for inflammation have suggested that non-surgical periodontal therapy reduces levels of markers for systemic inflammation. Therefore, it is advised that dental and general practitioners be aware that there might be an increased risk of periodontitis in patients experiencing overweight/obesity, because of an increase in systemic inflammation associated with overweight/obesity. In addition, they should also be aware that people with overweight/obesity are at high risk of cardiovascular diseases, and having periodontitis is an added burden to their risk of cardiovascular diseases. Evidence suggests that periodontal care reduces the risk of cardiovascular diseases and diabetes by improving CRP levels and improving glycemic control respectively. Therefore, general practitioners are advised to acknowledge the risk of

cardiovascular disease and diabetes in obese patients experiencing periodontitis, and that referrals of patients for periodontal risk assessment should be part of routine care and practice.

8.2 Implications for Policy

A high impact of periodontitis is reported worldwide and in Australia. Evidence-based research has reported linkages between periodontitis and health conditions including overweight/obesity, type 2 diabetes, cardiovascular diseases, pre-term birth weight, pregnancy associated complications, and dementia. Regardless of these findings, the dental profession remains marginalised and unable to sufficiently influence health policy and the health care system. The current model of dental practice is treatment (aesthetics and restoration) and consumerism focused. A population-focused approach is required to draw attention to the prevention of oral diseases and the education of the public on how oral health impacts general health. The practical application of a population-focused approach could be achieved through a universal, Medicare-based dental insurance system for Australians of all ages. This would help eliminate or reduce the inequalities in health care provision and delivery which result from social determinants of health, and also drive more equitable care. The overall impact of this policy would be greatly on: (i) improved knowledge on oral health and general health; (ii) better oral hygiene and periodontal health of Australians; and (iii) reduced burden of oral diseases and associated systemic complications through regular dental visits.

8.3 Future Directions

The result of this thesis determined a significant association between overweight/obesity and periodontitis in the systematic review, but not in the original studies based on the NSAOH 2004-06 dataset and the pilot study. Future research is still

required through the development of more rigorous data based on prospective cohort studies.

The conflicting findings of this study and previous work on overweight/obesity and periodontitis requires clarification and understanding of the true causal relationship between overweight/obesity and periodontitis. It is recommended that future studies should consider sampling for immunological biomarkers and oral microorganisms to understand the mediation effect of the complex factors in the relationship between overweight/obesity and periodontitis.

References

1. Brown P, Brunnhuber K, Chalkidou K, et al. How to formulate research recommendations. *BMJ* 2006; 333: 804-806. DOI: 10.1136/bmj.38987.492014.94.

2. Rutter H, Bes-Rastrollo M, De Henauw S, et al. Balancing upstream and downstream measures to tackle the obesity epidemic: a position statement from the European Association for the Study of Obesity. *Obesity Facts* 2017; 10: 61-63.

3. AIHW. *Overweight and obesity in Australia: a birth cohort analysis.* 2017. Canberra: AIHW.

4. Slade GD SA, Roberts-Thompson K. *Australia's dental generations: the National Survey of Adult Oral Health 2004–06.* 2007. Canberra: Australian Institute of Health and Welfare.

5. Suvan J, D'Aiuto F, Moles DR, et al. Association between overweight/obesity and periodontitis in adults. A systematic review. *Obesity Reviews* 2011; 12: e381-e404.

6. Anis AH, Zhang W, Bansback N, et al. Obesity and overweight in Canada: an updated cost-of-illness study. *Obesity Reviews* 2010; 11: 31-40.

7. Nascimento GG, Peres KG, Mittinty MN, et al. Obesity and Periodontal Outcomes: A Population-Based Cohort Study in Brazil. *Journal of Periodontology* 2016: 1-17. 2016/09/10. DOI: 10.1902/jop.2016.160361.

8. Yudkin J. Adipose tissue, insulin action and vascular disease: inflammatory signals. *International Journal of Obesity* 2003; 27: S25-S28.

9. Zimmermann GS, Bastos MF, Dias Goncalves TE, et al. Local and circulating levels of adipocytokines in obese and normal weight individuals with chronic periodontitis. *Journal of Periodontology* 2013; 84: 624-633.

10. Pradeep AR, Nagpal K, Karvekar S, et al. Levels of lipocalin-2 in crevicular fluid and tear fluid in chronic periodontitis and obesity subjects. *Journal of Investigative and Clinical Dentistry* 2015.

11. Arboleda S, Vargas M, Losada S, et al. Review of obesity and periodontitis: an epidemiological view. *British Dental Journal* 2019; 227: 235-239. DOI: 10.1038/s41415-019-0611-1.

12. Wang Y, Rimm EB, Stampfer MJ, et al. Comparison of abdominal adiposity and overall obesity in predicting risk of type 2 diabetes among men. *American Journal of Clinical Nutrition* 2005; 81: 555-563.

13. Wilson PW, D'Agostino RB, Sullivan L, et al. Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. *Archives of Internal Medicine (Chicago, Ill: 1908)* 2002; 162: 1867-1872. 2002/08/28.

14. Keller A, Rohde JF, Raymond K, et al. Association between periodontal disease and overweight and obesity: a systematic review. *Journal of Periodontology* 2015; 86: 766-776.

15. OCEBM. *OCEBM Levels of Evidence Working Group "The Oxford 2011 Levels of Evidence"*. 2011. Oxford Centre for Evidence-Based Medicine.

16. Loe H. The Gingival Index, the Plaque Index and the Retention Index Systems. *Journal of Periodontology* 1967; 38: Suppl:610-616. 1967/11/01. DOI: 10.1902/jop.1967.38.6.610.

17. Rubin DB. Inference and missing data. *Biometrika* 1976; 63: 581-592. DOI: 10.1093/biomet/63.3.581.

18. Hernan M and Robins J. Causal inference book. 2016. Boca Raton, FL: Chapman & Hall/CRC, 2017.

19. Jin L, Lamster I, Greenspan J, et al. Global burden of oral diseases: emerging concepts, management and interplay with systemic health. *Oral Diseases* 2016; 22: 609-619.

20. Macek MD and Tomar SL. Dental Care Visits among Dentate Adults with Diabetes and Periodontitis. *Journal of Public Health Dentistry* 2009; 69: 284-289. DOI: 10.1111/j.1752-7325.2009.00136.x.

21. Bergstrom J. Tobacco smoking and chronic destructive periodontal disease. *Odontology / the Society of the Nippon Dental University* 2004; 92: 1-8. 2004/10/19. DOI: 10.1007/s10266-004-0043-4.

22. Amaral CdSF, Vettore MV and Leão A. The relationship of alcohol dependence and alcohol consumption with periodontitis: a systematic review. *Journal of Dentistry* 2009; 37: 643-651.

23. Gjermo P, Rösing CK, Susin C, et al. Periodontal diseases in Central and South America. *Periodontology 2000* 2002; 29: 70-78.

24. Lim SS, Allen K, Bhutta ZA, et al. Measuring the health-related Sustainable Development Goals in 188 countries: a baseline analysis from the Global Burden of Disease Study 2015. *The Lancet* 2016; 388: 1813-1850.

25. Listl S, Galloway J, Mossey P, et al. Global economic impact of dental diseases. *Journal of Dental Research* 2015; 94: 1355-1361.

26. Roberts-Thomson K and Do L. *Oral health status. Australia's dental generations: The national survey of adult oral health*. 2007. Canberra: Australian Institute of Health and Welfare (Dental Statistics and Research Series No. 34): Cat. no. DEN 165.

27. Dye BA. Global periodontal disease epidemiology. *Periodontology 2000* 2012; 58: 10-25.

28. Löe H, Anerud A, Boysen H, et al. Natural history of periodontal disease in man. *Journal of Clinical Periodontology* 1986; 13: 431-440. DOI: 10.1111/j.1600-051X.1986.tb01487.x.

29. AAP. Periodontal disease: Fact sheet, https://www.perio.org/newsroom/periodontal-disease-fact-sheet (2017).

30. Laudenbach JM and Simon Z. Common dental and periodontal diseases: evaluation and management. *Medical Clinics* 2014; 98: 1239-1260.

31. Cope G. Gingivitis: symptoms, causes and treatment. *Dental Nursing* 2011; 7.

32. Buchwald S, Kocher T, Biffar R, et al. Tooth loss and periodontitis by socio-economic status and inflammation in a longitudinal population-based study. *Journal of Clinical Periodontology* 2013; 40: 203-211.

33. Goodson J, Tanner A, Haffajee A, et al. Patterns of progression and regression of advanced destructive periodontal disease. *Journal of Clinical Periodontology* 1982; 9: 472-481.

34. Bascones A, Noronha S, Gómez M, et al. Tissue destruction in periodontitis: bacteria or cytokines fault? *Quintessence International (Berlin, Germany : 1985)* 2005; 36: 299-306.

35. Page RC and Schroeder HE. Pathogenesis of inflammatory periodontal disease. A summary of current work. *Laboratory investigation; a Journal of Technical Methods and Pathology* 1976; 34: 235-249.

36. Jeffcoat MK and Reddy MS. Progression of Probing Attachment Loss in Adult Periodontitis*. *Journal of Periodontology* 1991; 62: 185-189.

37. Page RC, Simpson DM and Ammons WF. Host tissue response in chronic inflammatory periodontal disease IV. The periodontal and dental status of a group of aged great apes. *Journal of Periodontology* 1975; 46: 144-155.

38. Gemmell E, Marshall RI and Seymour GJ. Cytokines and prostaglandins in immune homeostasis and tissue destruction in periodontal disease. *Periodontol 2000* 1997; 14: 112-143. 1997/06/01.

39. Seymour GJ, Powell R and Davies W. The immunopathogenesis of progressive chronic inflammatory periodontal disease. *Journal of Oral Pathology & Medicine* 1979; 8: 249-265.

40. Lindhe J. *Clinical Periodontology and Implant Dentistry*. 1988.

41. Manson J. Bone morphology and bone loss in periodontal disease. *Journal of Clinical Periodontology* 1976; 3: 14-22.

42. Kinane DF. Causation and pathogenesis of periodontal disease. *Periodontology 2000* 2001; 25: 8-20.

43. Caton JG, Armitage G, Berglundh T, et al. A new classification scheme for periodontal and peri-implant diseases and conditions–Introduction and key changes from the 1999 classification. *Journal of Periodontology* 2018; 89: S1-S8.

44. Lang NP and Bartold PM. Periodontal health. *Journal of Clinical Periodontology* 2018; 45: S9-S16.

45. Trombelli L, Farina R, Silva CO, et al. Plaque-induced gingivitis: Case definition and diagnostic considerations. *Journal of Clinical Periodontology* 2018; 45: S44-S67.

46. Chapple IL, Mealey BL, Van Dyke TE, et al. Periodontal health and gingival diseases and conditions on an intact and a reduced periodontium: Consensus report of workgroup 1 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. *Journal of Periodontology* 2018; 89: S74-S84.

47. Papapanou PN, Sanz M, Buduneli N, et al. Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. *Journal of Periodontology* 2018; 89: S173-S182.

48. Tonetti MS, Greenwell H and Kornman KS. Staging and grading of periodontitis: Framework and proposal of a new classification and case definition. *Journal of Clinical Periodontology* 2018; 45: S149-S161.

49. Albandar JM, Susin C and Hughes FJ. Manifestations of systemic diseases and conditions that affect the periodontal attachment apparatus: Case definitions and diagnostic considerations. *Journal of Clinical Periodontology* 2018; 45: S171-S189.

50. Jepsen S, Caton JG, Albandar JM, et al. Periodontal manifestations of systemic diseases and developmental and acquired conditions: Consensus report of workgroup 3 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. *Journal of Clinical Periodontology* 2018; 45: S219-S229.

51. Herrera D, Retamal-Valdes B, Alonso B, et al. Acute periodontal lesions (periodontal abscesses and necrotizing periodontal diseases) and endo-periodontal lesions. *Journal of Clinical Periodontology* 2018; 45: S78-S94.

52. Armitage GC. Development of a classification system for periodontal diseases and conditions. *Annals of Periodontology* 1999; 4: 1-6.

53. Marsh PD. Dental plaque as a biofilm and a microbial community–implications for health and disease. *BMC Oral Health* 2006; 6: 1.

54. Wiebe CB and Putnins EE. The periodontal disease classification system of the American Academy of Periodontology-An update. *Journal-Canadian Dental Association* 2000; 66: 594-599.

55. AAP. *Proceedings of the World Workshop in Clinical Periodontics. .* 1989. Chicago The American Academy of Periodontology;.

56. Page RC and Eke PI. Case definitions for use in population-based surveillance of periodontitis. *Journal of Periodontology* 2007; 78: 1387-1399.

57. Tonetti M and Claffey N. Advances in the progression of periodontitis and proposal of definitions of a periodontitis case and disease progression for use in risk factor research. *Journal of Clinical Periodontology* 2005; 32: 210-213.

58. Page RC, Offenbacher S, Schroeder HE, et al. Advances in the pathogenesis of periodontitis: summary of developments, clinical implications and future directions. *Periodontology 2000* 1997; 14: 216-248.

59. Baelum V and López R. Defining a periodontitis case: analysis of a never-treated adult population. *Journal of Clinical Periodontology* 2012; 39: 10-19.

60. Eke P, Dye B, Wei L, et al. Prevalence of periodontitis in adults in the United States: 2009 and 2010. *Journal of Dental Research* 2012; 91: 914-920.

61. Löe H, Theilade E and Jensen SB. Experimental gingivitis in man. *Journal of Periodontology* 1965; 36: 177-187.

62. Ford PJ, Gamonal J and Seymour GJ. Immunological differences and similarities between chronic periodontitis and aggressive periodontitis. *Periodontol 2000* 2010; 53: 111-123. 2010/04/21. DOI: 10.1111/j.1600-0757.2010.00349.x.

63. Wilson M. *Microbial inhabitants of humans: their ecology and role in health and disease*. Cambridge University Press, 2005.

64. Marsh P. Microbial ecology of dental plaque and its significance in health and disease. *Advances in Dental Research* 1994; 8: 263-271.

65. Marsh P. Dental plaque as a microbial biofilm. *Caries Research* 2004; 38: 204-211.

66. Aas JA, Paster BJ, Stokes LN, et al. Defining the normal bacterial flora of the oral cavity. *Journal of Clinical Microbiology* 2005; 43: 5721-5732.

67. Marsh PD. Dental plaque: biological significance of a biofilm and community life-style. *Journal of Clinical Periodontology* 2005; 32 Suppl 6: 7-15. 2005/09/01. DOI: 10.1111/j.1600-051X.2005.00790.x.

68. Muto Y and Goto S. Transformation by extracellular DNA produced by Pseudomonas aeruginosa. *Microbiology and Immunology* 1986; 30: 621-628. 1986/01/01.

69. Zhang L and Mah T-F. Involvement of a novel efflux system in biofilm-specific resistance to antibiotics. *Journal of Bacteriology* 2008; 190: 4447-4452.

70. Borgström MK, Edwardsson S, Sullivan Å, et al. Dental plaque mass and acid production activity of the microbiota on teeth. *European Journal of Oral Sciences* 2000; 108: 412-417. DOI: 10.1034/j.1600-0722.2000.108005412.x.

71. Marsh P and Zaura E. Dental biofilm: ecological interactions in health and disease. *Journal of Clinical Periodontology* 2017; 44: S12-S22.

72. Botero Zuluaga L, Botero Botero A, Bedoya Trujillo JS, et al. Nonsurgical periodontal therapy. *Revista Facultad de Odontología Universidad de Antioquia* 2012; 23: 334-342.

73. Marsh PD and MV M. *Oral microbiology*. 5th edition ed.: Edinburgh, UK, Churchill Livingstone, 2009.

74. Zambon JJ. Periodontal diseases: microbial factors. *Annals of Periodontology* 1996; 1: 879-925.

75. Holt SC and Ebersole JL. Porphyromonas gingivalis, Treponema denticola, and Tannerella forsythia: the ‘red complex’, a prototype polybacterial pathogenic consortium in periodontitis. *Periodontology 2000* 2005; 38: 72-122.

76. Pérez-Chaparro PJ, Lafaurie GI, Gracieux P, et al. Distribution of Porphyromonas gingivalis fimA genotypes in isolates from subgingival plaque and blood sample during bacteremia. *Biomedica* 2009; 29: 298-306.

77. Kesavalu L, Sathishkumar S, Bakthavatchalu V, et al. Rat model of polymicrobial infection, immunity, and alveolar bone resorption in periodontal disease. *Infection and immunity* 2007; 75: 1704-1712.

78. Yamauchi T, Kamon J, Minokoshi Ya, et al. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. *Nature Medicine* 2002; 8: 1288-1295.

79. Sheiham A. Periodontal disease and oral cleanliness in tobacco smokers. *Journal of Periodontology* 1971; 42: 259-263.

80. Preber H, Linder L and Bergström J. Periodontal healing and periopathogenic microflora in smokers and non-smokers. *Journal of Clinical Periodontology* 1995; 22: 946-952. DOI: 10.1111/j.1600-051X.1995.tb01800.x.

81. Tomar SL and Asma S. Smoking-Attributable Periodontitis in the United States: Findings From NHANES III. *Journal of Periodontology* 2000; 71: 743-751. DOI: 10.1902/jop.2000.71.5.743.

82. G. DL, D. SG, F. RTK, et al. Smoking-attributable periodontal disease in the Australian adult population. *Journal of Clinical Periodontology* 2008; 35: 398-404. DOI: doi:10.1111/j.1600-051X.2008.01223.x.

83. Bergström J, Eliasson S and Dock J. Exposure to tobacco smoking and periodontal health. *Journal of Clinical Periodontology* 2000; 27: 61-68.

84. Johnson GK and Guthmiller JM. The impact of cigarette smoking on periodontal disease and treatment. *Periodontology 2000* 2007; 44: 178-194.

85. Grossi SG, Zambon JJ, Ho AW, et al. Assessment of risk for periodontal disease. I. Risk indicators for attachment loss. *Journal of Periodontology* 1994; 65: 260-267.

86. Grollmus ZN, Chavez MM and Donat FS. Periodontal disease associated to systemic genetic disorders. *Medicina Oral Patologica Oral Cirugia Bucal* 2007; 12: E211-E215.

87. Haber J. Smoking is a major risk factor for periodontitis. *Current Opinion in Periodontology* 1993: 12-18.

88. Giannopoulou C, Cappuyns I and Mombelli A. Effect of smoking on gingival crevicular fluid cytokine profile during experimental gingivitis. *Journal of Clinical Periodontology* 2003; 30: 996-1002.

89. Cho N, Shaw J, Karuranga S, et al. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Research and Clinical Practice* 2018; 138: 271-281.

90. ARCPOH. The relationship between diabetes and oral health among Australian adults. *Australian Dental Journal* 2008; 53: 93-96. DOI: 10.1111/j.1834-7819.2007.00014.x.

91. Campus G, Salem A, Uzzau S, et al. Diabetes and Periodontal Disease: A Case-Control Study. *Journal of Periodontology* 2005; 76: 418-425. DOI: 10.1902/jop.2005.76.3.418.

92. Emrich LJ, Shlossman M and Genco RJ. Periodontal Disease in Non-Insulin-Dependent Diabetes Mellitus. *Journal of Periodontology* 1991; 62: 123-131. DOI: 10.1902/jop.1991.62.2.123.

93. Grossi SG, Skrepcinski FB, DeCaro T, et al. Response to Periodontal Therapy in Diabetics and Smokers. *Journal of Periodontology* 1996; 67: 1094-1102. DOI: 10.1902/jop.1996.67.10s.1094.

94. Patil VA, Shivaraya R and Desai MH. Prevalence and Severity of Periodontal Disease in Type II Diabetes Mellitus (Noninsulin-dependent Diabetes Mellitus) Patients in Gulbarga, Karnataka, India: An Epidemiological Study. *Journal of Contemporary Dentistry* 2013; 3: 32-35.

95. Grossi SG and Genco RJ. Periodontal Disease and Diabetes Mellitus: A Two-Way Relationship*. *Annals of periodontology* 1998; 3: 51-61.

96. Thorstensson H, Kuylenstiema J and Hugoson A. Medical Status and complications in relation to periodontal disease experience in insulin-dependent diabetics. *Journal of Clinical Periodontology* 1996; 23: 194-202.

97. Katagiri S, Nitta H, Nagasawa T, et al. Effect of glycemic control on periodontitis in type 2 diabetic patients with periodontal disease. *Journal of Diabetes Investigation* 2013; 4: 320-325.

98. J. L, Q. C, M. S, et al. Association of oral microbiome with type 2 diabetes risk. *Journal of Periodontal Research* 2017; 52: 636-643. DOI: doi:10.1111/jre.12432.

99. Preshaw P, Alba A, Herrera D, et al. Periodontitis and diabetes: a two-way relationship. *Diabetologia* 2012; 55: 21-31.

100. Teshome A and Yitayeh A. The effect of periodontal therapy on glycemic control and fasting plasma glucose level in type 2 diabetic patients: systematic review and meta-analysis. *BMC oral health* 2017; 17: 31.

101. Winning L, Patterson CC, Neville CE, et al. Periodontitis and incident type 2 diabetes: a prospective cohort study. *Journal of Clinical Periodontology* 2017; 44: 266-274. DOI: 10.1111/jcpe.12691.

102. D'Aiuto F, Gkranias N, Bhowruth D, et al. Systemic effects of periodontitis treatment in patients with type 2 diabetes: a 12 month, single-centre, investigator-masked, randomised trial. *Lancet Diabetes and Endocrinology* 2018; 6: 954-965. 2018/11/27. DOI: 10.1016/s2213-8587(18)30038-x.

103. AIHW. *Risk factors contributing to chronic disease*. 2012. Canberra: AIHW.

104. WHO. Obesity and overweight, http://www.who.int/mediacentre/factsheets/fs311/en/ (2016).

105. Bergman RN, Stefanovski D, Buchanan TA, et al. A better index of body adiposity. *Obesity* 2011; 19: 1083-1089.

106. Goh LG, Dhaliwal SS, Welborn TA, et al. Anthropometric measurements of general and central obesity and the prediction of cardiovascular disease risk in women: a cross-sectional study. *BMJ Open* 2014; 4: e004138.

107. WHO. Global database on body mass index. 2012. *Global Database on Body Mass Index* 2012.

108. Okosun IS, Chandra KMD, Choi S, et al. Hypertension and Type 2 Diabetes Comorbidity in Adults in the United States: Risk of Overall and Regional Adiposity. *Obesity Research* 2001; 9: 1-9. DOI: 10.1038/oby.2001.1.

109. Ismail IS, Bebakar W and Kamaruddin N. Clinical Practice Guidelines on management of obesity 2004. *Putrajaya: Ministry of Health Malaysia, Academy of Medicine of Malaysia, Malaysian Association for the Study of Obesity, Malaysian Endocrine and Metabolic Society* 2004.

110. WHO. World Health Organization physical status: the use and interpretation of anthropometry. *World Health Organization, Geneva* 1995.

111. Low S, Chin MC, Ma S, et al. Rationale for redefining obesity in Asians. *Annals Academy of Medicine Singapore* 2009; 38: 66.

112. WHO. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *The Lancet* 2004; 363: 157-163. 2004/01/17. DOI: 10.1016/s0140-6736(03)15268-3.

113. Daniels SR. The use of BMI in the clinical setting. *Pediatrics* 2009; 124: S35-S41.

114. Chakraborty BM and Chakraborty R. Sensitivity and specificity of body mass index as a definition of the obesity component of metabolic syndrome. *Collegium antropologicum* 2007; 31: 943-947. 2008/01/26.

115. Romero-Corral A, Somers VK, Sierra-Johnson J, et al. Accuracy of body mass index in diagnosing obesity in the adult general population. *International Journal of Obesity* 2008; 32: 959-966.

116. Romero-Corral A, Somers VK, Sierra-Johnson J, et al. Diagnostic performance of body mass index to detect obesity in patients with coronary artery disease. *European Heart Journal* 2007; 28: 2087-2093.

117. Dhaliwal SS and Welborn TA. Central obesity and multivariable cardiovascular risk as assessed by the Framingham prediction scores. *The American Journal of Cardiology* 2009; 103: 1403-1407.

118. IDF. *The IDF consensus worldwide definition of the METABOLIC SYNDROME*. 2006. Belgium: International Diabetes Federation.

119. WHO C. Waist circumference and waist-hip ratio. 2008.

120. Song M-Y, Kim J, Horlick M, et al. Prepubertal Asians have less limb skeletal muscle. *Journal of Applied Physiology* 2002; 92: 2285-2291.

121. Ko GT, Chan JC, Cockram CS, et al. Prediction of hypertension, diabetes, dyslipidaemia or albuminuria using simple anthropometric indexes in Hong Kong Chinese. *International Journal of Obesity* 1999; 23: 1136-1142.

122. Bei-Fan Z. Predictive values of body mass index and waist circumference for risk factors of certain related diseases in Chinese adults: study on optimal cut-off points of body mass index and waist circumference in Chinese adults. *Asia Pacific Journal of Clinical Nutrition* 2002; 11: S685-S693.

123. Deurenberg P. Universal cut-off BMI points for obesity are not appropriate. *British Journal of Nutrition* 2001; 85: 135-136.

124. Misra A, Vikram N, Gupta R, et al. Waist circumference cutoff points and action levels for Asian Indians for identification of abdominal obesity. *International Journal of Obesity* 2006; 30: 106-111.

125. Janssen I, Heymsfield SB, Allison DB, et al. Body mass index and waist circumference independently contribute to the prediction of nonabdominal, abdominal subcutaneous, and visceral fat. *American Journal of Clinical Nutrition* 2002; 75: 683-688. 2002/03/28.

126. Kuk JL, Katzmarzyk PT, Nichaman MZ, et al. Visceral fat is an independent predictor of all-cause mortality in men. *Obesity* 2006; 14: 336-341.

127. Yusuf S, Hawken S, Ôunpuu S, et al. Obesity and the risk of myocardial infarction in 27 000 participants from 52 countries: a case-control study. *The Lancet* 2005; 366: 1640-1649.

128. NICE. *Obesity: identification, assessment and management*. 2014. UK: National Collaborating Centre for Primary Care and the Centre for Public Health Excellence at NICE.

129. Welborn TA, Dhaliwal SS and Bennett SA. Waist-hip ratio is the dominant risk factor predicting cardiovascular death in Australia. *Medical journal of Australia* 2003; 179: 580-585.

130. Saito T, Shimazaki Y, Koga T, et al. Relationship between upper body obesity and periodontitis. *Journal of Dental Research* 2001; 80: 1631-1636.

131. Khader YS, Bawadi HA, Haroun TF, et al. The association between periodontal disease and obesity among adults in Jordan. *Journal of Clinical Periodontology* 2009; 36: 18-24.

132. WHO. *Obesity: preventing and managing the global epidemic*. World Health Organization, 2000.

133. Browning LM, Hsieh SD and Ashwell M. A systematic review of waist-to-height ratio as a screening tool for the prediction of cardiovascular disease and diabetes: 0.5 could be a suitable global boundary value. *Nutr Res Rev* 2010; 23: 247-269. 2010/09/08. DOI: 10.1017/s0954422410000144.

134. Lee CM, Huxley RR, Wildman RP, et al. Indices of abdominal obesity are better discriminators of cardiovascular risk factors than BMI: a meta-analysis. *Journal of clinical epidemiology* 2008; 61: 646-653. 2008/03/25. DOI: 10.1016/j.jclinepi.2007.08.012.

135. Yoo E-G. Waist-to-height ratio as a screening tool for obesity and cardiometabolic risk. *Korean Journal of Pediatrics* 2016; 59: 425-431.

136. Ashwell M and Gibson S. Waist-to-height ratio as an indicator of 'early health risk': simpler and more predictive than using a 'matrix'based on BMI and waist circumference. *BMJ Open* 2016; 6: e010159.

137. Kuchler F and Variyam J. Mistakes were made: misperception as a barrier to reducing overweight. *International Journal of Obesity* 2003; 27: 856.

138. Robinson E and Oldham M. Weight status misperceptions among UK adults: the use of self-reported vs. measured BMI. *BMC Obesity* 2016; 3: 21.

139. Salcedo V, Gutiérrez-Fisac J, Guallar-Castillón P, et al. Trends in overweight and misperceived overweight in Spain from 1987 to 2007. *International Journal of Obesity* 2010; 34: 1759.

140. Duncan DT, Wolin KY, Scharoun-Lee M, et al. Does perception equal reality? Weight misperception in relation to weight-related attitudes and behaviors among overweight and obese US adults. *International Journal of Behavioral Nutrition and Physical Activity* 2011; 8: 20.

141. Yaemsiri S, Slining MM and Agarwal SK. Perceived weight status, overweight diagnosis, and weight control among US adults: the NHANES 2003-2008 Study. *International Journal of Obesity* 2011; 35: 1063.

142. Johnson F, Beeken RJ, Croker H, et al. Do weight perceptions among obese adults in Great Britain match clinical definitions? Analysis of cross-sectional surveys from 2007 and 2012. *BMJ Open* 2014; 4: e005561.

143. Wardle J, Haase AM and Steptoe A. Body image and weight control in young adults: international comparisons in university students from 22 countries. *International Journal of Obesity* 2006; 30: 644.

144. WHO. Epidemiology, http://www.who.int/topics/epidemiology/en/ (2010).

145. WHO. *Obesity and overweight*. 2017. Geneva, Switzerland: World Health Organization.

146. Flegal KM, Kruszon-Moran D, Carroll MD, et al. Trends in Obesity Among Adults in the United States, 2005 to 2014. *Journal of American Medical Association* 2016; 315: 2284-2291.

147. Craig R, Fuller E, Mindell J, et al. *Health Survey for England, 2014*. 2015.

148. Mensink G, Schienkiewitz A, Haftenberger M, et al. Overweight and obesity in Germany. *Bundesgesundheitsblatt - Health Research* 2013.

149. OECD. *Obesity Update* 2017. OECD.

150. WHO. *Obesity (body mass index >= 30) (age-standardized estimate) Data by WHO region*. 2014.

151. WHO. *Global Health Observatory (GHO) data – Overweight and obesity*. 2014.

152. Wan SC. *Overweight and Obesity in Asia*. 2014. Singapore: Gen Re.

153. Yoon KH, Lee JH, Kim JW, et al. Epidemic obesity and type 2 diabetes in Asia. *The Lancet* 2006; 368: 1681-1688. 2006/11/14. DOI: 10.1016/s0140-6736(06)69703-1.

154. Bastien M, Poirier P, Lemieux I, et al. Overview of epidemiology and contribution of obesity to cardiovascular disease. *Progress in Cardiovascular Diseases* 2014; 56: 369-381.

155. Finkelstein EA, daCosta DiBonaventura M, Burgess SM, et al. The costs of obesity in the workplace. *Journal of Occupational and Environmental Medicine* 2010; 52: 971-976.

156. APCSC. The burden of overweight and obesity in the Asia-Pacific region. *Obesity Reviews* 2007; 8: 191-196.

157. Davenport CB. Body-build and its inheritance. 1923. *Obesity Research* 1994; 2: 606-623. 1994/11/01.

158. Moon BC and Friedman JM. The molecular basis of the obese mutation in ob2J mice. *Genomics* 1997; 42: 152-156. 1997/05/15. DOI: 10.1006/geno.1997.4701.

159. Hinney A, Vogel CI and Hebebrand J. From monogenic to polygenic obesity: recent advances. *Eur Child Adolesc Psychiatry* 2010; 19: 297-310. 2010/02/04. DOI: 10.1007/s00787-010-0096-6.

160. Rankinen T, Zuberi A, Chagnon YC, et al. The human obesity gene map: the 2005 update. *Obesity (Silver Spring, Md)* 2006; 14: 529-644. 2006/06/03. DOI: 10.1038/oby.2006.71.

161. Farooqi IS and O'Rahilly S. Monogenic obesity in humans. *Annual review of medicine* 2005; 56: 443-458. 2005/01/22. DOI: 10.1146/annurev.med.56.062904.144924.

162. Moleres A, Martinez JA and Marti A. Genetics of Obesity. *Current Obesity Reports* 2013; 2: 23-31. journal article. DOI: 10.1007/s13679-012-0036-5.

163. Maples JM and Houmard JA. Physical activity for obesity. *Integrative Weight Management*. Springer, 2014, pp.251-260.

164. Gallanagh S, Quinn TJ, Alexander J, et al. Physical Activity in the Prevention and Treatment of Stroke. *ISRN Neurology* 2011; 2011: 953818. DOI: 10.5402/2011/953818.

165. WHO. *Global Strategy on Diet, Physical Activity and Health*. 2019. Geneva, Switzerland: World Health Organisation.

166. Dunstan D, Barr E, Healy G, et al. Television viewing time and mortality the australian diabetes, obesity and lifestyle study (AusDiab). *Circulation* 2010; 121: 384-391.

167. Casazza K, Fontaine KR, Astrup A, et al. Myths, presumptions, and facts about obesity. *New England Journal of Medicine* 2013; 368: 446-454.

168. Chaput JP, Klingenberg L, Astrup A, et al. Modern sedentary activities promote overconsumption of food in our current obesogenic environment. *Obesity Reviews* 2011; 12: e12-e20.

169. Haslam DW JW. Obesity. *The Lancet* 2005; 366: 1197-1209.

170. Stumvoll M, Goldstein BJ and Van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. *The Lancet* 2005; 365: 1333-1346.

171. Wilson PWF, D'Agostino RB, Sullivan L, et al. Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. *Archives of Internal Medicine* 2002; 162: 1867.

172. Eckel RH, Grundy SM and Zimmet PZ. The metabolic syndrome. *The Lancet* 2005; 365: 1415-1428.

173. Fujioka K. Pathophysiology of type 2 diabetes and the role of incretin hormones and beta-cell dysfunction. *JAAPA : official journal of the American Academy of Physician Assistants* 2007; Suppl: 3-8. 2008/01/25.

174. WHO. *Fact Sheet: Diabetes mellitus*. 2016. Geneva: WHO.

175. Samuel VT and Shulman GI. Mechanisms for insulin resistance: common threads and missing links. *Cell* 2012; 148: 852-871.

176. Bartelt A and Heeren J. Adipose tissue browning and metabolic health. *Nature Reviews Endocrinology* 2014; 10: 24-36.

177. Yates T and Khunti K. Epidemiology: The diabetes mellitus tsunami: worse than the 'Spanish flu' pandemic? *Nat Rev Endocrinol* 2016; 12: 377-378. 2016/05/21. DOI: 10.1038/nrendo.2016.74.

178. AIHW. *Diabetes*. 2019. Canberra, Australia: Australian Institute of Health and Welfare.

179. ABS. Australian Health Survey: updated results, http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/4364.0.55.003Chapter12011-2012 (2012).

180. Kolb H and Martin S. Environmental/lifestyle factors in the pathogenesis and prevention of type 2 diabetes. *BMC Medicine* 2017; 15: 131.

181. Waxman A. Why a global strategy on diet, physical activity and health? *Nutrition and Fitness: Mental Health, Aging, and the Implementation of a Healthy Diet and Physical Activity Lifestyle*. Karger Publishers, 2005, pp.162-166.

182. Wei M, Gibbons LW, Mitchell TL, et al. Alcohol intake and incidence of type 2 diabetes in men. *Diabetes Care* 2000; 23: 18-22.

183. Medina-RemOn A, Kirwan R, Lamuela-Raventos RM, et al. Dietary Patterns and the Risk of Obesity, Type 2 Diabetes Mellitus, Cardiovascular Diseases, Asthma, and Mental Health Problems. *Critical reviews in food science and nutrition* 2016: 0. 2016/04/30. DOI: 10.1080/10408398.2016.1158690.

184. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach: Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2015; 38: 140-149. DOI: 10.2337/dc14-2441.

185. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000; 321: 405-412. 2000/08/11.

186. RACGP. *General practice management of type 2 diabetes: 2016-2018*. 2016. East Melbourne, Vic: The Royal Australian College of General Practitioners. .

187. Boffetta P, McLerran D, Chen Y, et al. Body mass index and diabetes in Asia: a cross-sectional pooled analysis of 900,000 individuals in the Asia cohort consortium. *PloS one* 2011; 6: e19930.

188. Hu FB, Manson JE, Stampfer MJ, et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *New England Journal of Medicine* 2001; 345: 790-797.

189. Group D-DS and Group EDE. Age, body mass index and type 2 diabetes—associations modified by ethnicity. *Diabetologia* 2003; 46: 1063-1070.

190. Pan X-R, Li G-W, Hu Y-H, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance: the Da Qing IGT and Diabetes Study. *Diabetes Care* 1997; 20: 537-544.

191. WHO. Cardiovascular disease, http://www.who.int/cardiovascular_diseases/en/ (2016).

192. AIHW. *Australia's health 2016*. 2016. Canberra: Australian Institute of Health and Welfare.

193. North BJ and Sinclair DA. The intersection between aging and cardiovascular disease. *Circulation Research* 2012; 110: 1097-1108.

194. Ng M, Fleming T, Robinson M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. *The Lancet* 2014; 384: 766-781. DOI: https://doi.org/10.1016/S0140-6736(14)60460-8.

195. Hubert HB, Feinleib M, McNamara PM, et al. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation* 1983; 67: 968-977. 1983/05/01.

196. Rabkin SW, Mathewson FA and Hsu PH. Relation of body weight to development of ischemic heart disease in a cohort of young North American men after a 26 year observation period: the Manitoba Study. *The American Journal of Cardiology* 1977; 39: 452-458. 1977/03/01.

197. Calle EE, Rodriguez C, Walker-Thurmond K, et al. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *New England Journal of Medicine* 2003; 348: 1625-1638. 2003/04/25. DOI: 10.1056/NEJMoa021423.

198. Calle EE and Thun MJ. Obesity and cancer. *Oncogene* 2004; 23: 6365-6378.

199. Van Den Brandt PA, Spiegelman D, Yaun S-S, et al. Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. *American Journal of Epidemiology* 2000; 152: 514-527.

200. Kent S, Fusco F, Gray A, et al. Body mass index and healthcare costs: a systematic literature review of individual participant data studies. *Obesity Reviews* 2017.

201. Biener A, Cawley J and Meyerhoefer C. The Impact of Obesity on Medical Care Costs and Labor Market Outcomes in the US. *Clinical Chemistry* 2018; 64: 108-117. DOI: 10.1373/clinchem.2017.272450.

202. Colagiuri S, Lee CM, Colagiuri R, et al. The cost of overweight and obesity in Australia. *Medical Journal of Australia* 2010; 192: 260-264. 2010/03/06.

203. Proper KI, Singh AS, Van Mechelen W, et al. Sedentary behaviors and health outcomes among adults: a systematic review of prospective studies. *American Journal of Preventive Medicine* 2011; 40: 174-182.

204. van der Ploeg HP, Chey T, Korda RJ, et al. Sitting Time and All-Cause Mortality Risk in 222 497 Australian Adults. *JAMA Internal Medicine* 2012; 172: 494-500. DOI: 10.1001/archinternmed.2011.2174.

205. Amar S, Zhou Q, Shaik-Dasthagirisaheb Y, et al. Diet-induced obesity in mice causes changes in immune responses and bone loss manifested by bacterial challenge. *Proceedings of the National Academy of Sciences* 2007; 104: 20466-20471.

206. Cavagni J, Wagner TP, Gaio EJ, et al. Obesity may increase the occurrence of spontaneous periodontal disease in Wistar rats. *Archives of oral biology* 2013; 58: 1034-1039.

207. Virto L, Cano P, Jimenez-Ortega V, et al. Obesity and Periodontitis. An Experimental Study to Evaluate the Periodontal and Systemic Effects of the Co-Morbidity. *Journal of Periodontology* 2017: 1-15. 2017/09/16. DOI: 10.1902/jop.2017.170355.

208. Zuza EP, Garcia VG, Theodoro LH, et al. Influence of obesity on experimental periodontitis in rats: histopathological, histometric and immunohistochemical study. *Clinical Oral Investigation* 2017 2017/09/21. DOI: 10.1007/s00784-017-2207-y.

209. D'Aiuto F, Sabbah W, Netuveli G, et al. Association of the Metabolic Syndrome with Severe Periodontitis in a Large U.S. Population-Based Survey. *The Journal of Clinical Endocrinology & Metabolism* 2008; 93: 3989-3994. DOI: 10.1210/jc.2007-2522.

210. Dalla Vecchia CF, Susin C, Rösing CK, et al. Overweight and obesity as risk indicators for periodontitis in adults. *Journal of Periodontology* 2005; 76: 1721-1728.

211. Ekuni D, Yamamoto T, Koyama R, et al. Relationship between body mass index and periodontitis in young Japanese adults. *Journal of Periodontal Research* 2008; 43: 417-421. 2008/10/23.

212. Kim EJ, Jin BH and Bae KH. Periodontitis and obesity: a study of the Fourth Korean National Health and Nutrition Examination Survey. *Journal of Periodontology* 2011; 82: 533-542. 2010/11/04. DOI: 10.1902/jop.2010.100274.

213. Suvan JE, Petrie A, Nibali L, et al. Association between overweight/obesity and increased risk of periodontitis. *Journal of Clinical Periodontology* 2015; 42: 733-739. DOI: 10.1111/jcpe.12421.

214. Pischon N, Heng N, Bernimoulin JP, et al. Obesity, inflammation, and periodontal disease. *Journal of Dental Research* 2007; 86: 400-409.

215. CDC. Measuring healthy days. *Atlanta, Georgia: Centers for Disease Control and Prevention* 2000.

216. Kershaw EE and Flier JS. Adipose Tissue as an Endocrine Organ. *Journal of Clinical Endocrinology & Metabolism* 2004; 89: 2548-2556.

217. Beck JD and Offenbacher S. Systemic effects of periodontitis: epidemiology of periodontal disease and cardiovascular disease. *Journal of Periodontology* 2005; 76: 2089-2100.

218. Wood N, Johnson RB and Streckfus CF. Comparison of body composition and periodontal disease using nutritional assessment techniques: Third National Health and Nutrition Examination Survey (NHANES III). *Journal of Clinical Periodontology* 2003; 30: 321-327.

219. Haas BK. A multidisciplinary concept analysis of quality of life. *Western Journal of Nursing Research* 1999; 21: 728-742.

220. Galic S, Oakhill JS and Steinberg GR. Adipose tissue as an endocrine organ. *Molecular and cellular endocrinology* 2010; 316: 129-139. 2009/09/03. DOI: 10.1016/j.mce.2009.08.018.

221. Offenbacher S. Periodontal diseases: pathogenesis. *Annals of Periodontology* 1996; 1: 821-878.

222. Okada H and Murakami S. Cytokine expression in periodontal health and disease. *Critical Reviews in Oral Biology & Medicine* 1998; 9: 248-266.

223. Beck J, Garcia R, Heiss G, et al. Periodontal disease and cardiovascular disease. *Journal of Periodontology* 1996; 67: 1123-1137.

224. Nishimura F, Iwamoto Y, Mineshiba J, et al. Periodontal disease and diabetes mellitus: the role of tumor necrosis factor-α in a 2-way relationship. *Journal of Periodontology* 2003; 74: 97-102.

225. Genco RJ, Grossi SG, Ho A, et al. A proposed model linking inflammation to obesity, diabetes, and periodontal infections. *Journal of Periodontology* 2005; 76: 2075-2084.

226. Wilkinson RG and Marmot MG. *Social determinants of health: the solid facts*. World Health Organization, 2003.

227. Turrell G, Stanley L, De Looper M, et al. Health inequalities in Australia: morbidity, health behaviours, risk factors and health service use, http://www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=6442459734 (2006).

228. Marmot M. Social determinants of health inequalities. *The Lancet* 2005; 365: 1099-1104.

229. Bryant PH, Hess A and Bowen PG. Social Determinants of Health Related to Obesity. *The Journal for Nurse Practitioners* 2015; 11: 220-225.

230. Cui K, Bombardier C and Tomlinson GA. Contributions of Social Determinants of Health on Probability of Remission in Early and Established Rheumatoid Arthritis Patients. In: *Arthritis and Rheumatology* 2015, Wiley-Blackwell 111 River st, Hoboken 07030-5774, NJ USA.

231. Peres M and Heilmann A. Social inequalities in oral health: from evidence to action. 2015.

232. Busch M, Schienkiewitz A, Kroll L, et al. Trends in social inequalities in the prevalence of major cardiovascular disease among adults in Germany. In: *European Health Journal* 2015, pp.639-639.

233. AIHW. *Socioeconomic variation in periodontitis among Australian adults 2004–06*. 2010. Canberra: AIHW.

234. Pampel FC, Denney JT and Krueger PM. Obesity, SES and economic development: A test of the reversal hypothesis. *Social Science & Medicine (1982)* 2012; 74: 1073-1081. DOI: 10.1016/j.socscimed.2011.12.028.

235. Brennan D, Spencer A and Roberts-Thomson K. Periodontal disease among 45–54 year olds in Adelaide, South Australia. *Australian Dental Journal* 2007; 52: 55-60.

236. Kaye RT, S. BD and John SA. Social inequality in the use and comprehensiveness of dental services. *Australian Journal of Public Health* 1995; 19: 80-85. DOI: doi:10.1111/j.1753-6405.1995.tb00302.x.

237. Do LG, Slade GD, Roberts-Thomson KF, et al. Smoking-attributable periodontal disease in the Australian adult population. *Journal of Clinical Periodontology* 2008; 35: 398-404.

238. ABS. Overweight and Obesity in Adults in Australia: A Snapshot, 2007–08 http://www.abs.gov.au/ausstats/abs@.nsf/Products/993C26D57FBFEF72CA25789C0023DB5F?opendocument (2011).

239. Brennan D, Spencer A and Roberts-Thomson K. Caries experience among 45–54 year olds in Adelaide, South Australia. *Australian Dental Journal* 2007; 52: 122-127.

240. House NOHPC. Oral health messages for the Australian public. Findings of a national consensus workshop#. *Australian Dental Journal* 2011; 56: 331-335.

241. Do LG, Moysés SJ and Mathur M. 1.3 Patterns of oral health inequalities in middle-and low-income countries. *Social inequalities in oral health: from evidence to action* 2015; 26: 8.

242. Taani DQ. Periodontal awareness and knowledge, and pattern of dental attendance among adults in Jordan. *International Dental Journal* 2002; 52: 94-98.

243. Crocombe LA, Broadbent JM, Thomson WM, et al. Impact of dental visiting trajectory patterns on clinical oral health and oral health-related quality of life. *J Public Health Dent* 2012; 72: 36-44. 2012/02/10. DOI: 10.1111/j.1752-7325.2011.00281.x.

244. Crocombe LA, Broadbent JM, Thomson WM, et al. Dental visiting trajectory patterns and their antecedents. *J Public Health Dent* 2011; 71: 23-31. 2010/10/01. DOI: 10.1111/j.1752-7325.2010.00196.x.

245. Yildirim TT. Evaluating the Relationship of Dental Fear with Dental Health Status and Awareness. *Journal of Clinical and Diagnostic Research: JCDR* 2016; 10: ZC105.

246. Ng SK and Leung WK. A community study on the relationship of dental anxiety with oral health status and oral health‐related quality of life. *Community Dentistry and Oral Epidemiology* 2008; 36: 347-356.

247. Alkhalifa NS and Zahran DH. Reasons Preventing or Delaying Dental Visits in Taibah University Students. *British Journal of Medicine and Medical Research* 2016; 13.

248. Hill K, Chadwick B, Freeman R, et al. Adult Dental Health Survey 2009: relationships between dental attendance patterns, oral health behaviour and the current barriers to dental care. *British dental journal* 2013; 214: 25-32.

249. Chrisopolous S BK, Harford J. *Oral health and dental care in Australia: key facts and figures 2011*. 2011. Canberra: Australian Institute of Health and Welfare.

250. ES G, DN T, PG A, et al. Dental insurance, service use and health outcomes in Australia: a systematic review. *Australian Dental Journal* 2018; 63: 4-13. DOI: doi:10.1111/adj.12534.

251. Jura M and Kozak LP. Obesity and related consequences to ageing. *Age* 2016; 38: 23.

252. Duckett S. Australia's health system is enviable, but there's room for improvement, http://theconversation.com/australias-health-system-is-enviable-but-theres-room-for-improvement-81332 (2017).

253. Frencken JE, Sharma P, Stenhouse L, et al. Global epidemiology of dental caries and severe periodontitis – a comprehensive review. *Journal of Clinical Periodontology* 2017; 44: S94-S105. DOI: 10.1111/jcpe.12677.

254. Albandar J, Brunelle J and Kingman A. Destructive periodontal disease in adults 30 years of age and older in the United States, 1988-1994. *Journal of Periodontology* 1999; 70: 13-29.

255. Al-Zahrani MS, Bissada NF and Borawski EA. Obesity and periodontal disease in young, middle-aged, and older adults. *Journal of Periodontology* 2003; 74: 610-615.

256. Eremenko M, Pink C, Biffar R, et al. Cross-sectional association between physical strength, obesity, periodontitis and number of teeth in a general population. *Journal of Clinical Periodontology* 2016.

257. Lang NP, Schätzle MA and Löe H. Gingivitis as a risk factor in periodontal disease. *Journal of Clinical Periodontology* 2009; 36: 3-8.

258. Power ML and Schulkin J. Sex differences in fat storage, fat metabolism, and the health risks from obesity: possible evolutionary origins. *British Journal of Nutrition* 2008; 99: 931-940. 2007/11/06. DOI: 10.1017/s0007114507853347.

259. ABS. *National Health Survey: First Results, 2014–15*. . 2015. Canberra: Australian Bureau of Statistics.

260. Shiau HJ and Reynolds MA. Sex differences in destructive periodontal disease: a systematic review. *Journal of Periodontology* 2010; 81: 1379-1389.

261. Eke P, Liang W, O. TEG, et al. Risk Indicators for Periodontitis in US Adults: NHANES 2009 to 2012. *Journal of Periodontology* 2016; 87: 1174-1185. DOI: doi:10.1902/jop.2016.160013.

262. White D, Tsakos G, Pitts N, et al. Adult Dental Health Survey 2009: common oral health conditions and their impact on the population. *British dental journal* 2012; 213: 567.

263. ABS. Australian Standard Classification of Cultural and Ethnic Groups (ASCCEG), , http://www.abs.gov.au/ausstats/abs@.nsf/lookup/1249.0main+features22011 (2011).

264. National Heart L and Institute B. Managing overweight and obesity in adults: systematic evidence review from the obesity expert panel. 2013. *US Department of Health and Human Services: National Institutes of Health* 2013.

265. Albandar JM and Tinoco E. Global epidemiology of periodontal diseases in children and young persons. *Periodontology 2000* 2002; 29: 153-176.

266. ARCPOH. Periodontal diseases in the Australian adult population. *Australian Dental Journal* 2009; 54: 390.

267. Haisman R, Mason K and Holmes E. *Oral Health Conditions in Adults. Our Oral Health: Key findings of the 2009 New Zealand Oral Health Survey*. 2010. Wellington, New Zealand: Ministry of Health.

268. Manning M, Smith C and Mazerolle P. The societal costs of alcohol misuse in Australia. *Trends and issues in crime and criminal justice* 2013: 1.

269. Miller PG, Coomber K, Staiger P, et al. Review of rural and regional alcohol research in Australia. *Australian Journal of Rural Health* 2010; 18: 110-117. 2010/06/29. DOI: 10.1111/j.1440-1584.2010.01133.x.

270. Sayon-Orea C, Martinez-Gonzalez MA and Bes-Rastrollo M. Alcohol consumption and body weight: a systematic review. *Nutrition reviews* 2011; 69: 419-431. 2011/07/28. DOI: 10.1111/j.1753-4887.2011.00403.x.

271. Gay IC, Tran DT and Paquette DW. Alcohol intake and periodontitis in adults aged 30+ Years: NHANES 2009-2012. *Journal of Periodontology* 2018 2018/03/25. DOI: 10.1002/jper.17-0276.

272. Susin C, Wagner M, Haas A, et al. The association between alcohol consumption and periodontitis in southern Brazilian adults. *Journal of Periodontal Research* 2015; 50: 622-628.

273. WHO. *Prevalence of tobacco smoking: Global Health Observatory (GHO) data*. 2018. Geneva, Switzerland: World Health Organisation.

274. Bergstrom J. Smoking rate and periodontal disease prevalence: 40‐year trends in Sweden 1970–2010. *Journal of Clinical Periodontology* 2014; 41: 952-957.

275. Han DH, Lim S and Kim JB. The association of smoking and diabetes with periodontitis in a Korean population. *Journal of Periodontology* 2012; 83. DOI: 10.1902/jop.2012.110686.

276. Nishida N, Tanaka M, Hayashi N, et al. Determination of smoking and obesity as periodontitis risks using the classification and regression tree method. *Journal of Periodontology* 2005; 76. DOI: 10.1902/jop.2005.76.6.923.

277. Tian J, Venn A, Otahal P, et al. The association between quitting smoking and weight gain: a systematic review and meta-analysis of prospective cohort studies. *Obesity Reviews* 2015; 16: 883-901. 2015/06/27. DOI: 10.1111/obr.12304.

278. Leite FRM, Nascimento GG, Scheutz F, et al. Effect of Smoking on Periodontitis: A Systematic Review and Meta-regression. *American Journal of Preventive Medicine* 2018; 54: 831-841. DOI: https://doi.org/10.1016/j.amepre.2018.02.014.

279. WHO. *Healthy diet*. 2015. Geneva: WHO.

280. El Ghoch M, Calugi S and Dalle Grave R. The Effects of Low-Carbohydrate Diets on Psychosocial Outcomes in Obesity/Overweight: A Systematic Review of

Randomized, Controlled Studies. *Nutrients* 2016; 8 2016/07/02. DOI: 10.3390/nu8070402.

281. Foster GD, Wyatt HR, Hill JO, et al. A randomized trial of a low-carbohydrate diet for obesity. *The New England journal of medicine* 2003; 348: 2082-2090. 2003/05/23. DOI: 10.1056/NEJMoa022207.

282. Gardner CD, Offringa LC, Hartle JC, et al. Weight loss on low-fat vs. low-carbohydrate diets by insulin resistance status among overweight adults and adults with obesity: A randomized pilot trial. *Obesity (Silver Spring, Md)* 2016; 24: 79-86. 2015/12/08. DOI: 10.1002/oby.21331.

283. Baumgartner S, Imfeld T, Schicht O, et al. The impact of the stone age diet on gingival conditions in the absence of oral hygiene. *Journal of Periodontology* 2009; 80: 759-768. 2009/05/02. DOI: 10.1902/jop.2009.080376.

284. Woelber JP, Bremer K, Vach K, et al. An oral health optimized diet can reduce gingival and periodontal inflammation in humans - a randomized controlled pilot study. *BMC oral health* 2016; 17: 28. 2016/07/28. DOI: 10.1186/s12903-016-0257-1.

285. Koo SM, Seo D-G, Park YJ, et al. Association between consumption of milk and dairy products, calcium and riboflavin, and periodontitis in Korean adults: using the 2007-2010 Korea National Health and Nutrition Examination Surveys. *Journal of Nutrition and Health* 2014; 47: 258-267.

286. Soedamah-Muthu SS, Ding EL, Al-Delaimy WK, et al. Milk and dairy consumption and incidence of cardiovascular diseases and all-cause mortality: dose–response meta-analysis of prospective cohort studies. *American Journal of Clinical Nutrition* 2011; 93. DOI: 10.3945/ajcn.2010.29866.

287. Al-Zahrani MS. Increased intake of dairy products is related to lower periodontitis prevalence. *Journal of Periodontology* 2006; 77: 289-294.

288. Tanaka K, Miyake Y, Okubo H, et al. Calcium intake is associated with decreased prevalence of periodontal disease in young Japanese women. *Nutrition Journal* 2014; 13: 1.

289. Johnston Jr CC, Miller JZ, Slemenda CW, et al. Calcium supplementation and increases in bone mineral density in children. *New England Journal of Medicine* 1992; 327: 82-87.

290. Hull B. Health Topics. *Science* 2016.

291. Adegboye AR, Christensen LB, Holm-Pedersen P, et al. Intake of dairy products in relation to periodontitis in older Danish adults. *Nutrients* 2012; 4: 1219-1229.

292. Yudkin JS, Stehouwer C, Emeis J, et al. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? *Arteriosclerosis, Thrombosis, and Vascular biology* 1999; 19: 972-978.

293. Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003; 107: 499-511.

294. Menezes AMB, Oliveira PD, Wehrmeister FC, et al. Association between interleukin-6, C-reactive protein and adiponectin with adiposity: Findings from the 1993 pelotas (Brazil) birth cohort at 18 and 22years. *Cytokine* 2018; 110: 44-51. 2018/04/29. DOI: 10.1016/j.cyto.2018.04.020.

295. J. C, L. J and L. P. Obesity and C-reactive protein in various populations: a systematic review and meta-analysis. *Obesity Reviews* 2013; 14: 232-244. DOI: doi:10.1111/obr.12003.

296. Thanakun S and Izumi Y. Effect of Periodontitis on Adiponectin, C-Reactive Protein, and Immunoglobulin G Against Porphyromonas gingivalis in Thai People With Overweight or Obese Status. *Journal of Periodontology* 2016; 87: 566-576.

297. Demmer RT, Trinquart L, Zuk A, et al. The influence of anti-infective periodontal treatment on C-reactive protein: a systematic review and meta-analysis of randomized controlled trials. *PloS one* 2013; 8: e77441. 2013/10/25. DOI: 10.1371/journal.pone.0077441.

298. Poobalan A and Aucott L. Obesity among young adults in developing countries: a systematic overview. *Current Obesity Reports* 2016; 5: 2-13.

299. Huang TT, Drewnowski A, Kumanyika SK, et al. A systems-oriented multilevel framework for addressing obesity in the 21st century. *Preventing Chronic Diseases* 2009; 6.

300. Poobalan A, Aucott L, Precious E, et al. Weight loss interventions in young people (18 to 25 year olds): a systematic review. *Obesity Reviews* 2010; 11: 580-592.

301. Eckel RH, Grundy SM and Zimmet PZ. The metabolic syndrome. *Lancet* 2005; 365: 1415-1428.

302. Haslam DW JW. Obesity. *Lancet* 2005; 366: 1197-1209.

303. Stumvoll M, Goldstein BJ and Van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. *Lancet* 2005; 365: 1333-1346.

304. Wilson PWF, D'Agostino RB, Sullivan L, et al. Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. *Arch Internal Med* 2002; 162: 1867.

305. Li LW, Wong HM and McGrath CP. Longitudinal Association between Obesity and Dental Caries in Adolescents. *Journal of Pediatrics* 2017; 189: 149-154.e145. 2017/07/22. DOI: 10.1016/j.jpeds.2017.06.050.

306. Chaffee BW and Weston SJ. Association between chronic periodontal disease and obesity: a systematic review and meta-analysis. *Journal of Periodontology* 2010; 81: 1708-1724.

307. Moura-Grec PGd, Marsicano JA, Carvalho CAPd, et al. Obesity and periodontitis: systematic review and meta-analysis. *Ciência & Saúde Coletiva* 2014; 19: 1763-1772.

308. Suvan J, D'Aiuto F, Moles DR, et al. Association between overweight/obesity and periodontitis in adults. A systematic review. *Obes Rev* 2011; 12: e381-e404.

309. Maciel SS, Feres M, Gonçalves TED, et al. Does obesity influence the subgingival microbiota composition in periodontal health and disease? *Journal of Clinical Periodontology* 2016; 43: 1003-1012.

310. Zimmermann GS, Bastos MF, Dias Goncalves TE, et al. Local and circulating levels of adipocytokines in obese and normal weight individuals with chronic periodontitis. *J Periodontol* 2013; 84: 624-633.

311. Dye BA. Global periodontal disease epidemiology. *Periodontol 2000* 2012; 58: 10-25.

312. Genco RJ and Borgnakke WS. Risk factors for periodontal disease. *Periodontol 2000* 2013; 62: 59-94.

313. Eke PI, Dye BA, Wei L, et al. Update on prevalence of periodontitis in adults in the United States: NHANES 2009 to 2012. *Journal of Periodontology* 2015; 86: 611-622.

314. Amin Hel S. Relationship between overall and abdominal obesity and periodontal disease among young adults. *East Mediterranean Health Journal* 2010; 16: 429-433. 2010/08/28.

315. de Castilhos ED, Horta BL, Gigante DP, et al. Association between obesity and periodontal disease in young adults: a population-based birth cohort. *Journal of Clinical*

Periodontology 2012; 39: 717-724. 2012/06/08. DOI: 10.1111/j.1600-051X.2012.01906.x.

316. Kesim S, Cicek B, Aral CA, et al. Oral Health, Obesity Status and Nutritional Habits in Turkish Children and Adolescents: An Epidemiological Study. *Balkan medical journal* 2016; 33: 164-172. 2016/07/13. DOI: 10.5152/balkanmedj.2016.16699.

317. Lee KS, Lee SG, Kim EK, et al. Metabolic Syndrome Parameters in adolescents may be determinants for the future periodontal diseases. *Journal of Clinical Periodontology* 2015; 42: 105-112.

318. Irigoyen-Camacho ME, Sanchez-Perez L, Molina-Frechero N, et al. The relationship between body mass index and body fat percentage and periodontal status in Mexican adolescents. *Acta Odontologica Scandinavica* 2014; 72: 48-57.

319. Sarlati F, Akhondi N, Ettehad T, et al. Relationship between obesity and periodontal status in a sample of young Iranian adults. *International Dental Journal* 2008; 58: 36-40. 2008/03/21.

320. Franchini R, Petri A, Migliario M, et al. Poor oral hygiene and gingivitis are associated with obesity and overweight status in paediatric subjects. *Journal of Clinical Periodontology* 2011; 38: 1021-1028. 2011/07/29. DOI: 10.1111/j.1600-051X.2011.01770.x.

321. Markovic D, Ristic-Medic D, Vucic V, et al. Association between being overweight and oral health in Serbian schoolchildren. *International journal of paediatric dentistry* 2015; 25: 409-417. 2014/12/17. DOI: 10.1111/ipd.12147.

322. Galkina IV, Gavrilova OA, Piekalnits, II, et al. [Dental status in children and adolescents diagnosed with obesity]. *Stomatologiia* 2015; 94: 57-58. 2015/04/25. DOI: 10.17116/stomat201594157-58.

323. Lalla E, Cheng B, Lal S, et al. Diabetes mellitus promotes periodontal destruction in children. *Journal of Clinical Periodontology* 2007; 34: 294-298. 2007/03/24. DOI: 10.1111/j.1600-051X.2007.01054.x.

324. Lalla E, Cheng B, Lal S, et al. Periodontal changes in children and adolescents with diabetes: a case-control study. *Diabetes Care* 2006; 29: 295-299. 2006/01/31.

325. Irigoyen-Camacho ME, Sanchez-Perez L, Molina-Frechero N, et al. The relationship between body mass index and body fat percentage and periodontal status in Mexican adolescents. *Acta Odontol Scand* 2014; 72: 48-57. 2013/05/23. DOI: 10.3109/00016357.2013.797100.

326. Merchant AT, Jethwani M, Choi YH, et al. Associations between periodontal disease and selected risk factors of early complications among youth with type 1 and type 2 diabetes: a pilot study. *Pediatric diabetes* 2011; 12: 529-535. 2011/03/12. DOI: 10.1111/j.1399-5448.2010.00736.x.

327. Modeer T, Blomberg C, Wondimu B, et al. Association between obesity and periodontal risk indicators in adolescents. *International Journal of Pediatric Obesity* 2011; 6: e264-270. 2010/08/17. DOI: 10.3109/17477166.2010.495779.

328. Fadel HT, Pliaki A, Gronowitz E, et al. Clinical and biological indicators of dental caries and periodontal disease in adolescents with or without obesity. *Clinical Oral Investigation* 2014; 18: 359-368. 2013/03/22. DOI: 10.1007/s00784-013-0972-9.

329. Zeigler CC, Persson GR, Wondimu B, et al. Microbiota in the oral subgingival biofilm is associated with obesity in adolescence. *Obesity* 2012; 20: 157-164. 2011/10/15. DOI: 10.1038/oby.2011.305.

330. Zeigler CC, Wondimu B, Marcus C, et al. Pathological periodontal pockets are associated with raised diastolic blood pressure in obese adolescents. *BMC oral health* 2015; 15: 41. 2015/04/18. DOI: 10.1186/s12903-015-0026-6.

331. Furuta M, Ekuni D, Yamamoto T, et al. Relationship between periodontitis and hepatic abnormalities in young adults. *Acta Odontologica Scandinavica* 2010; 68: 27-33. 2009/11/03. DOI: 10.3109/00016350903291913.

332. Tomofuji T, Furuta M, Ekuni D, et al. Relationships between eating habits and periodontal condition in university students. *Journal of Periodontology* 2011; 82: 1642-1649. 2011/04/26. DOI: 10.1902/jop.2011.110061.

333. Kawabata Y, Ekuni D, Miyai H, et al. Relationship Between Prehypertension/Hypertension and Periodontal Disease: A Prospective Cohort Study. *American journal of hypertension* 2016; 29: 388-396. 2015/07/26. DOI: 10.1093/ajh/hpv117.

334. Lula EC, Ribeiro CC, Hugo FN, et al. Added sugars and periodontal disease in young adults: an analysis of NHANES III data. *American Journal of Clinical Nutrition* 2014; 100: 1182-1187. 2014/09/23. DOI: 10.3945/ajcn.114.089656.

335. Lundin M, Yucel-Lindberg T, Dahllof G, et al. Correlation between TNFalpha in gingival crevicular fluid and body mass index in obese subjects. *Acta Odontologica Scandinavica* 2004; 62: 273-277. 2005/04/22.

336. Al-Zahrani MS, Bissada NF and Borawskit EA. Obesity and periodontal disease in young, middle-aged, and older adults. *Journal of Periodontology* 2003; 74: 610-615. 2003/06/21. DOI: 10.1902/jop.2003.74.5.610.

337. Wood N, Johnson RB and Streckfus CF. Comparison of body composition and periodontal disease using nutritional assessment techniques: Third National Health and Nutrition Examination Survey (NHANES III). *J Clin Periodontol* 2003; 30: 321-327. 2003/04/16.

338. Reeves AF, Rees JM, Schiff M, et al. Total body weight and waist circumference associated with chronic periodontitis among adolescents in the United

States. *Archives of Pediatric Adolescent Medicine* 2006; 160: 894-899. 2006/09/06. DOI: 10.1001/archpedi.160.9.894.

339. Cole TJ, Bellizzi MC, Flegal KM, et al. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ* 2000; 320: 1240. DOI: 10.1136/bmj.320.7244.1240.

340. Consultation WE, Barba C, Cavalli-Sforza T, et al. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 2004; 363: 157-163.

341. Kuczmarski RJ OC G-SL, Flegal KM, Guo S, Wei R, Mei Z, Curtin LR, Roche AF, Johnson CL. *CDC Growth Charts: United States*. 2000. Hyattsville, Maryland: National Center for Health Statistics.

342. NIH. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. *Obesity Research* 1998; 6 Suppl 2: 51s-209s. 1998/11/14.

343. Organisation. WH. *Obesity: preventing and managing the global epidemic. Report of a WHO consultation*. 3-5 Jun 1997 1997. Geneva: WHO.

344. WHO. *Growth reference 5–19 years*. 2007. World Health Organisation.

345. Barba C, Cavalli-Sforza T, Cutter J, et al. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *The Lancet* 2004; 363: 157.

346. Ekuni D, Yamamoto T, Koyama R, et al. Relationship between body mass index and periodontitis in young Japanese adults. *Journal of Periodontal Research* 2008; 43: 417-421.

347. Carlos JP, Wolfe MD and Kingman A. The extent and severity index: a simple method for use in epidemiologic studies of periodontal disease. *Journal of Clinical Periodontology* 1986; 13: 500-505. 1986/05/01.

348. Loe H and Silness J. Periodontal disease in pregnancy. I. Prevalence and severity. *Acta Odontologica Scandinavica* 1963; 21: 533-551. 1963/12/01.

349. Silness J and Loe H. Periodontal disease in pregnancy. II. Correlation between oral hygiene and periodontal condition. *Acta Odontologica Scandanavia* 1964; 22: 121-135. 1964/02/01.

350. WHO. Oral health survey: Basic Method. 4th edition ed. Geneva: World Health Organization, 1997, pp.3.

351. O'Leary TJ, Drake RB and Naylor JE. The plaque control record. *Journal of Periodontology* 1972; 43: 38. 1972/01/01. DOI: 10.1902/jop.1972.43.1.38.

352. Ramfjord SP. Indices for Prevalence and Incidence of Periodontal Disease. *Journal of Periodontology* 1959; 30: 51-59. DOI: 10.1902/jop.1959.30.1.51.

353. WHO. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. *World Health Organization technical report series* 1995; 854: 1-452. 1995/01/01.

354. Rolland-Cachera MF, Sempe M, Guilloud-Bataille M, et al. Adiposity indices in children. *American Journal of Clinical Nutrition* 1982; 36: 178-184.

355. Greene JG and Vermillion JR. The simplified oral hygiene index. *JADA* 1964; 68: 7-13.

356. Ainamo J and Bay I. Problems and proposals for recording gingivitis and plaque. *International Dental Journal* 1975; 25: 229-235. 1975/12/01.

357. KCDC. *Guide to the utilization of the data from the fourth Korea National Health and Nutrition Examination Survey*. 2007. Seoul, Korea: Korea Centers for Disease Control and Prevention.

358. Cook S, Weitzman M, Auinger P, et al. Prevalence of a metabolic syndrome phenotype in adolescents: findings from the third National Health and Nutrition

Examination Survey, 1988-1994. *Archives of Pediatric Adolescent Medicine* 2003; 157: 821-827.

359. Matuliene G, Pjetursson BE, Salvi GE, et al. Influence of residual pockets on progression of periodontitis and tooth loss: results after 11 years of maintenance. *Journal of Clinical Periodontology* 2008; 35: 685-695.

360. Offenbacher S. Periodontal diseases: pathogenesis. *Ann Periodontol* 1996; 1: 821-878.

361. Okada H and Murakami S. Cytokine expression in periodontal health and disease. *Crit Rev Oral Biol Med* 1998; 9: 248-266.

362. Beck J, Garcia R, Heiss G, et al. Periodontal disease and cardiovascular disease. *J Periodontol* 1996; 67: 1123-1137.

363. Nishimura F, Iwamoto Y, Mineshiba J, et al. Periodontal disease and diabetes mellitus: the role of tumor necrosis factor-α in a 2-way relationship. *J Periodontol* 2003; 74: 97-102.

364. Genco RJ, Grossi SG, Ho A, et al. A proposed model linking inflammation to obesity, diabetes, and periodontal infections. *J Periodontol* 2005; 76: 2075-2084.

365. Eke PI, Page RC, Wei L, et al. Update of the case definitions for population-based surveillance of periodontitis. *J Periodontol* 2012; 83: 1449-1454. 2012/03/17. DOI: 10.1902/jop.2012.110664.

366. WHO. Adolescent health, http://www.who.int/topics/adolescent_health/en/ (2017).

367. Swinburn BA, Sacks G, Hall KD, et al. The global obesity pandemic: shaped by global drivers and local environments. *The Lancet* 2011; 378: 804-814.

368. AIHW. Impact of overweight and obesity as a risk factor for chronic conditions: Australian Burden of Disease Study. Canberra: AIHW, 2017.

369. Van Dyke TE and Van Winkelhoff AJ. Infection and inflammatory mechanisms. *Journal of Clinical Periodontology* 2013; 40: S1-S7.

370. Khan S, Taimur K and Awan KH. Chronic periodontitis and smoking. Prevalence and dose-response relationship. *Saudi Medical Journal* 2016; 37: 889-894.

371. Khan S, Barrington G, Bettiol S, et al. Is overweight/obesity a risk factor for periodontitis in young adults and adolescents?: a systematic review. *Obesity Reviews* 2018: n/a-n/a. DOI: 10.1111/obr.12668.

372. Fedewa MV, Das BM, Evans EM, et al. Change in weight and adiposity in college students: a systematic review and meta-analysis. *American Journal of Preventive Medicine* 2014; 47: 641-652.

373. FSANZ. AUSNUT 2011–13 Food Nutrient Database. Canberra: Food Standard Australia New Zealand, 2014.

374. Xyris software. FoodWorks, Dietary Analysis Package version 5, Highgate Hill, QLD, Australia. 2007.

375. StataCorp. *Stata Statistical Software: Release 15*. 2017. TX: StataCorp LLC.

376. Page RC and Eke PI. Case definitions for use in population-based surveillance of periodontitis. *Journal of Periodontology* 2007; 78: 1387-1399. 2007/08/19. DOI: 10.1902/jop.2007.060264.

377. Brown LJ and LÖE H. Prevalence, extent, severity and progression of periodontal disease. *Periodontology 2000* 1993; 2: 57-71.

378. Kapellas K, Mejia G, Bartold P, et al. Periodontal therapy and glycaemic control among individuals with type 2 diabetes: reflections from the PerioCardio study. *International Journal of Dental Hygiene* 2017; 15: e42-e51. DOI: 10.1111/idh.12234.

379. DOHA. *New national guidelines for alcohol consumption: Standard drink guide*. 2018. Canberra, Australia: Department of Health and Ageing, Australian Government.

380. AHA. Added Sugars, http://www.heart.org/HEARTORG/HealthyLiving/HealthyEating/Nutrition/Added-Sugars_UCM_305858_Article.jsp#.WnkSD6iWbct (2017).

381. Ylöstalo P, Suominen-Taipale L, Reunanen A, et al. Association between body weight and periodontal infection. *Journal of Clinical Periodontology* 2008; 35: 297-304. DOI: doi:10.1111/j.1600-051X.2008.01203.x.

382. Saito T, Shimazaki Y, Kiyohara Y, et al. Relationship between obesity, glucose tolerance, and periodontal disease in Japanese women: the Hisayama study. *Journal of Periodontal Research* 2005; 40: 346-353. DOI: 10.1111/j.1600-0765.2005.00813.x.

383. Bælum V, Pisuithanakan S, Teanpaisan R, et al. Periodontal conditions among adults in Southern Thailand. *Journal of Periodontal research* 2003; 38: 156-163.

384. Sambunjak D, Nickerson JW, Poklepovic T, et al. Flossing for the management of periodontal diseases and dental caries in adults. *Cochrane Database of Systematic Reviews* 2011.

385. WHO. *Guideline: sugars intake for adults and children*. World Health Organization, 2015.

386. Cekici A, Kantarci A, Hasturk H, et al. Inflammatory and immune pathways in the pathogenesis of periodontal disease. *Periodontology 2000* 2014; 64: 57-80.

387. Lertpimonchai A, Rattanasiri S, Arj-Ong Vallibhakara S, et al. The association between oral hygiene and periodontitis: a systematic review and meta-analysis. *International Dental Journal* 2017; 67: 332-343. DOI: doi:10.1111/idj.12317.

388. Casanova L, Hughes F and Preshaw P. Diabetes and periodontal disease: a two-way relationship. *British dental journal* 2014; 217: 433.

389. Vanderweele TJ and Vansteelandt S. Odds ratios for mediation analysis for a dichotomous outcome. *American Journal of Epidemiololgy* 2010; 172: 1339-1348. 2010/11/03. DOI: 10.1093/aje/kwq332.

390. Robins J. A new approach to causal inference in mortality studies with a sustained exposure period—application to control of the healthy worker survivor effect. *Mathematical Modelling* 1986; 7: 1393-1512. DOI: https://doi.org/10.1016/0270-0255(86)90088-6.

391. Baron RM and Kenny DA. The moderator–mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *Journal of personality and social psychology* 1986; 51: 1173.

392. Nascimento GG, Peres MA, Mittinty MN, et al. Diet-Induced Overweight and Obesity and Periodontitis Risk: An Application of the Parametric G-Formula in the 1982 Pelotas Birth Cohort. *American Journal of Epidemiology* 2017; 185: 442-451. 2017/02/09. DOI: 10.1093/aje/kww187.

393. WHO. Overweight and Obesity, http://www.who.int/mediacentre/factsheets/fs311/en/ (2016).

394. VanderWeele TJ and Vansteelandt S. Odds Ratios for Mediation Analysis for a Dichotomous Outcome. *American journal of epidemiology* 2010; 172: 1339-1348. DOI: 10.1093/aje/kwq332.

395. Nascimento GG, Leite FR, Do LG, et al. Is weight gain associated with the incidence of periodontitis? A systematic review and meta-analysis. *Journal of Clinical Periodontology* 2015; 42: 495-505.

396. Young LR and Nestle M. Reducing portion sizes to prevent obesity: a call to action. *American Journal of Preventive Medicine* 2012; 43: 565-568.

397. Webber L, Divajeva D, Marsh T, et al. The future burden of obesity-related diseases in the 53 WHO European-Region countries and the impact of effective interventions: a modelling study. *BMJ Open* 2014; 4: e004787.

398. Barrington GKSKKCLBS. Dietary sugars, obesity and dental caries in Australian Adults. *International Dental Journal* 2019.

399. Anwar A, Amir Q and Khan M. Chronic Periodontitis, A Silent Hazardous Disease. *Biomedica* 2014; 30: 34-39.

400. Khan S, Bettiol S, Kent K, et al. Obesity and periodontitis in Australian adults: A population-based cross-sectional study. *International Dental Journal* 2019. DOI: doi:10.1111/idj.12514.

401. Iwasaki M, Taylor GW, Moynihan P, et al. Dietary ratio of n-6 to n-3 polyunsaturated fatty acids and periodontal disease in community-based older Japanese: a 3-year follow-up study. *Prostaglandins, leukotrienes, and essential fatty acids* 2011; 85: 107-112. 2011/05/24. DOI: 10.1016/j.plefa.2011.04.002.

402. Andriankaja OM and Joshipura K. Potential association between prediabetic conditions and gingival and/or periodontal inflammation. *Journal of diabetes investigation* 2014; 5: 108-114. 2013/09/02. DOI: 10.1111/jdi.12122.

403. ANPHA. *OBESITY: SUGAR-SWEETENED BEVERAGES, OBESITY AND HEALTH*. 2014. Canberra: Australian National Preventive Health Agency.

404. Casanova L, Hughes FJ and Preshaw PM. Diabetes and periodontal disease: a two-way relationship. *British dental journal* 2014; 217: 433-437. 2014/10/25. DOI: 10.1038/sj.bdj.2014.907.

405. Alasqah M, Mokeem S, Alrahlah A, et al. Periodontal parameters in prediabetes, type 2 diabetes mellitus, and non-diabetic patients. *Brazilian oral research* 2018; 32: e81. 2018/08/09. DOI: 10.1590/1807-3107bor-2018.vol32.0081.

406. Lamster IB, Cheng B, Burkett S, et al. Periodontal findings in individuals with newly identified pre-diabetes or diabetes mellitus. *Journal of Clinical Periodontology* 2014; 41: 1055-1060. DOI: 10.1111/jcpe.12307.

407. Uusitupa M and Schwab U. Diet, Inflammation and Prediabetes—Impact of Quality of Diet. *Canadian Journal of Diabetes* 2013; 37: 327-331. DOI: https://doi.org/10.1016/j.jcjd.2013.07.029.

408. Bessell E, Fuller NR, Markovic TP, et al. Effects of alpha-cyclodextrin on cholesterol control and Compound K on glycaemic control in people with pre-diabetes: Protocol for a Phase III randomized controlled trial. *Clinical Obesity* 2019; 9: e12324. DOI: 10.1111/cob.12324.

409. R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing, 2016.

410. RStudio Team. RStudio: Integrated Development for R. Boston, MA2015.

411. Eke PI, Page RC, Wei L, et al. Update of the case definitions for population-based surveillance of periodontitis. *Journal of Periodontology* 2012; 83: 1449-1454.

412. Benguigui C, Bongard V, Ruidavets JB, et al. Metabolic syndrome, insulin resistance, and periodontitis: a cross-sectional study in a middle-aged French population. *Journal of Clinical Periodontology* 2010; 37: 601-608.

413. Khan S, Saub R, Vaithilingam RD, et al. Prevalence of chronic periodontitis in an obese population: a preliminary study. *BMC oral health* 2015; 15: 114.

414. ADA. Diagnosing Diabetes and Learning About Prediabetes, http://www.diabetes.org/diabetes-basics/diagnosis/ (2019).

415. AIHW. *Diabetes snapshot*. 2018. Australian Institute of Health and Welfare.

416. Johnson G, Martin JE and Timoshanko A. Preventing type 2 diabetes: scaling up to create a prevention system. *Medical journal of Australia* 2015; 202: 24-26.

417. Reichert S, Schlitt A, Beschow V, et al. Use of floss/interdental brushes is associated with lower risk for new cardiovascular events among patients with coronary heart disease. *Journal of Periodontal Research* 2015; 50: 180-188. DOI: 10.1111/jre.12191.

418. Foundation H. *Five ways to lower cholesterol*. 2018. Heart foundation.

419. Grunberger G, Jen K-LC and Artiss JD. The benefits of early intervention in obese diabetic patients with FBCx™ — a new dietary fibre. *Diabetes/Metabolism Research and Reviews* 2007; 23: 56-62. DOI: 10.1002/dmrr.687.

420. Hebebrand J and Hinney A. Environmental and genetic risk factors in obesity. *Child and Adolescent Psychiatric Clinics* 2009; 18: 83-94.

421. Hershenfield SM. *No association between periodontitis and obesity in a nationally representative sample of Canadian adults* University of Toronto Toronto, Canada, 2014.

422. Hershenfield SM. *No association between periodontitis and obesity in a nationally representative sample of Canadian adults*. University of Toronto, Canada, 2014.

423. Kingman A, Susin C and Albandar JM. Effect of partial recording protocols on severity estimates of periodontal disease. *Journal of Clinical Periodontology* 2008; 35: 659-667.

424. Kingman A and Albandar JM. Methodological aspects of epidemiological studies of periodontal diseases. *Periodontology 2000* 2002; 29: 11-30.

425. Susin C, Kingman A and Albandar JM. Effect of Partial Recording Protocols on Estimates of Prevalence of Periodontal Disease. *Journal of Periodontology* 2005; 76: 262-267. DOI: 10.1902/jop.2005.76.2.262.

426. Eke P, Thornton-Evans G, Wei L, et al. Accuracy of NHANES periodontal examination protocols. *Journal of Dental Research* 2010; 89: 1208-1213.

427. Eke PI, Dye B, Wei L, et al. Prevalence of periodontitis in adults in the United States: 2009 and 2010. *Journal of Dental Research* 2012; 91: 914-920.

428. Gibbs CH, Hirschfeld JW, Lee JG, et al. Description and clinical evaluation of a new computerized periodontal probe-the Florida Probe. *Journal of Clinical Periodontology* 1988; 15: 137-144.

429. Szklo M and Nieto FJ. *Epidemiology: beyond the basics*. Jones & Bartlett Publishers, 2014.

430. Prentice AM and Jebb SA. Beyond body mass index. *Obesity reviews* 2001; 2: 141-147.

431. IFCC. IFCC Standardization of HbA1c, http://www.ngsp.org/ifcc.asp (2010).

432. Sedgwick P. Bias in observational study designs: cross sectional studies. *BMJ* 2015; 350: h1286.

433. Bowling A. Mode of questionnaire administration can have serious effects on data quality. *Journal of Public Health* 2005; 27: 281-291.

434. Lee M-K and Jin H-J. Relationship between body mass index (BMI) and periodontal disease in Korean adult: The fifth Korea National Health and Nutrition Examination Survey (KNHANES V-1). *Journal of Korean society of Dental Hygiene* 2015; 15: 991-997.

435. Eke PI, Wei L, Thornton-Evans GO, et al. Risk indicators for periodontitis in US adults: NHANES 2009 to 2012. *Journal of Periodontology* 2016; 87: 1174-1185.

436. Crocombe L, Mejia G, Koster C, et al. Comparison of adult oral health in Australia, the USA, Germany and the UK. *Australian Dental Journal* 2009; 54: 147-153. DOI: 10.1111/j.1834-7819.2009.01108.x.

437. Sowa PM, Keller E, Stormon N, et al. The impact of a sugar-sweetened beverages tax on oral health and costs of dental care in Australia. *European Journal of Public Health* 2018; 29: 173-177. DOI: 10.1093/eurpub/cky087.

438. Billings M, Holtfreter B, Papapanou PN, et al. Age-dependent distribution of periodontitis in two countries: Findings from NHANES 2009 to 2014 and SHIP-TREND 2008 to 2012. *Journal of Clinical Periodontology* 2018; 45: S130-S148. DOI: 10.1111/jcpe.12944.

439. Eke PI, Wei L, Thornton-Evans GO, et al. Risk Indicators for Periodontitis in US Adults: NHANES 2009 to 2012. *Journal of Periodontology* 2016; 87: 1174-1185. DOI: 10.1902/jop.2016.160013.

440. Hugoson A, Nordery O, Slotte C, et al. Oral hygiene and gingivitis in a Swedish adult population 1973, 1983 and 1993. *Journal of Clinical Periodontology* 1998; 25: 807-812.

441. Kebschull M, Demmer R, Grün B, et al. Gingival tissue transcriptomes identify distinct periodontitis phenotypes. *Journal of Dental Research* 2014; 93: 459-468.

442. Roberts-Thomson K and Do L. *Oral health status*. Australian Institute of Health and Welfare (Media and Publishing Unit), 2007.

443. Bowen WH, Eastoe JE and Cock DJ. The effect of sugar solutions on the pH of plaque in caries-active monkeys (macaca irus). *Archives of oral biology* 1966; 11: 833-838. 1966/08/01.

444. Kanter R and Caballero B. Global Gender Disparities in Obesity: A Review. *Advances in Nutrition* 2012; 3: 491-498. DOI: 10.3945/an.112.002063.

445. Hales CM, Carroll MD, Fryar CD, et al. Prevalence of obesity among adults and youth: United States, 2015–2016. 2017.

446. WHO. *What do we mean by "sex" and "gender"?* . 2019.

447. ANHPHA. *Obesity: Prevalence trends in Austalia*. 2014. Canberra: Australian National Preventive Health Agency.

448. Devaux M and Sassi F. Social inequalities in obesity and overweight in 11 OECD countries. *The European Journal of Public Health* 2012: ckr058.

449. NHMRC. *Australian Dietary Guidelines: Providing the scientific evidence for healthier Australian diets*. 2013. Canberra: National Health and Medical Research Council.

Appendix A. Ethics approval for the NSAOH 2004-06

THE UNIVERSITY OF ADELAIDE
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OFFICE OF THE DEPUTY VICE-CHANCELLOR (RESEARCH)

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CRICOS Provider Number 00123M

29 March 2004

Professor GD Slade
Dentistry

Dear Professor Slade

PROJECT NO: *National survey of adult oral health 2004/05*
H-01-2004

I write to advise you that the Human Research Ethics Committee has approved the above project. Please refer to the enclosed endorsement sheet for further details and conditions that may be applicable to this approval.

Approval is current for one year. The expiry date for this project is: 31 March 2005

Where possible, subjects taking part in the study should be given a copy of the Information Sheet and the signed Consent Form to retain.

Please note that any changes to the project which might affect its continued ethical acceptability will invalidate the project's approval. In such cases an amended protocol must be submitted to the Committee for further approval. It is a condition of approval that you immediately report anything which might warrant review of ethical approval including (a) serious or unexpected adverse effects on participants (b) proposed changes in the protocol; and (c) unforeseen events that might affect continued ethical acceptability of the project. It is also a condition of approval that you inform the Committee, giving reasons, if the project is discontinued before the expected date of completion.

A reporting form is available from the Committee's website. This may be used to renew ethical approval or report on project status including completion.

Yours sincerely

pp CE MORTENSEN
Convenor
Human Research Ethics Committee

THE UNIVERSITY OF ADELAIDE
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OFFICE OF THE DEPUTY VICE-CHANCELLOR (RESEARCH)

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27 May 2004

Professor GD Slade
Dentistry

Dear Professor Slade

Re: Project No: H-01-2004 - National survey of adult oral health 2004/05

Thank you for the email dated 25.5.04 requesting a variation to the above project.

I write to advise you that on behalf of the Human Research Ethics Committee, I have approved the request to offer participants prior to their oral examination, the oral care gift pack.

The variation is granted in conjunction with the endorsement form of 24.3.04 and applies for the period until 31 March 2005.

Yours sincerely

CE MORTENSEN
Convenor
Human Research Ethics Committee

Appendix B. Ethics approval for the pilot study

THE UNIVERSITY OF SYDNEY

Nicholas Fuller (PhD)
The Boden Institute, Charles Perkins Centre

03 May 2017

Sharon Falleiro
The Research Development Office
Royal Prince Alfred Hospital
Missenden Road

Dear Ms Falleiro,

Re: Protocol No X14-0328 & HREC/14/RPAH/440 – "SFI 121: A double blinded, randomised controlled trial to determine a) the efficacy of a cyclodextrin on cholesterol control, and b) the efficacy of Compound K on glycaemic control (FBCx and GINST15) – Oral examination sub-study"

1. Protocol:
The ethics committee queried the collection of ATSI and the rationale for the collection.

Response: We have deleted the collection of ATSI data and this will no longer be completed. Please refer to page 131 ("Appendix S – Dental Data Collection Sheet").

2. Information sheet for dental sub-study:
   (i) Under the study procedures, please include a sentence about accessing their medical records.
   (ii) Under the heading, Further Information, please change Dr Khan's name to Shahrukh

Response: (i) Medical records will not be accessed for participants in this sub-study. Instead, a medical history will be collected by the dentist which is now reflected on page 2 under "Study procedures".

   (iii) Page 3 has been amended to read "Shahrukh Khan" instead of "Dr Shahrukh"

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Please find attached further documents for this study requiring approval:

1. Protocol Version 7_21 February 2017 based on Version 6_21 January 2016 (tracked and clean versions)
2. Information for Participants – Oral Examination Version 1_21 February 2017 (tracked and clean versions)

Yours sincerely,

Dr Nick Fuller (PhD)
Research Fellow – Clinical Trials Development & Analysis
The Boden Institute of Obesity, Nutrition, Exercise & Eating Disorders

Appendix C. Case report form for the pilot study

Diabetes prevention study

Oral Health Case Report Form

This Case Report Form (CRF) is to be completed during the Baseline oral health assessment.

All teeth should be recorded and referred to using the WHO/FDI Tooth Notation system*.

The order of the oral health assessment tasks in this CRF should be the order followed when performing them.

^^Demographic information, medications, medical history and family history data will be obtained from SFI-121 study questionnaires, so the tables here may require changes to match their data collected.

---

*World Health Organization (2013). Oral Health Surveys: Basic Methods. Geneva, World Health Organization Press.

Inclusion Criteria for Oral Assessments

Some conditions may limit the subject from participating in oral assessment of Periodontal Probing.

If any of the below conditions are present DO NOT perform the Periodontal Probing assessment, as they would require antibiotic prophylaxis to proceed. Other procedures are safe to proceed with.

Participants with prosthetic joints are safe to proceed with for all oral assessment tasks.

Cardiac condition w/ high risk of adverse outcome from endocarditis*	**Present**	**Excluded from Periodontal Probing^**
Prosthetic cardiac valve or prosthetic material for cardiac valve repair	☐ Yes ☐ No	☐ Yes ☐ No If answered yes above, don't progress to next steps and oral assessment visit ends here.
Previous infective endocarditis	☐ Yes ☐ No	
Congenital heart disease, only if; - Unrepaired cyanotic defects - Repaired defects w/ prosthetic material during first 6 months after surgery - Repaired defects with residual defects at or adjacent to the site of a prosthetic device	☐ Yes ☐ No	
Cardiac transplantation w/ development of valvulopathy	☐ Yes ☐ No	
Rheumatic heart disease (Indigenous Australians only)	☐ Yes ☐ No	

**Source for cardiac conditions with high risk of adverse outcome from endocarditis: Oral and Dental Expert Group. Therapeutic guidelines: oral and dental: Version 2. Melbourne: Therapeutic Guidelines Limited; 2012; Chapter: Antibiotic Prophylaxis; Pg. 102; Box 10.*

^Source for antibiotic prophylaxis recommendations for dental procedures: Oral and Dental Expert Group. Therapeutic guidelines: oral and dental: Version 2. Melbourne: Therapeutic Guidelines Limited; 2012; Chapter: Antibiotic Prophylaxis; Pg. 104; Table 8.

Plaque Index Assessment

Armamentarium

- Dental mirror & explorer
- Gauze x 1
- Air flow from empty syringe x 1

Scores for the Plaque Index (PI)* are taken from 4 surfaces of each designated tooth; mesial, distal, buccal and lingual/palatal. Missing teeth are not substituted, score these with 'X'. The tooth surface should be lightly dried with the air flow from an empty syringe. Use the explorer to assess thickness of plaque, then wipe with gauze before proceeding to the next surface.

*Plaque Index Scores are issued as follows:

Score 0	No plaque
Score 1	A film of plaque adhering to the free gingival margin and adjacent area of the tooth. The plaque may be seen *in situ* only after using the probe (explorer) on the tooth surface.
Score 2	Moderate accumulation of soft deposits within the gingival pocket, or on the tooth and gingival margin which can be seen with the naked eye.
Score 3	Abundance of soft matter within the gingival pocket and/or on the tooth and gingival margin

Plaque Index Score Recordings						
Surface	**16**	**12**	**24**	**36**	**32**	**44**
Mesial						
Distal						
Buccal						
Lingual/Palatal						
Averaged Score						
Total PI Score	(Average of all scores) =					

*Source: Silness, J. and H. Löe (1964). "Periodontal disease in pregnancy II. Correlation between oral hygiene and periodontal condition." Acta odontologica scandinavica **22**(1): 121-135.

DMFT Charting

Armamentarium:

- Dental mirror and explorer
- Gauze

	Score									
										Total SCORE
DMFT	D		M			F				=
dmft	d		e			f				=

Where DMFT refers to Decayed, Missing and Filled teeth in Permanent dentition and dmft refers to decayed, missing and filled teeth in primary dentition.

Source. WHO-Oral-Health-Surveys-Basic-Methods-5th-Edition-2013, Annex 1, Page 83.

Periodontal Charting Florida Probe System

Armamentarium

- Florida Probe System, Hand piece and tip
- Dental mirror
- Laptop

Perform this procedure with the patient laying in supine position and all PPE on. Use a dental mirror to aid in retraction and a head-lamp for ample light. Follow instructions from the Florida Probe system in order to complete the following measurements. Ensure the data is recorded and saved through the Florida Probe system on the laptop.

When inserting the Florida Probe tip ensure it stays parallel to the long axis of the tooth surface. Let the system exert the calibrated pressure needed in order to record the reading. Note any bleeding and/or suppuration during the recording and also record any recession.

Measurement/Data	Data entered
Patient ID number	☐Yes ☐ No ☐ Incomplete
Teeth present/Teeth missing	☐Yes ☐ No ☐ Incomplete
Full mouth 6-point periodontal chart recording (mm)	☐Yes ☐ No ☐ Incomplete
Full mouth clinical attachment level recording (mm)	☐Yes ☐ No ☐ Incomplete
Bleeding recorded	☐Yes ☐ No ☐ Incomplete
Time of data entry completion (24hr format):	:
Diagnosis	

Referral Required

Although these oral health assessment tasks in no way constitute as an oral examination, urgent oral issues or conditions may be noticed during the tasks and should be referred to a dental practice for appropriate management. If urgent issues, such as questionable lesions or abscess', are noticed please provide the participant with a written letter of referral and briefly explain the concern. All other non-urgent oral issues noticed should be verbally explained to participant, advising they seek a professional dental examination.

<table>
<tr><th colspan="3">Oral Health Issue</th><th>Urgent Referral Required</th><th>Referral Issued and explained to participant</th></tr>
<tr><td colspan="3">Describe the oral issue(s) noticed, including location, shape, concern:</td><td>☐ Yes

☐ No</td><td>☐ Yes

☐ No

☐ Not required</td></tr>
<tr><td>Urgent</td><td>Somewhat urgent</td><td>Non-urgent</td><td></td><td></td></tr>
</table>

Adverse Event

If an adverse event takes place during any of the oral health assessment tasks, follow with immediate appropriate action. Refer to the *Oral Health at CPC/RPA clinic* Risk Assessment and Safe Work Practice documents to minimise risk of adverse events. Once immediate action has been taken, and participant has been dismissed, note any adverse events in the table below.

Adverse Event	Time (24hr)	Action Taken	Follow-up Action required

Appendix D. Clinical Set-up

Appendix E. Bivariate analysis of extent of periodontitis, BMI and putative confounders

Appendix E. Bivariate analysis of the association between the extent of periodontitis (based on PD and CAL), BMI, and putative confounders

Characteristic	Extent of sites with PD≥4mm (%)	95%CI (Lower)	95%CI (Upper)	Extent of sites with CAL≥ 4mm (%)	95%CI (Lower)	95%CI (Upper)
Age						
15-44	2.3	1.5	3.2	3.5	2.7	4.3
45-59	3.5	2.4	4.8	14.5	12.5	16.5
60+	4.2*	2.9	5.7	37.4*	32.6	42.3
Sex						
Male	3.6*	2.5	4.7	13.5*	11.5	15.6
Female	2.3	1.7	2.8	9.6	8.2	10.9
Income						
≤30K	4.9*	3.0	6.9	25.1*	20.8	29.5
>30k-<60K	2.9	1.9	4.0	2.7	10.1	15.2
60K+	2.3	1.6	2.9	6.2	5.1	7.2
Education						
University/teaching/nursing	1.9	1.4	2.5	9.5*	7.6	11.2
Trade certificate/Dip/Cert	3.6	2.6	4.5	13.8	11.1	16.6
No post-secondary education	7.5*	2.6	17.5	22.9	14.3	31.5
Diabetes - Self-reported						
Yes	3.5	1.6	5.2	20.9*	12.5	29.2
No	2.9	2.2	3.5	11.2	9.9	12.5
Smoking						
Current	7.9*	4.5	11.1	17.3*	12.9	21.7
Former	2.8	2.2	3.5	16.5	13.8	19.3
Never	1.7	1.3	2.1	7.7	6.7	8.8
Alcohol						
≤2 drinks	2.4	1.8	2.9	11.8	10.1	13.6
> 2 drinks	4.1	2.6	5.6	11.3	9.1	13.6
Mouth-rinsing						
No	3.5	2.6	4.4	11.6	9.1	13.7
Yes	2.1*	1.5	2.7	11.5	10.3	12.9
Tooth brushing						
<2times/day	1.5	0.3	2.5	14.4	4.3	23.8
⩾ 2 times/day	2.9*	2.3	3.6	11.6	10.9	12.8
Flossing						
No	2.1	1.7	2.6	13.1*	11.1	15.1
Yes	3.6*	2.5	4.8	10.0	8.7	11.2
Usual reason for dental visit						
Check-up	1.7	1.3	2.1	8.9	7.7	10.3
Problem	4.7*	3.3	6.0	15.3*	13.1	17.5
						ca
BMI						
Underweight/Normal	2.2	1.4	2.9	8.6	7.0	10.2
Overweight/Obesity	3.2	2.4	3.9	14.0*	11.9	16.0
Added sugar	2.9*	2.3	3.2	12.5*	10.6	14.3

Appendix F. Multiple variable linear regression analysis of extent of CAL ≥4mm with confounding factors

Appendix F. Multiple variate linear regression analysis – Adjusted odds ratios for obesity and confounding factors (age, sex, income, education, smoking, flossing, type 2 diabetes, added sugar, and the usual reason for dental visit.

Characteristic	Odds ratio	95%CI (Lower)	95%CI (Upper)
BMI	-0.9	-3.7	2.0
Age	16.6*	13.2	20.0
Sex	2.1	1.4	5.6
Income	4.3*	2.2	6.4
Education	-0.3	-2.4	3.1
Diabetes - Self-reported	-1.2	-10.2	7.6
Smoking	3.9*	1.4	6.5
Flossing	-1.8	-5.0	1.3
Usual reason for dental visit	2.6	-0.3	5.5
Added sugar	0.1	-0.1	0.2