Title: Association between Obesity and Periodontitis in Australian adults: A Single Mediation Analysis

Running title: Obesity and periodontitis

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Summary of key findings: The direct effect of physical inactivity induced obesity on periodontitis was 13%. The indirect effect of obesity on periodontitis through dental visiting behaviour 3%.

Abstract

Background: Obesity and periodontitis are conditions with high burden and cost. This study aimed to unfold *“the proposed pathways through which the effect of obesity in the presence of health behaviours (dental visiting behaviour and diabetes) increases the risk of periodontitis?”*

Methods: The effect decomposition analysis using potential outcome approach was used to determine obesity related periodontitis risk using the Australian National Survey of Adult Oral Health 2004-06. A single mediation analysis for exposure “physical-inactivity induced obesity, mediator “dental visiting behaviour (a de facto measure of healthy behaviours)”, outcome “periodontitis”, and confounders “age, sex, household income, level of education, self-reported diabetes, alcohol-intake and smoking” was constructed for subset of 3715

participants, ≥ 30 years. Proposed pathways were set independently for each risk factor and in synergy. The STATA 15 Paramed library was used for analysis. Sensitivity analysis was conducted to detect unmeasured confounding using nonparametric approach.

Results: The average treatment effect of physical inactivity induced obesity to periodontitis is 14%. Pathway effect analysis using potential outcomes illustrated that the effect of obesity on periodontitis that was not mediated through poor dental visiting behaviour was 13%. Indirect effect of obesity-mediated through poor dental visiting behaviour on periodontitis was 3%.

Conclusion: The direct effect of physical inactivity induced obesity on periodontitis was higher than the indirect effect of obesity on periodontitis through dental visiting behaviour.

Clinical Implications: Establishing a pathway of causal relationship for obesity and periodontitis could help in developing management strategies that focuses on mediators.

Keywords: Mediation analysis, Obesity, Periodontitis, Risk factor, Public health, Periodontitis

Introduction

Obesity, including overweight, is an emerging epidemic (that has reached unprecedented proportions) of developing and developed nations including Australia¹. It is the second highest contributor to the burden of disease in Australia, with a prevalence of 63%². Obesity is associated with deterioration in health, greater risk of premature death, disability and chronic co-morbidities including type 2 diabetes³ and cardiovascular diseases⁴. These associated risks are also intermediate factors for periodontitis⁵. Systematic reviews and meta-analyses suggest the existence of an association between obesity and periodontitis [Odds ratio 1.2-4.5]^{6,7}.

Periodontitis is a chronic inflammatory condition that affects the supporting periodontal tissues and alveolar bone associated with the teeth⁸. The aetiological factor for periodontitis is dental plaque biofilm⁹. This results in a complex ecological interaction with the host immune-system response¹⁰, leading to metabolic changes in the bone and localisation of pro-inflammatory cytokines¹¹, under the influence of lifestyle factors^{12, 13} and chronic co-morbidities¹⁴.

Obesity potentially results in a persistent pro-inflammatory state¹⁵ that alters the micro-environment of the periodontal sites, favouring the growth and complexity of oral microflora¹⁶. Lipopolysaccharide from gram-negative bacteria in the periodontal sites can trigger 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 diabetes¹⁷. Reduced insulin sensitivity triggers the production of advanced glycation end products (AGE) that promotes the production of pro-inflammatory cytokines including leptin, TNF- α and IL-6, which act in the predisposition of periodontal inflammation^{15, 17}. This mechanism is expected to be delayed or discontinued in individuals who consume a diet with appropriate macronutrient and micronutrients, in particular low in sugar¹⁸, participate in regular dental visiting behaviours, and through motivation and practice of regular oral hygiene habits¹⁹. A study of health behaviours from eight European countries found that overweight/obese adults consumed more soft drinks, brushed less than two times a day, and had higher odds of problem-based dental visiting behaviour¹⁹. Thus, according to the principle of behavioural change and multiple behavioural research models, it could be suggested that for preventing periodontitis and reducing overweight/obesity-induced inflammation, healthy behaviour practices including dental visiting behaviour are necessary due to their potential mediation effects²⁰.

The association between obesity and periodontitis has been reported by studies using the conventional regression method ²¹. These methods are appropriate to determine the relationship between exposure, confounders and outcomes. However, when there are intermediate (mediator) variables on the exposure-outcome path, then use of traditional regression will yield biased estimates ²². It is from here we learn that between the path of exposure (obesity) and outcome (periodontitis) there are several other paths. Conventional regression methods in these situations yield incorrect results ²²⁻²⁵. To overcome some of the limitations of traditional regression analysis, methods including marginal structural modelling and G-formula have been developed to estimate the relationship between obesity and periodontitis ²³.

To study the mechanisms through which the exposure effects' the outcome, using observational cross-sectional study dataset, mediation analysis is presented as a suitable technique. Mediation allows the exposure effect to be decomposed into the direct effect and the indirect effect. Where direct effect refers to the effect of the exposure on the outcome and the indirect effect refers to the effect of the exposure through the intermediate variable(s) (mediator) on the outcome. To appropriately understand data generating mechanism between obesity and periodontitis, this study utilised the potential outcome approach that decomposes the average treatment effect into direct and indirect effects ^{23,26}.

Hence, this study aimed to explore the association relationship between obesity (related to physical inactivity) and periodontitis in Australia (a developed nation, with cultural and behavioural diversity) using single mediation analysis to answer this question “Does obesity cause periodontitis”? Furthermore, we also study the indirect effect of obesity through dental visiting behaviour (a de facto measure of healthy behaviours) on periodontitis.

Methods

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

Study design and sampling

This study is the secondary analysis of the NSAOH 2004-06 dataset where the analysis was limited to people 30 years and older. The NSAOH 2004-06 survey used a three-stage, stratified, clustered sampling design to draw a representative sample of the Australian population aged 15 years and older ²⁷. Full details of sampling, examination protocol and survey participation have been described previously ²⁷. 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).

Ethics approval and informed consent

The University of Adelaide's Human Research Ethics Committee provided ethics approval for this survey [H-01-2004]. The study was conducted according to the World Medical Association Declaration of Helsinki (version, 2008). Informed consent was obtained from all participants. Parents/guardian provided informed consent for people under the age of 18 years approved by the University of Adelaide Human Research Ethics Committee. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed for rigorous reporting of this research dataset.

Outcome

A standard examination of teeth was carried out for the measurement of periodontal parameters that included the 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 the 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 Centre for Disease Control and Prevention and American Academy of Periodontology case definition for periodontitis²⁸.

Anthropometric measure assessment

The survey participants self-reported body weight (kg) and height (cm) by filling out the questionnaire. These anthropometric measures were computed to calculate the body mass index (BMI) of the participants, using the World Health Organisation (WHO) definition for body mass index²⁹. The BMI were classified into two categories: (i) underweight/normal BMI as $<25 \text{ kg/m}^2$, and (ii) overweight/obese $\geq 25 \text{ kg/m}^2$.

This study aims to answer the question, “Does obesity causes periodontitis?” This question is inadequate when we try to interpret the meaning of potential outcome $Y^{a=1}$, which is the occurrence of periodontitis as if every person in the population is exposed to obesity. It results in an ill-defined potential outcome, which could mean too many different things and therefore, the causal effect is ill-defined. Thus, a well-defined intervention based on an unambiguous definition is required for the interpretation of potential outcome contrasts, where exposure ($a=1$) and exposure ($a=0$).

The WHO definition of BMI defines obesity as a snapshot in time for the cross-sectional study, and it does not provide information on how the person reached that level of BMI. For this scenario, we define people with $\text{BMI} < 25 \text{ kg/m}^2$ as “normal weight” and people with a $\text{BMI} \geq 25 \text{ kg/m}^2$ as “obese”. 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 obesity (based on BMI) using variables of added sugar and physical inactivity (at least one time of moderate physical activity in the last week) and tested the assumptions of consistency, exchangeability and positivity. We selected physical inactivity as the strongest intervening confounder for obesity (Figure 2). This study will use obesity interchangeably to physical inactivity induced obesity, i.e. “BMI more than 25kg/m² (overweight/obese) as a result of no moderate physical activity”. This definition led to the computation of two groups, i.e. (i) physical inactivity induced obesity group and (ii) recommended physical activity-induced normal weight group. Hence, for the purpose of this study physical inactivity induced obesity was denoted as obesity.

Mediators

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

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 (≤ 2 , > 2 standard drinks per day), age (15-44, 45-59, ≥ 60 years), income ($< \$30k$, $\$30k-\$60k$, $\geq \$60k$), 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 (≥ 2 times per day, < 2 times per day) and mouth rinsing (yes, no).

Direct acyclic graph

We acknowledge that numerous potential pathways exist for explaining the relationship between obesity and periodontitis³⁰. However, due to lack of availability of data not all possible mechanisms can be accommodated. Considering the available data in NSAOH, a possible directed acyclic graph (DAG) was drawn to predict the relationship between, the defined exposure A , outcome Y , mediator M and confounders C .

Figure 1 represents the DAG of this study, where exposure A was physical inactivity induced obesity (here after referred to as obesity in the rest of the document), outcome Y was periodontitis, the mediator was dental visiting behaviour (M), and confounders C were age (C_1), smoking (C_2), alcohol (C_3) and income (C_4). Figure 1 represents various pathways that represent the direct and indirect relationship of A and Y , under the influence of mediators (M). We came to this data generation mechanism based on evidence provided by previous studies and expert opinions. Assumptions of exchangeability and positivity were verified to determine that the intervention was well defined. Following the verification of these assumptions, mediation modelling was used.

Mediation assumptions and modelling

A single mediation analysis was used to decompose the average treatment effect of A on Y into natural direct and indirect effects. Direct and indirect effects were estimated using the counterfactual theory. The aim of the counterfactual theory is to get the magnitude and the direction of the effect correct after properly handling the confounding³¹. The direct effect

($A \rightarrow Y$) is defined as the effect of obesity (A) on periodontitis (Y) that is not mediated by dental visiting behaviour (M)³². The indirect effect is defined as the effect of obesity (A) that is mediated through dental visiting behaviour (M)³². A scenario using counterfactual theory was constructed to estimate the changes in the outcome (Appendix A). In addition to the consistency, positivity, exchangeability, and faithfulness, we also need to make the following four assumptions to decompose the average treatment effect^{23, 26}. These assumptions include;

1. There are no unmeasured confounders in the path of exposure, A , and outcome Y .
2. There is no unmeasured confounding between the mediator, M , and outcome Y .
3. There is no unmeasured confounding in between exposure, A and mediator, M .
4. None of the mediator–outcome confounders are affected by the exposure.

Survey Weight 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. The details of the population weighting strategy used by the NSAOH 2004-06 is discussed elsewhere²⁷.

Sensitivity analysis

Unmeasured confounders are the factors that might be associated with both exposure and outcome, and it might explain away the estimated association between the exposure and the outcome. In observational studies, the effect of observed confounding can be removed by using inverse probability treatment weighting or creating potential outcomes explicitly. However, nothing can be said about the unmeasured confounding. To make a causal claim of the estimated effect measure, one needs to conduct sensitivity analysis. To encounter this problem, sensitivity analysis (or “bias analysis”) is constructed using the E-value estimate²³.

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.²³

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 a mean age of 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 1. Around 43% participants had an annual income of \$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 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, were reported by 14.5% and 34.7% participants, respectively. Sixty percent people were estimated to be overweight/obese. Fifty-nine percent of people reported to brush their teeth twice or more daily. Mouth rinsing was common oral hygiene behaviour among 55% participants. Thirteen percent people reported their daily intake of added sugar was ≥ 30 g/day. Almost 77% people reported that they didn't perform any form of moderate physical activity within the last week.

Table 2 illustrates the results of a single mediation analysis. The results suggest that the total causal effect of obesity (A) to periodontitis (O) was 14%. The direct effect of obesity (A) on periodontitis (O) was 14% and the indirect effect of obesity to periodontitis was 3%

when the effect of obesity (O) was decomposed through dental visiting behaviour (M) on periodontitis.

Figure 3 shows the results of the sensitivity analysis in the context of obesity and periodontitis relationship. The sensitivity analysis suggested an E-value of 1.58 that suggested that the effect of unmeasured confounder in the relationship between obesity and periodontitis was low.

Discussion

To our knowledge, this study is the first to investigate the influence of obesity on periodontitis in the Australian adults' nationwide oral health data set using the cutting-edge research method of single mediation analysis. The findings of the study suggested that the direct effect of obesity (A) to periodontitis (O) was 14% when the exposure of the population was set for obese people with no moderate physical activity. The indirect effect of obesity through dental visiting behaviour on periodontitis was 1%.

A longitudinal study in the Brazilian population has reported a dose-response relationship between obesity and periodontitis using adjustment for time-varying covariates³³. Numerous systematic reviews and meta-analyses have also suggested a significant association between obesity and periodontitis^{6, 7, 34}.

There are studies that report no association between obesity and periodontitis. These include Castilhos et al., a study in a Brazilian population that reported findings of no association between obesity and periodontitis in young adults³⁵. The fourth Korean National Health and Nutrition Examination Survey (KNHANES) and Health 2000 Health Examination Survey of Finland also reported similar results where obesity was not associated with periodontitis in adults after adjusting for putative confounders^{36, 37}. However, these results

are not comparable to the current study because most of these previous studies used conventional regression method rather than causal models developed by Hernan and Robin²³ as discussed previously in the earlier section of this research paper.

A possible data generation mechanism to explain the effect of obesity on periodontitis is illustrated in Figure 4 where we assumed that the effect can also be through a de-facto measure of healthy behaviours. In an ideal situation, when a prospective longitudinal study data is available, generalised estimating equation modelling or random effects to study the joint/cumulative treatment effect could be used to model a life course analysis. In this scenario the treatment/exposure (obesity) remains the same over the period and outcome changes are repeatedly measured throughout the life course. However, in a real-life scenario, the aforementioned assumption is rejected, because BMI varies over the life course under the influence of lifestyle factors [diet, alcohol intake, and smoking] and is also time-dependent (e.g. due to physical activity the childhood obesity might change). Therefore, in the life course scenario, the standard statistical methods yield incorrect inference, with presence of time dependent exposures. Thus, Robin et al. developed methods such as G-estimation and Marginal structural models.

The current study hypothesised reduced dental visiting behaviour as an intermediary factor between obesity and periodontitis. This is due to several reasons. First, obesity is often associated with chronic co-morbidities that require medical attention that may influence patient to shift their prioritisation to general medical appointments rather than dental visits³⁸. Second, people with obesity experience high degree of stigmatisation, poor body imaging and have low self-esteem that leads to depression and vulnerability³⁹. Depression in obese people may contribute to disturbance in behavioural risk factors that include appetite and dietary pattern changes³⁹, reduced dental visiting behaviours that may significantly contribute to poor oral hygiene and pro-inflammatory state⁴⁰. These arguments are supported by the eight

European countries report that found that overweight and obese adults had 1.6 times higher problem-based dental visiting behaviour and poor oral hygiene habits ¹⁹. Dental visiting behaviour is an access to care measure that is significantly associated with poor oral hygiene ⁴¹, and dental plaque biofilm and host immune interaction ^{42, 43}, and adding to pre-existing obesity-related pro-inflammatory state ¹⁵. Moreover, from the policy perspective where no interventions for obesity can be thought of, one can think possible interventions for oral dentist visiting behaviours. These intervention may then allow reduce the indirect effect going from exposure through mediators to outcome.

A two-way relationship may exist between obesity and periodontitis based on the following mechanisms. Adipose tissues secrete cytokines such as tumour necrosis factor alpha (TNF- α) and interleukin 6 (IL-6) ⁴⁴. TNF- α is associated with inflammation in the periodontium, mainly released by monocytes and macrophages in the junctional epithelium circumscribed around the gingival sulcus ⁴⁵. It functions in the destruction of alveolar bone and cartilage in periodontal tissues ⁴⁶ and triggers the leucocytosis and synthesis of C-reactive protein (CRP) and amyloid A ⁴⁷. 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 ¹⁷. 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 ¹⁵ 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 ¹⁷.

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 misreport their weight status [men overestimate their height and women underestimate their

body weight] as compared to people of normal weight ⁴⁸; (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 longitudinal study design, to investigate the causality between 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 the inability to estimate the absolute sugar intake and total energy intake, and other macronutrients that constitutes the diet; (v) type 2 diabetes was tested as an intermediate variable [mediator] in the pilot DAG constructed for this study. However, due to the limitation of having less than 120 observations for type 2 diabetes in the NSAOH 2004-06 data, it was decided to remove type 2 diabetes from the DAG. It would be interesting to test the hypothesis on a mediation pathway in future studies.

Regardless of the limitations, this study has many strengths: 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. This study used a single mediation analysis that differentiates between confounders and mediators and recognises that unmeasured confounders that may affect the obesity and periodontitis relationship. This is better than regression analysis, in which the confounders and mediators of exposure (obesity) and outcome (periodontitis) are grouped together as putative confounders/mediators, limiting the ability to truly understand the effect of exposure on outcome.

Conclusion

No causal claims could be made on obesity and periodontitis relationship based on the outcomes of this study. It could be a result of several unmeasured confounders, and if they are added to the data generating mechanism, the estimated direct and indirect effect can be

explained effectively. Further research is required to estimate the causal relationship between obesity and periodontitis through longitudinal studies in the Australian population.

Public Health Implications

An integrated life course model of care needs to be developed where general practitioners and dentists work collaboratively towards health promotion and education of the people in regards to obesity and about the risk of periodontal disease has on the general health.

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

Competing Interest: We declare that we have no competing interests.

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Legend (Table and Figures)

- Table 1. Characteristics of participants
- Table 2. Single mediation analysis result
- Figure 1. Direct Acyclic Graph of Obesity (A), Periodontitis (O), Dental visiting behaviour (M) and Confounders (age, smoking, alcohol, income) (C).
- Figure 2. Nesting map of A (obesity) and C (Physical activity)
- Figure 3. E-Value of the joint minimum strength of association on the risk ratio scale that an unmeasured confounder must have with the obesity and periodontitis to fully explain away an observed treatment–outcome risk ratio of $RR = 1.14$
- Figure 4. Life course data generating mechanism for obesity and periodontitis for a single person, with a single time point snapshot at 30 years; where C= confounders; A= Obesity; Y=Periodontitis; M=Dental visiting behaviour.

Table 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 (≤ 36 g/day for men and ≤ 25 g/day for women)	86.7	[84.7– 88.5]
	High sugar (≥ 36 g/day for men and ≥ 25 g/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 2. Single mediation analysis result

Effect	Interpretation	Risk ratio Mean (SD)	Confidence Intervals
$E(Y_{1M1}/Y_{0M0})$	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
$E(Y_{1M1}/Y_{1M0})$	Indirect effect through M (dental visiting behaviour))	1.03	1.01, 1.07

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Figure 1. Direct Acyclic Graph of Obesity (X), Periodontitis (O), Dental visiting behaviour (M) and Confounders (age, smoking, alcohol, income) (C).

Author M

Figure 2. Nesting map of A (obesity) and C (Physical activity)

Author M:

Figure 3. E-Value of the joint minimum strength of association on the risk ratio scale that an unmeasured confounder must have with the obesity and periodontitis to fully explain away an observed treatment–outcome risk ratio of $RR = 1.14$

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Figure 4. Life course data generating mechanism for obesity and periodontitis for a single person, with a single time point snapshot at 30 years; where C= confounders; X= Obesity; Y=Periodontitis; M=Dental visiting behaviour.

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