UNIVERSIDADE FEDERAL DE PELOTAS
Faculdade de Odontologia
Programa de Pós-graduação em Odontologia

Tese

Impacto de sobrepeso e obesidade ao longo da vida na ocorrência de doença periodontal: evidências de revisões sistemáticas e de estudos transversais e longitudinais

Gustavo Giacomelli Nascimento

Pelotas, 2015

Gustavo Giacomelli Nascimento

Impacto de sobrepeso e obesidade ao longo da vida na ocorrência de doença periodontal: evidências de revisões sistemáticas e de estudos transversais e longitudinais

Tese apresentada ao Programa de Pós-graduação em Odontologia da Faculdade de Odontologia da Universidade Federal de Pelotas como requisito parcial para obtenção do título de Doutor em Odontologia.

Orientador: Prof. Dr. Flávio Fernando Demarco

Co-orientadores: Prof. Dr. Marco Aurélio Peres

Prof. Dr. Marcos Britto Corrêa

Pelotas, 2015

N244i Nascimento, Gustavo Giacomelli

Impacto do sobrepeso e obesidade ao longo da vida na ocorrência de doença periodontal: evidências de revisões sistemáticas e de estudos transversais e longitudinais. / Gustavo Giacomelli Nascimento; Flávio Fernando Demarco, orientador; Marco Aurélio Peres, coorientador; Marcos Britto Corrêa, coorientador. — Pelotas, 2015.

243 f. : il.

Tese (Doutorado em Odontologia) – Programa de Pós-Graduação em Odontologia, Faculdade de Odontologia – Universidade Federal de Pelotas, 2015.

1. Doença periodontal. 2. Obesidade. 3. Sobrepeso. 4. Estudos longitudinais. 5. Inferência causal. I. Demarco, Flávio Fernando, orient. II. Peres, Marco Aurélio; Corrêa, Marcos Britto, coorient. III. Título.

CDD 614.4

Elaborada por Maria Irani Coito CRB: 08/4440

Gustavo Giacomelli Nascimento

Impacto de sobrepeso e obesidade ao longo da vida na ocorrência de doença periodontal: evidências de revisões sistemáticas e de estudos transversais e longitudinais

Tese aprovada, como requisito parcial, para obtenção do grau de Doutor em Odontologia, Programa de Pós-Graduação em Odontologia, Faculdade de Odontologia, Universidade Federal de Pelotas.

Data da defesa: 08 de julho de 2015.

Banca Examinadora:

Prof. Dr. Flávio Fernando Demarco (Orientador)
Doutor em Odontologia pela Universidade de São Paulo

Prof. Dr. Cassiano Kuchenbecker Rösing
Doutor em Odontologia pela Universidade Estadual Paulista Júlio de Mesquita Filho

Prof. Dr. Aluísio Jardim Dornellas de Barros
Doutor em Epidemiologia pela London School of Hygiene and Tropical Medicine

Profa. Dra. Janaína Vieira dos Santos Motta
Doutora em Epidemiologia pela Universidade Federal de Pelotas

Profa. Dra. Andreia Morales Cascaes
Doutora em Epidemiologia pela Universidade Federal de Pelotas

Aos meus pais, Erio e Solange,
ao meu irmão, Gabriel, e ao Fábio.

Agradecimentos

Deixar a casa dos pais e a cidade natal em busca de um sonho não é uma tarefa fácil. É preciso sair da zona de conforto e acreditar que este é o melhor caminho a seguir. Muitos foram os momentos em que olhei para trás e me perguntei se estava tomando o rumo certo. Ao final deste caminho, percebo que o fim do doutorado não é o fim, mas apenas o começo e "*levo a certeza de que muito pouco sei, ou nada sei".*

E se hoje realizo este sonho, é devido ao apoio de pessoas que foram essenciais nas diferentes etapas desta trajetória. Assim, não tenho dúvidas de que escrever esta seção é a tarefa mais difícil de toda a tese. Digo isto, pois, neste espaço, não existem métodos analíticos ou diagramas causais que estimem a importância de cada pessoa nesta trajetória; a vida não apresenta tamanha objetividade. Aqui, é preciso deixar de lado o rigor acadêmico para sinceramente agradecer a todos que contribuíram para que este volume tivesse a atual forma.

Inicialmente, agradeço a **Deus**, por estar ao meu lado em todos os momentos. Acredito que, nada acontece por obra de coincidência, mas sim da Tua providência. Obrigado por guiar os meus passos e por me conduzir diante deste tortuoso caminho.

Aos meus pais, **Erio e Solange Nascimento**, e ao meu irmão, **Gabriel Nascimento**, fonte inesgotável de amor. Pai e mãe, minha eterna gratidão a vocês, que fizeram o possível e o impossível para que este momento acontecesse. Gabi, tu sabes o quanto és importante para mim. Vocês sempre me ensinaram que jamais devemos desistir dos nossos objetivos. Obrigado pelo amor e pelo carinho de sempre. Amo vocês!

Ao **Fábio Leite**, a pessoa que escolhi para compartilhar a vida. Fá, certamente, esta tese também é tua, pois sabes que eu não chegaria ao dia de hoje sem ti. Muitos foram os momentos, ao longo desses três anos e meio, que fizeste das minhas prioridades, as tuas. Obrigado por me tornar uma pessoa melhor, por

ser este companheiro de vida e por ser a “calmaria” em meio às minhas “tempestades”. *“I’ve had my run; Baby, I’m done; I gotta go home.” (Michael Bublé)*

Aos meus familiares, em especial aos meus tios e padrinhos **Dirceu e Vera Salvatti**, aos meus primos **Aline e Felipe Salvatti** e à minha prima e também madrinha **Patrícia Seben**. Obrigado por entenderem a minha ausência e por estarem ao meu lado em todos os momentos, mesmo que a distância. Vocês são

À minha avó, **Emma Giacomelli**, fonte do mais sincero amor. Eu sei, vó, que tu sempre estiveste comigo.

À família Manzolli-Leite, especialmente ao **Amauri,** à **Elza** e ao **Rafael Leite**. Agradeço pela acolhida e pelo carinho. Mesmo longe, vocês sempre estiverem “perto”.

Aos meus amigos de todas as épocas da vida que nunca deixaram que nossa amizade fosse abalada pela distância: **Ana Rosa De Toni**, **Luisa Cassiano**, **Caroline Weber**, **Priscila Pires**, **Tatiane Souza**, **Vitória Bernardes**. Obrigado por deixarem minha vida mais leve.

“Os amigos não precisam estar ao lado para justificar a lealdade. Mandar relatórios do que estão fazendo para mostrar preocupação. Os amigos são para toda a vida, ainda que não estejam conosco a vida inteira.” (Fabrício Carpinejar).

Aos meus amigos “pelotenses”: **Aline Almeida**, **Ana Paula Martins**, **Caio Dörr**, **Mabel Salas**, **Mariana Cadermatori**, **Luísa Jardim**, **Gabriela Pinto**, **Gabriela Basso, Fernanda Jostmeier**, **Lenise Seerig**, **Camila Ferrúa**, **Diogo Conceição**, **Rochele Castelli**. Vocês, meus amigos, são responsáveis por colorirem os dias cinzas de Pelotas, e moram em meu coração. “*Sinto hoje em Satolep, o que há muito não sentia...*” *(Vitor Ramil)*

A alguns amigos que acompanharam mais de perto minha trajetória acadêmica: **Profa. Dra. Cristiane Furuse**, **Prof. Dr. Frederico Martinho**, **Prof. Dr.**

Rafael Lund, **Prof. Dra. Luciana Pinto** e **Profa. Dra. Fernanda Faot**. Obrigado pelos ensinamentos, pelo incentivo e pela amizade de vocês.

À minha "família australiana": **Natália Peres**, **Bruno Tito**, **Dandara Haag**, **Helena Schuch**, **Gabriel Borges**, **Augusto Freitas**, **Andrea Freitas**, **Rodrigo Peres**, **Manoela Campos**, **David Chica**, **Sabrina Porto**, **Marco Peres** e **Karen Peres**. Vocês foram responsáveis por um ano de muito aprendizado e de muito companheirismo. Lembrarei com muito carinho de todos os momentos que dividimos durante este curto mas intenso período que passei do outro lado do mundo. Terão sempre um lugar especial em meu coração.

I am thankful to the "Ground Floor Group": **Addya Gupta**, **Ankur Singh**, **Claudia Lopez**, **Dandara Haag**, **Helena Schuch**, **Kamal Hanah**, **Nicole Mueller**, **Ninuk Haryani**, **Sofia Christofis**. I am so blessed for having such good friends as you. Thank you for your support and friendship throughout this year. I will miss you.

À Universidade Federal de Pelotas, na figura do magnífico reitor **Prof. Dr. Mauro Del Pino**, à Faculdade de Odontologia da UFPel, representada pela **Profa. Dra. Adriana Etges**, e ao Programa de Pós-graduação em Odontologia/UFPel, representado pelo **Prof. Dr. Maximiliano Cenci**.

À Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul e à Coordenação de Aperfeiçoamento de Pessoal de Nível Superior pelas bolsas de estudo no Brasil e na Austrália, respectivamente.

À equipe de campo do Estudo de Saúde Bucal-2013 da coorte de Pelotas de 1982, pelo trabalho em equipe; e aos membros da coorte de Pelotas de 1982, por abrirem suas casas para nos receber.

I am grateful to the University of Adelaide, especially to the Australian Research Centre for Population Oral Health. I am so proud of being part of this team. Thank you so much for every moment I've spent in this place. My special thanks to **A/Prof. Loc Do**, **Dr. Murthy Mittinty**, **Dr. Gloria Mejia**.

Finalmente, agradeço àqueles que tiveram papel fundamental para que eu pudesse “voar” - meus orientadores:

“Venham até a borda, ele disse.
Eles disseram: Nós temos medo.
Venham até a borda, ele insistiu.
Eles foram.
Ele os empurrou...
E eles voaram.” (Guillaume Apollinaire)

Ao meu orientador, **Prof. Dr. Flávio Demarco**, por me conduzir pelos caminhos acadêmicos da melhor forma possível. Foste não apenas um orientador, mas também um grande amigo e parceiro. Agradeço pela confiança que depositaste em mim desde o início desta caminhada e por todas as oportunidades que me proporcionaste. Sempre foste um exemplo pessoal e profissional a ser seguido. Saibas que tens minha admiração e minha gratidão. Foi um privilégio e um orgulho ter sido teu orientado. Obrigado por tudo o que fizeste por mim.

Ao meu co-orientador, **Prof. Dr. Marcos Corrêa**. Teus ensinamentos e tua amizade foram essenciais para que eu chegasse ao fim desta etapa. És um exemplo de pesquisador a ser seguido. Obrigado pelo aprendizado e pelos momentos divididos ao longo destes anos.

Aos meus co-orientadores, **Prof. Dr. Marco Peres e Profa. Dra. Karen Peres**. Vocês foram verdadeiros mestres no sentido mais amplo da palavra. Sou muito grato a vocês por todas as oportunidades de aprendizado e de crescimento profissional. Mais que pesquisadores, vocês são pessoas exemplares. Agradeço pelos conselhos, pelas discussões, pelo aprendizado, pelas oportunidades, pela amizade e pelos diversos momentos que compartilhamos fora do ambiente acadêmico (sempre regados a bom vinho). Serão sempre lembrados com carinho e admiração. A vocês, o meu mais sincero obrigado.

“Um homem da aldeia de Neguá, no litoral da Colômbia, conseguiu subir aos céus.
Quando voltou, contou. Disse que tinha contemplado, lá do alto, a vida humana.
E disse que somos um mar de fogueirinhas.
— O mundo é isso — revelou — Um montão de gente, um mar de fogueirinhas.
Cada pessoa brilha com luz própria entre todas as outras. Não existem duas fogueiras iguais.
Existem fogueiras grandes e fogueiras pequenas e fogueiras de todas as cores.
Existe gente de fogo sereno, que nem percebe o vento, e gente de fogo louco, que enche o ar de chispas. Alguns fogos, fogos bobos, não alumiam nem queimam; mas outros incendeiam a vida com tamanha vontade que é impossível olhar para eles sem pestanejar, e quem chegar perto pega fogo.”

(Eduardo Galeano, O Livro dos Abraços)

Resumo

NASCIMENTO, Gustavo Giacomelli. **Impacto de sobrepeso e obesidade ao longo da vida na ocorrência de doença periodontal: evidências de revisões sistemáticas e de estudos transversais e longitudinais.** 2015. 242f. Tese (Doutorado em Odontologia) – Programa de Pós-graduação em Odontologia, Universidade Federal de Pelotas, Pelotas, 2015.

As doenças periodontais afetam a gengiva e os tecidos dentários de suporte, sendo classificadas em gengivite, inflamação reversível da gengiva marginal, e periodontite, quando há destruição das estruturas que suportam o dente. Estas doenças possuem natureza infecciosa e o grau de destruição observado depende da resposta do sistema imune do hospedeiro. Enquanto algumas condições sistêmicas, como diabetes são indicadas como fatores de risco para o desenvolvimento e para a progressão das doenças periodontais, o papel de outras, como a obesidade, ainda não é totalmente claro. Obesidade caracteriza-se pelo acúmulo excessivo de gordura corporal responsável por causar danos à saúde geral, tendo sido apontada como um fator de risco para outras doenças sistêmicas como diabetes, doença cardiovascular e câncer. Revisões sistemáticas têm demonstrado a associação entre obesidade e doenças periodontais, especialmente em adultos. Os resultados destas revisões, entretanto, são basicamente provenientes de estudos transversais, o que impossibilita o estabelecimento de uma relação causal entre estas condições. Assim, as revisões sistemáticas que compõem esta tese têm como objetivo demonstrar os efeitos da obesidade nas condições periodontais. Na primeira revisão, buscou-se evidenciar o efeito do tratamento periodontal nos indivíduos obesos, e posteriormente, fazer uma comparação com o efeito do tratamento periodontal em indivíduos não-obesos. Os resultados, originados de poucos estudos, sugerem que o tratamento periodontal é efetivo para promover a melhora do quadro periodontal dos indivíduos obesos; ainda, que não há diferença entre o efeito da terapia periodontal entre obesos e não obesos. A segunda revisão sistemática explorou os efeitos do ganho de peso no desenvolvimento de novos casos de periodontite em adultos. Foram incluídos apenas cinco estudos prospectivos longitudinais que evidenciaram a associação entre o ganho de peso e a incidência de periodontite. Os achados demonstraram que os indivíduos que se tornaram obesos tiveram maior risco para desenvolver periodontite, seguido por aqueles com sobrepeso, quando comparados aos indivíduos que permaneceram eutróficos. Três artigos originais fazem parte desta tese: o primeiro, de desenho transversal, explora a associação entre sobrepeso/obesidade e sangramento gengival em escolares da cidade de Pelotas-RS. Os resultados demonstraram que, entre os meninos, o excesso de peso está associado ao aumento do sangramento gengival. Este estudo, embora transversal, demonstra a associação precoce entre sobrepeso/obesidade e condições periodontais. O segundo artigo original objetivou estimar o efeito controlado direto do sobrepeso/obesidade em desfechos periodontais (perda de inserção periodontal; sangramento à sondagem) em uma coorte de adultos da cidade de Florianópolis-SC (EpiFloripa) por meio de métodos de inferência causal (*marginal structural model with inverse-probability weighting)*. Os achados deste estudo evidenciaram o efeito

direto do sobrepeso/obesidade, especialmente da forma abdominal, em desfechos periodontais desfavoráveis. Finalmente, o último artigo deste volume pretendeu estimar o risco de periodontite na coorte de nascimentos de Pelotas de 1982. Neste estudo foram realizadas intervenções hipotéticas sobre o efeito do aumento do sobrepeso e da obesidade ao longo da vida, independente e em associação com hábitos não saudáveis, no risco de periodontite nesta população. Para isso, foi empregada a *g-formula* paramétrica, levando em consideração as variáveis tempo-dependentes. Os achados deste estudo sugerem que o aumento do sobrepeso e da obesidade aumentam o risco para periodontite. Além disso, quando o excesso de peso é combinado com outros hábitos não saudáveis, como fumo e dieta rica em gordura e carboidratos, o risco torna-se ainda maior. De forma geral, os resultados apresentados pelos artigos componentes desta tese suportam a associação entre excesso de peso e doença periodontal nas diferentes fases da vida. Ainda, os achados sugerem que existe uma relação causal entre sobrepeso/obesidade e doença periodontal em adultos.

Palavras-chave: doença periodontal; obesidade; sobrepeso; estudos longitudinais; inferência causal

Abstract

NASCIMENTO, Gustavo Giacomelli. **Impact of life-course overweight and obesity on periodontal disease: findings from cross-sectional study, longitudinal studies and systematic reviews.** 2015. 242p. Thesis (Doctor of Philosophy in Dentistry) – Post-graduate Program in Dentistry, Federal University of Pelotas, Pelotas, 2015.

Periodontal diseases affect the gingiva and the supporting tissues of the teeth. These diseases can be classified as gingivitis, a reversible inflammation of the marginal gingiva, and periodontitis, a destructive inflammation affecting the supporting structures of the teeth. Periodontal diseases are infectious conditions and depend on the host immune response. While some systemic conditions, such as diabetes are identified as a risk factor for development and progression of periodontal diseases, the role played by other systemic diseases, such as obesity, remains unclear. Obesity can be defined as a systemic disease characterized by excessive body fat accumulation that can lead to adverse impacts on health conditions. Studies have shown that obesity is also an important risk factor for other systemic diseases, such as diabetes, cardiovascular disease and cancer. Systematic reviews have demonstrated the association between obesity and periodontal diseases especially in adults. Results of these reviews, however, are originated from cross-sectional studies, which do not allow the establishment of causal relationship. Thus, the two systematic reviews included in this thesis aimed to estimate the effects of obesity on periodontal conditions. The first review aimed to look at the effects of periodontal therapy amongst obese individuals and to compare the effects of periodontal therapy of obese and non-obese subjects. Results, originated from few studies, suggest that periodontal therapy is effective to improve periodontal condition in obese individuals; also, that there is no difference between the effects of periodontal therapy in obese and in non-obese individuals. The second systematic review aimed to explore the effects of weight gain on the incidence of periodontitis in adults. Five prospective longitudinal studies were included. Pooled results demonstrated that individuals that became obese presented higher risk of periodontitis establishment, followed by those that became overweight comparing with individuals that remained eutrophic. Three original studies are part of this thesis: the first original article, a cross-sectional study, investigated the association between overweight/obesity and gingival bleeding in schoolchildren from Pelotas, Brazil. Results showed that excess of weight is associated with greater prevalence of gingivitis among boys. Even though this study presents a cross-sectional design, it demonstrates the precocious association between overweight/obesity and gingival bleeding. The second original article aimed to estimate the controlled direct effect of overweight/obesity on periodontal outcomes (clinical attachment loss; bleeding on probing) in a cohort of adults from Florianópolis, Brazil. Causal inference methods (marginal structural model with inverse-probability weighting) were applied. Results demonstrated a direct effect of overweight/obesity, especially central obesity, on unfavourable periodontal outcomes. Finally, the last original article of this thesis intended to estimate the risk of periodontitis in the 1982 Pelotas birth cohort. In this study hypothetical interventions on life-course overweight and obesity were set, independently and associated with unhealthy habits, to estimate the risk of periodontitis in this specific population. The parametric g-formula was employed

accounting for the time-varying variables. The findings suggest that the increase of overweight and obesity increase the risk of periodontitis. Furthermore, when excess of weight is associated with other unhealthy habits, such as smoking and high consumption of fat and carbohydrates, the risk is even greater. In summary, the results presented by the articles included in this thesis support the association between excess of weight and periodontal disease in different stages of life. Moreover, the findings suggest a causal relationship between overweight/obesity and periodontal disease in adults.

Key-words: periodontal diseases; obesity; overweight; longitudinal studies; causal inference

Sumário

Apresentação

A presente tese de doutorado foi estruturada de acordo com o Manual de Normas para trabalhos acadêmicos da Universidade Federal de Pelotas. A primeira seção deste volume é composta pelo projeto de pesquisa, devidamente qualificado em outubro de 2013, perante banca composta pelos seguintes membros: Prof. Dr. Flávio Fernando Demarco, Profa. Dra. Maria Cecília Formoso Assunção, e Profa. Dra. Fernanda de Oliveira Bello Corrêa. A versão incluída neste volume contempla as sugestões feitas pela banca examinadora.

Posteriormente ao projeto de pesquisa, é apresentado o relatório do trabalho de campo, no qual são descritas as atividades realizadas pelo doutorando durante o período do doutoramento. Nesta seção também está descrita a justificativa para as mudanças relativas ao projeto de pesquisa inicialmente proposto e para inclusão de novos artigos. Adicionalmente, encontra-se nesta seção o relato sobre as atribuições do doutorando na supervisão e no trabalho de campo do estudo de saúde bucal conduzido em 2013/14 com os membros da coorte de 1982, além das suas atividades durante seu período de estágio no exterior.

A terceira seção deste volume é composta por seis artigos científicos: um artigo de hipóteses, dois artigos de revisão e três artigos originais. Estes artigos, além de achados científicos, evidenciam a trajetória do doutorando durante seu período de doutoramento. Assim sendo, o primeiro artigo deste volume demonstra o primeiro contato do doutorando com o tema desta tese. O desenho amostral menos complexo favoreceu a compreensão do tema e das possíveis relações entre obesidade e doença periodontal. O segundo artigo reflete hipóteses trazidas pelo doutorando no momento de idealização do projeto de pesquisa inicialmente proposto. O primeiro artigo de revisão, por sua vez, apresenta evidências do efeito do tratamento periodontal nos parâmetros clínicos e imunológicos periodontais de indivíduos obesos, enquanto o segundo artigo de revisão demonstra o efeito do ganho de peso na incidência de periodontite. Finalmente, os dois últimos artigos originais evidenciam o efeito da obesidade sobre desfechos periodontais em dois estudos longitudinais a partir de abordagens analíticas de inferência causal. O quinto artigo demonstra o efeito direto da obesidade em desfechos periodontais em uma coorte de adultos da cidade de Florianópolis/SC (EpiFloripa) por meio de *Marginal Structural Model* com *inverse-probability weighting*. Finalmente, o último artigo que

compõe este volume estima o risco à periodontite na coorte de Pelotas de 1982. Além disso, simulam-se intervenções hipotéticas nesta população por meio da *g-formula* paramétrica. Assim, fica evidente, ao longo do volume, a temática comum a todos os artigos, assim como o aumento da complexidade analítica dos artigos apresentados.

Por fim, na última seção deste volume constam as considerações finais sobre os achados comuns dos artigos deste volume.

Projeto de Pesquisa

Gustavo Giacomelli Nascimento

Doenças periodontais e trajetória de obesidade ao longo da vida: estudo em uma coorte de nascimentos

Projeto de pesquisa a ser executado como requisito para obtenção do título de Doutor em Odontologia, pelo Programa de Pós-graduação em Odontologia da Universidade Federal de Pelotas

Orientador: Prof. Dr. Flávio Fernando Demarco
Co-orientadores: Prof. Dr. Marco Aurélio Peres
Prof. Dr. Marcos Britto Corrêa

Pelotas, RS, 2013

Banca examinadora

Prof. Dr. Flávio Fernando Demarco (Orientador)

Profa. Dra. Fernanda de Oliveira Bello Corrêa

Profa. Dra. Maria Cecília Formoso Assunção

Suplente: Profa. Dra. Marília Leão Goettems

Resumo

NASCIMENTO, Gustavo Giacomelli. **Doenças periodontais e trajetória de obesidade ao longo da vida: estudo em uma coorte de nascimentos.** 2013. 147p. Projeto de tese (Doutorado) – Programa de Pós-graduação em Odontologia, Universidade Federal de Pelotas, Pelotas, 2013.

As condições bucais mais prevalentes e importantes são cumulativas e crônicas na sua natureza, sendo necessário um longo período para a sua ocorrência. Os estudos com delineamento de coorte prospectiva caracterizam-se como os melhores desenhos metodológicos para o estudo destas condições. Os estudos de coorte com desfechos clínicos de saúde bucal são escassos, sendo as coortes de Pelotas, as únicas situadas em país de média e baixa renda com estudos publicados. A literatura tem demonstrado haver relações entre as doenças sistêmicas e as doenças bucais com resultados inconclusivos. Tem sido investigada a associação entre a obesidade e as doenças periodontais, uma vez que parecem haver fatores biológicos, comportamentais e sociais envolvidos nesta possível relação. Os fatores biológicos parecem estar ligados à elevação de algumas citocinas inflamatórias secretadas pelo tecido adiposo branco e pelos macrófagos nele infiltrados, como IL-1, IL-6 e TNF-α, essenciais ao início e à progressão das doenças periodontais. Em relação aos aspectos psicossociais, acredita-se que indivíduos provenientes da posição socioeconômica mais baixa possuem risco maior ao desenvolvimento de ambas condições, além de apresentarem hábitos de autocuidado mais negligentes, acentuando a possível relação entre as condições. Apenas um estudo na literatura avaliou o efeito de episódios de obesidade ao longo da vida, encontrando apenas associação com cálculo dentário. Entretanto, não há estudos que testem o impacto da obesidade de acordo com as três principais teorias do ciclo vital nas doenças periodontais. Assim, o presente trabalho tem como objetivo estudar a influência da trajetória da obesidade ao longo da vida nas doenças periodontais na vida adulta. De todos os indivíduos nascidos em 1982, uma subamostra de 720 pessoas é pertencente ao Estudo de Saúde Bucal-06, sendo estes, clinicamente examinados aos 31 anos. Em relação à saúde periodontal, serão avaliados a presença de sangramento gengival, de cálculo dental e será mensurada a perda de inserção clínica. Os exames serão realizados nos domicílios dos participantes por cirurgiões-dentistas devidamente calibrados e treinados. Variáveis, demográficas, socioeconômicas, comportamentais e de saúde bucal serão coletadas pela aplicação de questionário padronizado e testado previamente em outros estudos epidemiológicos. As condições de saúde geral, como peso, altura, circunferência abdominal, uso de serviços de saúde e auto avaliação de saúde serão obtidas do levantamento de saúde geral ocorrido no ano de 2012. Para análise da trajetória da obesidade serão utilizados os valores de Índice de Massa Corporal aos 4, aos 15, aos 23 e aos 31 anos de idade, e os valores de Circunferência Abdominal aos 15, aos 23 e aos 31 anos de idade. Para doença periodontal serão adotados dois desfechos principais: presença de sangramento gengival, e perda de inserção clínica de acordo com critério estabelecido tanto pelo Centro de Prevenção e Controle de Doenças – Academia Americana de Periodontia quanto pelo grupo de Estudo Multidisciplinar de Saúde e Desenvolvimento de Dunedin, Nova Zelândia. Todos os dados serão avaliados pelo software Stata versão 12.0 incluindo análises descritivas (frequências absolutas e relativas); bivariadas (teste Qui-quadrado para variáveis

categóricas nominais e Qui-quadrado de tendência linear para variáveis ordinais) e multivariáveis com adoção de modelos hierárquicos.

Palavras-chave: doença periodontal, obesidade, trajetória, marcadores biológicos, estudo de coorte.

Lista de Abreviaturas

AAP - Academia Americana de Periodontia
BoP - Sangramento à sondagem
CA - Circunferência abdominal
CAL - Perda de inserção clínica
CDC - *Center for Disease Control and Prevention*
CPI - Índice Periodontal Comunitário
CPO-D - Índice de dentes permanentes cariados, perdidos ou obturados
DCNT - Doenças Crônicas Não Transmissíveis
DP - Doenças Periodontais
ESB - Estudo de saúde bucal
ETM - Erro técnico de medida
FGB - Glicemia em jejum
GI - Índice gengival
GR - Recessão gengival
HDL - *High Density Lipoprotein*
HOMA-IR - Modelo de avaliação da homeostase
IL - Interleucina
IMC - Índice de massa corporal
INF - Interferon
ISI - Institute for Scientific Information
LDL - *Low density lipoprotein*
LILACS - Literatura Latino-Americana e do Caribe em Ciências da Saúde
MCP - Proteína quimiotática para monócitos
MESH - *Medical Subject Headings*
NHANES - *National Health and Nutrition Examination Survey*
NIDR - *National Institute for Dental Research*
OMS - Organização Mundial de Saúde
PAI - Inibidor do ativador do plasminogênio
PCR - Proteína C-Reativa
PD - Profundidade de sondagem
PGR - Progranulina
POF - Pesquisa de Orçamentos Familiares
RCQ - Relação cintura quadril
RCA - Relação cintura altura
SD - Desvio-padrão
S-IgA - Imunoglobulina A secretória
SciELO - *Scientific Eletronic Library Online*
TAB - Tecido adiposo branco
TAM - Tecido adiposo marrom
TGR - Triglicérides plasmático
TNF - Fator de necrose tumoral
UFPel - Universidade Federal de Pelotas
VIGITEL - Vigilância de Fatores de Risco e de Proteção para Doenças Crônicas por Inquérito Telefônico

Lista de Figuras

Sumário

1 Introdução

A epidemia de obesidade tem acometido tanto países de alta renda quanto países de média e baixa renda e tem gerado preocupação nas agências de saúde mundiais, uma vez que esta condição possui relevante impacto na morbidade, na mortalidade e nos gastos de saúde (WHO, 2000). A Organização Mundial de Saúde (OMS) reconheceu a obesidade como um fator predisponente a diversas doenças crônicas, como doenças cardiovasculares e câncer. Dados do sistema de Vigilância de Fatores de Risco e de Proteção para Doenças Crônicas por Inquérito Telefônico do ano de 2012 (VIGITEL) demonstraram que aproximadamente 50% da população das capitais brasileiras acima de 18 anos está com excesso de peso. Quando avaliam-se somente os dados relativos à obesidade, sem considerar o sobrepeso, 17% da população encontra-se nesta condição. Fatores comportamentais, como hábitos dietéticos e prática de atividade física, e nível socioeconômico estão intimamente ligados a esta condição (VIGITEL, 2013).

As doenças periodontais são doenças crônicas, de origem inflamatória causada essencialmente por microrganismos específicos (ARMITAGE, 1999). A progressão destas doenças está intimamente ligada à interação entre o sistema imune do hospedeiro e a carga bacteriana presente nos sítios acometidos (LAINE et al., 2013). Condições sistêmicas como diabetes e obesidade têm sido apontadas como fatores de risco às doenças periodontais, uma vez que há um desequilíbrio nesta relação de interação (GENCO; BORGNAKKE, 2013). Dentre as condições periodontais, destacam-se a gengivite induzida por biofilme bacteriano e a periodontite crônica, as formas mais prevalentes na população. A gengivite é caracterizada pelo inflamação gengival causada pela presença do biofilme, com posterior crescimento do contorno gengival, coloração avermelhada acentuada e sangramento após estímulo (MARIOTTI, 1999). A periodontite crônica, por sua vez, caracteriza-se pela perda da inserção gengival e do osso alveolar, frutos da inflamação gengival e da diminuição da resistência dos tecidos periodontais à sondagem (ANDRUKHOV et al., 2013)

A literatura tem reportado haver associação entre o padrão corporal e as doenças periodontais, com maior risco aos indivíduos com excesso de peso. Estes estudos, em sua maioria, são conduzidos em adultos e em idosos, devido à cronicidade das doenças periodontais. Poucos estudos, porém, trazem dados

referentes a adultos jovens, uma vez que, muitas vezes, não há manifestação das doenças periodontais nesta população específica. DICKIE DE CASTILHOS e colaboradores (DICKIE DE CASTILHOS et al., 2012) encontraram associação entre obesidade/sobrepeso com presença de sangramento gengival e de cálculo dentário na coorte de Pelotas de 1982 aos 24 anos, mostrando já haver efeitos do excesso de peso no desenvolvimento das doenças periodontais. Além disso, Al-Zahrani e colaboradores (AL-ZAHRANI et al., 2003) demonstraram que obesidade esteve associada com maior perda de inserção periodontal apenas entre adultos jovens em estudo conduzido nos Estados Unidos, reforçando a hipótese de que a associação entre perda de inserção clínica e obesidade tem início precoce no ciclo vital.

Assim, diante de escassos dados que apresentem informação sobre a possível associação entre obesidade e DP em indivíduos jovens, e diante da falta de estudos que trabalhem com o efeito cumulativo da obesidade ao longo vida sobre as doenças periodontias, este trabalho objetiva investigar a possível relação entre trajetórias de obesidade e doença periodontal em uma coorte de nascimentos.

2 Revisão da Literatura

2.1 Exposições de risco ao longo da vida

A epidemiologia do ciclo vital é definida como o estudo dos efeitos ao longo prazo de exposições físicas e sociais ocorridas durante a gestação, a infância, a adolescência, ao início da vida adulta e seus riscos às doenças crônicas (KUH; BEN-SHLOMO, 2004). Estes estudos buscam estabelecer relações causais entre exposições e desfechos, levando em consideração a duração e o tempo de desenvolvimento da doença (KUH; BEN-SHLOMO, 2004). As doenças crônicas, incluindo as mais prevalentes doenças bucais, devido à sua natureza, se desenvolvem depois de um período relativamente longo, o que gera um desencontro entre a exposição, o início da doença e os primeiros sinais clínicos (NICOLAU et al., 2007). Estes fatos sugerem que as exposições ocorridas no início da vida podem desempenhar um importante papel no desenvolvimento de doenças, antes de haver qualquer manifestação clínica da condição. Além disso, o fato de que muitos fatores de risco possuem sua própria história natural reforça a relevância do tempo no estudo do desenvolvimento de doença crônicas (KUH; BEN-SHLOMO, 2004).

Considerando a variedade e o número de exposições ao longo da vida, e a importância da duração e do período do ciclo vital, a relação entre exposição e desfecho não ocorre de maneira linear. KUH e BEN-SHLOMO (2004) sumarizaram os principais modelos para esclarecer o entendimento da relação entre a exposição e o desfecho ao longo da vida. O modelo de *programação biológica* preconizado por Baker é a primeira formulação de teoria do modelo do *período crítico* (BAKER, 1992). Segundo o autor, eventos intrauterinos ou da primeira infância seriam os responsáveis pelo aparecimento de doenças ao longo da vida. Assim, o modelo do *período crítico* considera o período do ciclo vital da exposição como a peça chave da teoria. A ideia é que a exposição, durante um específico período do crescimento ou do desenvolvimento, fisicamente altera algumas estruturas fundamentais do sistema corporal, resultando em um dano irreversível levando ao posterior desenvolvimento de determinada doença. (KUH; BEN-SHLOMO, 2004).

O segundo modelo, *período crítico com efeito modificador*, considera que as exposições ocorridas nos primeiros estágios da vida interagem com exposições ao longo da vida, aumentando ou diminuindo o risco ao desenvolvimento de doenças

crônicas. Isto sugere que fatores ocorridos tardiamente podem modificar o risco ocorrido precocemente (KUH; BEN-SHLOMO, 2004). Diferentemente destes dois modelos, o modelo de *acúmulo de risco* sugere que as injúrias são acumuladas incrementalmente ao longo vida, e que, após determinados eventos, levam a episódios de adoecimento, juntamente com condições e comportamentos adversos, potencializando o risco para o desenvolvimento de doenças crônicas (KUH; BEN-SHLOMO, 2004). Este mecanismo cumulativo propõe que o número, a duração e a severidade da exposição geram um dano cumulativo ao sistema biológico. De acordo com KUH e BEN-SHLOMO (2004) este acúmulo pode ser causado por exposições independentes, ou seja, o indivíduo é exposto a uma série de eventos desconexos em cada estágio específico de vida, e estas exposições combinadas potencializam o risco para o desenvolvimento de doenças crônicas. Entretanto, autores têm sugerido que estas exposições tenham maior probabilidade de acontecer de maneira "agrupada" ao longo da vida, constituindo o chamado modelo de *acúmulo de risco com risco agrupado*.

O modelo de *cadeia de risco* é outra versão do modelo de acúmulo de risco, caracterizado por eventos em cadeia, onde uma exposição adversa/benéfica leva a outra exposição benéfica/adversa. Este quadro dinâmico propõe uma interação entre fatores intrínsecos como recursos sociais individuais e comportamentos, e entre fatores extrínsecos como influência sociocultural, material, e estrutura familiar. Embora os processo de risco intrínsecos não sejam ignorados, este modelo enfatiza o processo de riscos extrínsecos, sugerindo que os eventos externos afetam a chance de um indivíduo experimentar eventos futuros subsequentes, que tendem a gerar mudanças no risco para o desenvolvimento de doenças crônicas (KUH; BEN-SHLOMO, 2004). NICOLAU e colaboradores (2007) aplicaram os diferentes modelos propostos às doenças crônicas em saúde bucal, como demonstrado na Fig. 1.

Os modelos propostos por KUH e BEN-SHLOMO (2004) são uma tentativa de esclarecer o quadro altamente complexo e dinâmico do ciclo vital. Estes modelos não são exclusivos, e pressupõe-se que a combinação total ou parcial deles são o ponto chave desta interação.

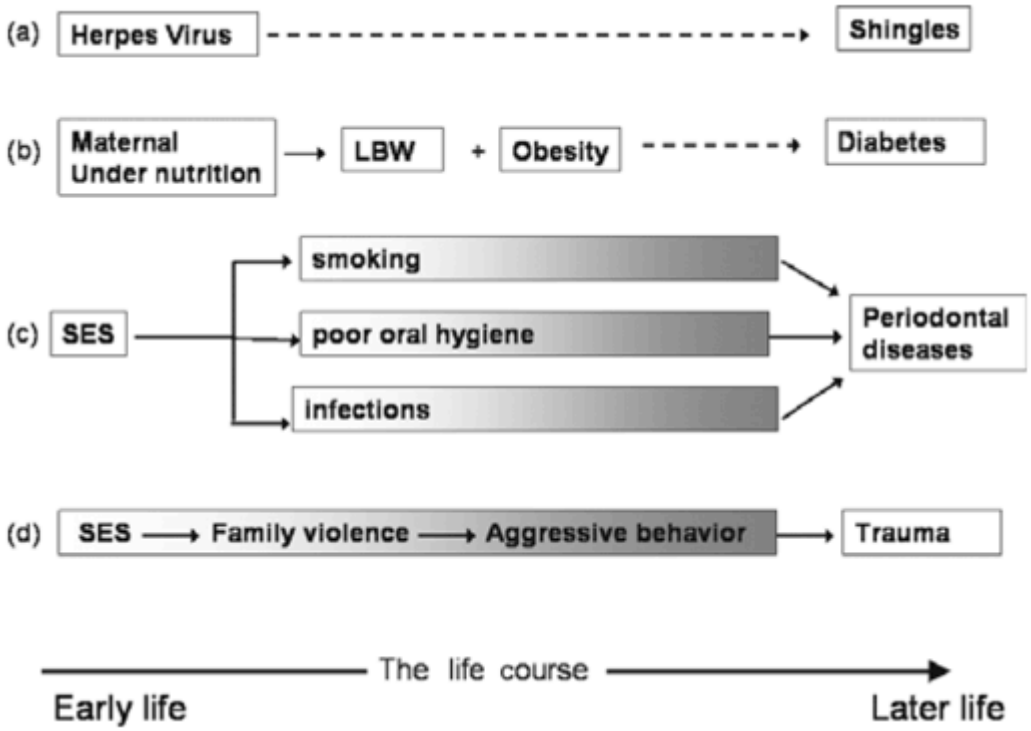


Figura 1 - Esquema exemplificando os diferentes modelos entre exposições precoces e doenças crônicas gerais e bucais. Modelo do período crítico (*Herpes virus*: vírus do herpes; *Shingles*: herpes zoster) (a); Modelo do período crítico com efeito modificador (*Maternal undernutrition*: Desnutrição materna; *LBW*: baixo peso ao nascer; *Obesity*: obesidade; *Diabetes*: debates mellitus) (b); Modelo do acúmulo de risco agrupado (*SES*: posição socioeconômica; *Smoking*: fumo; *Poor oral hygiene*: higiene bucal deficiente; *Infections*: infecções; *Periodontal diseases*: doenças periodontais) (c); Modelo de cadeia de risco (*SES*: posição socioeconômica; *Family violence*: violência familiar; *Aggressive behavior*: comportamento agressivo; *Trauma*: trauma) (d). Retirado de NICOLAU et al., 2007.

2.2 Doenças Crônicas não Transmissíveis

A transição demográfica, descrita como uma alteração na estrutura populacional associada ao desenvolvimento socioeconômico, é acompanhada de um fenômeno denominado transição epidemiológica, caracterizado pela mudança no padrão da distribuição das doenças na população, em função do maior envelhecimento, característico da transição demográfica (POPKIN, 2006). Associado a isto, observa-se também a alteração nos padrões dietéticos e nutricionais, associados ao aumento na prevalência de doenças crônicas (AMUNA; ZOTOR, 2008).

As doenças crônicas não transmissíveis (DCNT) representam um problema de saúde pública de ordem nacional e mundial (SCHMIDT et al., 2011). Segundo

dados da Organização Mundial da Saúde (OMS), as DCNT, que no passado, acometiam, especialmente, países desenvolvidos, são a causa para cerca de 80% das mortes em países de baixa e de média renda (WHO, 2005). No Brasil, a realidade está próxima à estimativa feita pela OMS, uma vez que, em 2007, as DCNT foram responsáveis por aproximadamente 70% dos óbitos no país (SCHMIDT, et al., 2011). Compreende-se que esta mudança ocorreu em um contexto de desenvolvimento econômico e social, marcado pela melhoria das condições de saúde da população. Aliados a isto, o crescimento da renda, a industrialização, o maior acesso aos alimentos processados e a globalização de hábitos não saudáveis contribuíram para que ocorresse uma relevante transição nutricional, condição de risco às DCTN (SCHMIDT, et al., 2011). Estas condições, além de terem um importante impacto na qualidade de vida da população, ainda acentuam problemas de ordem social, contribuindo para o aumento da pobreza e das desigualdades, uma vez que, estas doenças representam o maior custo de internações hospitalares no âmbito do Sistema Único de Saúde (SCHMIDT, et al., 2011).

A expressão das doenças de natureza crônica ocorre após décadas do início à exposição aos seus fatores de risco, e é precedida de complexas alterações biológicas conhecidas como síndrome metabólica (ALBERTI et al., 2009). Dentre as alterações, destacam-se hipertensão arterial sistêmica, elevados níveis de triglicérides, baixos níveis de colesterol HDL (*high density lipoprotein)* e obesidade, sobretudo, central. Não bastassem estas condições, associam-se ainda hábitos de vida não-saudáveis, como etilismo, tabagismo e sedentarismo, elementos de risco ao desenvolvimento das doenças crônicas não transmissíveis. Mesmo com o elevado número de evidências demonstrando esta relação, o mecanismo de fisiopatologia ainda apresenta pontos a ser explorados e explicados nestas condições (BUETTNER; SCHOLMERICH; BOLLHEIMER, 2007).

2.3 Obesidade

Dentre as alterações da denominada Síndrome Metabólica, destaca-se a obesidade. Esta condição caracteriza-se por danos à condição de saúde causados pelo acúmulo excessivo ou anormal de gordura corpórea (KOPELMAN, 2000). A obesidade não pode ser considerada como uma simples desordem, mas sim, um

grupo heterogêneo de condições com múltiplas e complexas causas. O peso corporal é, então, determinado pela interação entre fatores biológicos, ambientais, sociais e comportamentais, agindo na regulação entre o armazenamento e o gasto energético.

Diversas são as causas atribuídas à etiologia da obesidade, destacando fatores psicossociais, comportamentais e biológicos. Embora o componente genético tenha um papel inquestionável na etiologia da obesidade, o notável aumento na prevalência desta condição pode ser melhor explicado por mudanças sociais e comportamentais, resultados da transição sociodemográfica (KOPELMAN, 2000) (Fig. 2).

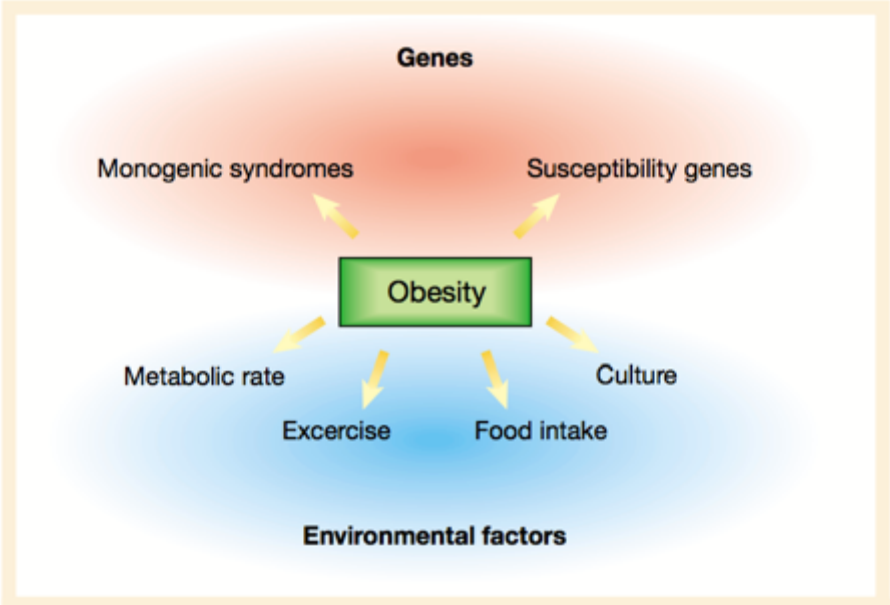


Figura 2 - Fatores influenciadores ao desenvolvimento da obesidade (*Monogenic syndromes*: síndromes monogênicas; *Susceptibillity genes*: susceptibilidade genética; *Culture*: cultura; *Food intake*: ingestão de alimentos; *Excercise*: atividade física; *Metabolic rate*: taxa metabólica). Retirado de KOPELMAN, 2000.

A epidemia da obesidade era uma realidade predominante dos países ricos e desenvolvidos (ALVES et al., 2013). Ao passo que países de baixa e de média renda começam a se tornar mais globalizados, há uma mudança considerável no padrão nutricional, e nos hábitos de vida, acarretando, consequentemente, uma significante elevação da prevalência desta doença. Assim, após a década de 1990, a obesidade assume taxas nunca antes observadas, e continuadamente crescentes (POPKIN, 2006). Nos países de alta renda, como Reino Unido, Austrália e Estados Unidos, a obesidade atinge mais de um terço da população, e taxas semelhantes são observadas em países em de renda média, como México e África do Sul (POPKIN, 2006). Outro dado que chama a atenção é o crescimento desta doença nestes

países, chegando a uma taxa de aumento anual superior a 1%. Nos Estados Unidos, de acordo com avaliação nacional (NHANES), estima-se que em 2015, cerca de 75% da população apresentará obesidade ou sobrepeso (WANG; BEYDOUN, 2007) (Fig. 3).

No Brasil, dados da Pesquisa de Orçamentos Familiares (POF 2008-2009) revelaram que aproximadamente 50% da população adulta apresenta sobrepeso, e cerca de 15% está obesa. Os dados deste levantamento permitem também observar a mudança nos hábitos nutricionais dos brasileiros, com aumento considerável no consumo de lipídeos totais e ácidos graxos saturados, aliado à diminuição no consumo de frutas, hortaliças e leguminosas (LEVY-COSTA et al., 2005). Além disso, observou-se um aumento substancial na ingesta de alimentos altamente processados, de alto teor energético e elevada composição de açúcares e ácidos graxos saturados (MONTEIRO et al., 2011). Essa alteração no padrão alimentar dos brasileiros é evidenciada pela crescente prevalência não somente das DCNT, mas também do excesso de peso da população (LEVY-COSTA, et al., 2005). Dados do sistema de Vigilância de Fatores de Risco e de Proteção para Doenças Crônicas por Inquérito Telefônico para o ano de 2012 (VIGITEL, 2013) demonstram que 51% da população adulta, acima de 18 anos, está com excesso de peso em 2012, um aumento de 8 pontos percentuais desde o último levantamento em 2006. Os dados ainda mostram que há uma diferença na distribuição desta condição de acordo com o gênero: enquanto em mulheres o excesso de peso atinge 48%, entre os homens, este percentual chega a 54%. Há também uma variação de acordo com a faixa etária dos entrevistados, aumentando de 28% na faixa etária dos 18 aos 24 anos para 55% na faixa dos 35 aos 44 anos. Na cidade de Pelotas, em recente estudo, observou-se também o aumento considerável dos índices de obesidade e sobrepeso, especialmente nos últimos anos, acompanhando a tendência nacional e mundial (LINHARES et al., 2012). Os autores encontraram uma prevalência de obesidade (IMC ≥ 30kg/m^2) de 21,7% entre os homens e de 29,2% entre as mulheres.

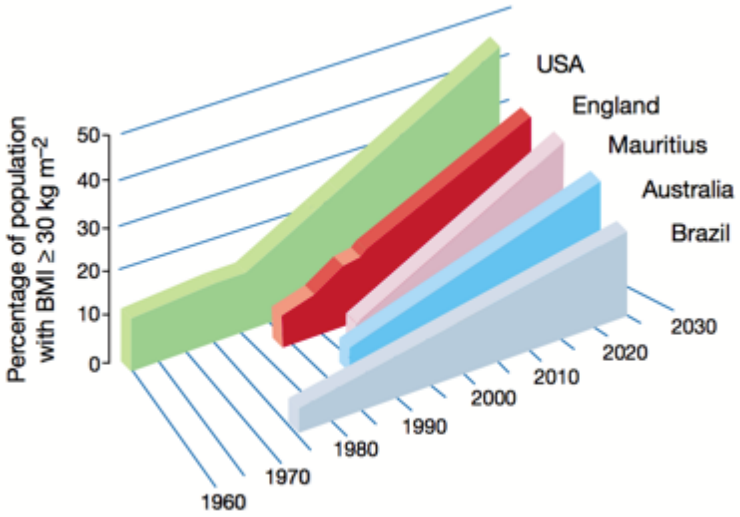


Figura 3 - Taxas de prevalência de obesidade (IMC ≥ 30) passadas, atuais e projetadas (1960 a 2025) para os Estados Unidos, Inglaterra, País de Gales, Ilhas Maurício, Austrália e Brasil. KOPELMAN, 2000.

O VIGITEL 2013 apresenta ainda dados de acordo com o sexo e com a escolaridade dos brasileiros. Aproximadamente 45% das pessoas com 12 anos ou mais anos de estudo apresentaram consumo regular de frutas e de hortaliças, enquanto, entre aqueles que estudaram até oito anos, o percentual reduz para 29%. Ainda, o consumo de gordura saturada foi mais comum entre as pessoas com menor escolaridade: 32% comem carne com excesso de gordura e 53% bebem leite integral regularmente. Entre a população com maior escolaridade, os percentuais registrados estão abaixo da média nacional, com 27% e 47%, respectivamente. O inquérito ainda demonstrou menores frequências de obesidade e de sobrepeso entre os indivíduos com maior escolaridade, assim, o crescente aumento da escolaridade dos brasileiros registrado nos últimos anos pode representar uma expectativa positiva em relação ao controle destas condições.

2.3.1 Mensuração da massa lipídica corpórea

Diversas técnicas podem ser empregadas para a determinação da distribuição da gordura corpórea. Entre as mais utilizadas em estudos epidemiológicos, destacam-se o índice de massa corporal (IMC), a relação cintura-quadril (RQC), a determinação da circunferência abdominal (CA) e o método de bioimpedância.

O índice de massa corporal consiste em um valor calculado por meio da fórmula: peso (Kg)/altura ao quadrado (m). A partir deste valor, faixas pré-determinadas indicam o padrão corpóreo do indivíduo acima de 19 anos – Abaixo de 18,5: déficit de peso; 19 a 24,9: peso normal ou saudável; 25 a 29.9: sobrepeso grau 1; 30 a 39.9: obesidade ou sobrepeso grau 2; acima de 40: obesidade mórbida ou sobrepeso grau 3 (KOPELMAN, 2000). Para crianças e adolescentes, o cálculo do IMC deve ser feito pelo escore Z relativo à idade e ao sexo do sujeito (WHO, 2007).

Esta classificação graduada do padrão corpóreo fornece uma importante informação sobre o aumento da gordura corporal. Isto permite significantes comparações intra e inter populacionais, além de permitir a identificação de indivíduos e de grupos de risco. Este índice também possibilita o estabelecimento de prioridades para intervenção a nível individual e coletivo, propiciando uma posterior avaliação da efetividade das intervenções propostas (KOPELMAN, 2000). Como principais limitações deste índice, destacam-se sua incapacidade de distinção entre massa adiposa e massa magra (tecido ósseo e muscular), e de identificação localização da massa adiposa no organismo (SNIJDER et al., 2006).

O acúmulo excessivo de gordura na região abdominal está intimamente ligado à deposição de tecido adiposo nas vísceras, sendo a obesidade visceral considerada um importante fator de risco a doenças cadiovasculares – hiperglicemia, assim como à elevação do nível sérico de triglicerídeos (LINHARES et al., 2012). A circunferência abdominal consiste na medida da circunferência localizada no ponto médio entre a parte inferior da última costela e a parte superior da pelves. Já a relação cintura-quadril representa a razão entre a circunferência abdominal e a circunferência do quadril. Ambas medidas fornecem informações mais precisas sobre a localização gordura corporal, pois possui boa capacidade de estimar a gordura visceral intra-abdominal (SNIJDER, et al., 2006). Para CA há a definição dos seguintes pontos de corte, com distinção entre os sexos: normal ou eutrófico (homem <94cm, mulher <80cm); grau 1 (homem ≥94cm e <102cm, mulher ≥80cm e <88cm); grau 2 (homem ≥102cm, mulher ≥88cm) (LEAN; HAN; MORRISON, 1995). Já para a RCQ, a literatura sugere que sejam classificados como obesos homens que apresentem valores maiores ou iguais a 0,90 e mulheres 0,80 (SUK et al., 2003). Outro índice que está amplamente sendo utilizado em países de alta renda é a relação cintura-altura (RCA). Este método trabalha somente

com a gordura abdominal, uma vez que consiste em estabelecer como categoria de risco indivíduos que apresentem valor de circunferência abdominal maior que a metade do valor da altura. Desta forma, este método tem sido apontado como o mais simples e preciso, uma vez que a altura do indivíduo é constante, e a única variável é a medida circunferência abdominal (HSIEH; YOSHINAGA, et al., 1995). Sua desvantagem consiste na não determinação da gordura visceral, já que apenas mede o diâmetro abdominal. Segundo estudo que comparou as principais formas de mensuração da gordura corporal (IMC, CA, RCQ, RCA), indicou que há diferenças para sensibilidade e especificidade das formas de mensuração entre os sexos: para homens, os métodos mais precisos foram CA e RCQ; já para mulheres, CA e RCAlt (BENER et al., 2013).

A bioimpedância é um método rápido, barato e não-invasivo de avaliação da composição corporal, sendo assim, extremamente indicado para estudos epidemiológicos (LINTSI, KAARMA et al., 2004). Esta técnica baseia-se no princípio de que os componentes corporais oferecem resistência diferenciada à passagem da corrente elétrica. A resistência é uma função do formato do corpo, conteúdo e volume dos tecidos condutivos. Sendo assim, massa magra e massa gorda conduzem corrente de forma diferente, principalmente por diferenças na quantidade de água desses tecidos. Primeiramente, a bioimpedância estima a quantidade de água corporal total. A seguir, conhecendo-se o nível de hidratação da massa magra pode-se calcular a quantidade de massa magra e consequentemente a massa gorda.

2.3.2 Tecido adiposo e seu papel no sistema imune

O tecido adiposo humano é constituído pelo tecido adiposo branco (TAB) e pelo tecido adiposo marrom (TAM). O TAB, localizado perifericamente nas regiões subcutânea e visceral, armazena energia na forma de triglicérides, participando da regulação do balanço energético mediante processos de lipogênese e de lipólise. O TAM, por sua vez, é localizado no sistema nervosa central, apresentando funções termogênicas fruto do maior número de mitocôndrias existentes em sua estrutura (KERSHAW; FLIER, 2004).

Evidências têm demonstrado que o TAB, antes reconhecido órgão passivo de acúmulo de energia, é um importante órgão de função endócrina metabolicamente

ativo, capaz de secretar e de expressar diversas substâncias bioativas, adipocinas, com ação local e sistêmica (KERSHAW; FLIER, 2004, TILG; MOSCHEN, 2006).

A resposta inflamatória clássica representa uma reação aguda frente ao desafio infeccioso ou ao dano tecidual, tendendo a evoluir para a homeostase, uma vez removido seu agente causador (MEDZHITOV, 2008). Entretanto, há uma alteração deste processo clássico diante do quadro de obesidade, já que não há manifestação dos sintomas típicos – calor, tumor, rubor, dor e perda de função – caracterizando-se por uma reação crônica de baixa intensidade (HOTAMISLIGIL, 2006). Aliado a isso, inclui-se em seu desenvolvimento hábitos relacionados a hábitos de vida, como a prática de exercícios físicos e a qualidade da dieta (EGGER; DIXON, 2010).

Esta resposta inflamatória alterada está intimamente relacionada com a hipertrofia do tecido adiposo, especialmente o TAB, responsável pela produção de uma gama de citocinas, em sua maioria pró-inflamatórias, como a IL (interleucina)-1β, a IL-6, o fator de necrose tumoral (TNF)-α e a proteína quimiotática para monócitos (MCP)-1, e de adipocinas, como a resistina e a leptina (CANCELLO; CLEMENT, 2006). Concomitante a isto, a obesidade também está associada à diminuição na produção de adiponectina, adipocina usualmente considerada um importante fator de propriedades anti-inflamatórias (STEFAN; STUMVOLL, 2002).

Ainda não há evidências sobre a relação causal entre a obesidade e a inflamação. Em tese, assume-se que a inflamação é um estado consequente à obesidade, embora alguns autores suportem a hipótese de a obesidade ser o resultado de uma doença inflamatória. De fato, sabe-se que obesidade e inflamação estão associadas, e apresentam condição cíclica no agravamento de ambas, estabelecendo uma relação de retroalimentação (CANCELLO; CLEMENT, 2006).

Algumas teorias tentam explicar a origem da infamação crônica na obesidade (NEELS; OLEFSKY, 2006). Acredita-se que o ganho de peso leve à hipertrofia dos adipócitos, comprimindo, assim, os vasos sanguíneos, dificultando o adequado suprimento do tecido adiposo (XU et al., 2003). Desta forma, ocorreria hipóxia local, com a sequente morte de células adiposas, sendo este quadro, então, responsável por desencadear a cascata de sinalização inflamatória, e o processo de angiogênese, para formação de novos vasos no local (LOLMEDE et al., 2003). Entende-se que a condição de hipóxia *per se* seja suficiente para estimular a quimiotaxia de macrófagos e para induzir a expressão de genes pró-inflamatórios.

Portanto, a elevação dos níveis dos marcadores pró-inflamatórios observados na obesidade – TNF-α, IL-1, IL-6, MCP-1 – seria proveniente da produção destes pelos próprios adipócitos e pelos macrófagos infiltrados em resposta à hipóxia (CANCELLO; CLEMENT, 2006) (Fig. 4). Concomitante a estas alterações, os fatores secretados pelo TAB acabam estimulando a produção de marcadores pró-inflamatórios agudos em outros órgãos, como a proteína C-Reativa (PCR), produzida no fígado pelo estímulo da IL-6 secretada pelos adipócitos (MOHAN et al., 2005).

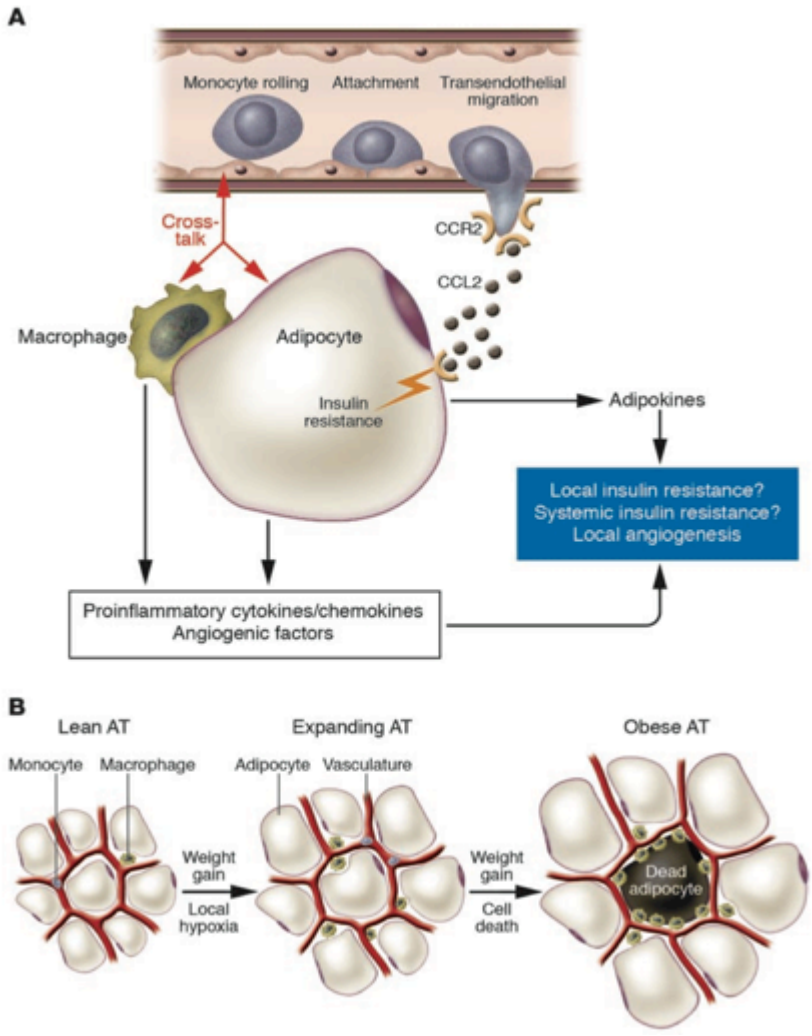


Figura 4 - Itinerário do macrófago na infiltração tecidual. (A) Infiltrado macrófago ocorre após rolamento e inserção dos monócitos ativados por células endoteliais. Estes monócitos, após diapedese se diferenciam em macrófagos. Inter-relação entre adipócitos, macrófagos, e células endoteliais podem agravar o estado inflamatório, resultando em aumento na secreção de citocinas pró-inflamatórias, adipocinas e fatores angiogênicos. (B) Expansão do tecido adiposo durante o ganho de peso, ocasionando hipóxia dos adipócitos. Macrófagos localizados predominantemente ao redor dos adipócitos. Retirado de NEELS; OLEFSKY, 2006.

A proteína C-Reativa (PCR), de origem hepática, é um marcador inespecífico de inflamação sistêmica associada à fase aguda de resposta frente ao estímulo causador. Atualmente, este marcador tem sido estudado à exaustão, uma vez que ele além de apresentar-se como forte candidato da ligação entre o processo inflamatório crônico e o processo aterosclerótico (DANESH et al., 2004), ainda apresenta propriedades pró-inflamatórias (DASU et al., 2007). Esta proteína, em ensaios altamente sensíveis, tem demonstrado ser um relevante preditor para eventos cardiovasculares, especialmente quando seus elevados níveis persistem por períodos crônicos associados a outros fatores de risco, como fumo e sedentarismo (NAZMI et al., 2010). Na obesidade, esta proteína tem sua produção estimulada pela IL-6 produzida pelas células adiposas, sendo os níveis deste marcador diretamente proporcionais ao índice de massa corporal, e à adiponectina, adipocina com potencial anti-inflamatório (BULLO et al., 2003) (Fig. 5). Assim, é esperada uma concentração elevada deste marcador em casos de obesidade, observando-se sua diminuição com a progressiva perda de massa adiposa (TRAYHURN; WOOD, 2004). A Tabela 1 resume os principais marcadores biológicos envolvidos no processo inflamatório da obesidade, com seus efeitos a nível local e sistêmico.

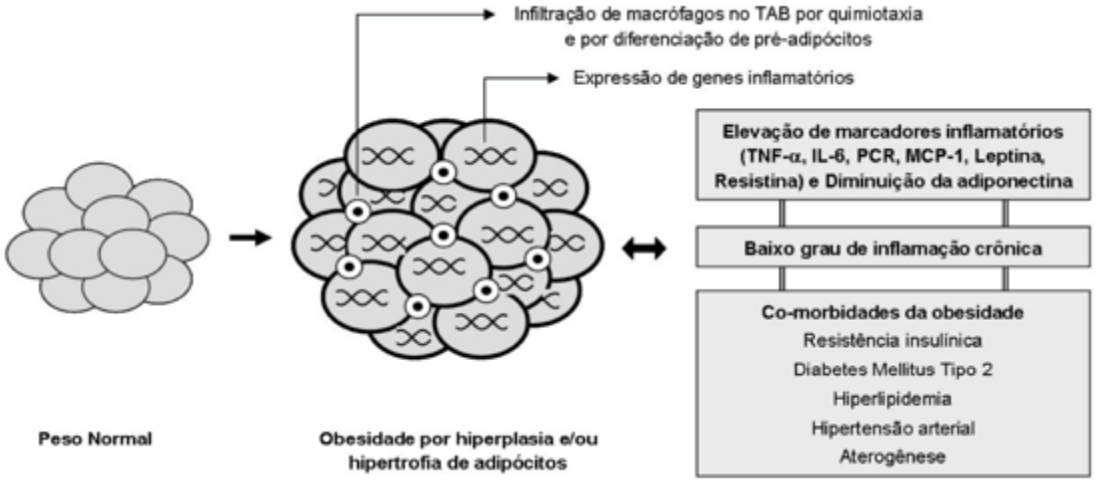


Figura 5 - Relação de citocinas pró-inflamatórias envolvidas na obesidade e no processo inflamatório. Retirado de LEITE et al., 2009.

Tabela 1 - Relação de citocinas envolvidas na obesidade e na inflamação, com seus respectivos efeitos e comportamentos. Retirado de LEITE et al., 2009.

Adipocinas	Comportamento na obesidade	Efeitos
TNF-α	Aumentado	↑ Produção de citocinas
		↑ Lipólise (↓LPL, ↓lipogênese)
		↓ Captação de glicose (↓ GLUT-4)
		Resistência insulínica
		Propriedades aterogênicas
IL-6	Aumentado	Obesidade
		↑ Lipólise
		↑ Resistência insulínica
		Proteínas hepáticas de fase aguda (PCR)
PCR	Aumentado	Diretamente proporcional ao IMC
		Obesidade e risco de diabetes mellitus tipo 2 e doenças cardiovasculares
		Inversamente proporcional a adiponectina
MCP-1	Aumentado	Proteína quimioatrativa de monócitos e macrófagos
		Papel na infiltração de macrófagos
		↓ Captação de glicose
		Resistência insulínica
		Propriedades aterogênicas
Leptina	Aumentado	Níveis proporcionais à adiposidade
		↑ Produção de citocinas
		↑ Adesão e fagocitose de macrófagos
		Efeito regulador sobre a pressão sangüínea
Resistina	Aumentado	↑ Resistência insulínica
Adiponectina	Diminuído	Ação antiinflamatória
		↑ Sensibilidade à insulina
		Favorece a oxidação dos AG
		Atenua a progressão de aterosclerose

2.4 Doenças Periodontais

Há diversas classificações para as doenças periodontais, sendo as formas mais prevalentes, a gengivite induzida por biofilme bacteriano e a periodontite crônica (ANDRUKHOV et al., 2013). A gengivite induzida por biofilme bacteriano tem como condição a presença do biofilme para iniciar ou exacerbar a severidade da doença. Esta situação é caracterizada pela inflamação da gengiva marginal, apresentando crescimento do contorno gengival, coloração avermelhada acentuada, aumento do exsudato gengival e sangramento após estímulo. Seus sinais clínicos e sintomas estão associados com níveis de inserção estáveis, sem perda da inserção clínica. A reversão da gengivite induzida por biofilme bacteriano se dá pela remoção do fator etiológico, destacando a reversibilidade da condição inflamatória

(MARIOTTI, 1999). A periodontite crônica caracteriza-se pela inflamação gengival com sangramento à sondagem na área da bolsa gengival, associada à diminuição da resistência dos tecidos periodontais à sondagem, o que leva à formação da bolsa periodontal, juntamente com a perda da inserção gengival e do osso alveolar (CAL). A progressão desta doença é contínua e com breves episódios de exacerbação localizada e regressão ocasional, apresentando, assim uma natureza cíclica (GENCO; BORGNAKKE, 2013).

A periodontite possui origem em uma condição inflamatória crônica dos tecidos de suporte dos dentes causada por microrganismos anaeróbicos gram-negativos específicos (ARMITAGE, 1999). A progressão da periodontite é dependente da interação entre o sistema imunológico do hospedeiro e a carga e a virulência bacteriana (LAINE et al., 2013). Condições sistêmicas, como diabetes e obesidade, podem exacerbar a progressão da doença, uma vez que promovem desequilíbrio nesta relação (GENCO; BORGNAKKE, 2013). Assim, lipopolissacarídeos e outros produtos bacterianos, após terem acesso aos tecidos gengivais, iniciam e perpetuam a resposta inflamatória do hospedeiro, resultando na elevada produção de citocinas pró-inflamatórias, as quais contribuem para destruição do ligamento periodontal e do osso alveolar, e futuramente para a possível perda do elemento dentário (PUSSINEN et al., 2004).

De acordo com a Academia Americana de Periodontia (AAP), a periodontite crônica pode ser clinicamente classificada de acordo com a severidade e a extensão dos sítios afetados. Para a extensão da doença, o a forma localizada envolveria até 30% dos sítios presentes, já a forma generalizada, mais de 30% dos sítios. A severidade pode ser diferenciada de acordo com a perda de inserção clínica em leve (1-2mm CAL), moderada (3-4mm CAL) ou severa (≥ 5mm CAL) (FLEMMIG, 1999). A classificação desta doença é um instrumento útil para a determinação do prognóstico e para o estabelecimento do plano de tratamento e de manutenção ao longo prazo.

Para estudos epidemiológicos, entretanto, há significante falta de padronização do diagnóstico da periodontite, o que pode representar uma barreira para a comparação entre os diferentes estudos (BORRELL; PAPAPANOU, 2005, LOCKHART et al., 2012). Alguns estudos têm usado uma combinação de sinais clínicos e sintomas, como sangramento à sondagem (BoP), profundidade de sondagem (PD) e perda de inserção clínica (CAL), associados ao sinal radiográfico

de perda óssea alveolar (LOCKER; LEAKE, 1993). Devido à dificuldade de obtenção de todos estes dados, alguns estudos têm utilizado a combinação dos indicadores da doença, CAL e PD, sob justificativa de que estas medidas representam tanto o efeito cumulativo da destruição tecidual (CAL), quanto à situação atual da doença (PD) (ARBES; AGUSTSDOTTIR; SLADE, 2001). Ainda mais complexa é a determinação dos valores limítrofes usados para a definição dos "casos", independente dos indicadores usados, assim como as definições das doenças incidentes ou progressivas (BORRELL; PAPAPANOU, 2005). A Associação Americana de Periodontia e o Centro para Controle e Prevenção de Doenças (*Center for Disease Control & Prevention – CDC*) têm sugerido que em estudos epidemiológicos a seguinte classificação da doença seja seguida: periodontite leve: ≥ 2 sítios interproximais com CAL ≥ 3mm, e ≥ 2 sítios interproximais com PD ≥ 4mm (não no mesmo dente), ou 1 sítio com PD ≥ 5 mm; periodontite moderada: ≥ 2 sítios interproximais com CAL ≥ 4mm (não no mesmo dente), ou ≥ 2 sítios interproximais com PD ≥ 5mm (não no mesmo dente); periodontite severa: ≥ 2 sítios interproximais com CAL ≥ 6mm (não no mesmo dente), e ≥ 1 sítio interproximal com PD ≥ 5mm (EKE et al., 2012). Nos estudos provenientes de uma coorte de nascidos vivos da Nova Zelândia, Shearer e colaboradores (2011) usaram a seguinte definição para os desfechos de doença periodontal: ≥ 1 sítio com CAL ≥ 4mm; ≥ 2 sítios com CAL ≥ 4mm; ≥ sítios com CAL ≥ 5mm.

Outra limitação que dificulta a comparação entre os diferentes estudos epidemiológicos, é a adoção de exames de "boca completa" ou "parcial". Estudos epidemiológicos populacionais de larga escala do tipo *survey* têm usado o protocolo de registro parcial, como o *National Health and Nutrition Examination Survey* (NHANES III) e o SB Brasil 2010, onde assume-se que estas medidas são representativas da situação bucal completa (ALBANDAR; BRUNELLE; KINGMAN, 1999). Além disso, este tipo de estudo tem como objetivo principal estimar a prevalência e a severidade da doença, o que permite o uso de protocolo parcial. Diferentes autores têm documentado que o uso do protocolo de exame bucal parcial geralmente tende a subestimar tanto a prevalência quanto a severidade da doença (KINGMAN; ALBANDAR, 2002; PERES et al., 2012), o que poderia representar um importante viés e uma maior dificuldade em inferir os reais risco e prognóstico (BORRELL; PAPAPANOU, 2005). Como os estudos epidemiológicos analíticos buscam estabelecer possíveis fatores mediadores das condições periodontais

tendem a usar o exame de boca completa, como o Estudo de Saúde Bucal de 2006 em uma coorte de nascidos vivos na cidade de Pelotas (DICKIE DE CASTILHOS et al., 2012) e o Estudo Multidisciplinar de Saúde e de Desenvolvimento de Dunedin – Nova Zelândia (SHEARER et al., 2011). Assim, fica evidente a necessidade de uniformização de critérios para determinação da prevalência e da incidência da periodontite.

A determinação da prevalência desta patologia em diferentes populações tem sido impactada pela variação nos critérios clínicos de avaliação. Nos Estados Unidos, no NHANES 2009-2010, cerca de 47% da amostra, representando 65 milhões de adultos, tinha periodontite, distribuída em 8,7%, 30,0% e 8,5% com severidade leve, moderada e severa respectivamente, gerando preocupação entre os órgãos de saúde, como o Centro para Controle e Prevenção de Doenças (*Center for Disease Control and Prevention – CDC)* (EKE et al., 2012). Em uma coorte de nascimentos na Nova Zelândia, foi observado aumento na prevalência e na severidade da doença periodontal dos 26 aos 32 anos (THOMSON et al., 2006), com elevação no número de sítios com perda de inserção, passando de 30,2% aos 26 anos para 42,4% aos 32, assim como progressão desta perda em dentes anteriormente acometidos. Em relação à classificação da severidade da doença, observou-se 29,3% da amostra apresentava periodontite, sendo 28,8% na sua forma leve e 0,5% nas formas moderada e severa combinadas aos 26 anos, e 45% da amostra com periodontite, sendo 41,3% na forma leve e 3,7% aos 32 anos. Os autores concluíram que há significante diferença no padrão da doença periodontal observado, com o avanço da idade da terceira para a quarta década de vida.

No Brasil, a proporção de adultos entre 35 e 44 anos que apresentam perda de inserção clínica maior que 4mm é de aproximadamente 18,2%, refletindo a alta prevalência desta patologia entre a população brasileira (BRASIL, 2011). No estudo de Porto Alegre, realizado por SUSIN e colaboradores (SUSIN et al., 2011), a prevalência de CAL ≥3mm e de CAL ≥5mm foi de 50,4% e de 17,4% respectivamente, entre os 621 indivíduos examinados com idade entre 14-29 anos. Na coorte de 1982 de Pelotas, aos 24 anos, os participantes apresentaram prevalência de gengivite, definido como sangramento gengival, cálculo dentário e bolsa periodontal de 37,5%, 87,4% e 3,3% respectivamente (DICKIE DE CASTILHOS, et al., 2012). Assim, estima-se que de maneira análoga ao ocorrido em Dunedin, em novo acompanhamento na coorte de nascidos em 1982 haja um

incremento da carga da doença, uma vez que os indivíduos apresentam idade mais avançada. Destaca-se ainda, a mudança significativa na estimativa da doença, uma vez que há a adoção de exame de boca completa com mensuração de valores contínuos da CAL, dando real dimensão da doença.

2.5 Hipotética Causalidade entre Obesidade e Doença Periodontal

A literatura tem evidenciado a associação positiva entre as doenças periodontais e a obesidade (DICKIE DE CASTILHOS et al., 2012; REEVES et al., 2006). Como a obesidade provoca alterações no metabolismo tecidual e celular que geram alterações a nível sistêmico, isto pode levar à modificação da doença periodontal. Além disso, fatores psicossociais, assim como comportamentais também parecem explicar esta relação.

Do ponto de vista biológico, alguns autores atribuem esta associação à exacerbação de citocinas pró-inflamatórias sistêmicas nos tecidos periodontais (CHAFFEE; WESTON, 2010). Sabe-se que o tecido adiposo branco é responsável pela secreção de adipocinas, substâncias responsáveis pelo estado de inflamação crônico, assim como pela alteração na resposta imunológica (KOPELMAN, 2000). Dentre as citocinas presentes no processo inflamatório, destacam-se o TNF-α e a IL-6, produzidos por células adiposas e por macrófagos lá localizados, e que desempenha um importante papel na progressão da periodontite (PRESHAW; TAYLOR, 2011). A PCR também parece estar envolvida neste processo, uma vez que seus níveis encontram-se aumentados em pacientes obesos (BULLO, et al., 2003) e em pacientes com doença periodontal (WU et al., 2000). Outras adipocinas, como a leptina e a resistina, também parecem estar envolvidas nesta interação, uma vez que estas proteínas estão associadas à secreção de citocinas pró-inflamatórias, à ativação e à manutenção do processo inflamatório (ZIMMERMANN et al., 2013). Estudos têm apontado que indivíduos obesos com a presença de doença periodontal apresentam elevados níveis dos marcadores acima, ocorrendo uma diminuição destes valores tanto com o tratamento periodontal, quanto com a perda de massa adiposa, assim, nota-se o processo de retroalimentação destas condições (ZUZA et al., 2011).

Ainda, mesmo diante de um quadro pró-inflamatório, indivíduos obesos apresentam prejuízo da resposta imune inata, inclusive da resposta inflamatória,

frente ao processo infeccioso (SCHMIDT, et al., 2011). O reconhecimento dos patógenos e a consequente produção de mediadores inflamatórios por células do sistema imune inato são fatores indispensáveis para a efetiva eliminação do agente patogênico (KARLSSON; BECK, 2010). Assim, disfunções na resposta inata podem aumentar a o risco e a gravidade das infecções. Estudos em seres humanos têm corroborado estes achados, uma vez que indivíduos obesos têm apresentado maior risco à morte por H1N1, além de apresentar maior risco a infecções secundárias em casos de hospitalização (MORGAN et al., 2010).

Esta deficiência na resposta imune frente aos desafios infecciosos parece estar ligada ao início e à progressão da doença periodontal em obesos, uma vez que doença periodontal pode resultar em exposições sistemáticas a bactérias, a endotoxinas lipopolissacarídeas, e a outros produtos bacterianos que influenciam não só a homeostase, mas também o metabolismo lipídico. Isto porque a área de superfície total das bolsas em pacientes com periodontite é estimada entre 08 e 20cm^2, podendo o sulco gengival comportar cerca de 200mg de biofilme, totalizando em uma grande quantidade de micro-organismos capazes de constantemente invadir os tecidos periodontais subjacentes (SOCRANSKY, 1970). A perda de integridade do epitélio na bolsa periodontal gera regiões de ulceração no interior da bolsa, oportunizando uma estreita proximidade do biofilme bacteriano com a circulação sanguínea (HUJOEL et al., 2001). Ademais, essa constante ruptura do epitélio da bolsa oportuniza a translocação bacteriana gerando, consequentemente, a bacteremia transitória (DURACK, 1995). Procedimentos como escovação dentária e raspagem periodontal foram suficientes para permitir que bactérias bucais fossem encontradas na corrente sanguínea, e quanto maior a severidade da doença, maior a exposição e a contagem dos periodontopatógenos circulantes (SILVER; MARTIN; MCBRIDE, 1977). Em uma revisão sistemática, foi observada forte relação entre bacteremia local e escovação dental diária, não estando esta associação presente para o uso do fio dental, independente da condição gengival (TOMAS et al., 2012). Tendo em vista a natureza cíclica da doença periodontal, com episódios de exacerbação e remissão e a constante invasão bacteriana nas bolsas periodontais, há uma variação nos níveis dos mediadores inflamatórios, com valores aumentados nas fases agudas da doença (WU et al., 2000).

Além de fatores biológicos, fatores sociodemográficos parecem estar envolvidos nesta interação, e a relação entre posição socioeconômica e as

condições de saúde já está bem elucidada na literatura científica. A saúde bucal tem sido apontada como um forte marcador socioeconômico e comportamental podendo ser considerada para o estudo das iniquidades sociais em saúde (OLIVEIRA et al., 2013). Thomson e colaboradores (THOMSON; SHEIHAM; SPENCER, 2012) afirmaram que a prevalência e a severidade das doenças periodontais está intimamente ligada à renda familiar e ao nível educacional materno. A obesidade, por sua vez, está também associada ao padrão sociodemográfico, onde observa-se maior prevalência desta condição nos indivíduos do padrão socioeconômico mais baixo (GIBBS; FORSTE, 2013). Assim, é possível atribuir parte da variação socioeconômica observada na periodontite aos indivíduos menos favorecidos financeiramente (THOMSON; SHEIHAM; SPENCER, 2012). Além disso, ambas doenças compartilham fatores de risco comuns, como tabagismo, consumo de álcool, hábitos nutricionais e estresse psicológico (GENCO; BORGNAKKE, 2013). Reeves e colaboradores (REEVES et al., 2006) encontraram associação positiva entre a obesidade, o estresse psicológico e as doenças periodontais. O estresse psicológico relacionado ao excesso de peso pode afetar hábitos de higiene, como escovação dentária, uso de fio dental e procura por serviços de saúde (MELLIN et al., 2002).

O impacto do emagrecimento sobre as condições periodontais ainda tem sido pouco estudado. Por dificuldades metodológicas, o acompanhamento da perda de peso tem sido feita de forma pontual, em períodos após cirurgia bariátrica, onde há acentuada perda de peso em um curto espaço de tempo. Os autores têm demonstrado haver melhora significativa das condições periodontais após a perda de peso, reforçando a associação entre ambas condições (PATARO et al., 2012; LAKKIS et al., 2012). Os autores ainda sugerem que o emagrecimento não traz somente mudanças biológicas, mas também comportamentais e psicológicas, como adoção de hábitos dietéticos saudáveis, hábitos de higiene geral e bucal regulares, refletindo em maior autocuidado destes indivíduos.

Há apenas um estudo na literatura que avaliou o impacto de diferentes episódios de obesidade e sua associação com sangramento gengival, bolsa periodontal, e cálculo dentário (DICKE DE CASTILHOS et al., 2012). Os autores trabalharam com medidas de IMC e de CA em três diferentes períodos da vida de indivíduos da coorte de Pelotas de 1982: aos 15, aos 18 e aos 23 anos. Após ajuste para possíveis fatores de mediação e de confusão, apresentar dois episódios de

obesidade demonstrou associação com a presença de cálculo dental, um fator de risco ao desenvolvimento de periodontite ao longo da vida (SUSIN et al., 2011). Este estudo, porém, apresenta importantes limitações em relação ao exame periodontal, uma vez que foi usada uma modificação do índice CPI para a mensuração da doença. Este índice, inicialmente criado para verificar a necessidade de tratamento periodontal a nível populacional, apresenta os valores de PS de forma categórica, não dando uma real dimensão da doença. Além disso, o único valor registrado consiste na PD, e não na CAL, o que leva à subestimação da doença, uma vez que não mede suas sequelas e sua real dimensão.

Desta forma, faz-se necessária a avaliação da trajetória de obesidade, por meio de diferentes episódios ao longo da vida, com dados clínicos de CAL, BoP e cálculo dentário, além de sua possível relação com a incidência da doença em adultos jovens, uma vez que não há estudos na literatura que abordem o assunto.

3 Hipóteses

Baseado no que foi previamente apresentado, e diante da falta de literatura que trabalhe com trajetórias de obesidade ao longo da vida, serão testadas algumas hipóteses acerca da possível associação entre obesidade e doença periodontal de acordo com as teorias do ciclo vital, de maneira semelhante ao realizado por PERES e colaboradores, quando estudaram a associação entre trajetória da posição socioeconômica e cárie dentária (PERES et al., 2011). Serão levados em consideração três teorias de exposições durante o ciclo vital: teoria do período crítico, teoria do período crítico com efeito modificador e teoria do acúmulo de risco. É importante destacar que a possível explicação entre a associação entre obesidade e doença periodontal se dá por mecanismos biológicos, comportamentais e sociais, destacando a complexidade desta relação.

De acordo com a teoria do período crítico, evento experimentados na primeira infância terão consequências ao longo da vida. Estudos têm sugerido que ser obeso na infância é um fator de risco à obesidade e à resistência à insulina na vida adulta, demonstrando a relevância deste evento quando ocorrido de forma precoce (ADAIR et al., 2013). Desta forma, pressupõe-se que crianças obesas terão aumento da inflamação crônica sistêmica, e consequentemente, da susceptibilidade à infecção local, levando ao precoce sangramento gengival, fator de risco à periodontite na idade adulta. Assim, de acordo com esta teoria, espera-se que crianças que se encontravam obesas na infância, independente da perda de peso, tenham maior carga de doença periodontal na vida adulta.

Se considerarmos o modelo do período crítico com efeito modificador, espera-se que indivíduos que apresentavam-se obesos na infância e que mantiveram esta condição na adolescência e na fase adulta apresentem maior severidade de doença periodontal, tendo em vista os aspectos biológicos e comportamentais de ambas condições. Entretanto, se houver perda de peso durante a vida, estes indivíduos apresentarão carga de doença periodontal de forma similar àqueles indivíduos que nunca apresentaram episódios de obesidade, uma vez que hábitos saudáveis tendem a ser adquiridos, assim como baixa dos níveis inflamatórios sistêmicos. Espera-se, assim, que a “mobilidade” entre as diferentes composições corporais possa ter influência na doença periodontal.

Se pensarmos nesta possível associação considerando o modelo de acúmulo de risco, pressupõe-se que indivíduos que experimentaram maior número de episódios de obesidade serão aqueles que apresentarão maior severidade de sangramento gengival e de perda de inserção clínica. Isto porque houve um período prolongado de exposição aos fatores de risco às DP em indivíduos obesos, levando ao desenvolvimento e à manutenção de situação periodontal desfavorável. Ainda considerando este modelo, indivíduos que emagreceram na adolescência terão menor severidade de DP que aqueles que emagreceram apenas na fase adulta, pois os últimos ficaram expostos tanto à inflamação crônica quando a hábitos não saudáveis por um período maior que os primeiros. Embora DICKIE DE CASTILHOS e colaboradores (2012) não tenham encontrado associação entre episódios de obesidade e doença periodontal, espera-se que, com a mudança da forma de diagnóstico da DP além do envelhecimento dos membros da coorte, esta associação possa ser melhor avaliada.

4 Objetivos

4.1 Objetivo Geral

Estudar, aos 31 anos, a relação entre trajetória de obesidade e doença periodontal na coorte de nascidos vivos de Pelotas de 1982.

4.2 Objetivos Específicos

Estimar a prevalência e da doença periodontal em adultos jovens;

Estimar a prevalência de obesidade e sobrepeso em adultos jovens;

Estimar a incidência de obesidade e sobrepeso entre os 24 e os 31 anos;

Investigar a associação entre perda de inserção clínica e sobrepeso, obesidade central e abdominal;

Investigar a associação entre sangramento gengival e sobrepeso, obesidade central e abdominal;

Testar as teorias do ciclo vital na associação entre obesidade e sangramento gengival aos 31 anos;

Testar as teorias do ciclo vital na associação entre obesidade e perda de inserção clínica aos 31 anos;

Conhecer o efeito dos mediadores inflamatórios ligados à associação das doenças periodontais com excesso de peso corporal.

5 Métodos

5.1 Artigos propostos

Serão propostos inicialmente, como fruto da tese, três artigos científicos publicados em periódicos:

1. Relação entre marcadores inflamatórios da obesidade e das doenças periodontais: revisão sistemática da literatura;
2. Associação entre trajetória de obesidade e sangramento gengival na quarta década de vida: estudo em uma coorte de nascimentos;
3. Associação entre doença periodontal e trajetória de obesidade segundo teorias do ciclo vital em uma coorte de nascidos vivos.

5.2 Revisão Sistemática

Com o objetivo de identificar os estudos existentes sobre os mecanismos biológicos e marcadores inflamatórios relacionados às doenças periodontais e à obesidade e ao sobrepeso com fatores associados, será realizada uma revisão sistemática da literatura nas bases *PubMed Central*, Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS), *Scientific Eletronic Library Online* (SciELO), *Web of Knowledge (ISI)*. Os seguintes passos serão seguidos: realização de buscas utilizando diferentes estratégias; leitura dos títulos e resumos; identificação de artigos que preencham os critérios de inclusão e aquisição dos textos na íntegra. De acordo com a relevância e adequação ao estudo, os artigos serão utilizados nesta revisão de literatura.

Para o desfecho serão utilizados os termos *Periodontal Diseases, Gingivitis, Periodontitis,* presentes na relação de termos *Medical Subject Headings* (MeSH), associados com os termos *Obesity, Overweight, Body Fat Distribution, Abdominal Fat, Intra-Abdominal Fat, Obesity, Abdominal.* Como descritores das exposições serão usados os termos MeSH *interleukin-6, C-reactive protein, adiponectin, leptin, resistin, tumoral necrosis factor-alpha* (tab. 2)*.* Serão selecionados todos os artigos publicados em idioma inglês, espanhol ou português. Não serão usados limites para a data de publicação.

Em busca preliminar, foram encontrados 205 artigos com a associação entre as doenças periodontais e o padrão corporal. Quando acrescentados os segundos descritores, a busca totalizou 34 artigos, que terão seus títulos e resumos avaliados. A tab. 3 apresenta os principais artigos selecionados e seus resultados.

Tabela 2 - Estratégia de busca no *Pubmed*

		Artigos Encontrados	Artigos avaliados
#1	(((((((("Periodontal Diseases"[Mesh]) OR "Gingivitis"[Mesh]) OR "Periodontitis"[Mesh]))))) AND (((((((("Obesity"[Mesh]) OR ("Obesity, Abdominal"[Mesh]) OR ("Overweight"[Mesh]) OR ("Body Fat Distribution"[Mesh]) OR ("Abdominal Fat"[Mesh]) OR ("Intra-Abdominal Fat"[Mesh]))))))))	205	-
#2	#1 + AND ((((((("Adiponectin"[Mesh]) OR "Resistin"[Mesh]) OR "Leptin"[Mesh]) OR "Interleukin-6"[Mesh]) OR "Tumor Necrosis Factor-alpha"[Mesh]) OR "C-Reactive Protein"[Mesh] OR "Cytokines"[Mesh])	34	-
#3	#1 + #2 AND ("Therapeutics"[Mesh]) OR (Therapy OR Treatment OR Intervention OR Surgical OR Non-surgical OR Healing)	18	18

Tabela 3 - Principais artigos selecionados para a revisão sistemática da literatura.

Autor e ano	País	Tipo do estudo/ Amostra	Indicadores de obesidade	Indicadores de doenças periodontais	Marcadores inflamatórios envolvidos	Resultados
Saito et al., 2008	Japão	Estudo transversal. 76 indivíduos entre 50-59 anos (76 mulheres.	IMC; CA; RCQ; Bioimpedância.	Exame de boca inteira. PD.	Adiponectina; Resistina.	Participantes com periodontite (1 dente com PD≥6 e 3 dentes com PD≥4): Maior IMC e maiores níveis de resistina.
Zuza et al., 2011	Brasil	Ensaio clínico. 27 indivíduos obesos (IMC≥30) entre 40-50 anos (seis homens e 21 mulheres); 25 não-obesos (IMC<25) entre 40-50 anos (8 homens e 17 mulheres).	IMC; CA; RCQ; Bioimpedância.	Exame de boca inteira com seis sítios por dente. IPV; GI; PoB; PD; CAL.	FGB; Hemoglobina glicada; IL-1β; IL-6; TNF-α; INF- γ.	IMC≥30: maiores níveis de IL-1β; IL-6; TNF-α. Após tratamento periodontal: IL-6; TNF-α.
Akman et al., 2012	Turquia	Estudo transversal. 200 indivíduos (95 homens e 105 mulheres) com idade entre 18-61 anos	Índice de massa corporal (IMC) Relação Cintura/quadril (RCQ)	Exame de boca inteira com quatro sítios por dente (mésio-vestibular; vestibular; disto-vestibular e lingual) Índice de Placa Visível (IPV); Profundidade de Sondagem (PD); Perda de inserção (CAL); Sangramento à sondagem (PoB).	Triglicérides plasmático (TRG); Colesterol total; Colesterol HDL; Glicemia (FGB); TNF-α; PCR; PAI-1.	IMC≥25: Maiores níveis de FGB, TRG, CRP, PAI-1, IPV e CAL. Maiores níveis de TRG e de PAI-1: Maiores IPV, PD e CAL.
Benguigui et al., 2012	França	Estudo transversal. 186 indivíduos	IMC, CA	Exame de boca inteira com quatro sítios por dente. Perda dentária;	HDL; LDL; PCR;	IMC≥25: Maiores níveis de HOMA-IR, LDL e PCR e maiores IPV e PD.

		entre 35-64 anos (102 homens e 84 mulheres).		IPV; PD; CAL; Sangramento marginal (GI).	HOMA-IR.	
Dickie de Castilhos et al., 2012	Brasil	Estudo transversal. 720 indivíduos com 24 anos (379 homens e 339 mulheres)	IMC; CA.	Exame de boca inteira com seis sítios por dente. CPI; PoB; Cálculo dentário.	PCR	IMC≥25: maiores níveis de PCR; maior risco para PoB e cálculo dentário.
Pradeep et al., 2012	Índia	Estudo transversal. 40 indivíduos entre 25-45 anos (20 homens e 20 mulheres).	IMC; CA.	GI; PD; CAL.	PCR; Progranulina (PGR)	IMC≥25 e WC≥90 homens e WC≥80 mulheres e periodontite crônica (GI; PD≥5; CAL≥3): níveis mais elevados do PCR e PGR.
Altay et al., 2013	Turquia	Ensaio clínico. Casos: 30 indivíduos obesos com dislipidemia; Controle: 100 pacientes não obesos. Pacientes ≥25 anos; com DP.	IMC; Circunferência abdominal (CA).	Presença de ≥5 dentes com ≥1 sítios com PD ≥5mm; CAL≥2mm e PoB.	TRG; Colesterol total; HDL; LDL; Lipoproteína-A; PCR; FGB; IL-6; TNF-α; leptina e insulina (HOMA-IR).	Após tratamento periodontal, IMC ≥25: menores níveis de HOMA-IR, IL-6, TNF-α. IMC<25: menores níveis de IL-6.

Autor e ano	País	Tipo do estudo/ Amostra	Indicadores de obesidade	Indicadores de doenças periodontais	Marcadores inflamatórios envolvidos	Resultados
Buchwald et al., 2013	Alemanha	Estudo longitudinal. 2806 indivíduos entre 20-80 anos (1346 homens e 1460 mulheres)	IMC	Protocolo parcial de boca dividida com quatro sítios por dente. CAL.	PCR	PCR e obesidade estiveram associados com incidência de CAL entre os indivíduos.
Fadel et al., 2013	Suécia	Estudo caso-controle. Casos: 28 adolescentes obesos (IMC≥30) entre 14 e 18 anos (14 homens e 14 mulheres) Controles: 27 adolescentes eutróficos (IMC=20) entre 14 e 16 anos (15 homens e 12 mulheres)	IMC; CA; RCQ.	Exame de boca inteira com quatro sítios por dente. GI; IPV; PD.	CRP; S-IgA	IMC≥30: Maiores níveis de S-IgA e gengivite. Sem relação com CRP.

Autor e ano	País	Tipo do estudo/ Amostra	Indicadores de obesidade	Indicadores de doenças periodontais	Marçadores inflamatórios envolvidos	Resultados
Pradeep et al., 2013	Índia	Estudo transversal. 40 indivíduos entre 25-45 anos (20 homens e 20 mulheres).	IMC; WC.	GI; PS; PI.	PCR; MCP-4.	IMC≥25 e WC≥90 homens e WC≥80 mulheres e periodontite crônica (GI; PD≥5; CAL≥3): níveis mais elevados do PCR e MCP-4.

5.3 Estudo de Saúde Bucal

O delineamento deste estudo é de uma coorte prospectiva de nascimentos. Em 1982, todos os nascimentos hospitalares que ocorreram na cidade de Pelotas, Rio Grande do Sul, foram identificados e os 5.914 nascidos vivos, cuja família residia na área urbana da cidade, foram pesados e as mães entrevistadas. Esta população foi acompanhada 11 vezes até 2013. Detalhes sobre a metodologia do projeto já foram previamente publicados (VICTORA; BARROS, 2006).

Em 1997, quando os participantes da coorte completaram 15 anos de idade, foram selecionados sistematicamente 70 setores censitários (27% do total) da área urbana de Pelotas e visitadas todas as casas nestes setores. Foram encontrados 1076 indivíduos pertencentes à coorte, dos quais obteve-se uma amostra probabilística aleatória de 900 adolescentes de 15 anos de idade para o estudo de saúde bucal de 1997 (ESB-97). O ESB-97 foi composto de aplicação de um questionário sobre hábitos de higiene bucal, utilização de serviços odontológicos, dor de origem dental e de exames odontológicos que avaliaram a presença de cárie dentária e os problemas de oclusão dos adolescentes.

Os 888 adolescentes participantes (98,7%) do ESB-97 foram contatados em 2006 para uma nova visita e exames odontológicos (ESB-06). Foi aplicado novamente um questionário contendo perguntas referentes ao uso de serviços odontológicos, episódios de dor de origem dental e aos hábitos comportamentais relacionados à higiene bucal. Além disso, no exame clínico foram coletadas informações sobre diversas condições de saúde bucal, como cárie dentária, lesões bucais e presença de cálculo dentário, de sangramento gengival e de bolsa periodontal, de acordo com os critérios do CPI. No final deste estudo um total de 720 indivíduos foi avaliado, representando uma taxa de resposta de 80% em relação ao ESB-97. Esta será a amostra convidada a participar deste novo estudo.

5.4 Equipe e Logística

Os exames referentes à saúde sistêmica foram devidamente conduzidos por pesquisadores do Programa de Pós-graduação em Epidemiologia da UFPel ao longo do ano de 2012.

Em relação à saúde bucal, a coleta de dados será realizada por meio de entrevistas individuais e exames odontológicos a serem realizados nos domicílios

dos adultos pertencentes à amostra da coorte. Os examinadores serão cirurgiões-dentistas com experiência prévia em estudos epidemiológicos. Os entrevistadores serão alunos de graduação da Faculdade de Odontologia (UFPel), também com experiência neste tipo de atividade. A equipe de trabalho de campo será composta por seis examinadores e seis entrevistadores, além dos supervisores do trabalho de campo e auxiliares para digitação e arquivamento de material.

A seleção e o treinamento da equipe serão realizados pelos coordenadores do estudo. Será elaborado um manual de instruções do estudo que servirá como guia para os entrevistadores no caso de dúvidas no preenchimento ou codificação do questionário. Também serão apresentadas orientações sobre a postura e forma de abordagem do entrevistador. Todos os examinadores e entrevistadores serão treinados e calibrados seguindo metodologia previamente descrita (PERES; TRAEBERT; MARCENES, 2001). A reprodutibilidade diagnóstica será aferida pela estatística Kappa (variáveis categóricas) e por meio do coeficiente de correlação intra-classe (variáveis contínuas e discretas) considerando satisfatório o valor de 0,60 para os critérios de profundidade de sondagem (PD) recessão gengival (GR) e perda de inserção clínica (CAL). Para calibração dos examinadores, 30 voluntários não pertencentes ao estudo serão clinicamente examinados.

Estima-se a realização de uma média de 50 a 60 entrevistas e exames completos por semana, o que totaliza aproximadamente quatro meses de trabalho de campo, incluindo o treinamento, pré-teste e estudo piloto. Estão previstas reuniões semanais de avaliação entre a equipe de campo e os supervisores e coordenadores do estudo.

Os exames serão realizados nos domicílios dos participantes, com uso de luz artificial (fotóforos acoplados à cabeça), material de exame (espelho plano, sondas periodontais, espátulas de madeira, gaze) devidamente esterilizados na Faculdade de Odontologia da UFPel. Todos os examinadores estarão devidamente paramentados respeitando as normas de biossegurança preconizadas pela Organização Mundial da Saúde.

5.4.1 Pré-teste

Embora todas as questões do questionário já tenham sido usadas em outras pesquisas, será realizado pré-teste do questionário em 20 adultos da mesma faixa

etária da pesquisa em área de abrangência de uma Unidade de Saúde do Município. O pré-teste visa a adequar o questionário para o trabalho de campo propriamente dito.

5.4.2 Controle de qualidade

Os supervisores do estudo realizarão a aplicação de uma versão resumida do questionário, por via telefônica, em 10% da amostra (70 pessoas) com o objetivo de medir a reprodutibilidade. Os dados serão duplamente digitados por digitadores distintos.

6 Variáveis em estudo

6.1 Condições de saúde bucal

As condições de saúde bucal serão coletadas nos domicílios dos participantes por meio de exames clínicos que serão realizados por cirurgiões-dentistas devidamente treinados e calibrados. As condições periodontais avaliadas serão sangramento gengival à sondagem (PoB), cálculo dental, profundidade de sondagem (PD), recessão gengival (GR) e perda de inserção clínica (CAL).

6.1.1 Sangramento gengival

O sangramento à sondagem será aferido pelo exame de seis sítios (mésio-vestibular, médio-vestibular, disto-vestibular, mésio-lingual/palatal, médio-lingual/palatal e disto-lingual/palatal) em todos os dentes presentes com exceção dos terceiros molares (SUSIN et al., 2011). Será usada uma sonda periodontal milimetrada modelo *NIDR* (*National Institute for Dental Research*) com marcação colorida em 2, 4, 6, 8 e 10mm, usada em diversos levantamentos epidemiológicos já descritos (SHEARER, et al., 2011, THOMSON, et al., 2006). Para avaliação do sangramento gengival, será considerado o número de sítios com sangramento gengival presente os indivíduos que apresentarem sangramento gengival até 10 segundos após a sondagem. A variável será apresentada de forma dicotômica: presença ou ausência de sangramento gengival por sítio. A proporção de sítios e de

dentes com sangramento gengival dentre o total de sítios e de dentes presentes também serão calculadas.

6.1.2 Cálculo dental

O cálculo dental supragengival será aferido pelo exame de seis sítios (mésio-vestibular, médio-vestibular, disto-vestibular, mésio-lingual/palatal, médio-lingual/palatal e disto-lingual/palatal) em todos os dentes presentes com exceção dos terceiros molares (SUSIN et al., 2011). Será usada uma sonda periodontal milimetrada modelo *NIDR* (*National Institute for Dental Research*) com marcação colorida em 2, 4, 6, 8 e 10mm, usada em diversos levantamentos epidemiológicos já descritos (SHEARER, et al., 2011, THOMSON, et al., 2006). Serão considerados com cálculo dental presente os indivíduos que apresentarem cálculo dental supragengival. A variável será apresentada de forma dicotômica: presença ou ausência de cálculo dental por sítio. A proporção de sítios e de dentes com cálculo dental dentre o total de sítios e de dentes presentes também serão calculadas.

6.1.3 Doença periodontal

Doença periodontal será definida a partir de diferentes combinações das medidas de profundidade de sondagem, recessão gengival e perda de inserção clínica (SAVAGE et al., 2009). Para a medida de profundidade de sondagem será a distância entre a margem gengival e a porção mais apical sondável da bolsa periodontal registrada em milímetros de forma contínua. Como recessão gengival, será considerada a distância entre a junção amelocementária e o nível gengival, registrada em milímetros de forma contínua. A perda de inserção clínica será definida como a soma entre a profundidade de sondagem e a recessão gengival, apresentada também de forma contínua. A recessão gengival será registrada como valor negativo nos casos em que a margem gengival estiver recobrindo a junção cemento-esmalte em mais de 01mm, como nos casos de hiperplasia gengival.

Serão examinados seis sítios por dente (disto-lingual, lingual, mésio-lingual, mésio-vestibular, vestibular e disto-vestibular) de todos os dentes com exceção dos terceiros molares (SUSIN, et al., 2011).

Para a definição da presença da doença, serão considerados os critérios usados por Shearer e colaboradores (SHEARER, et al., 2011) usando três definições de casos: um ou mais sítios com 4+mm CAL; dois ou mais sítios com 4+mm CAL; e um ou mais sítios com 5+mm CAL; e os critérios definidos pelo CDC-AAP descritos anteriormente.

6.2 Condição de saúde geral

6.2.1 Padrão corporal

Para determinação do padrão corporal, serão utilizados dados de diferentes levantamentos de saúde geral já ocorridos. Para determinação do IMC dos participantes aos 4 e aos 15 anos, serão obtidos os valores do escore Z peso/idade, altura/idade e peso altura das visitas ocorrida em 1986 e em 1997, onde será definido o padrão corporal relativo à idade, com o uso do software *Anthro* disponibilizado pela Organização Mundial da Saúde (versão 3.2.2, Janeiro de 2011). Para análise da trajetória do padrão corporal do participante, será calculado o índice de massa corporal aos 26 e aos 30 anos. Para o uso da CA, serão usados os dados obtidos aos 15, aos 18, aos 23 e aos 31 anos, de acordo com os critérios definidos (LEAN; HAN; MORRISON, 1995). Serão usadas medidas da circunferência da cintura, além do índice de massa corporal. Os três desfechos serão analisados como variáveis contínuas e categóricas, usando critérios determinados para a classificação do padrão corporal. Cada uma destas variáveis será analisada separadamente conforme o sexo.

Assim, estabelecer-se-ão quatro diferentes trajetórias dos 4 aos 30 anos de idade para IMC e dos 15 aos 30 anos para CA: excesso de peso-eutróficos (excesso de massa corporal aos 4 anos (IMC)/15 anos (CA) e eutrofia aos 30); eutróficos-excesso de peso (eutrofia aos 4 anos (IMC)/15 anos (CA) e excesso de massa corporal aos 30 anos); sempre eutróficos; sempre com excesso de peso (WHO, 2007).

Durante o ano de 2012, no estudo de saúde geral ocorrido no Centro de Pesquisas Epidemiológicas, todos os participantes tiveram sua altura e massa corpórea medidos como primeira etapa dos exames realizados. Estes valores foram anotados em seu crachá. O índice de massa corporal será determinado pela

fórmula: massa corpórea (Kg)/quadrado da altura (m) e será expresso em Kg/m^2. Esta variável será categorizada de acordo com os parâmetros da Organização Mundial da Saúde (WHO, 2000).

Para a aferição da circunferência da cintura e do quadril, cada indivíduo ficou em posição ereta com os pés levemente separados e os braços soltos ao lado do corpo. A cintura foi medida na parte mais estreita do tronco, diretamente sobre a pele. Para indivíduos sem cintura visível, foi medida a circunferência no ponto médio entre a crista ilíaca e a última costela. O quadril foi medido na extensão máxima das nádegas (nos planos anteroposterior e lateral) com o indivíduo usando apenas um avental sobre a roupa íntima. O avental era de um material fino e leve, tendo como objetivo evitar o uso de roupas volumosas durante o exame e proteger a intimidade do entrevistado. As medidas foram efetuadas mantendo a fita com firmeza no plano horizontal evitando a compressão do tecido subcutâneo. Os entrevistadores foram treinados e padronizados na medição da cintura e do quadril até que ficassem dentro dos limites máximos de erro permitido. Estes limites foram estabelecidos conforme o erro técnico de medida (ETM) de um instrutor experiente em avaliações deste tipo (padrão ouro). Maiores informações sobre a metodologia de padronização das medidas estão descritas na tese de González-Chica (GONZÁLEZ CHICA, 2009).

6.3 Demais variáveis independentes

As variáveis independentes que serão utilizadas no estudo foram obtidas dos diferentes acompanhamentos da coorte (tab. 4).

Renda familiar ao nascimento (1982): coletada em salários mínimos, segundo grupos (<1; 1,1 a 3,0; 3,1 a 6,0; 6,1 a 10 e >10).

Nível de escolaridade do participante (2012): a variável será agrupada em quatro categorias (>12; de 9 a 11; de 5 a 8; ≤ 4 anos).

Fumo atual (≥ 1 cigarro por dia) (2004): será incluído nas análises como variável dicotômica (sim/não).

Consumo de álcool (2004): este item será avaliado como variável categórica (não bebe; bebe 1 unidade/dia; bebe >1 unidade/dia).

Consumo de fibras (2004): será avaliado como variável dicotômica (baixo consumo de fibras sim/não).

Consumo de gorduras (2004): será avaliado como variável categórica (consumo muito baixo, baixo, dieta americana, alto e muito alto).

Uso do fio dental (2006): obtida de forma dicotômica (uso do fio dental sim/não).

Utilização de serviços odontológicos (2006): obtida por meio da pergunta “Tu consultaste com o dentista nos últimos 12 meses?” (sim ou não).

Serão usadas como variáveis de mediação:

Níveis sistêmicos de Proteína C-Reativa (2004): A variável será apresentada como variável categórica de acordo com os seguintes critérios: nível baixo: 1,0 mg/L; nível moderado: 1,01 a 3,0 mg/L; nível elevado: 3,01 a 10,0 mg/L. Valores de PCR acima de 10mg/L serão excluídos, uma vez que estes valores indicam inflamação aguda (PEARSON et al., 2003).

Presença de cálculo dentário (2004): Será considerada presença ou ausência de cálculo dentário por pessoa.

Tabela 4 - Apresentação das variáveis independentes.

Levantamentos de Saúde Geral	**Variáveis**	**Mensuração**
1982		
	Renda Familiar	<1; 1,1 a 3,0 3,1 a 6,0 6,1 a 10 >10 salários mínimos
1986		
	Estado nutricional	IMC ≤ 1SD IMC >1 e <2 SD IMC ≥2 SD
1997		
	Estado nutricional	IMC ≤ 1SD IMC >1 e <2 SD IMC ≥2 SD CA
2004		
	Tabagismo	Sim/Não
	Consumo de gordura	Muito baixo Baixo Dieta americana Alto Muito alto
	Consumo de fibras	Baixo consumo Alto consumo
	Consumo de álcool	Não bebe Bebe 1 unidade/dia Bebe >1 unidade/dia
	Proteína C-Reativa	Nível baixo Nível intermediário Nível elevado
	Estado nutricional	IMC <18,5 IMC >19 e <24,9 IMC >25 e <29.9 IMC >30 e <39.9 IMC >40 CA
2012		
	Estado nutricional	IMC <18,5 IMC >19 e <24,9 IMC >25 e <29.9 IMC >30 e <39.9 IMC >40 CA
	Escolaridade do indivíduo	>12 9 a 11 5 a 8 ≤ 4 anos
Estudos de Saúde Bucal		
2006		
	Utilização do serviço odontológico	Sim/Não
	Uso de fio dental	Sim/Não
	Cálculo Dentário	Ausência/Presença
	Sangramento gengival	Ausência/Presença
	Bolsa Periodontal	Ausência de bolsa Bolsa Rasa Bolsa Moderada Bolsa Profunda

6.4 Modelo Conceitual

As variáveis sociodemográficas – sexo, renda ao nascer e escolaridade atual – serão ordenadas na porção mais distal para ajuste do modelo. A posição socioeconômica apresenta uma conhecida relação com os desfechos de saúde bucal e de saúde geral. Os padrões sociais dos desfechos bucais são similares àqueles observados nos desfechos de saúde bucal. THOMSON (2012) indicou que variáveis socioeconômicas, como baixa renda familiar e baixa escolaridade, estão intimamente ligadas à severidade e à extensão das doenças periodontais. De forma similar, estudos têm demonstrado que crianças menos favorecidas apresentam maior risco à obesidade e ao sobrepeso na vida (SHIBLI et al., 2008). Existem evidências de que as condições socioeconômicas na infância teriam repercussão sobre o estado de saúde e de nutrição na vida adulta, afetando inclusive os padrões de mortalidade (GALOBARDES et al., 2004).

As variáveis intermediárias serão compostas por hábitos comportamentais, como padrão alimentar, tabagismo, consumo de álcool, uso de fio dental e uso de serviços. Variáveis relacionadas à dieta estão intimamente ligadas à obesidade e à doença periodontal. ALVES e colaboradores (2012) e SAXLIN e colaboradores (2008) relataram que a dieta está ligadas às doenças bucais como cárie dentária e doença periodontal, fato que justifica a inclusão destas variáveis. Além disso, hábitos dietéticos, influenciam de forma significativa a resposta inflamatória, exacerbando a reação biológica envolvida na associação entre obesidade e doença periodontal (MARTINEZ-PABON et al., 2013). O tabagismo está ligado de forma relevante tanto à obesidade quanto à DP, como bem elucidado pela literatura e tem sido amplamente usado como fator de confusão em estudos que investigam esta associação (DICKIE DE CASTILHOS et al., 2012). O consumo de álcool também parece estar envolvido tanto com a obesidade quanto com a progressão da doença periodontal, medida por meio da perda de inserção clínica (GENCO; BORGNAKKE, 2013). Embora o uso do fio dental e a utilização dos serviços odontológicos não estejam ligados à obesidade, estas variáveis podem ser usadas como fortes indicadores de hábitos de higiene bucal, razão de sua inclusão para ajuste do modelo.

Os níveis de PCR assim como a presença de cálculo dentário estão intimamente ligados aos desfechos periodontais e à obesidade, razão de sua

inclusão como variáveis proximais no modelo. DICKIE DE CASTILHOS e colaboradores (2012) encontraram associação entre elevados níveis de PCR e sangramento gengival nos indivíduos desta coorte aos 24 anos. Este aumento da inflamação sistêmica pode ser considerada como um fator de risco não apenas ao excesso de peso, como também às doenças periodontais, uma vez que a inflamação crônica é responsável por modificar o sistema imune nato, deixando o indivíduos mais susceptível a doenças infecciosas, como as doenças periodontais (FRANCHINI et al., 2011). A presença de cálculo apresenta forte associação com as periodontopatias sendo relacionado com episódios de obesidade na coorte de 1982 de Pelotas aos 24 anos (DICKIE DE CASTILHOS et al., 2012). Embora a presença de cálculo não possa ser utilizada como um indicador de doença, ela pode ser considerada como um fator de risco ao sangramento gengival e à perda de inserção clínica, uma vez que atua como importante fator retentivo do biofilme bacteriano (SUSIN et al., 2011).

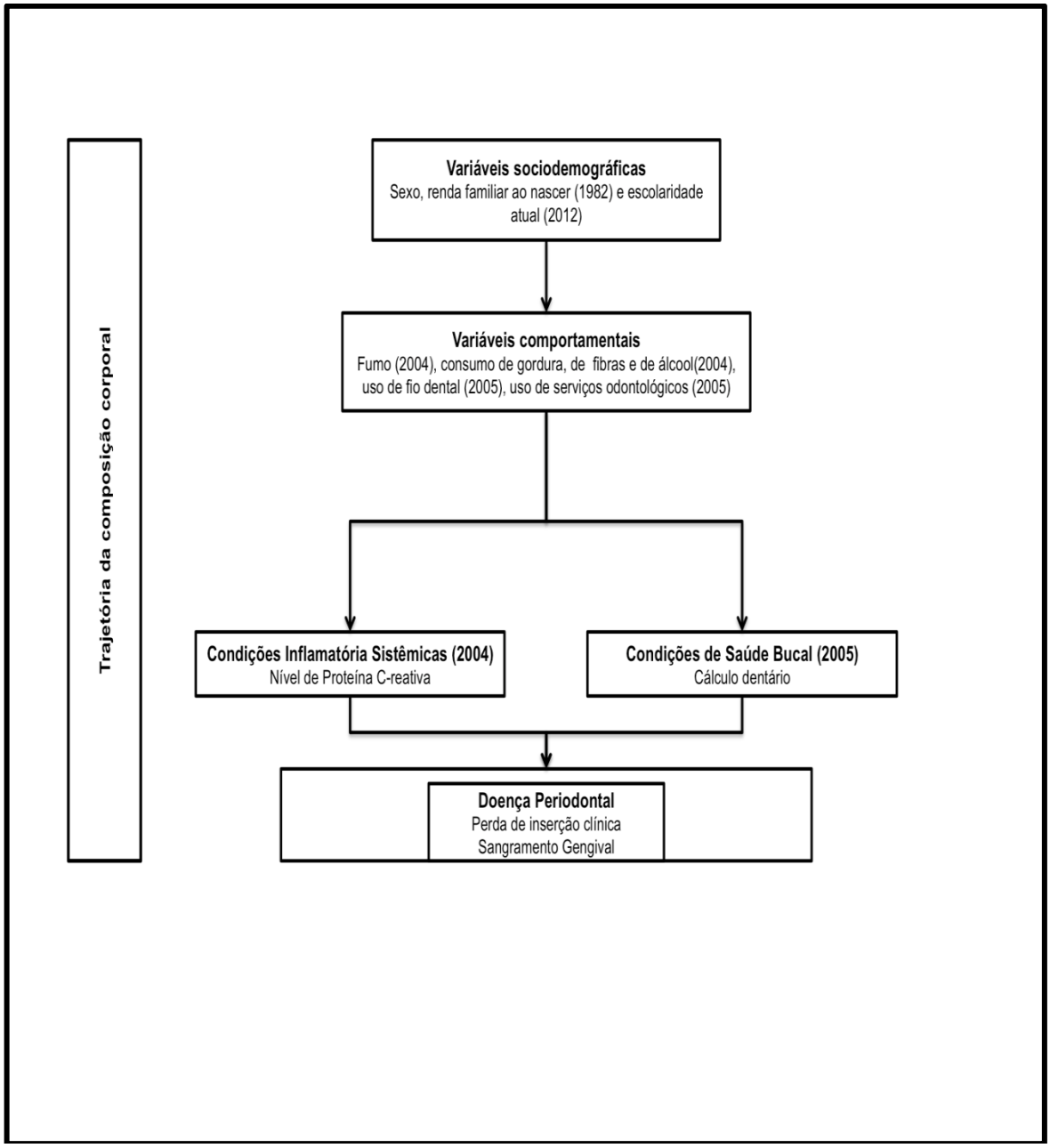


Figura 6 - Modelo conceitual de organização para entrada das variáveis no modelo.

6.5 Análise dos dados

Os dados serão duplamente digitados no software EpiData 3.1 recorrendo-se à entrada dupla e, posteriormente, à comparação dos arquivos de dados gerados, a fim de detectar e corrigir erros. Posteriormente, o software STATA versão 12.0 será utilizado para análise dos dados. Será realizada uma análise descritiva para determinar a frequência relativa e absoluta das variáveis relativas aos diferentes desfechos estudados. As associações entre variáveis serão avaliadas através de análise bivariada (teste Qui-quadrado para variáveis categóricas nominais e Qui-quadrado de tendência linear para variáveis ordinais). Na análise multivariada, será utilizada regressão de Poisson com variância robusta, estimando-se as razões de prevalência e seus intervalos de confiança de 95%.

Para a análise multivariável serão realizadas análises de mediação com técnicas estatísticas apropriadas, sendo adotado modelo teórico hierárquico (Fig. 6), onde as variáveis independentes serão ordenadas em blocos que determinarão a entrada das mesmas na análise estatística. Somente as variáveis que, na análise bivariada, apresentarem valor P<0,25 serão incluídas nos modelos.

6.6 Questões éticas

Este projeto foi submetido ao Comitê de Ética em Pesquisa da Faculdade de Medicina da UFPel e aprovado sob parecer 384.332. Todas as entrevistas e exames serão realizados após assinatura de termo de consentimento livre e esclarecido. De forma similar ao acompanhamento de saúde bucal de 2006, um projeto de Extensão será criado junto ao Programa de Pós-graduação em Odontologia, para que seja realizado o atendimento clínico das necessidades de tratamento diagnosticadas.

7 Referências

ADAIR, L. S.; FALL, C. H. D.; OSMOND, C.; STEIN, A. D.; MARTORELL, R.; RAMIREZ-ZEA, M.; SACHDEV, H. S.; DAHLY, D. L.; BAS, I.; NORRIS, S. A.; MICKLESFIELD, L.; HALLAL, P.; VICTORA, C. G. Associations of linear growth and relative weight gain during early life with adult health and human capital in countries of low and middle income: findings from five birth cohort studies **Lancet**, v. 382, n. 9891, p. 525-534, 2013.

AKMAN, P. T.; FENTOGLU, O.; YILMAZ, I.; ARPAK, N. Serum Plasminogen Activator Inhibitor-1 and Tumor Necrosis Factor-a Levels in Obesity and Periodontal Disease **J Periodontol**, v. 83, n. 8, 1057-1062, 2012.

ALBANDAR, J. M.; BRUNELLE, J. A.; KINGMAN, A. Destructive periodontal disease in adults 30 years of age and older in the United States, 1988-1994 **J Periodontol**, v.70, n.1, p.13-29, 1999.

ALBERTI, K. G.; ECKEL, R. H.; GRUNDY, S. M.; ZIMMET, P. Z.; CLEEMAN, J. I.; DONATO, K. A.; FRUCHART, J. C.; JAMES, W. P.; LORIA, C. M.; SMITH, S. C., JR.; INTERNATIONAL DIABETES FEDERATION TASK FORCE ON, E.; PREVENTION; HATIONAL HEART, L.; BLOOD, I.; AMERICAN HEART, A.; WORLD HEART, F.; INTERNATIONAL ATHEROSCLEROSIS, S.; INTERNATIONAL ASSOCIATION FOR THE STUDY OF, O. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity **Circulation**, v.120, n.16, p.1640-1645, 2009.

ALTAY, U.; GÜRGAN, C. A.; AGBAHT, K. Changes in Inflammatory and Metabolic Parameters After Periodontal Treatment in Patients With and Without Obesity **J Periodontol**, v. 84, n. 1, p. 13-23, 2013.

ALVES, L. S.; SUSIN, C.; DAME-TEIXEIRA, N.; MALTZ, M. Overweight and obesity are not associated with dental caries among 12-year-old South Brazilian schoolchildren **Community Dent Oral Epidemiol**, v.41, n.3, p.224-231, 2013.

AL-ZAHRANI, M. S.; BISSADA, N. F.; BORAWSKI, E. A. Obesity and periodontal disease in young, middle-aged and older adults **J Periodontol**, v. 74, n. 5, p. 610-615, 2003.

AMUNA, P.; ZOTOR, F. B. Epidemiological and nutrition transition in developing countries: impact on human health and development **Proc Nutr Soc**, v.67, n.1, p.82-90, 2008.

ANDRUKHOV, O.; HARIRIAN, H.; BERTL, K.; RAUSCH, W. D.; BANTLEON, H. P.; MORITZ, A.; RAUSHC-FAN, X. Nitric oxide production, systemic inflammation and lipid metabolism in periodontitis patients: possible gender aspect **J Clin Periodontol**, v. 40, n. 10, p. 916-923, 2013.

ARBES, S. J., JR.; AGUSTSDOTTIR, H.; SLADE, G. D. Environmental tobacco smoke and periodontal disease in the United States **Am J Public Health**, v.91, n.2, p.253-257, 2001.

BARKER, D. J. P. **Foetal and infant origin of adult disease.** London: BMJ Publishing Group, 1992.

BENER, A.; YOUSAFZAI, M. T.; DARWISH, S.; AL-HAMAQ, A. O.; NASRALLA, E. A.; ABDUL-GHANI, M. Obesity index that better predict metabolic syndrome: body mass index, waist circumference, waist hip ratio or waist height ratio **J Obes**, v. Ahead of print, 2013.

BENGUIGUI, C.; BONGARD, V.; RUIDAVETS, J. B.; CHAMONTIN, B.; FERRIÈRES, J.; AMAR, J. Evaluation of oral health related to body mass index **Oral Dis**, v. 18, n. 8, 748-755, 2012.

BORRELL, L. N.; PAPAPANOU, P. N. Analytical epidemiology of periodontitis **J Clin Periodontol**, v.32 Suppl 6, p.132-158, 2005.

BRASIL. **SB Brasil 2010. Pesquisa Nacional de Saúde Bucal - Resultados Principais**. 2011. 92f. Ministério da Saúde, Brasília.

BRASIL. **Dados da Pesquisa de Vigilância de Fatores de Risco e de Proteção para Doenças Crônicas por Inquérito Telefônico (VIGITEL)**. 2013. Ministério da Saúde, Brasília.

BUCHWALD, S.; KOCHER, T.; BIFFAR, R.; HARB, A.; HOLTFRETER, B.; MEISEL, P. Tooth loss and periodontitis by socio-economic status and inflammation in a longitudinal population-based study **J Clin Periodontol**, v. 40, n. 3, p. 203-211, 2013.

BUETTNER, R.; SCHOLMERICH, J.; BOLLHEIMER, L. C. High-fat diets: modeling the metabolic disorders of human obesity in rodents **Obesity (Silver Spring)**, v.15, n.4, p.798-808, 2007.

BULLO, M.; GARCIA-LORDA, P.; MEGIAS, I.; SALAS-SALVADO, J. Systemic inflammation, adipose tissue tumor necrosis factor, and leptin expression **Obes Res**, v.11, n.4, p.525-531, 2003.

CANCELLO, R.; CLEMENT, K. Is obesity an inflammatory illness? Role of low-grade inflammation and macrophage infiltration in human white adipose tissue **BJOG**, v.113, n.10, p.1141-1147, 2006.

CHAFFEE, B. W.; WESTON, S. J. Association between chronic periodontal disease and obesity: a systematic review and meta-analysis **J Periodontol**, v.81, n.12, p.1708-1724, 2010.

DANESH, J.; WHEELER, J. G.; HIRSCHFIELD, G. M.; EDA, S.; EIRIKSDOTTIR, G.; RUMLEY, A.; LOWE, G. D.; PEPYS, M. B.; GUDNASON, V. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease **N Engl J Med**, v.350, n.14, p.1387-1397, 2004.

DASU, M. R.; DEVARAJ, S.; DU CLOS, T. W.; JIALAL, I. The biological effects of CRP are not attributable to endotoxin contamination: evidence from TLR4 knockdown human aortic endothelial cells **J Lipid Res**, v.48, n.3, p.509-512, 2007.

DICKIE DE CASTILHOS, E.; HORTA, B. L.; GIGANTE, D. P.; DEMARCO, F. F.; PERES, K. G.; PERES, M. A. Association between obesity and periodontal disease in young adults: a population-based birth cohort **J Clin Periodontol**, v.39, n.8, p.717-724, 2012.

EGGER, G.; DIXON, J. Inflammatory effects of nutritional stimuli: further support for the need for a big picture approach to tackling obesity and chronic disease **Obes Rev**, v.11, n.2, p.137-149, 2010.

EKE, P. I.; DYE, B. A.; WEI, L.; THORNTON-EVANS, G. O.; GENCO, R. J.; CDC PERIODONTAL DISEASE SURVEILLANCE WORKGROUP: JAMES BECK, G. D. R. P. Prevalence of periodontitis in adults in the United States: 2009 and 2010 **J Dent Res**, v.91, n.10, p.914-920, 2012.

EKE, P. I.; PAGE, R. C.; WEI, L.; THORNTON-EVANS, G.; GENCO, R. J. Update of the case definitions for population-based surveillance of periodontitis **J Periodontol**, v.83, n.12, p.1449-1454, 2012.

FADEL, H. T.; PLIAKI, A.; GRONOWITZ, E.; MÅRILD, S.; RAMBERG, P.; DAHLÈN, G.; YUCEL-LINDBERG, T.; HEIJL, L.; BIRKHED, D. Clinical and biological indicators of dental caries and periodontal disease in adolescents with or without obesity **Clin Oral Invest**, Ahead of print, 2013.

FLEMMIG, T. F. Periodontitis **Ann Periodontol**, v.4, n.1, p.32-38, 1999.

FRANCHINI, R.; PETRI, A.; MIGLIARIO, M.; RIMONDINI, L. Poor oral hygiene and gingivitis are associated with obesity and overweight status in paediatric subjects **J Clin Periodontol**, v. 38, n. 11, p. 1021-1028, 2011.

GALOBARDES, B.; LYNCH, J. W.; DAVEY SMITH, G. Childhood socioeconomic circumstances and cause-specific mortality in adulthood: systematic review and interpretation **Epidemiol Rev**, v. 26, p. 7-21, 2004.

GENCO, R. J.; BORGNAKKE, W. S. Risk factors for periodontal disease **Periodontol 2000**, v.62, n.1, p.59-94, 2013.

GIBBS, B. G.; FORSTE, R. Socioeconomic status, infant feeding practices and early childhood obesity **Pediatr Obes**, 2013.

GONZÁLEZ CHICA, D. A. **Efeito de condições sociodemográficas e do crescimento precoce sobre a obesidade abdominal em adultos jovens:**

resultados da coorte de Pelotas de 1982. 2009. (Doutorado) - Universidade Federal de Pelotas, Pelotas.

HSIEH, S. D.; YOSHINAGA, H. Waist/height ratio as a simple and useful predictor of coronary hearte disease risk factors in women. **Intern Med**, v. 34, n. 12, p. 1147-1152, 1995.

HOTAMISLIGIL, G. S. Inflammation and metabolic disorders **Nature**, v.444, n.7121, p.860-867, 2006.

HUJOEL, P. P.; CUNHA-CRUZ, J.; KRESSIN, N. R. Spurious associations in oral epidemiological research: the case of dental flossing and obesity **J Clin Periodontol**, v.33, n.8, p.520-523, 2006.

KARLSSON, E. A.; BECK, M. A. The burden of obesity on infectious disease **Exp Biol Med (Maywood)**, v.235, n.12, p.1412-1424, 2010.

KERSHAW, E. E.; FLIER, J. S. Adipose tissue as an endocrine organ **J Clin Endocrinol Metab**, v.89, n.6, p.2548-2556, 2004.

KINGMAN, A.; ALBANDAR, J. M. Methodological aspects of epidemiological studies of periodontal diseases **Periodontol 2000**, v.29, p.11-30, 2002.

KOPELMAN, P. G. Obesity as a medical problem **Nature**, v.404, n.6778, p.635-643, 2000.

KUH, D.; BEN-SHLMO, Y. **The life course approach to chronic epidemiology**. 2 ed. Oxford: Oxford University Press, 2004.

LAKKIS, D.; BISSADA, N. F.; SABER, A.; KHAITAN, L.; PALOMO, L.; NARENDRAN, S.; AL-ZAHRANI, M. S. Response to periodontal therapy in patients who had weight loss after bariatric surgery and obese counterparts: a pilot study **J Periodontol**, v. 83, n. 3, p. 684-689, 2012.

LAINE, M. L.; MOUSTAKIS, V.; KOUMAKIS, L.; POTAMIAS, G.; LOOS, B. G. Modeling susceptibility to periodontitis **J Dent Res**, v.92, n.1, p.45-50, 2013.

LEAN, M. E.; HAN, T. S.; MORRISON, C. E. Waist circumference as a measure for indicating need for weight management **BMJ**, v.311, n.6998, p.158-161, 1995.

LEITE, L. D.; ROCHA, E. D. M.; BRANDÃO-NETO, J. Obesidade: uma doença inflamatória. **Rev Cienc e Saúde**, v. 2, n. 2, p. 85-95, 2009.

LEVY-COSTA, R. B.; SICHIERI, R.; PONTES NDOS, S.; MONTEIRO, C. A. [Household food availability in Brazil: distribution and trends (1974-2003)] **Rev Saude Publica**, v.39, n.4, p.530-540, 2005.

LINDHE, Jan et al. **Tratato de Periodontia Clínica e Implantologia Oral**. 4 ed. Rio de Janeiro: Guanabara Koogan, 2005. 1013p.

LINDHE, J.; NYMAN, S. The effect of plaque control and surgical pocket elimination on the establishment and maintenance of periodontal health. A longitudinal study of periodontal therapy in cases of advanced disease **J Clin Periodontol**, v.2, n.2, p.67-79, 1975.

LINHARES RDA, S.; HORTA, B. L.; GIGANTE, D. P.; DIAS-DA-COSTA, J. S.; OLINTO, M. T. [Distribution of general and abdominal obesity in adults in a city in southern Brazil] **Cad Saude Publica**, v.28, n.3, p.438-447, 2012.

LINTSI. M.; KAARMA, H.; KULL, I. Comparison of hand-to-hand bioimpedance and anthropometry equations versus dual-energy X-ray absorptiometry for the assessment of body fat percentage in 17-18-year-old conscripts **Clin Physiol Funct Imaging**, v.24, n.2, p.85-90, 2004.

LOCKER, D.; LEAKE, J. L. Risk indicators and risk markers for periodontal disease experience in older adults living independently in Ontario, Canada **J Dent Res**, v.72, n.1, p.9-17, 1993.

LOCKHART, P. B.; BOLGER, A. F.; PAPAPANOU, P. N.; OSINBOWALE, O.; TREVISAN, M.; LEVISON, M. E.; TAUBERT, K. A.; NEWBURGER, J. W.; GORNIK, H. L.; GEWITZ, M. H.; WILSON, W. R.; SMITH, S. C., JR.; BADDOUR, L. M. Periodontal disease and atherosclerotic vascular disease: does the evidence support an independent association?: a scientific statement from the American Heart Association **Circulation**, v.125, n.20, p.2520-2544, 2012.

LOLMEDE, K.; DURAND DE SAINT FRONT, V.; GALITZKY, J.; LAFONTAN, M.; BOULOUMIE, A. Effects of hypoxia on the expression of proangiogenic factors in differentiated 3T3-F442A adipocytes **Int J Obes Relat Metab Disord**, v.27, n.10, p.1187-1195, 2003.

MARIOTTI, A. Dental plaque-induced gingival diseases **Ann Periodontol**, v.4, n.1, p.7-19, 1999.

MARTINEZ-PABON, M. C.; DUQUE-AGUDELO, L.; DIAZ-GIL, J. D.; ISAZA-GUZMAN, D. M.; TOBON-ARROYAVE, S. I. Comparison of the effect of two sugar-substituted chewing gums on different caries- and gingivitis-related variables: a double-blind, randomized, controlled clinical trial **Clin Oral Invest**, Ahead of print, 2013.

MEDZHITOV, R. Origin and physiological roles of inflammation **Nature**, v.454, n.7203, p.428-435, 2008.

MELLIN, A. E.; NEUMARK-SZTAINER, D.; STORY, M.; IRELAND, M.; RESNICK, M. D. Unhealthy behaviors and psychosocial difficulties among overweight adolescents: the potential impact of familial factors **J Adolesc Health**, v.31, n.2, p.145-153, 2002.

MOHAN, V.; DEEPA, R.; VELMURUGAN, K.; PREMALATHA, G. Association of C-reactive protein with body fat, diabetes and coronary artery disease in Asian Indians:

the Chennai Urban Rural Epidemiology Study (CURES-6) **Diabet Med**, v.22, n.7, p.863-870, 2005.

MONTEIRO, C. A.; LEVY, R. B.; CLARO, R. M.; DE CASTRO, I. R.; CANNON, G. Increasing consumption of ultra-processed foods and likely impact on human health: evidence from Brazil **Public Health Nutr**, v.14, n.1, p.5-13, 2011.

MORGAN, O. W.; BRAMLEY, A.; FOWLKES, A.; FREEDMAN, D. S.; TAYLOR, T. H.; GARGIULLO, P.; BELAY, B.; JAIN, S.; COX, C.; KAMIMOTO, L.; FIORE, A.; FINELLI, L.; OLSEN, S. J.; FRY, A. M. Morbid obesity as a risk factor for hospitalization and death due to 2009 pandemic influenza A(H1N1) disease **PLoS One**, v.5, n.3, p.e9694, 2010.

NAZMI, A.; OLIVEIRA, I. O.; HORTA, B. L.; GIGANTE, D. P.; VICTORA, C. G. Lifecourse socioeconomic trajectories and C-reactive protein levels in young adults: findings from a Brazilian birth cohort **Soc Sci Med**, v.70, n.8, p.1229-1236, 2010.

NEELS, J. G.; OLEFSKY, J. M. Inflamed fat: what starts the fire? **J Clin Invest**, v.116, n.1, p.33-35, 2006.

NICOLAU, B.; THOMSON, W. M.; STEELE, J. G.; ALLISON, P. J. Life-course epidemiology: concepts and theoretical models and its relevance to chronic oral conditions **Community Dent Oral Epidemiol** v. 35, p. 241-249, 2007.

OLIVEIRA, L. J. C.; NASCIMENTO, G. G.; CORREA, M. B.; GOETTEMS, M. L.; TARQUINIO, S. B.; TORRIANI, D. D.; DEMARCO, F. F. Iniquidades em saúde bucal: escolares beneficiários do Bolsa Família são mais vulneráveis? **Rev Saude Publica**, No prelo, 2013.

PATARO, A. L.; COSTA, F. O.; CORTELLI, S. C.; CORTELLI, J. R.; DUPIM SOUZA, A. C.; NOGUEIRA GUIMARÃES ABREU, M. H.; GIRUNDI, M. G.; COSTA, J. E. Influence of obesity and bariatric surgery on the periodontal condition **J Periodontol**, v. 83, n. 3, p. 257-266, 2012.

PEARSON, T. A.; MENSAH, G. A.; ALEXANDER, R. W.; ANDERSON, J. L.; CANNON, R. O., 3RD; CRIQUI, M.; FADL, Y. Y.; FORTMANN, S. P.; HONG, Y.; MYERS, G. L.; RIFAI, N.; SMITH, S. C., JR.; TAUBERT, K.; TRACY, R. P.; VINICOR, F.; CENTERS FOR DISEASE, C.; PREVENTION; AMERICAN HEART, A. 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**, v.107, n.3, p.499-511, 2003.

PERES, M. A.; TRAEBERT, J.; MARCENES, W. [Calibration of examiners for dental caries epidemiologic studies] **Cad Saude Publica**, v.17, n.1, p.153-159, 2001.

PERES, M. A.; PERES, K. G.; THOMSON, W. M.; BROADBENT, J. M.; GIGANTE, D. P.; HORTA, B. L. The Influence of Family Income Trajectories From Birth to Adulthood on Adult Oral Health: Findings From the 1982 Pelotas Birth Cohort **Am J Public Health**, v. 101, n. 4, p. 730-736, 2011.

PERES, M. A.; PERES, K. G.; CASCAES, A. M.; CORREA, M. B.; DEMARCO, F. F.; HALLAL, P. C.; HORTA, B. L.; GIGANTE, D. P.; MENEZES, A. B. Validity of partial protocols to assess the prevalence of periodontal outcomes and associated sociodemographic and behavior factors in adolescents and young adults **J Periodontol**, v. 83, n. 3, p. 369-378, 2012.

POPKIN, B. M. Global nutrition dynamics: the world is shifting rapidly toward a diet linked with noncommunicable diseases **Am J Clin Nutr**, v.84, n.2, p.289-298, 2006.

PRADEEP, A. R.; PRIYANKA, N.; PRASAD, M. V.; KALRA, N.; KUMARI, N. Association of progranulin and high sensitivity CRP concentrations in gingival crevicular fluid and serum in chronic periodontitis subjects with and without obesity **Dis Markers**, v. 33, n. 4, p. 207-213, 2012.

PRADEEP, A. R.; KUMARI, N.; KALRA, N.; PRIYANKA, N. Correlation of MCP-4 and high-sensitivity C-reactive protein as a marker of inflammation in obesity and chronic periodontitis **Cytokines**, v. 61, n. 3, p. 772-777, 2013.

PRESHAW, P. M.; TAYLOR, J. J. How has research into cytokine interactions and their role in driving immune responses impacted our understanding of periodontitis? **J Clin Periodontol**, v.38 Suppl 11, p.60-84, 2011.

REEVES, A. F.; REES, J. M.; SCHIFF, M.; HUJOEL, P. Total body weight and waist circumference associated with chronic periodontitis among adolescents in the United States **Arch Pediatr Adolesc Med**, v.160, n.9, p.894-899, 2006.

SAXLIN, T.; SUOMINEN-TAIPALE, L.; KATTAINEN, A.; MARNIEMI, J.; KNUUTTILA, M.; YLÖSTALO, P. Association between serum lipid levels and periodontal infection **J Clin Periodontol**, v. 35, n. 12, p. 1040-1047, 2008.

SAITO, T.; YAMAGUCHI, N.; SHIMAZAKI, Y.; HAYASHIDA, H.; YONEMOTO, K.; DOI, Y.; KIYOHARA, Y.; IIDA, M.; YAMASHITA, Y. Serum levels of resistin and adiponectin in women with periodontitis: the Hisayama study **J Dent Res**, v. 87, n. 4, p.319-322, 2008.

SCHMIDT, M. I.; DUNCAN, B. B.; AZEVEDO E SILVA, G.; MENEZES, A. M.; MONTEIRO, C. A.; BARRETO, S. M.; CHOR, D.; MENEZES, P. R. Chronic non-communicable diseases in Brazil: burden and current challenges **Lancet**, v.377, n.9781, p.1949-1961, 2011.

SCHROEDER, H. E.; LINDHE, J. Conversion of stable established gingivitis in the dog into destructive periodontitis **Arch Oral Biol**, v.20, n.12, p.775-782, 1975.

SHEARER, D. M.; THOMSON, W. M.; CASPI, A.; MOFFITT, T. E.; BROADBENT, J. M.; POULTON, R. Inter-generational continuity in periodontal health: findings from the Dunedin family history study **J Clin Periodontol**, v.38, n.4, p.301-309, 2011.

SHIBLI, R.; RUBIN, L.; AKONS, H.; SHAOUL, R. Morbidity of overweight (>or=85th percentile) in the first 2 years of life **Pediatrics**, v. 122, n. 2, p. 267-272, 2008.

SNIJDER, M. B.; VAN DAM, R. M.; VISSER, M.; SEIDELL, J. C. What aspects of body fat are particularly hazardous and how do we measure them? **Int J Epidemiol**, v.35, n.1, p.83-92, 2006.

STEFAN, N.; STUMVOLL, M. Adiponectin--its role in metabolism and beyond **Horm Metab Res**, v.34, n.9, p.469-474, 2002.

SUK, S. H.; SACCO, R. L.; BODEN-ALBALA, B.; CHEUN, J. F.; PITTMAN, J. G.; ELKIND, M. S.; PAIK, M. C.; NORTHERN MANHATTAN STROKE, S. Abdominal obesity and risk of ischemic stroke: the Northern Manhattan Stroke Study **Stroke**, v.34, n.7, p.1586-1592, 2003.

SUSIN, C.; HAAS, A. N.; VALLE, P. M.; OPPERMANN, R. V.; ALBANDAR, J. M. Prevalence and risk indicators for chronic periodontitis in adolescents and young adults in south Brazil **J Clin Periodontol**, v.38, n.4, p.326-333, 2011.

THOMSON, W. M.; BROADBENT, J. M.; POULTON, R.; BECK, J. D. Changes in periodontal disease experience from 26 to 32 years of age in a birth cohort **J Periodontol**, v.77, n.6, p.947-954, 2006.

THOMSON, W. M.; SHEIHAM, A.; SPENCER, A. J. Sociobehavioral aspects of periodontal disease **Periodontol 2000**, v.60, n.1, p.54-63, 2012.

TILG, H.; MOSCHEN, A. R. Adipocytokines: mediators linking adipose tissue, inflammation and immunity **Nat Rev Immunol**, v.6, n.10, p.772-783, 2006.

TRAYHURN, P.; WOOD, I. S. Adipokines: inflammation and the pleiotropic role of white adipose tissue **Br J Nutr**, v.92, n.3, p.347-355, 2004.

VICTORA, C. G.; BARROS, F. C. Cohort profile: the 1982 Pelotas (Brazil) birth cohort study **Int J Epidemiol**, v.35, n.2, p.237-242, 2006.

WANG, Y.; BEYDOUN, M. A. The obesity epidemic in the United States--gender, age, socioeconomic, racial/ethnic, and geographic characteristics: a systematic review and meta-regression analysis **Epidemiol Rev**, v.29, p.6-28, 2007.

WORLD HEALTH ORGANIZATION. **Obesity: Preventing and Managing the Global Epidemic**. WHO Techincal Report Series. 2000. Geneva.

WORLD HEALTH ORGANIZATION. **Preventing chronic diseases: a vital investment**. World Health Organization. 2005. Geneva.

WORLD HEALTH ORGANIZATION. **Growth reference 5–19 years.** Disponível em: http://www.who.int/growthref/who2007_bmi_for_ age/en/index.html (último acesso em 20 de maio de 2013).

WU, T.; TREVISAN, M.; GENCO, R. J.; FALKNER, K. L.; DORN, J. P.; SEMPOS, C. T. Examination of the relation between periodontal health status and cardiovascular

risk factors: serum total and high density lipoprotein cholesterol, C-reactive protein, and plasma fibrinogen **Am J Epidemiol**, v.151, n.3, p.273-282, 2000.

XU, H.; BARNES, G. T.; YANG, Q.; TAN, G.; YANG, D.; CHOU, C. J.; SOLE, J.; NICHOLS, A.; ROSS, J. S.; TARTAGLIA, L. A.; CHEN, H. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance **J Clin Invest**, v.112, n.12, p.1821-1830, 2003.

ZIMMERMANN, G. S.; BASTOS, M. F.; DIAS GONCALVES, T. E.; CHAMBRONE, L.; DUARTE, P. M. Local and circulating levels of adipocytokines in obese and normal weight individuals with chronic periodontitis **J Periodontol**, v.84, n.5, p.624-633, 2013.

ZUZA, E. P.; BARROSO, E. M.; CARRARETO, A. L.; PIRES, J. R.; CARLOS, I. Z.; THEODORO, L. H.; TOLEDO, B. E. The role of obesity as a modifying factor in patients undergoing non-surgical periodontal therapy **J Periodontol**, v.82, n.5, p.676-682, 2011.

8 Orçamento

O projeto apresentado contará com o seguinte financiamento:

1) Edital MCT-CNPq/MS-SCTIE-DECIT/MS-SAS-DAB Nº10/2012 Saúde Bucal

Processo: 402357/2012-3

Condições de saúde geral, socioeconômicas, comportamentais, clínicas e de acesso a serviços ao longo do ciclo vital: associação com saúde bucal em uma coorte de nascidos vivos no Sul do Brasil.

Proponente: Flávio Fernando Demarco

Co-proponentes: Bernardo Horta; Denise Gigante; Marco Peres; Karen Peres; Sandra Tarquínio; Marcos Britto Corrêa

Valor Aprovado: R$ 59.021,30

8.1 Orçamento Detalhado

Item	Quantidade	Valor (Reais)
Material de Consumo		
Espátulas de madeira	6 pacotes	10,80
Gaze	1pacote	25,00
Caixas de metal	4 unidades	216,98
Material para autoclavagem	400 peças	720,00
Lanternas portáteis para exame	4 unidades	60,00
Pilhas	20 unidades	80,00
Luvas	8 caixas	106,40
Toucas	60 unidades	75,00
Toalhas de papel	10 rolos	20,00
Jalecos	8 unidades	160,00
Sacos de lixo	90 unidades	20,00
Total		1.496,00
Material Permanente		
Sondas Periodontal CPI	100 unidades	3.000,00
Odontoscópio n. 5	100 unidades	1.000,00
Computador notebook Dell Novo Inspiron 14	10 unidades	26.990,00
Software Stata 12.0	1 unidade	3.200,00
Software Stat Transfer	1 unidade	460,00
Total		34.650,00
Pessoa Física		
Digitador	1	754,00
Examinadores/entrevistadores de campo	8	18.025,00 (valor base R$25,00 por visita domiciliar por dupla incluindo transporte)
Secretaria	1	2.898,12
Revisão de inglês	1	300,00
Total		21.777,12
Pessoa Jurídica		
Inscrição em congressos	2	250,00
Transporte e hospedagem para congressos	2	650,00
Total		900,00
TOTAL		59.021,30

9 Cronograma

Etapa	Trimestre									
	1º	2º	3º	4º	5º	6º	7º	8º	9º	10º
Revisão da literatura										
Planejamento da Pesquisa e Submissão ao CEP										
Elaboração do projeto										
Coleta dos dados										
Análise dos dados										
Atendimento Clínico										
Redação da tese										
Defesa da tese										
Submissão dos artigos										

Apêndices

Apêndice A – Termo de Consentimento Livre e Esclarecido

UNIVERSIDADE FEDERAL DE PELOTAS

PROGRAMAS DE PÓS-GRADUAÇÃO EM

EPIDEMIOLOGIA E ODONTOLOGIA

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO – TCLE

O Sr.(a) está sendo convidado a participar da pesquisa **"Condições de saúde geral, socioeconômicas, comportamentais e de acesso a serviços ao longo do ciclo vital: impacto na saúde bucal em uma coorte de nascidos vivos no Sul do Brasil**". Sua colaboração neste estudo é MUITO IMPORTANTE, mas a decisão de participar é VOLUNTÁRIA, o que significa que o Sr.(a) terá o direito de decidir se quer ou não participar, bem como de desistir de fazê-lo a qualquer momento.

Esta pesquisa tem como objetivo conhecer a situação de saúde geral e de saúde bucal dos adultos que estão sendo acompanhados neste estudo de coorte e sua relação com condições socioeconômicas, demográficas, de acesso a serviços e qualidade de vida.

Garantimos que será mantida a CONFIDENCIALIDADE das informações e o ANONIMATO. Ou seja, o seu nome não será mencionado em qualquer hipótese ou circunstância, mesmo em publicações científicas. NÃO HÁ RISCOS quanto à sua participação e o BENEFÍCIO será conhecer a realidade da saúde dos moradores de Pelotas, a qual poderá melhorar os serviços de saúde em sua comunidade.

Será realizada uma entrevista e verificaremos algumas condições de saúde da sua boca, como por exemplo, a presença de cárie e a existência de sangramento nas gengivas. Este exame será realizado por dentistas e não oferece nenhum risco, não causa dor alguma e todos os instrumentos utilizados estarão esterilizados ou serão descartáveis. Em caso de dúvida o(a) senhor(a) poderá entrar em contato com Professor Flávio Fernando Demarco, coordenador desta pesquisa, nos Programas de Pós-Graduação em Odontologia e Epidemiologia da UFPel, pelo telefone (53) 3222 4162 – ramal 130 ou e-mail: ffdemarco@gmail.com.

Eu,.....

declaro estar esclarecido(a) sobre os termos apresentados e consinto por minha livre e espontânea vontade em participar desta pesquisa e assino o presente documento em duas vias de igual teor e forma, ficando uma em minha posse.

Pelotas, _____ de _____ de 2013.

_____

(Assinatura do participante)

Apêndice B – Entrevista sobre Saúde Bucal

CENTRO DE PESQUISAS EPIDEMIOLÓGICAS - UFPEL

AMOSTRA DA COORTE DE 1982 – ACOMPANHAMENTO 2013

SAÚDE BUCAL

FOLHA DE ROSTO

Nome do indivíduo _____

Número da coorte: __ __ __ __ __ __ - __

Data de nascimento: __ __/__ __/ __ __ __ __

Endereço:_____

_____

Ponto de referência:_____

_____

Telefones:
Tel 1 _____

Tel 2 _____

Tel 3 _____

Telefones Novos:
Tel 1 _____

Tel 2 _____

Tel 3 _____

Tem email? Não ( ) Sim ( )

Se sim, email? _____@_____

Outra pessoa da família tem email? Não ( ) Sim ( )
Se sim, quem? _____

Email? _____@_____

COORTE 1982
AVALIAÇÃO DE SAÚDE BUCAL AOS 31 ANOS / 2013
BLOCO A – IDENTIFICAÇÃO

ENTREVISTADOR: _____ cód __ __ DATA DE ENTREVISTA:___ / ___ / ___

Número do indivíduo *qes*
__ __ __ __ __ __ - __

IDENTIFICAÇÃO:

"Sr(a) <NOME DA PESSOA **> estamos trabalhando no estudo sobre saúde bucal dos adultos nascidos em 1982 em Pelotas, realizado pelo Centro de Pesquisas Epidemiológicas da UFPel. Você faz parte desse estudo desde seu nascimento e já foi visitado(a) outras vezes, e agora estamos fazendo uma pesquisa sobre a saúde bucal. Desta vez, só estamos avaliando as pessoas que já tiveram sua saúde bucal avaliada aos 15 anos (1997) e aos 24 anos (2006). Nós gostaríamos de fazer umas perguntas sobre coisas relacionadas à sua saúde bucal. Queremos também examinar seus dentes e a sua boca. Este questionário não possui respostas certas ou erradas e é muito importante para o estudo que o(a) Sr.(a). responda da maneira mais exata possível. As informações prestadas são de caráter sigiloso e seu nome não será associado com qualquer uma das respostas. Podemos conversar?"** *Se a resposta for afirmativa, dar o consentimento para o entrevistado assinar.*

BLOCO A – HÁBITOS

1. Você costuma escovar os dentes com pasta de dentes ? [C01]

_____

Nunca 1
Sim às vezes 2
1 vez ao dia todos os dias 3
2 vezes ao dia todos os dias 4
3 vezes ao dia ou + todos os dias 5
IGN 9

2. Qual o tipo de água você bebe geralmente? [C02]

(5) Outra**.** Qual**?** _____

água direto da torneira 1
água da torneira filtrada/filtro 2
água mineral 3
água de poço 4
outra 5
IGN 9

3. Você usa fio dental [C03]

Ler as alternativas

Nunca 0
Às vezes 1
Sempre 2
NSA 8
IGN 9

BLOCO D –CONSULTA COM DENTISTA		
4. Alguma vez na vida foi ao consultório do dentista? ***Se (0)*** ➔ *pule para a questão* ***Se (9)*** ➔ *pule para a questão*	[D04]	Não 0 Sim 1 IGN 9
5. Quando você consultou o dentista pela última vez?	[D05]	Menos de 1 1 a 2 anos 2 3 ou mais anos 3 NSA 8 IGN 9
6. Qual foi o motivo da sua última consulta com o dentista? (18) Outros_____	[D06]	Consulta de rotina/prevenção/revisão 10 Dor 11 Dente quebrado/trauma 12 Cavidades nos dentes/cárie/restauração/obturação 13 Ferida, caroço ou manchas na boca 14 Rosto inchado 15 Problemas na gengiva 16 Extrações/arrancar o dente (devido à cárie) 17 Outros 18 NSA 88 IGN 99
7. Onde você foi atendido? Outro _____	[D07]	Posto de Saúde 0 Faculdade de Odontologia 1 No local de trabalho 2 Consultório particular 3 Convênio 4 Outro 5 NSA 8 IGN 9
8. Você tem medo de ir ao dentista? *Ler as alternativas*	[D08]	Não 0 Um pouco 1 Sim 2 Sim, muito 3 IGN 9
9. Você acha que atualmente necessita ir ao dentista? ***Se (0)*** ➔ *pule para a questão...* ***Se (2)*** ➔ *pule para a questão ...* ***Se (9)*** ➔ *pule para a questão* **...**	[D09]	Não 0 Sim 1 Está em tratamento com dentista 2 IGN 9

10. Necessita ir a uma consulta com o dentista por qual motivo? [D10]

*Após essa pergunta pule para **44***

Consulta de rotina/manutenção 10
Dor 11
Dente quebrado/trauma 12
Cavidades nos dentes/cárie/restauração/obturação 13
Ferida, caroço ou manchas na boca 14
Rosto inchado 15
Problemas na gengiva 16
Extrações/arrancar o dente (devido à cárie) 17
Outros 18
NSA 88
IGN 99

11. Não precisa ir a uma consulta com o dentista por qual motivo? [D11]

Por que está tudo bem com seus dentes 0
Embora ele/a tenha algum problema, isso pode esperar 1
Outro 2
IGN 8

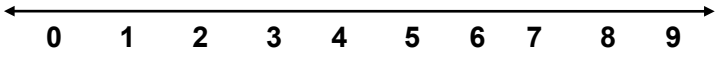
(2) Outro_____

12. Desde os últimos 6 meses, sentiu dor de dente? [D12]

Não (Marcar 88 nas questões 13 e 14) 0
Sim 1
NSA 8
IGN 9

13. Você poderia apontar na linha abaixo o quanto esta dor lhe doeu? Você deve pensar que 0 (zero) significa nenhuma dor e 10 (dez) uma dor muito forte *(anotar o número diretamente na coluna da direita)* [D13]

(88) NSA
(99) IGN



14. Qual foi a principal causa da sua dor de dente? *(marcar uma alternativa)* [D14]

Buraco ou cavidade no dente 11
Quando comi ou bebi alimentos quentes, frios ou doces 12
Quando mastiguei alimentos duros (cenoura, maça, etc) 13
Aparelho ortodôntico fixo ou móvel no dente 14
Quando obturei um dente 15
Quando fiz tratamento de canal 16
Quando tirei (extrai) um dente 17
Quando um dente quebrou 18
Coloquei uma prótese 19
Gengiva 20
Outra razão 21
NSA 88
IGN99

15. Você já realizou tratamento de canal na sua vida?	[D15]	Não 0 Sim, uma vez 1 Sim, mais de uma vez 2 NSA 8 IGN 9
16. Considerando a aparência de seus dentes o senhor está *(ler as alternativas)*?		Muito satisfeito 0 Satisfeito 1 Nem satisfeito, nem insatisfeito 2 Insatisfeito 3 Muito Insatisfeito 4
17. Considerando a cor de seus dentes o senhor está *(ler as alternativas)*?	satisfeito 0	Muito Satisfeito 1 Nem satisfeito, nem insatisfeito 2 Insatisfeito 3 Muito Insatisfeito 4
18. Você já considerou que seus dentes estavam escuros e fez tratamento para clareá-los (branqueá-los)?		Não 0 Sim, uma vez 1 Sim, mais de uma vez 2 NSA 8 IGN 9
19. Você já considerou que seus dentes estavam mal posicionados amontoados?		Não 0 Sim, um pouco 1 Sim, muito 2 NSA 8 IGN 9
20. Você já usou aparelho (fixo ou móvel) nos dentes?		Não 0 Sim 1 NSA 8 IGN 9
21. Você já quebrou alguma vez algum dente da frente?		Não 0 Sim, uma vez 1 Sim, mais de uma vez 2 NSA 8 IGN 9
22. Você deseja fazer algum destes tratamentos para melhorar a aparência dos seus dentes?		
a. Tratamento ortodôntico (aparelho dentário):		(0) Não (1) Sim (8) Não sei
b. Restaurações:		(0) Não (1) Sim (8) Não sei
c. Clareamento:		(0) Não (1) Sim (8) Não sei
d. Implante e/ou Prótese*:*		(0) Não (1) Sim (8) Não sei

23 Você está satisfeito com a sua aparência?	Muito satisfeito 0 Satisfeito 1 Nem satisfeito, nem insatisfeito 2 Insatisfeito 3 Muito insatisfeito 4
24. Comparado com pessoas da sua idade, você considera a saúde dos teus dentes, da boca e gengivas:	Muito boa 0 Boa 1 Regular 2 Ruim 3 Péssima 4

BLOCO E – SATISFAÇÃO E PROBLEMAS BUCAIS

28. Problemas com dentes, boca e maxilares (ossos da boca) e seus tratamentos podem afetar o bem-estar e a vida diária das pessoas e suas famílias. Para cada uma das seguintes questões, por favor, escolha as opções de respostas que melhor descreve as suas experiências. Considere toda sua vida, desde o nascimento até agora, quando responder cada pergunta. *Após cada pergunta ler as opções:*

(1) nunca, (2) quase nunca, (3) às vezes (de vez em quando), (4) com frequência, (5) com muita frequência, (9) não sei

1. Você teve problemas para falar alguma palavra?**?**	[OHIP1]	1	2	3	4	5	9
2. você sentiu que o sabor dos alimentos tem piorado?	[OHIP2]	1	2	3	4	5	9
3. você sentiu dores em sua boca ou nos seus dentes?	[OHIP3]	1	2	3	4	5	9
4. você se sentiu incomodada ao comer algum alimento?	[OHIP4]	1	2	3	4	5	9
5. você ficou preocupado/a?	[OHIP5]	1	2	3	4	5	9
6. você se sentiu estressado/a?	[OHIP6]	1	2	3	4	5	9
7. sua alimentação ficou prejudicada?	[OHIP7]	1	2	3	4	5	9
8. você teve que parar suas refeições?	[OHIP8]	1	2	3	4	5	9
9. você encontrou dificuldade para relaxar?	[OHIP9]	1	2	3	4	5	9
10. você se sentiu envergonhado/a?	[OHIP10]	1	2	3	4	5	9
11. você ficou irritado/a com outras pessoas?	[OHIP11]	1	2	3	4	5	9
12. você teve dificuldade para realizar suas atividades diárias?	[OHIP12]	1	2	3	4	5	9
13. você sentiu que a vida, em geral, ficou pior?	[OHIP13]	1	2	3	4	5	9
14. você ficou totalmente incapaz de fazer suas atividades diárias?	[OHIP14]	1	2	3	4	5	9

Desgaste dental / DTM

29. Alguém já ouviu você apertando (rangendo) os dentes?	[DTM1]	Não 0 Sim 1 IGN 9
30. Você já acordou de manhã com a sua mandíbula cansada, dolorida ou com dificuldade de abrir?	[DTM2]	Não 0 Sim 1 IGN 9
31. Seus dentes ou gengiva doem ao acordar de manhã?	[DTM3]	Não 0 Sim 1 IGN 9
32. Você já teve dor do lado da cabeça ao acordar de manhã?	[DTM4]	Não 0 Sim 1 IGN 9
33. Você já percebeu estar desgastando os dentes durante o dia?	[DTM5]	Não 0 Sim 1 IGN 9
34. Você já notou estar fazendo apertamento dos seus dentes durante o dia?	[DTM6]	Não 0 Sim 1 IGN 9
35. Você já notou ruído semelhante a casca de ovo se quebrando ou estalo próximo ao ouvido?	[DTM7]	Não 0 Sim 1 IGN 9

Apêndice C – Ficha de Exame Clínico

FICHA DE EXAME

Data exame: ___/___/_____

EXAMINADOR ☐☐ NUM ☐☐☐☐☐☐

Nome:_____

Uso e Nec. Prót.

USO ☐ Sup ☐ Inf NEC ☐ Sup ☐ Inf

TAD

12	11	21	22	32	31	41	42

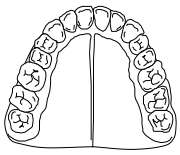
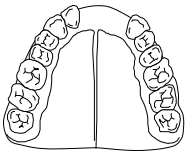
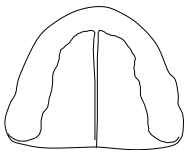
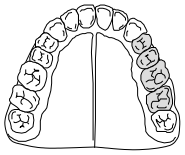
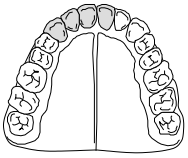
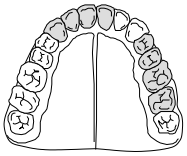
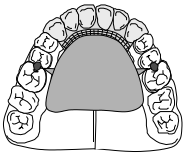
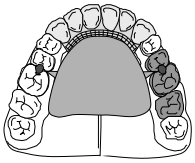
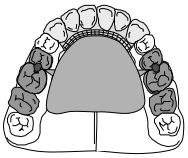
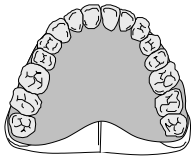
Outro:

Condição da Coroa

18	17	16	15	14	13	12	11	Face	21	22	23	24	25	26	27	28
								O								
								M								
								V								
								D								
								L								
								R								
								LCNC								
48	47	46	45	44	43	42	41	Face	31	32	33	34	35	36	37	38
								O								
								M								
								V								
								D								
								L								
								R								
								LCNC								

Condição Periodontal

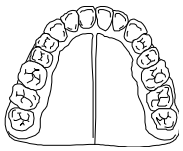
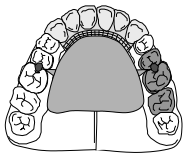
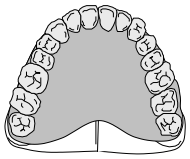
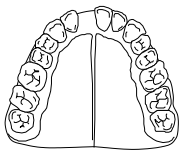
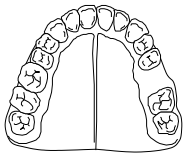
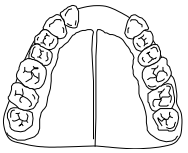
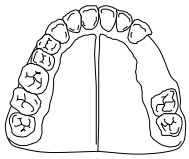
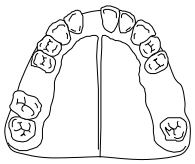
	17				16				15				14				13				12				11			
Sítio	D	V	M	P	D	V	M	P	D	V	M	P	D	V	M	P	D	V	M	P	D	V	M	P	D	V	M	P
Sangr.																												
Cálc.																												
NG																												
PS																												
PIP																												
	21				22				23				24				25				26				27			
Sítio	M	V	D	P	M	V	D	P	M	V	D	P	M	V	D	P	M	V	D	P	M	V	D	P	M	V	D	P
Sangr.																												
Cálc.																												
NG																												
PS																												
PIP																												
	37				36				35				34				33				32				31			
Sítio	D	V	M	P	D	V	M	P	D	V	M	P	D	V	M	P	D	V	M	P	D	V	M	P	D	V	M	P
Sangr.																												
Cálc.																												
NG																												
PS																												
PIP																												
	41				42				43				44				45				46				47			
Sítio	M	V	D	P	M	V	D	P	M	V	D	P	M	V	D	P	M	V	D	P	M	V	D	P	M	V	D	P
Sangr.																												
Cálc.																												
NG																												
PS																												
PIP																												

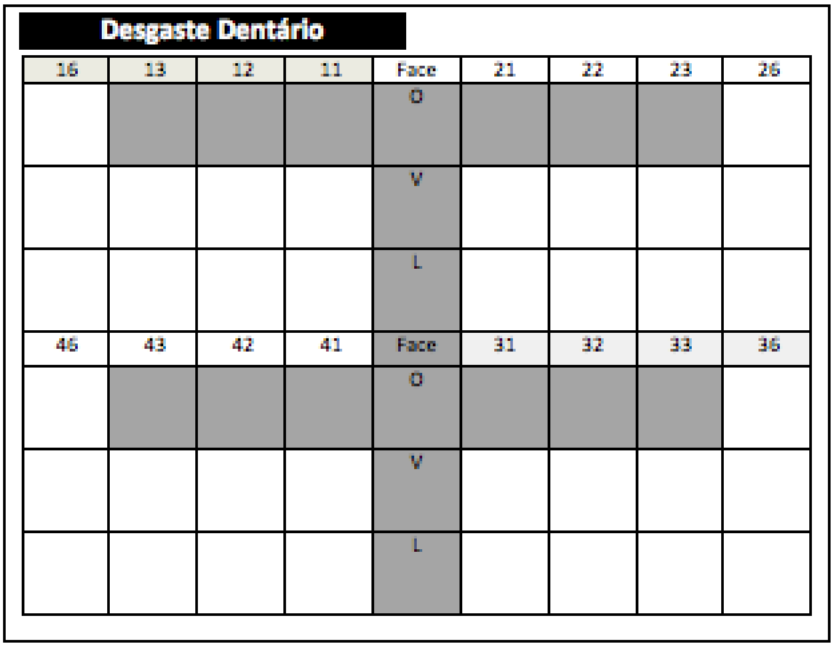
Uso de Prótese Superior				**OUPS |___|**
Uso de Prótese Inferior				**OUPI |___|**
Código	**Critério**	**Exemplos**		
0	Não usa prótese dentária	 Nenhum espaço protético	 Desdentado parcial, mas sem prótese presente	 Desdentado total e sem prótese presente
1	Usa uma ponte fixa	 Uma ponte fixa posterior	 Uma ponte fixa anterior	
2	Usa mais do que uma ponte fixa	 Duas pontes fixas em pontos diferentes (anterior e posterior)		
3	Usa prótese parcial removível	 Prótese Parcial Removível anterior		
4	Usa uma ou mais pontes fixas **e** uma ou mais próteses parciais removíveis	 Prótese removível anterior e ponte fixa posterior	 Prótese removível anterior e duas pontes fixas posteriores	
5	Usa prótese dentária total			

		Prótese total		
9	Sem informação			

Necessidade de Prótese Superior
ONPS |___|

Necessidade de Prótese Inferior
ONPI |___|

Código	Critério	Exemplos		
0	Não necessita de prótese dentária	 Todos os dentes presentes	 Espaços protéticos presentes com prótese	 Desdentado total mas com presença de prótese
1	Necessita uma prótese, *fixa ou removível*, para substituição de **um elemento**	 Espaço protético unitário anterior	 Espaço protético unitário posterior	
2	Necessita uma prótese, *fixa ou removível*, para substituição de **mais de um elemento**	 Espaço protético anterior de mais de um elemento	 Espaço protético posterior de mais de um elemento	
3	Necessita uma combinação de próteses, *fixas e/ou removíveis*, para substituição de um e/ou mais de um elemento		Espaços protéticos em vários pontos da boca	



Escore	Critério
0	Ausência de desgaste em dentina
1	Dentina apenas visível (incluindo cupping) ou dentina exposta menos de 1/3 da superfície
2	Dentina exposta maior a 1/3 da superfície
3	Exposição da polpa ou dentina secundária

AVALIAÇÃO DAS RESTAURAÇÕES

**Obs.: Em caso de critério 8 (NSA) para a pergunta MAT, pular para o dente seguinte e marcar 8 (NSA) em todas as outras questões para o referido dente*

DENTE 17

1. Tipo de material utilizado?	**17MAT |___|**
2. Tipo de cavidade?	**17CAV |___|**
3. A quanto tempo tu fizeste esta restauração?	**17TEM |___|**
4. Classificação da restauração?	**17CLAS |___|**
5. Razão da classificação insatisfatória?	**17RAZ |___|**

DENTE 16

1. Tipo de material utilizado?	**16MAT |___|**
2. Tipo de cavidade?	**16CAV |___|**
3. A quanto tempo tu fizeste esta restauração?	**16TEM |___|**
4. Classificação da restauração?	**16CLAS |___|**
5. Razão da classificação insatisfatória?	**16RAZ |___|**

DENTE 15

1. Tipo de material utilizado?	**15MAT |___|**
2. Tipo de cavidade?	**15CAV |___|**
3. A quanto tempo tu fizeste esta restauração?	**15TEM |___|**
4. Classificação da restauração?	**15CLAS |___|**
5. Razão da classificação insatisfatória?	**15RAZ |___|**

DENTE 14

1. Tipo de material utilizado?	**14MAT |___|**
2. Tipo de cavidade?	**14CAV |___|**
3. A quanto tempo tu fizeste esta restauração?	**14TEM |___|**
4. Classificação da restauração?	**14CLAS |___|**
5. Razão da classificação insatisfatória?	**14RAZ |___|**

DENTE 27

1. Tipo de material utilizado?	**27MAT |___|**
2. Tipo de cavidade?	**27CAV |___|**
3. A quanto tempo tu fizeste esta restauração?	**27TEM |___|**
4. Classificação da restauração?	**27CLAS |___|**
5. Razão da classificação insatisfatória?	**27RAZ |___|**

DENTE 26

1. Tipo de material utilizado?	**26MAT |___|**
2. Tipo de cavidade?	**26CAV |___|**
3. A quanto tempo tu fizeste esta restauração?	**26TEM |___|**
4. Classificação da restauração?	**26CLAS |___|**
5. Razão da classificação insatisfatória?	**26RAZ |___|**

DENTE 25

1. Tipo de material utilizado?	**25MAT |___|**
2. Tipo de cavidade?	**25CAV |___|**
3. A quanto tempo tu fizeste esta restauração?	**25TEM |___|**
4. Classificação da restauração?	**25CLAS |___|**
5. Razão da classificação insatisfatória?	**25RAZ |___|**

DENTE 24

1. Tipo de material utilizado?	**24MAT |___|**
2. Tipo de cavidade?	**24CAV |___|**
3. A quanto tempo tu fizeste esta restauração?	**24TEM |___|**
4. Classificação da restauração?	**24CLAS |___|**
5. Razão da classificação insatisfatória?	**24RAZ |___|**

**Obs.: Em caso de critério 8 (NSA) para a pergunta MAT, pular para o dente seguinte e marcar 8 (NSA) em todas as outras questões para o referido dente*

DENTE 37

1. Tipo de material utilizado?	**37MAT |___|**
2. Tipo de cavidade?	**37CAV |___|**
3. A quanto tempo tu fizeste esta restauração?	**37TEM |___|**
4. Classificação da restauração?	**37CLAS |___|**
5. Razão da classificação insatisfatória?	**37RAZ |___|**

DENTE 36

1. Tipo de material utilizado?	**36MAT |___|**
2. Tipo de cavidade?	**36CAV |___|**
3. A quanto tempo tu fizeste esta restauração?	**36TEM |___|**
4. Classificação da restauração?	**36CLAS |___|**
5. Razão da classificação insatisfatória?	**36RAZ |___|**

DENTE 35

1. Tipo de material utilizado?	**35MAT |___|**
2. Tipo de cavidade?	**35CAV |___|**
3. A quanto tempo tu fizeste esta restauração?	**35TEM |___|**
4. Classificação da restauração?	**35CLAS |___|**
5. Razão da classificação insatisfatória?	**35RAZ |___|**

DENTE 34

1. Tipo de material utilizado?	**34MAT |___|**
2. Tipo de cavidade?	**34CAV |___|**
3. A quanto tempo tu fizeste esta restauração?	**34TEM |___|**
4. Classificação da restauração?	**34CLAS |___|**
5. Razão da classificação insatisfatória?	**34RAZ |___|**

DENTE 47

1. Tipo de material utilizado?	**47MAT |___|**
2. Tipo de cavidade?	**47CAV |___|**
3. A quanto tempo tu fizeste esta restauração?	**47TEM |___|**
4. Classificação da restauração?	**47CLAS |___|**
5. Razão da classificação insatisfatória?	**47RAZ |___|**

DENTE 46

1. Tipo de material utilizado?	**46MAT |___|**
2. Tipo de cavidade?	**46CAV |___|**
3. A quanto tempo tu fizeste esta restauração?	**46TEM |___|**
4. Classificação da restauração?	**46CLAS |___|**
5. Razão da classificação insatisfatória?	**46RAZ |___|**

DENTE 45

1. Tipo de material utilizado?	**45MAT |___|**
2. Tipo de cavidade?	**45CAV |___|**
3. A quanto tempo tu fizeste esta restauração?	**45TEM |___|**
4. Classificação da restauração?	**45CLAS |___|**
5. Razão da classificação insatisfatória?	**45RAZ |___|**

DENTE 44

1. Tipo de material utilizado?	**44MAT |___|**
2. Tipo de cavidade?	**44CAV |___|**
3. A quanto tempo tu fizeste esta restauração?	**44TEM |___|**
4. Classificação da restauração?	**44CLAS |___|**
5. Razão da classificação insatisfatória?	**44RAZ |___|**

LESÕES BUCAIS (Avaliação do examinador)		
1. Presença de lesão bucal? (0) Não (*marque 8 OU 88 nas questões de 2 a 9 e passe para a questão11).* (1) Sim (9) IGN		**LB |___|**
2. Localização da lesão 1		**LBLOC1 |___|**
(11) Língua (12) Assoalho da boca (13) Mucosa jugal (14) Palato (15) Gengiva (16) Lábio (17) Maxila (18) Mandíbula (19) Outras:_____ (99) IGN		
3. – Tipo de lesão 1		
Úlcera	(1) sim (2) não (8) NSA (9) IGN	**ULC1 |___|**
Mancha avermelhada	(1) sim (2) não (8) NSA (9) IGN	**MVER1 |___|**
Mancha acastanhada/enegrecida	(1) sim (2) não (8) NSA (9) IGN	**MCAS1 |___|**
Placa branca	(1) sim (2) não (8) NSA (9) IGN	**PBRA1 |___|**
Erosão	(1) sim (2) não (8) NSA (9) IGN	**EROS1 |___|**
Pápula/nódulo	(1) sim (2) não (8) NSA (9) IGN	**PAPU1 |___|**
Vesícula/bolha	(1) sim (2) não (8) NSA (9) IGN	**VESI1 |___|**
4. Qual o tamanho da lesão 1?*(Usar uma escala em milímetros)* (88) NSA		**LBTAMAN1 |___|**
5. Tu já tinhas percebido esta ferida ou machucado na tua boca? Há quanto tempo?		**LBTEMP1 |___|**
(11) Não, nunca (12) Menos de 1 mês (13) Entre 1 mês a 3 meses (14) Entre 3 a 6 meses (15) Entre 6 meses a 1 ano (16) De 1 a 2 anos (17) Mais que 2 anos (99) IGN		
6. Localização da lesão 2		**LBLOC2 |___|**
(11) Língua (12) Assoalho da boca (13) Mucosa jugal (14) Palato (15) Gengiva (16) Lábio (17) Maxila (18) Mandíbula (19) Outras:_____ (99) IGN		

7. – Tipo de lesão 2		
Úlcera	(1) sim (2) não (8) NSA (9) IGN	**ULC2 |___|**
Mancha avermelhada	(1) sim (2) não (8) NSA (9) IGN	**MVER2 |___|**
Mancha acastanhada/enegrecida	(1) sim (2) não (8) NSA (9) IGN	**MCAS2 |___|**
Placa branca	(1) sim (2) não (8) NSA (9) IGN	**PBRA2 |___|**
Erosão	(1) sim (2) não (8) NSA (9) IGN	**EROS1 |___|**
Pápula/nódulo	(1) sim (2) não (8) NSA (9) IGN	**PAPU2 |___|**
Vesícula/bolha	(1) sim (2) não (8) NSA (9) IGN	**VESI2 |___|**
8. Qual o tamanho da lesão 2? *(Usar uma escala em milímetros)* (88) NSA		**LBTAMAN2 |___|**
9. Tu já tinhas percebido esta ferida ou machucado na tua boca? Há quanto tempo?		**LBTEMP2 |___|**
(11) Não, nunca (12) Menos de 1 mês (13) Entre 1 mês a 3 meses (14) Entre 3 a 6 meses (15) Entre 6 meses a 1 ano (16) De 1 a 2 anos (17) Mais que 2 anos (99) IGN		
10. Tu relacionas algum destes sintomas citados a seguir com a tua lesão? *(ler as alternativas, anotando dois números: o primeiro correspondente à alternativa e o segundo ao número da lesão – 1 ou 2)*		
(11) Dor	**(1) sim (2) não (8) NSA (9) IGN**	**DOR |___|**
(12) Ardência (queimação)	**(1) sim (2) não (8) NSA (9) IGN**	**ARD |___|**
(13) Coceira	**(1) sim (2) não (8) NSA (9) IGN**	**COC |___|**
(14) Desconforto	**(1) sim (2) não (8) NSA (9) IGN**	**DESC |___|**
11. Tu costumas examinar a tua boca?		**LBAUTEX |___|**
(0) Nunca (1) Sim (2) Às vezes (9) IGN		

Relatório do Trabalho de Campo

O presente relatório está dividido em quatro partes correspondendo às etapas do trabalho desenvolvido pelo doutorando. A primeira parte explica as mudanças ocorridas nos objetivos da tese. A segunda traz explicações sobre inclusão de novos artigos a este volume. Por sua vez, a terceira parte deste relatório traz as funções do doutorando no trabalho de campo do Estudo de Saúde Bucal-13 aninhado à coorte de Pelotas de 1982. Finalmente, o último item apresenta os pontos relativos ao período de doutorado sanduíche na Universidade de Adelaide, Austrália.

1 Mudanças ocorridas no Projeto de Pesquisa

Ao finalizar a leitura do projeto, fica evidente o interesse que tínhamos em estudar o efeito da obesidade ao longo da vida nos desfechos periodontais da vida adulta. O objetivo inicial desta tese era testar se as teorias de *life-course epidemiology* poderiam ser aplicadas para explicar a relação entre obesidade e doenças periodontais. Entretanto, após um contato do doutorando com técnicas analíticas de inferência causal, foi necessária a adequação dos objetivos iniciais desta tese.

Os modelos analíticos que testam as teorias da epidemiologia do ciclo vital apresentam limitações com relação aos seus achados, uma vez que não consideram o caráter longitudinal das variáveis *time-varying*. Assim, há uma discussão sobre a validade dos achados originados destas análises. Por sua vez, as análises de inferência causal parecem gerar estimativas mais fiéis à realidade por dois aspectos principais: a) há distinção entre mediadores e confundidores no modelo analítico; b) estimativas criadas a partir de probabilidades geradas em um universo contrafactual. Estas características foram consideradas extremamente relevantes ao doutorando e aos seus orientadores no momento de decisão da técnica analítica a ser usada nos artigos originais incorporados a esta tese. Além disso, destaca-se o pioneirismo dos autores em utilizar esta abordagem analítica em desfechos de saúde bucal. Diante destes fatos, justifica-se a opção pela mudança dos objetivos iniciais desta tese.

2 Inclusão de novos artigos à tese

O projeto de pesquisa apresentado no capítulo anterior deste volume descreve apenas as questões metodológicas relativas ao Estudo de Saúde Bucal de 2013 da coorte de 1982. Entretanto, esta tese, além de artigos, traz também a trajetória do doutorando no seu período de doutoramento. O primeiro artigo incluído neste volume representa o primeiro contato do doutorando com o tema desta tese. Nele explorou-se a relação entre obesidade e sangramento gengival em escolares da cidade de Pelotas. Este artigo, embora apresente desenho transversal, evidencia o impacto da obesidade sobre as condições periodontais em fases precoces da vida, algo que não seria possível de verificar com os dados da coorte de Pelotas de 1982. Assim sendo, acreditamos ser pertinente a inclusão deste trabalho neste volume.

Como parte do aprendizado de técnicas analíticas para inferência causal, o Professor Marco Peres propos que um artigo prévio ao artigo analítico com os dados da coorte de Pelotas de 1982 fosse realizado com os dados do EpiFloripa, uma coorte de adultos da cidade de Florianópolis. Neste artigo, o objetivo central foi verificar o efeito da mudança de estado nutricional, especialmente do ganho de peso, em desfechos periodontais nesta coorte representativa da população de Florianópolis. Acreditamos que seria essencial o contato com técnicas analíticas de inferência causal em um cenário menos complexo que aquele da coorte de Pelotas de 1982, uma vez que o EpiFloripa apresenta dados de dois momentos distintos em um intervalo de tempo relativamente curto (três anos). Assim, o desenvolvimento deste estudo foi um passo importante para que o doutorando desenvolvesse o último estudo analítico desta tese, fato que justifica a inclusão deste artigo neste volume.

É importante ressaltar que mesmo aqueles artigos não planejados previamente têm a temática comum aos demais artigos desta tese: obesidade e doença periodontal. Além disso, como dito anteriormente, estes artigos evidenciam a trajetória percorrida pelo doutorando durante o seu doutoramento, com o aumento da complexidade das abordagens analíticas adotadas.

3 Participação no trabalho de campo do Estudo de Saúde Bucal de 2013 (ESB-13)

Em conjunto com a doutoranda do Programa de Pós-graduação em Epidemiologia, Lenise Menzes Seerig, o doutorando realizou a supervisão do trabalho de campo do Estudo de Saúde Bucal de 2013. Adicionalmente, também participou do presente estudo como examinador. O trabalho de campo iniciou no mês de outubro de 2013 e finalizou no mês de março de 2014. A etapa de calibração e treinamento da equipe teve duração de uma semana e realizou-se entre os dias 02 e 06 de setembro de 2013. Neste momento, foram apresentados aos examinadores e entrevistadores o questionário assim como a ficha de exame clínico. Os supervisores de campo instruíram os demais membros da equipe sobre forma de abordagem aos participantes, identificação e conduta a ser seguida no momento das entrevistas. A calibração ocorreu em indivíduos com idade entre 25 e 40 anos não pertencentes à coorte de 1982. Um examinador padrão-ouro foi determinado pelos coordenadores do levantamento. Cada examinador foi orientado a realizar o exame clínico odontológico completo em 20 indivíduos, os quais foram anotados pelo candidato a anotador. Os resultados obtidos com este processo revelaram os seguintes índices Kappa e de correlação intraclasse: Uso e necessidade de prótese dentário (Kappa 0.84); Índice de Estética Dental – DAI (Kappa 0.65); Índice de Superfícies Cariadas, Perdidas ou Obturadas – CPO-S (Kappa 0.89); Profundidade de Sondagem Periodontal (Índice de correlação intra-classe 0.85). Como resultado deste processo, seis examinadores (alunos de mestrado e doutorado do Programa de Pós-graduação em Odontologia) e 10 anotadores (alunos de mestrado do Programa de Pós-graduação em Odontologia e alunos de graduação em Odontologia) apresentaram-se calibrados e prontos para ir a campo.

A partir de listas fornecidas pelo Programa de Pós-graduação em Epidemiologia, buscou-se todos os 888 membros da coorte que haviam participado do Estudo de Saúde Bucal de 1997 (ESB-97), fazendo-os um novo convite para participar do ESB-13. Auxiliados pela secretária, os supervisores de campo providenciaram um número de contato telefônico para cada um dos indivíduos participantes. Assim, estabeleceu-se o primeiro contato, onde foi realizado o convite para participação deste novo levantamento. Em caso de aceite, foram obtidas preferências de data e horário para realização das entrevistas e dos exames

clínicos. Em caso de inexistência de número telefônico, contato via rede social (*Facebook*) foi realizado com os participantes localizados. Quando não se obteve retorno dos participantes em nenhuma destas formas de contato, os examinadores de campo visitaram o domícilio destes indivíduos baseados nos dados obtidos nos levantamentos prévios. Desta forma, os participantes encontrados em suas residências tiveram seus dados atualizados, sendo convidados para participar do estudo.

A secretária ficou responsável pelo agendamento das visitas aos domicílio dos participantes para realização da entrevista e do exame clínico. Para o trabalho de campo especificamente, cada examinador e cada anotador disponibilizou uma agenda semanal, incluindo fins de semana, com horários disponíveis para realização das visitas. De acordo com esta agenda, o supervisor de campo organizava a dupla "examinador/anotador" responsável pela visita. Além disso, o supervisor enviava os dados dos participantes para o e-mail da dupla responsável, com os dados da entrevista a ser realizada. Sempre que possível, com a finalidade de otimizar o processo de trabalho e de reduzir custos, o supervisor de campo agrupava de acordo com a área geográfica o maior número de entrevistas. Devido à peculiaridade desta coorte, alguns participantes preferiam ser entrevistados na sede do Centro de Pesquisas Epidemiológicas, localizada no centro do município de Pelotas. Nestes casos, a dupla "examinador/anotador" fazia seu deslocamento até este local, onde realizava a entrevista.

Os participantes da coorte que não mais residiam na cidade de Pelotas também foram contatados. Foi oferecida uma ajuda de deslocamento a estes participantes para que eles comparecessem ao Centro de Pesquisas Epidemiológicas. Devido ao número significativo de participantes em Caxias do Sul, Rio Grande e na Região Metropolitana de Porto Alegre, uma dupla composta por examinador e anotador também foi deslocada a estas localidades.

As duplas de examinadores e anotadores iam a campo identificadas por colete com o logo do Centro de Pesquisas Epidemiológicas e da Universidade Federal de Pelotas e por crachás com o respectivo nome. Além disso, levavam consigo o material necessário para o exame clínico (sonda periodontal PCP-2, odontoscópio plano n^{o}5, luvas, gaze, gorro e máscara) além de um *netbook*, onde eram anotadas as entrevistas e os dados provenientes do exame clínico, e do termo de consentimento livre e esclarecido. O referido termo era lido e assinado previamente

à entrevista. A duração média de cada visita foi de 25 minutos, desde a chegada da dupla “examinador/anotador” até a finalização do exame clínico.

O controle do número de entrevistas era realizado semanalmente pelos supervisores de campo, e discutidos com o restante da equipe. O controle de qualidade também foi de responsabilidade dos supervisores de campo. Após a realização das entrevistas, 10% dos participantes foi aleatoriamente selecionado para a realização de um questionário por telefone, contendo 10 questões selecionadas da entrevista. Os supervisores de campo ficaram responsáveis por esta tarefa, assim como por, verificar a satisfação dos participantes quanto ao trabalho da dupla que o entrevistou. Os resultados mostraram boa concordância das respostas, com índice Kappa superior a 0,80 para todas as perguntas. No que se refere à satisfação, a nota média foi de 9,3, variando de 7,0 a 10,0.

Após a conclusão do trabalho de campo, foi oferecido tratamento odontológico a todos os indivíduos que apresentaram necessidade de tratamento. Os participantes foram contatados via telefone para agendamento de consulta odontológica de acordo com as suas necessidades específicas. Foram oferecidos tratamentos nas áreas de Dentística Restauradora, Prótese Dentária, Endodontia, Periodontia e Estomatologia.

Ao doutorando couberam as seguintes atribuições enquanto supervisor de campo:

- Organizar material teórico (manual de campo);
- Agendar as visitas;
- Distribuir as visitas agendadas diariamente às duplas;
- Organizar diariamente a logística das visitas;
- Suprir material para realização das entrevistas (material de consumo, termos de consentimento livre e esclarecido, organizar esterilização dos materiais).

Na função de examinador de campo, o doutorando foi responsável por:

- Realizar exames odontológicos no domicílio e no Centro de Pesquisas Epidemiológicas;
- Realizar entrevistas;
- Realizar exames odontológicos no domicílio dos participantes da Região Metropolitana de Porto Alegre;

- Realizar o tratamento odontológico daqueles participantes que demandaram tal necessidade.

4 Período de Doutorado Sanduíche

Como parte do seu treinamento, o doutorando passou 11 meses do seu curso de doutoramento no *Australian Research Centre for Population Oral Health (ARCPOH)*, da Universidade de Adelaide, Austrália. Este centro de pesquisa é reconhecido internacionalmente pelos estudos desenvolvidos na área de epidemiologia em saúde bucal. Neste período, o Professor Marco Peres e a Professora Associada Karen Peres foram responsáveis pela orientação direta do doutorando. Foram colaboradores deste processo o Professor Mark Bartold (*School of Dentistry*), o Professor Associado Loc Do (ARCPOH), a Dra. Gloria Mejia (*ARCPOH*) e o Dr. Murthy Mittinty (*School of Population Health*). Durante o período do seu estágio sanduíche, o doutorando dedicou tempo ao aprendizado de técnicas analíticas causais e de mediação. Ainda, participou de seminários, conferências, cursos, "*journal clubs*", e apresentou dois seminários no centro de pesquisa.

Artigo 1

Artigo Original publicado no periódico *Journal of Clinical Periodontology*

J Clin Periodontol 2013; 40: 1072–1078 doi: 10.1111/jcpe.12163

Journal of Clinical Periodontology

Are obesity and overweight associated with gingivitis occurrence in Brazilian schoolchildren?

Gustavo G. Nascimento[1], Lenise M. Seerig[2], Fabiana Vargas-Ferreira[2], Fernanda O. B. Correa[1], Fábio R. M. Leite[1] and Flávio F. Demarco[1,2]

[1]Graduate Program in Dentistry, School of Dentistry, Federal University of Pelotas, Pelotas, Brazil; [2]Graduate Program in Epidemiology, Federal University of Pelotas, Pelotas, Brazil

Nascimento GG, Seerig LM, Vargas-Ferreira F, Correa FOB, Leite FRM, Demarco FF. Are obesity and overweight associated with gingivitis occurrence in Brazilian schoolchildren?. J Clin Periodontol 2013; 40: 1072–1078. doi: 10.1111/jcpe.12163.

Abstract

Aim: This cross-sectional study aimed to assess the relationship between weight status and gingival inflammation in Brazilian schoolchildren aged 8- to 12-year old, when controlling for potential confounders.

Methods: Overall, 1211 children aged 8- to 12-year old from public and private schools in Southern Brazil were selected by a two-stage cluster method. Questionnaires were used to assess socio-demographic data and oral hygiene habits. Oral examination evaluated presence of plaque and gingival bleeding. Anthropometric measures were collected to obtain body mass index. Multivariate Poisson regression was used for data analysis (Prevalence Ratio/95% Confidence Interval).

Results: Prevalence of gingivitis was 44.0%. Mean and median values of gingival bleeding sites were 3.10 and 2.0 respectively. Obese/overweight children totalized 34.6%. In multivariate adjusted analysis, sex (PR 0.86; 95%CI 0.75;0.98), maternal schooling (PR 1.09; 95% CI 1.01;1.18), plaque (PR 1.37; 95% CI 1.26;1.50), dental caries experience (PR 1.16; 95% CI 1.01;1.36) and bleeding during tooth brushing (PR 1.27; 95% CI 1.11;1.48) were associated with the outcome. In the sex-stratified analysis, overweight/obese boys presented a greater risk for gingivitis (PR 1.22 95% CI 1.01;1.48).

Conclusions: Gingivitis was not associated with obesity/overweight in the total sample. Gender differences seem to influence the relationship between gingivitis and obesity/overweight; a stronger association was noted among boys than girls.

Key words: epidemiology; obesity; overweight; paediatrics; periodontal diseases

Accepted for publication 1 September 2013

Conflict of interest and source of funding statement

The authors declare that they have no conflict of interests. The Brazilian National Council for Scientific and Technological Development (CNPq) provided research grant (process #402350/2008-1 and 79996/2008-5) to the Principal Investigator (FFD).

Obesity/overweight is defined as a disease in which body fat is excessively accumulated and may adversely affect general health (World Health Organization 2000). The disease is not a problem exclusive of adults from developed countries, since the proportion of children and adolescents with excessive fat accumulation has increased significantly also in developing countries (Kopelman 2000, Fadel et al. 2013). In Brazil, obesity/overweight in childhood and adolescence has risen in the last decades, with 32% of schoolchildren aged 12-year old affected by this condition in 2009 (Brazilian Institute of Geography & Statistic 2010). As a result, many physical and psychological diseases are precociously emerging. Adiposity is a well-known risk factor to many systemic diseases,

such as hypertension (Chaffee & Weston 2010), type 2 diabetes mellitus (Khader et al. 2009), cardiovascular disease (Chaffee & Weston 2010) and other life-threatening diseases. Thus, these age-dependent comorbidities can begin earlier in life than once believed, especially due to a change in the behavioural and dietary patterns (Reeves et al. 2006).

Periodontal diseases are mostly chronic inflammatory conditions from infectious nature induced by dental biofilm accumulation on teeth surfaces. Among children and adolescents, the most prevalent periodontal disease is the plaque-induced gingivitis, a site-specific condition (Lopez et al. 2006, Chiapinotto et al. 2013). Once gingivitis progression is dependent on the balance between host defence and bacterial load and virulence, an alteration in this relationship induced by systemic conditions may exacerbate the periodontal disease progression, resulting in collagen fibres destruction and alveolar bone loss (Genco & Borgnakke 2013). There are common risk factors for periodontal disease and obesity, such as smoke, dietary habits, alcohol consumption, psychological stress, among others (Genco & Borgnakke 2013).

Reports have hypothesized the interaction between obesity and periodontal disease, for example, variations and alterations in host defence, impaired glucose tolerance, increased response to psychological stress, and secretion of pro-inflammatory cytokines (Range et al. 2013).

Periodontal disease and obesity/overweight have been exhaustively studied in the last years in adults. Nevertheless, few studies were conducted investigating this relationship in children and adolescents. Epidemiological studies presented inconclusive data; Reeves et al. (2006) found a greater risk for periodontal disease only among obese young adults aged 17–21-year old, whereas 13- to 16-year-old adolescents did not present any association between both conditions. Franchini et al. (2011) did not observe an association between the gingival inflammation itself and obesity/overweight. Nevertheless, obese adolescents demonstrated bad oral hygiene, what is closely linked to the periodontal inflammation, with special regards to obese boys, who presented higher biofilm accumulation, a direct risk factor for periodontal disease, compared with obese girls (Franchini et al. 2011). Kâ et al. (2013) presented data proposing a close relationship between metabolic syndromes, which includes obesity, and gingivitis among children aged 8- to 10-year old. The authors, however, only detected this association among boys, suggesting that gender could be an influencing factor in this complex interaction. However, there is no consensus in the literature about the strength of this association between males and females, especially in early life, once Kwon et al. (2011) observed this association only among 19-year-old females.

Considering these controversial results and the need of further investigation about this topic, this study aimed to assess the relationship between weight status and periodontal disease in Brazilian schoolchildren aged 8- to 12-year old, when controlling for potential confounders.

Methods

Sample

This cross-sectional study was conducted in 2010 with children aged 8- to 12-year old, in Pelotas, southern Brazil. The city population is estimated in 330,000 people (Brazilian Institute of Geography & Statistics 2010) and the city presents 25 private and 91 public schools, with approximately 25,000 schoolchildren regularly attending school within the age range studied.

In order to select a representative sample of schoolchildren, a cluster selection sample was adopted with an estimated design effect of 2. The following parameters were used for the sample calculation (prevalence and association): prevalence of gingivitis 83.8 per cent (Chiapinotto et al. 2013), a standard error of 3 per cent, 95 per cent CI, power of 80 per cent, a design effect of 1.4, and adding 10 per cent to losses. The minimum sample size required for this study was 891 schoolchildren. To select the sample, 20 public private and public schools were randomly selected, considering the number of children in each school and the proportion of schools in the city. In each of the selected schools, children aged 8- to 12-year old, enrolled in grade 2–6 of primary education, were invited to participate. Detailed information about the methodology used has been already described (Goettems et al. 2013).

Data collection

Data collection was obtained at schools, and was composed by structured questionnaires sent to the parents, with socio-demographic information; interview with the children and clinical and oral examinations. Six examiners, previously trained and calibrated, with experience in epidemiological studies performed the oral examinations. Calibration process was composed by 40 h of theoretical activities and discussions about the outcomes, with the diagnostic based on photographic images, according to Goettems et al. (2013).

A benchmark dental examiner conducted the complete examiner training and the calibration process. Clinical examinations were carried out under artificial light, using CPI periodontal probe – "ball point" – (World Health Organization 1997) and dental mirrors. Dental caries experience (DMF-T ≥ 1) considered the DMF-T index. To assess the presence of dental plaque and gingival bleeding, the visible plaque index and gingival bleeding index, described by Ainamo & Bay (1975), were respectively used. The presence of gingival bleeding, gingivitis and dental plaque were adjusted to assess the contra-lateral incisors and first molars chosen randomly (Susin et al. 2005). The outcome of gingivitis occurrence was analysed by median (Kazemnejad et al. 2008, Chiapinotto et al. 2013).

In addition, anthropometric measures were taken to obtain the body mass index (BMI). The Cole criteria were used to determine the weight status considering child's sex and age (Cole et al. 2000).

Data analysis

Data were double-typed in the Epi Data 3.1 database, and transferred to STATA version 11.0 (Stata Corp., College Station, TX, USA). Data were submitted to descriptive and

bivariate analyses, chi-square and chi-square for linear trend when appropriate, in order to verify an association between the outcomes with the independent variables. After, a multivariate Poisson regression model was performed, considering the cluster sample design (prevalence ratio and 95%CI). For variable selection the stepwise method with backward selection was used. Variables with $p < 0.25$ were included in the fitting model, and estimated their Prevalence Ratio (PR) and their 95% confidence of interval. Variables with $p \leq 0.05$ were maintained in the adjusted model. The variables "age" and "BMI" were maintained in all multivariate models independently of their *p*-values. The variable "age" was used as a discrete variable in the bivariate analysis to show the distribution of sample; for the multivariate Poisson regression, this variable was grouped in two different categories according to the biological life course: childhood (8- to 10-year old) and adolescence (11- to 12-year old) (Jokovic et al. 2002). The variable "BMI" was kept since it was the main independent variable studied and it could be related to gender. Analyses were also stratified by sex, to investigate the effects of independent variables according to gender.

Ethics

The study was submitted and approved by the Ethics Committee of the Federal University of Pelotas School of Dentistry, Brazil. Only children with written consent form signed by their parents were included in the study.

Results

The response rate was 69.2% of total sample, and 1211 children were evaluated. The major reasons for participation refusal were as follows: lack of consent form signed by parents and absence of children at school in the examination day.

Table 1 presents the descriptive and univariate analyses of the evaluated population. A total of 574 (47.4%) boys and 637 (52.6%) girls were examined. In relation to skin colour, most of the children were white (72.8%) and 65.1% had between 8 and 10 year old. Regarding maternal schooling, 53.3% of the mothers had 9 or more years of school. In the last year, 75.7% of the children visited the dentist. Almost all children, brushed their teeth regularly, and 59% brushed once a day. The prevalence of gingivitis was 44.0% (95%CI 41.2;46.9). The mean of affected sites by visible plaque was 4.74 (± SD 4.10), varying from 0 to 20 sites with plaque and median of 4.0. Regarding gingival bleeding, mean of bleeding sites was 3.10 (± SD 3.22), varying from 0 to 19 and with median of 2.0. This value was considered a cut-point for the outcome gingivitis occurrence. Children with excessive fat accumulation (obesity and overweight) totalized 34.6% of the studied sample.

Table 1. Sample distribution and prevalence of gingivitis according to socio-demographic and biological variables, Pelotas, Brazil, 2011. (N = 1,211)

		Total		Gingivitis		*p*-value
		N	(%)	N	(%)	
Sex	Male	574	47.4	267	46.5	0.107*
	Female	637	52.6	267	41.9	
Skin colour	White	858	72.8	371	43.7	0.502*
	Dark-skinned Black	189	16.1	90	48.1	
	Light-skinned black	128	11.0	54	42.5	
Type of school	Public	958	79.0	445	46.4	0.001*
	Private	253	21.0	89	35.2	
Years	8	182	15.0	70	39.6	0.082†
	9	312	25.8	136	43.9	
	10	295	24.3	131	44.4	
	11	259	21.4	120	46.3	
	12	163	13.5	77	48.1	
Household income	1	246	23.7	93	38.0	0.002†
	2	271	26.1	111	41.6	
	3	241	23.2	110	45.8	
	4	279	26.9	140	50.5	
Maternal schooling	≥12	502	43.0	194	38.8	<0.0001†
	9–11	121	10.3	45	37.5	
	5–8	127	11.0	60	47.6	
	≤4	426	36.2	212	50.5	
Last visit to dentist	<1 year	905	75.7	254	41.8	0.248*
	More than 1 year	291	24.3	134	46.7	
Frequency of tooth brushing (times/daily)	1	697	59.0	294	42.7	0.226*
	2	106	9.0	52	49.5	
	3	382	32.0	179	47.0	
Body Mass Index (BMI)	Normal	787	65.4	344	43.7	0.766*
	Overweight/obese	417	34.6	186	44.6	
Visible plaque (tertiles)	0 to 2 sites	430	36.0	125	29.3	<0.001*
	3 to 5 sites	380	31.5	166	44.1	
	≥6 sites	399	33.0	243	29.3	
Dental caries experience	No	495	41.3	193	39.0	0.002*
	Yes	704	58.7	338	48.0	
Bleeding during tooth brushing	No	804	67.8	327	40.7	0.001*
	Yes	382	32.2	194	50.8	
Gingival inflammation (Bleeding sites)	0–2 sites	680	56.0	–	–	
	≥3	534	44.0	–	–	
Total		1211	100	534	44.0	

*Chi-square test.
†Chi-square test for linear trend.

Gingival inflammation was associated with the type of school – public or private ($p = 0.001$), maternal schooling ($p < 0.0001$), household income ($p = 0.002$), dental caries experience ($p = 0.002$), gingival bleeding and visible plaque ($p < 0.001$). BMI was maintained in the multivariate model independently of the *p*-value.

Table 2 presents the crude and adjusted prevalence ratios of multivariate Poisson regression for gingivitis according to the exposed variables. In crude analysis, gingivitis was associated with type of school, household income, lower maternal schooling, presence of visible plaque in higher number of sites, dental caries experience and

Table 2. Crude (C) and adjusted (A) Prevalence Ratios (PR) for gingivitis occurrence in schoolchildren, according to variables. Pelotas, RS, 2010

Variables	Gingivitis occurence			
	PR[c] (95%IC)	*p*	PR[a] (95%IC)	*p*-value
Sex		0.107		0.033
Male	1		1	
Female	0.91 (0.80;1.03)		0.86 (0.75;0.98)	
Age (years)		0.188		–
8–10	1		–	
11–12	1.09 (0.96;1.24)		–	
Type of School		<0.001		–
Public	1.33 (1.11;1.59)		–	
Private	1.0		–	
Household Income		<0.001		–
1 (poorer)	1.09 (0.88;1.36)		–	
2	1.21 (0.98; 1.49)		–	
3	1.33 (1.09;1.62)		–	
4 (richer)	1.0			
Maternal schooling (years)		<0.001		0.003
≥12	1.0		1.0	
9–11	1.17 (0.90;1.52)		1.13 (0.86;1.49)	
5–8	1.23 (0.93;1.62)		1.21 (0.91;1.61)	
≤4	1.45 (1.12;1.86)		1.33 (1.02;1.74)	
Last visit to dentist		0.160		–
<1 year	1		–	
More than 1 year	1.12 (0.96;1.30)		–	
Frequency of tooth brushing (times/daily)	1.16 (0.94;1.43)	0.144	–	–
1				
2	1.10 (0.96;1.26)		–	
3	1.0		–	
Visible plaque		<0.001		<0.001
0–2 sites	1.0		1.0	
3–5 sites	1.51 (1.25;1.82)		1.47 (1.22;1.78)	
≥6 sites	2.08 (1.76;2.46)		1.90 (1.59;2.27)	
Caries Experience		0.002		0.036
No	1.0		1.0	
Yes	1.23 (1.07;1.40)		1.16 (1.01;1.36)	
Bleeding during tooth brushing		0.001		<0.001
No	1.0		1.0	
Yes	1.24 (1.09;1.42)		1.27 (1.11;1.48)	
Body mass index		0.766		0.659**
Normal	1.0		1.0	
Overweight/obese	1.02 (0.89;1.16)		1.03 (0.89;1.18)	

**Variables maintained in the final model independently of the *p*-value.

self-reported bleeding during tooth brushing. After adjustment, sex (PR 0.86; 95%CI 0.75;0.98), maternal schooling (PR 1.09; 95% CI 1.01;1.18), visible plaque (PR 1.37; 95% CI 1.26;1.50), dental caries experience (PR 1.16; 95% CI 1.01;1.36) and bleeding during tooth brushing (PR 1.27; 95% CI 1.11;1.48) were associated with the outcome.

Among boys, adjusted Poisson regression revealed that obese/overweight schoolchildren presented a greater chance of having gingivitis (PR 1.22; 95% CI 1.01;1.48). The outcome was also associated with lower household income (PR 0.90; 95% CI 0.82;0.98), lower maternal schooling (PR 1.10; 95% CI 1.03;1.17), higher visible plaque (PR 1.39; 95% CI 1.23;1.56), higher caries experience (PR 1.22; 95% CI 1.01;1.51) and bleeding during brushing (PR 1.17; 95% CI 1.15;1.20) (Table 3). Among girls, the weight status was not associated in the final model, while lower maternal schooling (PR 1.11; 95% CI 1.01; 1.22), higher visible plaque (PR 1.35; 95% CI 1.20;1.53), higher caries experience (PR 1.22; 95% CI 1.01; 1.48) and bleeding during brushing (PR 1.22; 95% CI 1.01;1.47) remained associated (Table 4).

Discussion

This study evaluated the association of gingivitis and obesity among schoolchildren aged 8- to 12-year old, when controlling for possible confounders. In this study, occurrence of gingivitis was classified according to the number of sites affected by marginal bleeding (percentile 50). Our results demonstrated that gingival inflammation was associated with sex, low level of maternal schooling, presence of visible plaque, caries experience and bleeding during tooth brushing. On the stratified analysis, after adjustment, only obese/overweight boys presented a greater chance of having gingivitis, but such association was not observed for girls. In addition, gingivitis was associated with lower income and lower maternal schooling, higher prevalence of caries and bleeding during brushing. These variables were used for controlling and most of them were discussed in deep in another study from the same survey (Goettems et al. 2013).

Socio-economic factors have a close relationship with oral and general health outcomes. Social patterns of oral health outcomes are almost identical to the social gradients found in general health outcomes (Thomson 2012). According to Thomson (2012), the study of oral health is a useful way to understand social inequalities, due to the cumulative and chronic characteristics of oral conditions. Peres et al. (2009), in a cohort study in the city of Pelotas, demonstrated that mothers with low educational level tended to have children with a greater DMF-T, while Thomson et al. (2012) indicated that low household income and low parental education levels are intimately linked to the severity and extension of periodontal diseases. The same way, obesity and overweight in childhood are associated with low socio-economic status, and low levels of parental education (Gibbs & Forste 2013). Many reports demonstrated that obese children with disadvantaged background presented a greater risk for not only later obesity but also early morbidity (Shibli et al. 2008).

As previously described by many reports, gingivitis is one of the most prevalent diseases among children

Table 3. Crude (c) and adjusted (a) Prevalence Ratios (PR) for gingivitis occurrence among boys. Pelotas, RS, 2010

Variables	Gingivitis occurence			
	PR[c] (95%IC)	P	PR[a] (95%IC)	*p*-value
Age (years)		0.762		0.704**
8–10	1		1.0	
11–12	1.03 (0.85;1.24)		1.03 (0.85;1.27)	
Type of school		0.035		–
Public	1.31 (1.02;1.70)		–	
Private	1.0		–	
Household income		<0.001		0.023
1 (Poorest)	1.0		1.0	
2	0.81 (0.67–0.97)		1.01 (0.80;1.28)	
3	0.80 (0.67;0.97)		0.77 (0.58;1.02)	
4 (Richest)	0.72 (0.59;0.88)		0.76 (0.57;1.03)	
Maternal schooling (years)		0.030		0.007
≥12	1.0		1.0	
9–11	1.07 (0.75;1.52)		0.98 (0.74;1.31)	
5–8	0.93 (0.63;1.36)		1.27 (0.58;1.02)	
≤4	1.33 (0.96;1.84)		1.15 (1.01;1.33)	
Last visit to dentist		0.290		–
<1 year	1		–	
More than 1 year	1.11 (0.91;1.36)		–	
Frequency of tooth brushing (times/daily)		0.351		–
1	1.16 (0.94;1.43)		–	
2	1.10 (0.96;1.26)		–	
3	1.0		–	
Visible plaque		<0.001		<0.001
0 to 2 sites	1.0		1.0	
3 to 5 sites	1.48 (1.15;1.89)		1.50 (1.24;1.81)	
≥6 sites	2.10 (1.67;2.63)		1.93 (1.62;2.30)	
Dental caries experience		0.024		0.048
No	1.0		1.0	
Yes	1.24 (1.03;1.50)		1.22 (1.01;1.51)	
Bleeding during tooth brushing		0.022		0.024
No	1.0		1.0	
Yes	1.46 (1.12;1.89)		1.17 (1.15–1.20)	
Body mass index		0.197		0.043
Normal	1.0		1.0	
Overweight/obese	1.13 (0.94;1.36)		1.22 (1.01;1.48)	

**Variables maintained in the final model independently of the *p*-value.

and adolescents, so does dental caries. An interesting finding is the association of dental caries experience with gingivitis, in the adjusted model, with both sexes. It is well known that some habits are related to those conditions, since dental caries and gingival inflammation are the result of a complex interaction, composed by biological, environmental and social factors (Thomson 2012). The interface between dental caries and gingivitis is not a consensus in the literature. Even though both diseases are quite prevalent in childhood, their association remains unclear. Our results have shown that children with DMF-T ≥ 1 presented a greater chance of presenting gingival inflammation. A reasonable explanation for this fact could be related to plaque accumulation on tooth surface in both conditions, consequence of poorer oral self-care measures, associated with bad dietary habits and plaque maturation (Martinez-Pabon et al. 2013). Moreover, in proximal surfaces, not filled dental cavities, restoration marginal gaps and calculus could work as retentive factors for plaque accumulation what might increase the risk for gingivitis development in those specific sites (Ekstrand et al. 1998).

The relationship between obesity and oral health in childhood is still inconclusive. While in adults, there is a clear association with obesity and periodontal disease, in children and adolescents there is no consensus. Our results indicated that excessive fat accumulation is not related with gingival inflammation in the total sample. Reeves et al. (2006) in a recent study found that weight status influences the development of periodontitis in adolescents and young adults aged 17- to 21-year old. The authors, however, did not find this association in younger children, probably due to the chronic condition of obesity and periodontitis. The association of weight status and gingivitis was observed only in the subgroup analysis, with a positive association among boys. These results are in accordance with Kâ et al. (2013) who found similar differences among gender, with a stronger association among male children aged 8-10-year. Commonly, gender impacts a number of individual characteristics such as genetics, hormone status, nutrition and general and oral health habits, which may promote different responses of exposure and susceptibility. Reports have revealed that in adults, the relationship between weight status and periodontal disease is more robust among women, especially after the fifth or sixth decades of life. Probably, this fact is observed because, in early life, females have less fat accumulation than males, what is not supported in the long-life, when an increase of obesity prevalence is observed among women (Furuta et al. 2013). In addition, another factor that could be linked with the association of obesity and gingivitis only in boys is related to the pattern of oral hygiene at this age, once girls are more concerned about healthy lifestyle even in early life (Honne et al. 2012).

There are many hypotheses about the relationship between periodontal disease and obesity. Obese subjects tend to present unhealthy dietary habits, with higher consumption of sugar and fat, increasing the risk for periodontal disease (Al-Zahrani et al. 2003). The adipose tissue can represent a reservoir of pro-inflammatory cytokines, such as IL-1β, IL-8 and C-reactive protein, inducing a chronic immunological response by the host (Genco et al. 2005). The unbalance in the inflammatory response can affect the periodontal tissues even in early life (Reeves et al. 2006). Thus, we hypothesized that the combination of metabolic and inflammatory profiles, with neglected attitude towards oral and general health self-care, like poor

Table 4. Crude (c) and adjusted (a) Prevalence Ratios (PR) for gingivitis occurrence among girls. Pelotas, RS, 2010

Variables	Gingivitis occurence			
	PR[c] (95%IC)	*p*	PR[a] (95%IC)	*p*-value
Age (years)		0.108		0.108**
8–10	1		1.0	
11–12	1.15 (0.96;1.38)		1.16 (0.96;1.39)	
Type of School		<0.035		–
Public	1.31 (1.02;1.70)		–	
Private	1.0		–	
Household Income		0.278		–
1 (Poorest)	1.0		–	
2	1.07 (0.81–1.42)		–	
3	0.93 (0.68;1.27)		–	
4 (Richest)	1.21 (0.92;1.60)		–	
Maternal schooling (years)		<0.003		0.020
≥12	1.0		1.0	
9–11	1.30 (0.86;1.95)		1.26 (0.83;1.92)	
5–8	1.61 (1.07;2.43)		1.58 (1.04;2.41)	
≤4	1.62 (1.08;2.41)		1.49 (1.01;2.24)	
Last visit to dentist		0.290		–
<1 year	1		–	
More than 1 year	1.06 (0.87;1.31)		–	
Frequency of tooth brushing (times/daily)	0.92 (0.69;1.22)	0.191	–	–
1				
2	0.85 (0.64;1.11)		–	
3	1.0		–	
Visible plaque (tertiles)		<0.001		<0.001
0–2 sites	1.0		1.0	
3–5 sites	1.56 (1.17;2.07)		1.51 (1.10;2.06)	
≥6 sites	2.11 (1.63;2.73)		1.86 (1.40;2.48)	
Dental caries experience		0.050		0.045
No	1.0		1.0	
Yes	1.20 (1.01;1.45)		1.22 (1.01;1.48)	
Bleeding during tooth brushing		0.019		0.036
No	1.0		1.0	
Yes	1.24 (1.03;1.50)		1.22 (1.01;1.47)	
Body mass index		0.390		0.655**
Normal	1.0		1.0	
Overweight/obese	0.91 (0.76;1.11)		0.96 (0.78;1.16)	

**Variables maintained in the final model independently of the *p*-value.

oral hygiene, poor dietary habits and socioeconomic status can play an important role in the interface of weight status and periodontal disease (Franchini et al. 2011, Thomson et al. 2012).

Gingivitis, as a chronic condition, is the first stage in the evolution of periodontal diseases, and its prevention is necessary, since it is not possible to foresee which affected sites will evolve to destructive disease. A recent cohort study demonstrated that overweight and obesity are associated with gingival inflammation and dental calculus in young adults, showing the evolution of periodontal conditions over the years (Dickie de Castilhos et al. 2012). According to Susin et al. (2011) presence of dental calculus and gingival bleeding in adolescents are considered risk factors for the development of chronic and aggressive periodontitis, reinforcing the importance of controlling these factors in early life. Since periodontal disease and obesity/overweight may be associated and share key risk factors, adopting treatments based on common risk approach should be more rationale instead of focusing in one specific disease (Sheiham & Watt 2000). Moreover, establishment of healthy habits in childhood could be an important factor for disease prevention in adult life, especially in chronic conditions (Sheiham et al. 2011).

This study presents some important limitations that should be considered. First of all, as we used a cross-sectional design for the study, the causal and temporal associations of gingivitis and weight status remain unclear, once it is not possible to determine which condition was firstly established. Although this type of study is not indicated for the establishment of causal relationship, it provides useful data for further longitudinal investigations. The lack of criteria to diagnose gingivitis might be an obstacle for comparison among different studies in the literature. The Visible Plaque and Gingival Bleeding indexes (Ainamo & Bay 1975) used in this study, followed the same protocols already defined in previous epidemiologic evaluations conducted with schoolchildren population (Kazemnejad et al. 2008). Adoption of a partial register protocol (Peres et al. 2012) was selected considering that the mixed dentition could overestimate the prevalence of gingival inflammation, due to the physiological effect of eruption. Finally, the refusal rate obtained in our study could represent a sample biased, once non-examined children could present a different profile in relation to the outcome and the independent variables.

Regardless the limitations, this study presented valuable data in terms of possible interaction between general and oral health. In summary, there is no association between obesity/overweight and gingivitis in the total sample. A positive association was only observed in boys, but not in girls, demonstrating a potential influence of gender difference in this relationship. Our findings could be a baseline not only for further investigations, but also for the establishment of public policies, based on a holistic understanding of the health-disease process.

Acknowledgements

The authors are grateful to the State Secretary of Education, the Municipal Secretary of Education, and the Direction of Private Schools, which allowed this study to be performed.

References

Ainamo, J. & Bay, I. (1975) Problems and proposals for recording gingivitis and plaque. *International Dental Journal* **25**, 229–235.

Al-Zahrani, M. S., Bissada, N. F. & Borawskit, E. A. (2003) Obesity and periodontal disease in young, middle-aged, and older adults. *Journal of Periodontology* **74**, 610–615.

Brazilian Institute of Geography and Statistic (2010) Household budget survey 2008–2009. Anthropometry and nutritional status among children, adolescents and adults in Brazil; 1–130. [WWW document] http://www.ibge.gov.br/home/estatistica/populacao/condicaodevida/pof/2008_2009_encaa/pof_20082009_encaa.pdf [last accessed 20 June 2013].

Brazilian Institute of Geography and Statistics (2010) Synthesis of social indicators. An analysis of living conditions;1–317. [WWW document] http://www.ibge. gov.br/home/estatistica/populacao/condicaodevida/indicadoresminimos/sinteseindicsociais2010/SIS_ 2010.pdf [last accessed 20 June 2013].

Chaffee, B. W. & Weston, S. J. (2010) Association between chronic periodontal disease and obesity: a systematic review and meta-analysis. *Journal of Periodontology* **81**, 1708–1724.

Chiapinotto, F. A., Vargas-Ferreira, F., Demarco, F. F., Correa, F. O. & Masotti, A. S. (2013) Risk factors for gingivitis in a group of Brazilian schoolchildren. *Journal of Public Health Dentistry* **73**, 9–17.

Cole, T. J., Bellizzi, M. C., Flegal, K. M. & Dietz, W. H. (2000) Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ* **320**, 1240–1243.

Dickie de Castilhos, E., Horta, B. L., Gigante, D. P., Demarco, F. F., Peres, K. G. & Peres, M. A. (2012) Association between obesity and periodontal disease in young adults: a population-based birth cohort. *Journal of Clinical Periodontology* **39**, 717–724.

Ekstrand, K. R., Bruun, G. & Bruun, M. (1998) Plaque and gingival status as indicators for caries progression on approximal surfaces. *Caries Research* **32**, 41–45.

Fadel, H. T., Pliaki, A., Gronowitz, E., Marild, S., Ramberg, P., Dahlen, G., Yucel-Lindberg, T., Heijl, L. & Birkhed, D. (2013) Clinical and biological indicators of dental caries and periodontal disease in adolescents with or without obesity. *Clinical Oral Investigations*. doi: 10.1007/s00784-013-0972-9.

Franchini, R., Petri, A., Migliario, M. & Rimondini, L. (2011) Poor oral hygiene and gingivitis are associated with obesity and overweight status in paediatric subjects. *Journal of Clinical Periodontology* **38**, 1021–1028.

Furuta, M., Shimazaki, Y., Takeshita, T., Shibata, Y., Akifusa, S., Eshima, N., Kiyohara, Y., Ninomiya, T., Hirakawa, Y., Mukai, N., Nagata, M. & Yamashita, Y. (2013) Gender differences in the association between metabolic syndrome and periodontal disease: the Hisayama Study. *Journal of Clinical Periodontology* **40**, 743–752.

Genco, R. J. & Borgnakke, W. S. (2013) Risk factors for periodontal disease. *Periodontology 2000* **62**, 59–94.

Genco, R. J., Grossi, S. G., Ho, A., Nishimura, F. & Murayama, Y. (2005) A proposed model linking inflammation to obesity, diabetes, and periodontal infections. *Journal of Periodontology* **76**, 2075–2084.

Gibbs, B. G. & Forste, R. (2013) Socioeconomic status, infant feeding practices and early childhood obesity. *Pediatric Obesity*. doi: 10.1111/j.2047-6310.2013.00155.x.

Goettems, M. L., Correa, M. B., Vargas-Ferreira, F., Torriani, D. D., Marques, M., Domingues, M. R., Hallal, P. C. & Demarco, F. F. (2013) Methods and logistics of a multidisciplinary survey of schoolchildren from Pelotas, in the Southern Region of Brazil. *Cadernos de Saude Publica* **29**, 867–878.

Honne, T., Pentapati, K., Kumar, N. & Acharya, S. (2012) Relationship between obesity/overweight status, sugar consumption and dental caries among adolescents in South India. *International Journal of Dental Hygiene* **10**, 240–244.

Jokovic, A., Locker, D., Stephens, M., Kenny, D., Thompson, B. & Guyatt, G. (2002) Validity and reliability of a questionnaire for measuring child oral-health-related quality of life. *Journal of Dental Research* **81**, 459–463.

Kâ, K., Rousseau, M. C., Lambert, M., Tremblay, A., Tran, S. D., Henderson, M. & Nicolau, B. (2013) Metabolic syndrome and gingival inflammation in Caucasian children with a family history of obesity. *Journal of Clinical Periodontology* **40**, 986–993.

Kazemnejad, A., Zayeri, F., Rokn, A. R. & Kharazifard, M. J. (2008) Prevalence and risk indicators of periodontal disease among high-school students in Tehran. *East Mediterranean Health Journal* **14**, 119–125.

Khader, Y. S., Bawadi, H. A., Haroun, T. F., Alomari, M. & Tayyem, R. F. (2009) The association between periodontal disease and obesity among adults in Jordan. *Journal of Clinical Periodontology* **36**, 18–24.

Kopelman, P. G. (2000) Obesity as a medical problem. *Nature* **404**, 635–643.

Kwon, Y. E., Ha, J. E., Paik, D. I., Jin, B. H. & Bae, K. H. (2011) The relationship between periodontitis and metabolic syndrome among a Korean nationally representative sample of adults. *Journal of Clinical Periodontology* **38**, 781–786.

Lopez, R., Fernandez, O. & Baelum, V. (2006) Social gradients in periodontal diseases among adolescents. *Community Dentistry and Oral Epidemiology* **34**, 184–196.

Martinez-Pabon, M. C., Duque-Agudelo, L., Diaz-Gil, J. D., Isaza-Guzman, D. M. & Tobon-Arroyave, S. I. (2013) Comparison of the effect of two sugar-substituted chewing gums on different caries- and gingivitis-related variables: a double-blind, randomized, controlled clinical trial. *Clinical Oral Investigations*. doi:10.1007/s00784-013-0989-0.

Peres, M. A., Barros, A. J., Peres, K. G., Araujo, C. L. & Menezes, A. M. (2009) Life course dental caries determinants and predictors in children aged 12 years: a population-based birth cohort. *Community Dentistry and Oral Epidemiology* **37**, 123–133.

Peres, M. A., Peres, K. G., Cascaes, A. M., Correa, M. B., Demarco, F. F., Hallal, P. C., Horta, B. L., Gigante, D. P. & Menezes, A. B. (2012) Validity of partial protocols to assess the prevalence of periodontal outcomes and associated sociodemographic and behavior factors in adolescents and young adults. *Journal of Periodontology* **83**, 369–378.

Range, H., Poitou, C., Boillot, A., Ciangura, C., Katsahian, S., Lacorte, J. M., Czernichow, S., Meilhac, O., Bouchard, P. & Chaussain, C. (2013) Orosomucoid, a new biomarker in the association between obesity and periodontitis. *PLoS ONE* **8**, e57645.

Reeves, A. F., Rees, J. M., Schiff, M. & Hujoel, P. (2006) Total body weight and waist circumference associated with chronic periodontitis among adolescents in the United States. *Archives of Pediatric & Adolescent Medicine* **160**, 894–899.

Sheiham, A., Alexander, D., Cohen, L., Marinho, V., Moyses, S., Petersen, P. E., Spencer, J., Watt, R. G. & Weyant, R. (2011) Global oral health inequalities: task group–implementation and delivery of oral health strategies. *Advances in Dental Research* **23**, 259–267.

Sheiham, A. & Watt, R. G. (2000) The common risk factor approach: a rational basis for promoting oral health. *Community Dentistry and Oral Epidemiology* **28**, 399–406.

Shibli, R., Rubin, L., Akons, H. & Shaoul, R. (2008) Morbidity of overweight (>or=85th percentile) in the first 2 years of life. *Pediatrics* **122**, 267–272.

Susin, C., Haas, A. N., Valle, P. M., Oppermann, R. V. & Albandar, J. M. (2011) Prevalence and risk indicators for chronic periodontitis in adolescents and young adults in south Brazil. *Journal of Clinical Periodontology* **38**, 326–333.

Susin, C., Kingman, A. & Albandar, J. M. (2005) Effect of partial recording protocols on estimates of prevalence of periodontal disease. *Journal of Periodontology* **76**, 262–267.

Thomson, W. M. (2012) Social inequality in oral health. *Community Dentistry and Oral Epidemiology* **40** (Suppl 2), 28–32.

Thomson, W. M., Sheiham, A. & Spencer, A. J. (2012) Sociobehavioral aspects of periodontal disease. *Periodontology 2000* **60**, 54–63.

World Health Organization (1997) *Oral Health Survey: Basic Methods. Report of a WHO Consultation*. World Health Organization, 4th ed., Geneva.

World Health Organization (2000) *Obesity: Preventing and Managing the Global Epidemic. Report of a WHO Consultation World Health Organization Technical Report Series*. 894, i–xii, 1–253, World Health Organization, Geneva.

Address:
Flávio F. Demarco
Graduate Program in Dentistry
School of Dentistry
Federal University of Pelotas
457, Gonçalves Chaves St. room 506
Pelotas/RS – Brazil
96015-560
E-mail: ffdemarco@gmail.com

Clinical Relevance

Scientific relevance for the study: Association between obesity and periodontal disease has been reported mainly in adults, with scarce studies in the paediatric population.

Principal findings: Obesity and overweight were associated with gingivitis among boys. Social factors, oral hygiene factors and dental caries experience were also associated with gingival inflammation in both genders.

Practical implications: Young obese boys have a higher risk of developing gingivitis, risk factor for periodontitis. Common risk approach is recommended, once obesity and gingivitis share common risk factors; also, longitudinal studies with this specific population are needed.

Artigo 2

Brazilian Dental Journal (2014) 25(2): 87-89
http://dx.doi.org/10.1590/0103-6440201300019

ISSN 0103-6440

Relationship Between Periodontal Disease and Obesity: The Role of Life-Course Events

Gustavo G. Nascimento[1], Fábio R. Leite[1], Marcos B. Correa[1], Bernardo L. Horta[2], Marco A. Peres[3], Flávio F. Demarco[1,2]

[1]Postgraduate Program in Dentistry, UFPel - Federal University of Pelotas, Pelotas, RS, Brazil
[2]Postgraduate Program in Epidemiology, UFPel - Federal University of Pelotas, Pelotas, RS, Brazil
[3]Australian Research Centre for Population Oral Health, ARCPOH - The University of Adelaide, Australia

Correspondence: Prof. Dr. Flávio Fernando Demarco, Rua Gonçalves Chaves, 457, 5º andar, Centro, 96015-560 Pelotas, RS, Brasil. Tel: +55-53-3225-6741. e-mail: ffdemarco@gmail.com

Periodontal disease is ranked among the 10 most prevalent chronic diseases worldwide, and is considered a major public health problem. Its etiology has been associated with local and general conditions that could interfere in the host immune response. Obesity, like periodontal disease, has emerged as a prevalent chronic disease in high-, low- and medium-income countries, recognized as risk factor for cardiovascular disease and cancer. A relationship between periodontal health and obesity may exist, but the mechanism that would explain this association remains unclear. Life-course epidemiology could be a useful instrument to investigate a casual association between early exposures and later outcomes, being appropriate for understanding the establishment of chronic conditions. This approach comprehends different theories, considering the time, the duration and the intensity of early exposition, and its impact on the development of chronic diseases in later life. Thus, the aim of this study is to hypothesize the different life-course epidemiology theories to explain the possible association between periodontal health and nutritional status in adulthood.

Key Words: Periodontal disease, obesity, epidemiology

Introduction

Periodontal disease is mainly a chronic inflammatory condition induced by dental biofilm accumulation on tooth surfaces (1). It is a highly prevalent condition worldwide and represents a major public health problem for developed and developing countries (2). It figures among the 10 most prevalent chronic diseases (2). There are different clinical manifestations of periodontal conditions, such as gingivitis, an acute inflammation of gingival soft tissue caused by bacteria accumulation along the gingival margin; and periodontitis, a more advanced inflammatory form of periodontal disease, in which breakdown of the supporting tissues of the teeth occurs (3). Periodontitis is clinically characterized by periodontal pockets resulting from an attachment loss, which progressively can lead to loosening and ultimately loss of the teeth. Tooth loss is a worldwide public health problem caused mainly by dental caries and periodontal disease, the last especially in later adulthood, with impacts on quality of life (4). Periodontal destruction may be caused by local factors, such as dental biofilm, and systemic factors, like diabetes, HIV infection or other diseases that may depress the host immune response (3).

Evidence suggests that obesity associated with periodontal disease seems to exist, as several studies have observed this association in different life-course stages, since childhood to adulthood (5-8). Focusing on the biological aspects, a low-grade inflammation caused by excessive adipose tissue might be responsible for important alterations in the oral conditions. It has also been suggested that there is a high production of pro-inflammatory cytokines, such as interleukin (IL)-1β, tumor necrosis factor (TNF)-α, IL-6, by the adipocytes and macrophages of the white adipose tissue (9). These cytokines play a significant role in the development and progression of periodontal disease because the release of inflammatory cytokines is closely linked to a higher susceptibility to bacterial infection, caused by an alteration in the host immune response (10,11).

In order to identify the role of early exposures in the development of chronic diseases in later life, life-course epidemiology provides different tools that may help understanding the possible mechanisms involved in this relationship. Life-course epidemiology has been defined as the study of long-term effects of physical and social exposures that influence the development of chronic diseases across life course of individuals (12). It aims to establish potential causal links between exposures and outcomes, considering the duration and timing of the exposure (13).

Although many studies have explored the association between obesity and periodontal disease, the literature is scarce on prospective studies focused on this theme. The aim of this paper is to discuss on the relationship between obesity and periodontal disease according to four different life-course epidemiology theories: a) critical period (programming model); b) critical period with modifier

effect model; c) accumulation of risk model; d) chain-of-risk model (13,14).

Life-Course Epidemiology Approach

Critical Period Model

This model emphasizes that an exposure occurred in a specific period of life affecting some body structure or system and causing irreversible or permanent damage or disease later in life (12,15).

If one considers that this model explains the association between obesity and periodontal disease, subjects who presented obesity or overweight at a certain time period, e.g. childhood, will present higher prevalence of periodontal disease and more severe clinical attachment loss, resulting in worse periodontal condition compared with those that were eutrophic in early life. According to this theory, obesity in early life would permanently affect periodontal tissues, and he weight of the subject in adulthood is not relevant for the development of periodontal disease.

Critical Period with Modifier Effect Model

This model considers that the exposure at a certain age could interact with events that happened during different life periods, enhancing or decreasing the likelihood of developing a chronic condition (12,13). Therefore, this model assumes the possibility of risk change or "mobility" across the classes during life-course.

Taking this model into account, subjects would present a compatible periodontal situation respecting the trajectory of weight status during life course. The hypothesis of this study is that different outcomes are expected according to the different obesity/overweight trajectories during life: a) Subjects who were obese/overweight in early life and gained weight in adulthood would present the most severe clinical attachment loss and consequently the worst periodontal condition, since the early deleterious effects of obesity on periodontal health would be aggravated by the later weight gain, exacerbating the deficiency in host immune response already caused by early obesity event; b) individuals that were obese/overweight in early life and lost weight in adulthood would present the second worst periodontal condition, since even with the effects of obesity exposure in early life, with enduring damages to the periodontal tissue and the host defense mechanism, the decrease of inflammatory cytokine levels in later life, would increase the intensity of host response in front of a potential pathogen infection; c) subjects who were eutrophic in childhood and adolescence, but gained weight in adulthood would have better periodontal conditions than always obese subjects and obese earlier in life, but worse than the never obese individuals, because that exposure to inflammatory cytokines in later life would be less harmful than in early life, as this later exposure would not modify permanently the biological properties of periodontal tissues; d) always eutrophic subjects would present the best periodontal condition among the established trajectories.

Accumulation of Risk Model

The third model suggests that injuries are accumulated incrementally through the life-course. It considers that the number, duration and severity of exposures have a cumulative effect on the chronic disease development (12).

In this way, the disease load will be related to the amount of time that the subject was exposed to the risk condition. Therefore, periodontal disease development in adulthood would be directly proportional to the number of obesity episodes during life, independent from the life period when obesity/overweight occurred. In sum, subjects who were obese for a longer period of time would have a higher risk of periodontal diseases. Therefore, subjects with more episodes (longer periods of time) of obesity would be the ones with the most severe clinical attachment loss reflecting the worst periodontal status.

Chain-of-Risk Model

The fourth life-course model is a modified version of the accumulation of risk model and basically considers that one adverse or beneficial exposure conducts to other benefic/adverse event as a chain of events, impacting in health conditions. This model takes into consideration a complex interaction between exposures, such as individual social resources and extrinsic factors, e.g. social environment (13).

Considering the possible association between nutritional status and periodontal disease, obese subjects are expected to present low self-esteem, influencing directly in the oral and general health self-care, with neglected attitudes, like poor oral hygiene and poor dietary habits. Associated with these factors, obese individuals present altered metabolic and inflammatory profiles, like increased levels of C-reactive protein and pro-inflammatory cytokines, which would exert a major role in the periodontal disease development and progression.

Final Considerations

Based on the above, the hypothesis of this study is that life-course epidemiology has an important role in understanding the possible association of nutritional status and periodontal disease in later life. Accordingly, prospective studies are required to verify the sequence of events in the life course that may affect the development of chronic oral conditions. Such investigations could provide basis for the most appropriated time to start preventive strategies in order to reduce disease occurrence and severity, saving public resources and improving the quality of life

of individuals and populations.

Resumo

As doenças periodontais apresentam-se entre as dez doenças crônicas mais prevalentes mundialmente, sendo consideradas um relevante problema de saúde pública. Sua etiologia tem sido associada com fatores locais e com fatores sistêmicos que poderiam influenciar na resposta imune do hospedeiro. A obesidade, de forma semelhante à doença periodontal, emergiu como uma doença crônica altamente prevalente, tanto em países de alta renda, como em países de média e de baixa renda, sendo considerada um conhecido fator de risco às doenças cardiovasculares e ao câncer. Há uma possível relação entre as doenças periodontais e a obesidade, mas os mecanismos envolvidos nesta associação permanecem desconhecidos. A epidemiologia do ciclo vital pode ser considerada um eficiente instrumento para investigar associações causais entre exposições precoces e desfechos tardios, sendo apropriada para a compreensão do estabelecimento de doenças crônicas. Esta abordagem abrange diferentes teorias, considerando o tempo, a duração e a intensidade da exposição, e o seu impacto no desenvolvimento de doenças crônicas em fases tardias da vida. Assim, o objetivo deste estudo é fazer hipóteses sobre as diferentes teorias da epidemiologia do ciclo vital para explicar a possível associação entre a saúde periodontal e o estado nutricional na vida adulta.

Acknowledgements

The authors would like to thank the Brazilian government agency CNPq for the research funding (Process #403257/2012-3).

References

1. Genco RJ, Borgnakke WS. Risk factors for periodontal disease. Periodontol 2000 2013;62:59-94.
2. Petersen PE, Ogawa H. The global burden of periodontal disease: towards integration with chronic disease prevention and control. Periodontol 2000 2012;60:15-39.
3. Petersen PE, Baehni PC. Periodontal health and global public health. Periodontol 2000 2012;60:7-14.
4. Van Dyke TE, van Winkelhoff AJ. Infection and inflammatory mechanisms. J Clin Periodontol 2013;40:S1-S7.
5. Nascimento GG, Seerig LM, Vargas-Ferreira F, Correa FO, Leite FR, Demarco FF. Are obesity and overweight associated with gingivitis occurrence in Brazilian schoolchildren? J Clin Periodontol 2013;40:1072-1078.
6. Ka K, Rousseau MC, Lambert M, Tremblay A, Tran SD, Henderson M, et al.. Metabolic syndrome and gingival inflammation in Caucasian children with a family history of obesity. J Clin Periodontol 2013;40:986-993.
7. Dickie de Castilhos E, Horta BL, Gigante DP, Demarco FF, Peres KG, Peres MA. Association between obesity and periodontal disease in young adults: a population-based birth cohort. J Clin Periodontol 2012;39:717-724.
8. Han DH, Lim SY, Sun BC, Paek DM, Kim HD. Visceral fat area-defined obesity and periodontitis among Koreans. J Clin Periodontol 2010;37:172-179.
9. Cancello R, Clement K. Is obesity an inflammatory illness? Role of low-grade inflammation and macrophage infiltration in human white adipose tissue. BJOG 2006;113:1141-1147.
10. Karlsson EA, Beck MA. The burden of obesity on infectious disease. Exp Biol Med 2010;235:1412-1424.
11. Reynolds MA. Modifiable risk factors in periodontitis: at the intersection of aging and disease. Periodontol 2000 2014;64:7-19.
12. Kuh D, Ben-Shlomo Y. A life course approach to chronic disease epidemiology. 2nd ed. Oxford: Oxford University Press; 2004.
13. Nicolau B, Thomson WM, Steele JG, Allison PJ. Life-course epidemiology: concepts and theoretical models and its relevance to chronic oral conditions. Community Dent Oral Epidemiol 2007;35:241-249.
14. Demarco FF, Peres KG, Peres MA. Life course epidemiology and its implication for oral health. Braz Oral Res 2014 [Epub ahead of print. DOI: 10.1590/S1806-83242014.50000006].
15. Barker DJP. Mothers, babies and health in later life. 2nd ed. Edinburgh: Churchill Livingstone; 1998.

Received March 17, 2014
Accepted May 7, 2014

Artigo 3

Artigo de Revisão submetido ao periódico *Clinical Oral Investigations*

Does periodontal treatment have an effect on clinical and immunological parameters of periodontal disease in obese subjects? A systematic review and meta-analysis

Gustavo G. Nascimento[1,2,] Fábio R. M. Leite[1,2,] Marcos B. Correa[1,] Marco A. Peres[2,] Flávio F. Demarco[1,3]

[1] Post-Graduate Program in Dentistry, Federal University of Pelotas, Pelotas, Brazil

[2] Australian Research Centre for Population Oral Health (ARCPOH), School of Dentistry, The University of Adelaide, South Australia, 5005

[3] Post-Graduate Program in Epidemiology, Federal University of Pelotas, Pelotas, Brazil

Corresponding Author
Gustavo G. Nascimento
457, Gonçalves Chaves St, 5th floor
Pelotas, RS, Brazil
ZIP 96015-560
gustavo.gnascimento@hotmail.com

Abstract

Aim: To systematically review the literature to answer the questions: i)“Is periodontal treatment effective to improve clinical and immunological conditions in obese subjects?”; ii)“Do obese subjects present different clinical and immunological response after periodontal therapy when compared to non-obese subjects?”

Methods: Searches were performed in six databases up to August 2014. Interventional studies were included if the following data were described: (1) Obesity/overweight assessment; (2) Definition of periodontal disease; (3) Periodontal therapy; (4) Inflammatory marker in serum/plasma; and/or clinical parameters of periodontal disease. Assessment of quality was performed with the Downs and Black scale. Meta-analyses were conducted with the available data.

Results: Of 489 articles, 5 were included, and only 3 proceeded to meta-analysis of clinical outcomes. Included studies presented fair methodological quality. Statistical analysis demonstrated that periodontal therapy in obese subjects was effective to improve clinical outcomes. No clinical differences between post-therapy results of obese and non-obese were observed. Effects of periodontal therapy on inflammatory markers remain unclear.

Conclusions: Periodontal treatment seems to be effective to improve healing in obese individuals. No differences on periodontal healing between obese and non-obese subjects were observed; however, only limited and fragile base of evidence was available for analysis.

Clinical Relevance: Periodontal treatment is effective to improve clinical and immunological periodontal parameters in adults. Also, obesity seems to not modify the periodontal healing after treatment.

Key words: Periodontal therapy; Periodontitis; Obesity; Nutritional Status; Cytokines

Introduction

A plausible biologic relationship between obesity and periodontal disease may exist. Studies in adults and in children have investigated this possible relationship, and majority of them found a positive association between both conditions [1-3]. In addition, systematic reviews have exhaustedly explored this connection, supporting the evidences from clinical and epidemiological studies [4, 5]. However, the causal mechanisms behind this positive association remain unclear, once the cross-sectional design adopted by most of the studies does not allow a temporal relationship between presumed exposure and outcome [6].

Some mechanisms try to explain this association, considering different approaches such the socioeconomic, the behavioral, the life-course but always emphasizing the biologic one [7]. In essence, the white adipose tissue (WAT) is responsible for secretion of many inflammatory cytokines, such as interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, C-reactive protein (CRP) and specific adipocytokines such as leptin and adiponectin [8]. Additionally, some adipocytes could suffer hypoxia due to WAT hypertrophy. The dead adipocytes have the potential to secret pro-inflammatory cytokines and to increase the chemoattraction of monocytes to the WAT, exacerbating the cytokine secretion. Serum increase of pro-inflammatory mediators is responsible for producing a low-grade systemic inflammation and insulin resistance, influencing the host immune response [9]. Thus, the ability to identify and combat possible infectious agents is totally unbalanced, becoming the obese subjects more susceptible to systemic infections [10]. It has been shown that toll-like receptors (TLR) in periodontal tissues of obese subjects are desensitized by pro-inflammatory cytokines, which become less effective to periodontopathogen recognition, resulting in development and progression of periodontal diseases [5].

Periodontal therapy conceptually aims to eliminate both living bacteria in the microbial biofilm and calcified biofilm microorganisms. From a practical point of view, this therapy intends to reduce the number of biofilm microorganisms and disturb the ecology the microbial biofilm. As a consequence, the host immune response can better cope with the remaining microorganisms, decreasing the inflammatory load present in the affected sites [11]. The response of periodontal therapy in obese subjects has been discretely studied. As similarly observed in type II diabetes,

periodontal therapy success may present some specificities due to the potential modifier effect caused by obesity on periodontal tissues [12]. Previously conducted reports presented a low number of patients enrolled, and a lack of consensus between the clinical results; hence the effects of periodontal therapy on clinical and immunological parameters of obese subjects are not totally clear. Two systematic reviews have been published on the topic, but their results should be carefully considered. The first included observational and interventional studies without performing a meta-analysis, which limits the authors' results [13]. The later included participants with systemic disease affecting the periodontal response, such as diabetes. Even thought the authors had mentioned they intended to control their results, it was not possible [14]. Furthermore, since nor the first neither the later reviews assessed the effects of periodontal therapy in obese subjects, the question of whether obesity impacts on periodontal healing remains to be answered.

Since obesity may interfere on periodontal disease development and progression and given the knowledge obtained from diabetes studies, it is unsure the effects of periodontal therapy on obese subjects. Also, it is expected that obese individuals might present different clinical and immunological outcomes after periodontal therapy when compared to eutrophic subjects. Based on that, the aim of the present study was to systematically review the literature in order to explore the clinical and systemic immunological impact of periodontal therapy on obese subjects. Also, to compare obese and non-obese individuals regarding the clinical parameters and immunological markers level after periodontal treatment.

Methods

Review Questions

Is periodontal treatment effective to improve clinical and immunological conditions in obese subjects?

Are clinical and immunological responses after periodontal therapy of obese subjects different when compared to non-obese subjects?

Inclusion and Exclusion Criteria

Potential articles to be included in this review were independently examined by two reviewers (GGN and FRML) according to the following inclusion criteria:

1. Interventional studies assessing the effects of periodontal therapy on obese individuals and/or comparing the effects of periodontal therapy on obese and non-obese subjects;
2. Adults enrolled in the study (≥18year-old);
3. Obesity/overweight assessment (e.g. body mass index, waist/hip ratio, waist circumference);
4. Definition of periodontal disease;
5. Presence of periodontal therapy (Non-surgical therapy: supra, sub gingival scaling and root planing; Surgical therapy: open flap debridement with or without the use of regenerative materials);
6. Evaluation of at least one inflammatory marker in serum; and/or evaluation of clinical parameters of periodontal disease before and after periodontal therapy.

Additionally, the following exclusion criteria were observed:

1. Use of systemic medication (anti-inflammatory, antibiotics) 6-months previous to periodontal therapy;
2. Presence of systemic conditions that could affect the progression of periodontitis and/or gain/loss of weight;
3. Cell culture or animal studies;
4. Observational studies;
5. Letters to the editor, reviews and conference abstracts.

In cases of disagreement, articles were discussed between the reviewers until a consensus was reached.

Strategy Search

Literature was searched in a structured way to identify papers that analyzed the effect of periodontal therapy in clinical and/or immunological parameters in obese/overweight and eutrophic subjects. Electronic database searches in PubMed via Medline, Scopus, Embase, Web of Knowledge, Latin-American and Caribbean

Center on Health Sciences Information (LILACS) and Scientific Electronic Library Online (SciELO) were performed up to and including August 2014. Initially, the search was conducted on PubMed via Medline using the following strategy: “Periodontal Diseases”[Mesh] OR “Periodontitis”[Mesh] OR “Gingivitis”[Mesh]) AND “Obesity”[Mesh] OR “Obesity, Abdominal”[Mesh] OR “Body Fat Distribution”[Mesh] OR “Abdominal Fat”[Mesh] OR “Intra-Abdominal Fat”[Mesh] AND “Therapeutics”[Mesh] OR “Root Planing”[Mesh] OR “Dental Scaling”[Mesh] OR “Periodontal Debridement”[Mesh] OR “Periodontal Treatment” OR “Periodontal Therapy”. Search strategies used in other databases can be found in the appendix. No date and language restrictions were applied. Duplicate studies were identified and discarded using the software EndNote X7 (Thomson Reuters, Carlsbad, California, United States, 2013). Titles, abstracts and key words of potential articles were screened independently considering the inclusion and exclusion criteria by two reviewers. Lists were compared and in case of disagreement, a consensus was reached by discussion. Assessment of the full articles retrieved after an initial screening was performed independently by the same two reviewers. In addition to the electronic search, a hand search was performed in the reference list of all included studies by the same reviewers. Predefined data-collection worksheets were employed for the assessment of each selected publication.

Data extraction and quality assessment

Articles with potential to be included in the study were submitted to a detailed analysis comprehending information regarding author’s name and year of publication, inflammatory markers evaluated, study design with sample size, periodontal disease definition, obesity definition, mean age of enrolled subjects, follow-up period, type of periodontal therapy and main results. In addition, in order to perform a meta-analysis, results regarding mean values and standard deviation of inflammatory markers and/or clinical parameters were registered. Authors were contacted in order to clarify any queries on the study methodology or result.

With the intention to assess quality of selected studies, the scale proposed by Downs and Black [15] was used. As with previous studies [16], this checklist was modified slightly: the scoring for question 27 on power was simplified to zero or one-point, according to presence or absence of sufficient power in the study to detect a

clinically significant effect. Therefore, articles reporting power of less than 0.80 with alpha at 0.05 obtained a zero score. The maximum rate for this modified scale was 28 with all specific items scored as either yes (= 1) or no/unable to determine (= 0), with the exception of item 5, “Are the distributions of principals confounders in each group of subjects to be compared clearly described?” in which responses were rated as yes (=2), partially (=1) and no (=0). The ranges of scores were grouped into four different categories as follows: Excellent (26 to 28), good (20 to 25), fair (15 to 19) and poor (14 and less) [16]. Articles were evaluated by the same two reviewers independently, and in case of disagreement, a consensus was obtained after discussion.

Statistical Analysis

Each clinical sign of periodontal disease was considered an independent outcome as follows: percentage of sites with bleeding on probing (BoP), probing depth (PD) and clinical attachment level (CAL). Data regarding systemic inflammatory markers were not available to be included in the pooled analysis. In order to answer our review questions, different analyses were performed: 1. to observe the effect of periodontal therapy only among obese subjects; 2. to compare the effect of periodontal treatment between obese and non-obese. Meta-analyses were performed at the longest follow-up. When heterogeneity was not statistically significant (P>0.05), the fixed-effects model was used; otherwise, the random-effects model was employed [17]. The software RevMan 5.2 (The Nordic Cochrane Center, Copenhagen, Denmark, 2011) was used to perform the meta-analyses.

Results

Results from the literature search comprised 489 articles. One hundred forty-four articles were duplicated and removed, remaining 345 articles for consideration. After that, title, abstracts and key words were evaluated and 335 articles excluded. Finally, 10 articles were fully read, and five included in the final review (Figure 1). Excluded articles and main reason for exclusion are presented in Table 1.

Main results of included articles are present in Table 2. Of all included studies, two of them evaluated serum levels of C-reactive protein [18, 19], two determined the

levels of IL-6 and TNF-α [20, 19], two evaluated levels of leptin [19, 21] and only one assessed levels of IL-1 and INF-ɣ [20] and levels of adiponectin [21].

All studies presented clinical data of periodontal parameters at baseline and after treatment in obese and in non-obese subjects. Two of them found no difference on periodontal response between obese and normal-weight individuals [18, 20], whereas the remaining studies observed a worse periodontal healing in obese [22, 21, 19]. Three studies also evaluated the levels of circulating pro-inflammatory cytokines with obese subjects presenting significantly higher levels than their counterparts at baseline [18-20]. Additionally, all studies detected clinical and biochemical differences after periodontal therapy in comparison with baseline values.

The assessment of quality of included studies revealed that all of them were classified as fair quality with values ranging from 15 to 19.

Three studies presented available data to be included in the meta-analysis considering the effects of periodontal treatment on some clinical parameters of periodontal disease [20, 19, 21]; one study presented data only concerning BoP [20]. The latter authors were contacted in order to obtain data of remaining outcomes; nevertheless, the original dataset was not available. Other authors were also contacted to collect missing data, but no response was obtained. Even with the reduced number of studies enrolled, the effect of periodontal therapy could be observed in obese subjects, comparing all clinical parameters at baseline and follow-up (BoP: $P<0.0001$, I^2 0%; PD: $P<0.0001$, I^2 0%; CAL: $P<0.0001$, I^2 0%). In all analyses, as no heterogeneity was observed, the fixed model was employed. Considering the effects of periodontal therapy on clinical signs of periodontal disease of obese and non-obese subjects after periodontal treatment, no difference could be observed for all evaluated parameters (BoP: $P=0.19$, I^2 0%; PD: $P=0.93$, I^2 83%; CAL: $P=0.92$, I^2 87%). As heterogeneity was present only for PD and CAL, the random-effects model was used for those analyses.

Discussion

The results of this systematic review and meta-analysis demonstrated that periodontal therapy could improve clinical signs of periodontal disease in obese subjects. Additionally, this systemic condition seems to exert no influence on periodontal healing, when comparing after-treatment results of this group with non-

obese subjects. It is evident that our results should be carefully considered, once few studies presented available data to be included in the systematic review. Additionally, all articles were classified as fair quality, reinforcing our concerns with the obtained results.

Periodontal therapy seems to be an effective method to improve clinical signs of periodontal disease among obese individuals. Even though the effects of periodontal therapy on serum levels of inflammatory markers could not be measured in this review, it is expected a decrease of pro-inflammatory cytokines at least in gingival crevicular fluid. This local alteration could be responsible for improving the immune response towards inflammation resolution in the site-level, promoting periodontal healing. Similar findings were observed among type II diabetes individuals; even though both conditions have distinct etiological pathways [12]. Type II diabetes, besides altering the host immune response by increasing the levels of inflammatory markers, also interferes with both the delivery of nutrition and the migration of defensive immune cells to the gingival tissues. This, in turn, reduces the oxygen diffusion and elimination of metabolic waste, exacerbating the disease [23].

Surprisingly our findings comparing the post-treatment results of obese and non-obese subjects suggested that obesity did not modify the effects of periodontal treatment. However, it is worth pointing out that only one study followed-up the enrolled subjects up to 06 months [21], against 02 to 03 months in the others. This study revealed that obese subjects presented lower improvement of clinical parameters, suggesting that obesity could modify periodontal healing in the long-term. Thus, given that periodontal healing can occur until 24 months after therapy [24] and that it is influenced by local and systemic factors, it is not possible to assume that periodontal therapy would have similar outcomes in obese and in non-obese in the long-term. Additionally, as periodontal disease development and resolution are strongly influenced by oral habits [25], and since obese patients are more likely to present neglected general and oral health hygiene habits, it is not possible to presume the long-term effects of the therapy in this specific group [26].

Considering the effects of periodontal therapy in pro-inflammatory cytokines, no statistical analysis could be performed in our study. Many pro-inflammatory cytokines were investigated, such as IL-1β, IL-6, TNF-α, as well as, specific adipokines, like leptin and adiponectin. Despite this variety of mediators studied, results presented no consensus, once in some reports therapy was responsible for

decreasing serum levels of the studied protein, whereas in others not. Even with an improvement of periodontal status among enrolled obese patients post-therapy when compared to baseline, many of them retained several inflamed residual periodontal pockets, which might be responsible for maintaining serum levels of pro-inflammatory cytokines. It was also observed a lack of goal to be achieved by plaque or BoP levels in order to classify patients as clinically healthy at the end of therapy. Hence, our results suggest that the effect of periodontal treatment on systemic mediators of obese subjects should be further investigated.

Even with many reports in the medical field suggesting that obesity may influence the immune-inflammatory response [27], this is not evident in the periodontal tissues. Some investigators have studied the effects of adipokines in this process, looking at the role played by the interaction between leptin, visfatin and adiponectin [28, 29]. According to Deschner and colleagues [30], the increase in the first two cytokines, combined with the decrease in the last one could be considered a “pathomechanistic link between obesity and compromised periodontal healing”.

In the present review, several limitations should be taken into consideration. Firstly, the results obtained in the meta-analysis are fragile, once few studies presented data to be analyzed. Even with other studies presenting potential data to be pooled, authors did not respond to any request. Secondly, the small number of studies precluded the assessment of heterogeneity by using meta-regression and subgroup analyses, as well as the assessment of publication bias by using funnel plot and the Egger’s test. Thirdly, it was not possible to combine the results of immunological markers possibly affected by periodontal therapy. Thus, it was not possible to measure quantitatively the effects of periodontal treatment on these mediators. Fourthly, the low number of subjects enrolled in the included studies and the short follow-up could misrepresent the actual impact of obesity on the healing of periodontal tissues. As most studies did not present a sample size calculation, it was not possible to determine if the absence of difference in periodontal healing after therapy between obese and non-obese subjects was real or if it was due to a lack of statistical power to identify it. Fifthly, it is worth pointing out that the design of included studies could also have misrepresented our findings. Even though it has been shown that obese subjects tend to present neglected hygiene habits and low socioeconomic status [31, 32], no study concerned about pairing subjects enrolled in obese and non-obese groups. This might have compromised the comparability

between groups. Finally, all studies presented a fair quality, signaling that included studies also presented important limitations in their designs and findings.

In summary, and considering the limits of this systematic review, only restricted information comparing the effects of periodontal therapy on obese and non-obese is available in the current literature. Overall, our results suggest that periodontal therapy is effective to improve clinical outcomes of periodontal disease in obese subjects. Additionally, obesity seems not exert a modifier effect on periodontal healing, once obese and non-obese subjects presented similar improvement of clinical conditions post-therapy. Nevertheless, interventional prospective case-controls with long-term follow-up, larger number of subjects enrolled and more solid methodological aspects are required for further investigations.

Conflict of Interest

The authors deny any conflict of interest.

Acknowledgments

The authors are grateful to the Coordination for the Improvement of Higher Education Personnel (CAPES) for the scholarship provided to GGN (#BEX 13810/13-8) and to the National Counsel of Technological and Scientific Development (CNPq) for the scholarship provided to FRML (#BEX 229279/2013-9).

References

1. Han DH, Lim SY, Sun BC, Paek DM, Kim HD (2010) Visceral fat area-defined obesity and periodontitis among Koreans. J Clin Periodontol 37:172-179. doi:10.1111/j.1600-051X.2009.01515.x

2. Furuta M, Shimazaki Y, Takeshita T, Shibata Y, Akifusa S, Eshima N, Kiyohara Y, Ninomiya T, Hirakawa Y, Mukai N, Nagata M, Yamashita Y (2013) Gender differences in the association between metabolic syndrome and periodontal disease: the Hisayama Study. J Clin Periodontol 40:743-752. doi:10.1111/jcpe.12119

3. Nascimento GG, Seerig LM, Vargas-Ferreira F, Correa FO, Leite FR, Demarco FF (2013) Are obesity and overweight associated with gingivitis occurrence in Brazilian schoolchildren? J Clin Periodontol 40:1072-1078. doi:10.1111/jcpe.12163

4. Chaffee BW, Weston SJ (2010) Association between chronic periodontal disease and obesity: a systematic review and meta-analysis. J Periodontol 81:1708-1724. doi:10.1902/jop.2010.100321

5. Suvan J, D'Aiuto F, Moles DR, Petrie A, Donos N (2011) Association between overweight/obesity and periodontitis in adults. A systematic review. Obes Rev 12:e381-404. doi:10.1111/j.1467-789X.2010.00808.x

6. Khader YS, Bawadi HA, Haroun TF, Alomari M, Tayyem RF (2009) The association between periodontal disease and obesity among adults in Jordan. J Clin Periodontol 36:18-24. doi:10.1111/j.1600-051X.2008.01345.x

7. Nascimento GG, Leite FR, Correa MB, Horta BL, Peres MA, Demarco FF (2014) Relationship between periodontal disease and obesity: the role of life-course events. Braz Dent J 25:87-89

8. Kopelman PG (2000) Obesity as a medical problem. Nature 404:635-643. doi:10.1038/35007508

9. Cancello R, Clement K (2006) Is obesity an inflammatory illness? Role of low-grade inflammation and macrophage infiltration in human white adipose tissue. BJOG 113:1141-1147. doi:10.1111/j.1471-0528.2006.01004.x

10. Bullo M, Garcia-Lorda P, Megias I, Salas-Salvado J (2003) Systemic inflammation, adipose tissue tumor necrosis factor, and leptin expression. Obes Res 11:525-531. doi:10.1038/oby.2003.74

11. Adriaens PA, Adriaens LM (2004) Effects of nonsurgical periodontal therapy on hard and soft tissues. Periodontol 2000 36:121-145. doi:10.1111/j.1600-0757.2004.03676.x

12. Correa FO, Goncalves D, Figueredo CM, Bastos AS, Gustafsson A, Orrico SR (2010) Effect of periodontal treatment on metabolic control, systemic inflammation and cytokines in patients with type 2 diabetes. J Clin Periodontol 37:53-58. doi:10.1111/j.1600-051X.2009.01498.x

13. Keller A, Rohde JF, Raymond K, Heitmann BL (2015) The Association Between Periodontal Disease and Overweight and Obesity: A Systematic Review. J Periodontol:1-15. doi:10.1902/jop.2015.140589

14. Papageorgiou SN, Reichert C, Jager A, Deschner J (2015) Effect of overweight/obesity on response to periodontal treatment: systematic review and a meta-analysis. J Clin Periodontol. doi:10.1111/jcpe.12365

15. Downs SH, Black N (1998) The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health 52:377-384

16. Tan L, Wang MJ, Modini M, Joyce S, Mykletun A, Christensen H, Harvey SB (2014) Preventing the development of depression at work: a systematic review and meta-analysis of universal interventions in the workplace. BMC Med 12:74. doi:10.1186/1741-7015-12-74

17. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7:177-188

18. Al-Zahrani MS, Alghamdi HS (2012) Effect of periodontal treatment on serum C-reactive protein level in obese and normal-weight women affected with chronic periodontitis. Saudi Med J 33:309-314

19. Altay U, Gurgan CA, Agbaht K (2013) Changes in inflammatory and metabolic parameters after periodontal treatment in patients with and without obesity. J Periodontol 84:13-23. doi:10.1902/jop.2012.110646

20. Zuza EP, Barroso EM, Carrareto AL, Pires JR, Carlos IZ, Theodoro LH, Toledo BE (2011) The role of obesity as a modifying factor in patients undergoing non-surgical periodontal therapy. J Periodontol 82:676-682. doi:10.1902/jop.2010.100545

21. Dias Goncalves TE, Feres M, Zimmermann GS, Faveri M, Figueiredo LC, Braga PG, Duarte PM (2014) Effects of Scaling and Root Planing on Clinical Response and

Serum Levels of Adipocytokines in Obese Patients With Chronic Periodontitis. J Periodontol:1-12. doi:10.1902/jop.2014.140266

22. Suvan J, Petrie A, Moles DR, Nibali L, Patel K, Darbar U, Donos N, Tonetti M, D'Aiuto F (2014) Body mass index as a predictive factor of periodontal therapy outcomes. Journal of Dental Research 93:49-54. doi:10.1177/0022034513511084

23. Kumar M, Mishra L, Mohanty R, Nayak R (2014) "Diabetes and gum disease: The diabolic duo". Diabetes Metab Syndr 8:255-258. doi:10.1016/j.dsx.2014.09.022

24. Graziani F, Laurell L, Tonetti M, Gottlow J, Berglundh T (2005) Periodontal wound healing following GTR therapy of dehiscence-type defects in the monkey: short-, medium- and long-term healing. J Clin Periodontol 32:905-914. doi:10.1111/j.1600-051X.2005.00789.x

25. van der Weijden F, Slot DE (2011) Oral hygiene in the prevention of periodontal diseases: the evidence. Periodontol 2000 55:104-123. doi:10.1111/j.1600-0757.2009.00337.x

26. Franchini R, Petri A, Migliario M, Rimondini L (2011) Poor oral hygiene and gingivitis are associated with obesity and overweight status in paediatric subjects. J Clin Periodontol 38:1021-1028. doi:10.1111/j.1600-051X.2011.01770.x

27. Karlsson EA, Beck MA (2010) The burden of obesity on infectious disease. Exp Biol Med (Maywood) 235:1412-1424. doi:10.1258/ebm.2010.010227

28. Nokhbehsaim M, Keser S, Jager A, Jepsen S, Deschner J (2013) Regulation of regenerative periodontal healing by NAMPT. Mediators Inflamm 2013:202530. doi:10.1155/2013/202530

29. Nokhbehsaim M, Keser S, Nogueira AV, Cirelli JA, Jepsen S, Jager A, Eick S, Deschner J (2014) Beneficial Effects of Adiponectin on Periodontal Ligament Cells under Normal and Regenerative Conditions. J Diabetes Res 2014:796565. doi:10.1155/2014/796565

30. Deschner J, Eick S, Damanaki A, Nokhbehsaim M (2014) The Role of Adipokines in Periodontal Infection and Healing. Mol Oral Microbiol. doi:10.1111/omi.12070

31. Adair LS, Fall CH, Osmond C, Stein AD, Martorell R, Ramirez-Zea M, Sachdev HS, Dahly DL, Bas I, Norris SA, Micklesfield L, Hallal P, Victora CG, group C (2013) Associations of linear growth and relative weight gain during early life with adult health and human capital in countries of low and middle income: findings from five birth cohort studies. Lancet 382:525-534. doi:10.1016/S0140-6736(13)60103-8

32. Thomson WM, Sheiham A, Spencer AJ (2012) Sociobehavioral aspects of periodontal disease. Periodontol 2000 60:54-63. doi:10.1111/j.1600-0757.2011.00405.x

Figure Captions

Fig. 1 Flow-chart of identification and selection process of studies

Fig. 2 Clinical outcomes before and after periodontal therapy in obese subjects. A. Bleeding on Probing (%); B. Probing Depth (PD); C. Clinical Attachment Loss (CAL)

Fig. 3 Post-therapy clinical outcomes in obese and non-obese subjects. A. Bleeding on Probing (%); B. Probing Depth (PD); C. Clinical Attachment Loss (CAL)

Figures

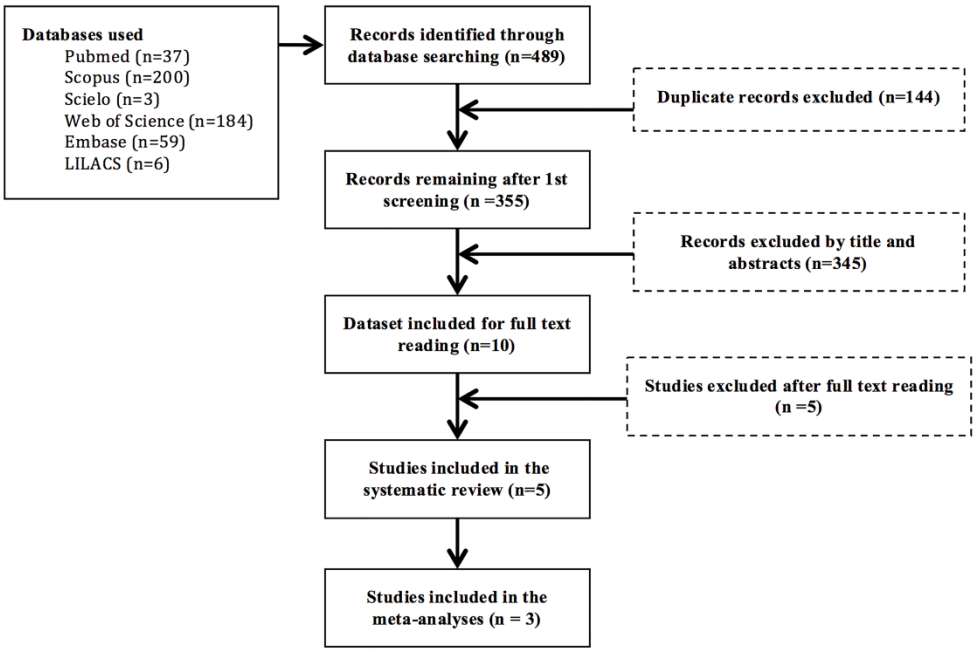


Fig. 1 Flow-chart of identification and selection process of studies

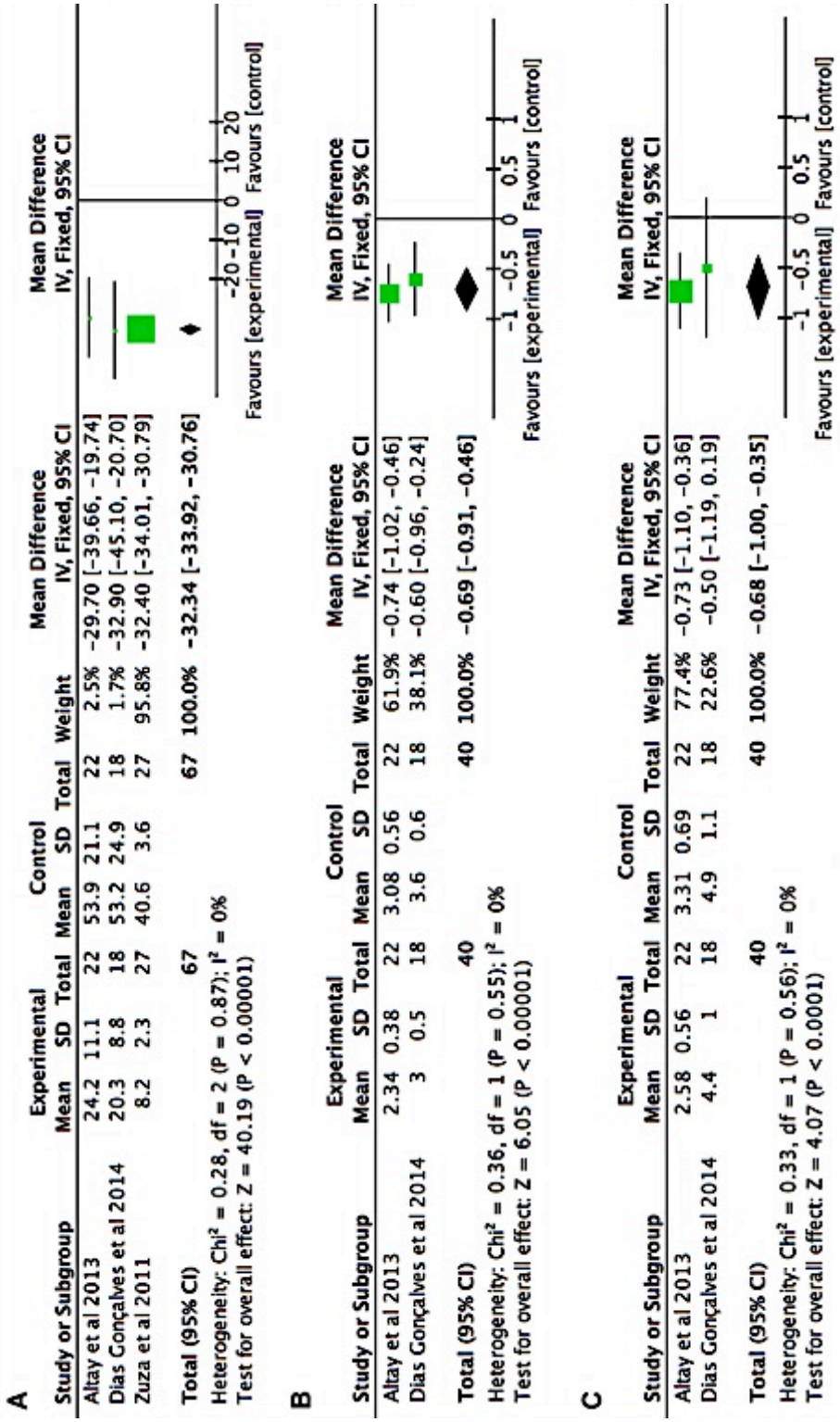


Fig. 2 Clinical outcomes before and after periodontal therapy in obese subjects. A. Bleeding on Probing (%); B. Probing Depth (PD); C. Clinical Attachment Loss (CAL)

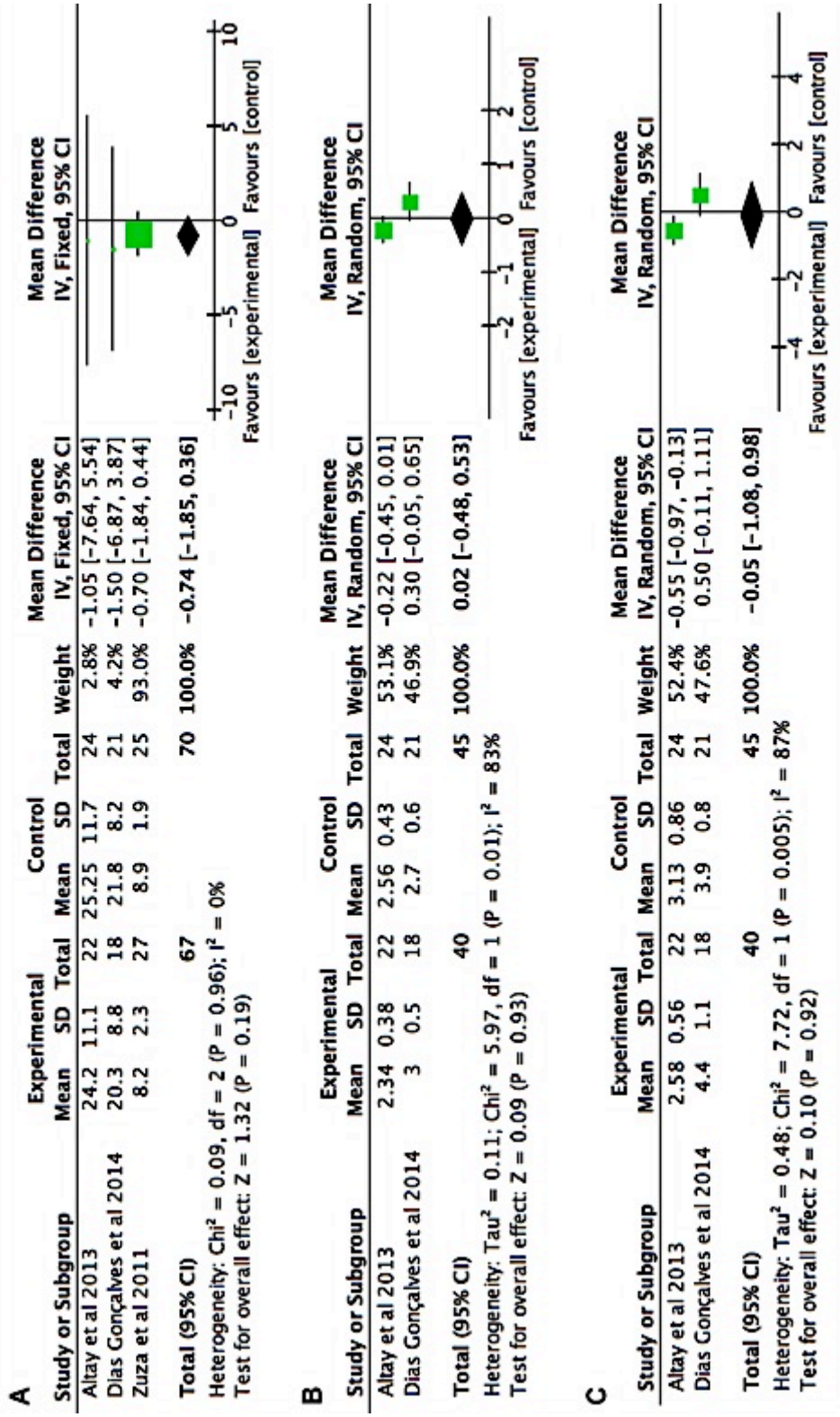


Fig. 3 Post-therapy clinical outcomes in obese and non-obese subjects. A. Bleeding on Probing (%); B. Probing Depth (PD); C. Clinical Attachment Loss (CAL)

Tables

Table 1. Main reasons for exclusion of studies

Study	**Main reason for exclusion**
Acharya et al., 2010	No data available considering only obese subjects
Eldin et al., 2013	No definition of periodontal disease
López et al., 2012	No data available considering only obese subjects
Offenbacher et al., 2009	No data available considering only obese subjects
Pavez Correa et al., 2011	Presence of subjects with systemic disease (Diabetes Mellitus)

Table 2. Main findings of studies that fulfilled all inclusion criteria

Study	Inflammatory markers evaluated	Clinical parameters evaluated	Study design and population	Periodontal disease definition	Obesity definition	Mean age	Follow-up period	Type periodontal therapy (Surgical/non-surgical)	Pro-inflammatory cytokines results	Clinical periodontal parameters results	Observation
Al-Zahrani and AlGhamdi, 2012	Serum C-reactive protein	BoP (%); PD (mm); CAL (mm).	Interventional: Obese with CP (20); Non-obese with CP (20).	CAL≥3mm in ≥30% of sites.	BMI: Normal weight: 18.5-25; Obese: ≥ 30.	Overall: 43.7; Obese: 44; Non-obese: 43.4.	02 months	Non-surgical: scaling and root planing + OHI	Highest levels of CRP: obese with periodontal disease at baseline. Periodontal therapy significantly reduced CRP levels in both groups. No differences were found in final levels of CRP between both groups after therapy.	Periodontal therapy was effective to improve clinical parameters in obese and non-obese with no differences observed.	Sample size composed only by women. No data available before and after treatment separated by weight status.
Altay et al., 2013	Serum IL-6; TNF-α; C-reactive protein; Leptin	BoP (%); PD (mm); CAL (mm).	Interventional: Obese with CP (22); Non-obese with CP (24).	≥5 teeth with ≥1 site with PD≥5mm, CAL≥2mm and BoP.	BMI: Obesity class I: 30-34.9; class II: 35-39.9; class III: ≥40. WC: >102 males; >88 females.	Obese: 45.6; Non-obese: 42.5	03 months	Non-surgical: scaling and root planing + OHI + chlorhexidine 0.12% (14 days)	Highest levels of TNF-α, leptin: obese with PD at baseline. Periodontal therapy significantly reduced IL-6, TNF-α and leptin levels in obese; and IL-6 in normal-weight. After treatment, obese subjects presented greater	Post-therapy results revealed that obese and non-obese presented similar clinical outcomes of periodontal disease, except for CAL. Obese subjects presented lower CAL	Included in meta-analysis.

									values of Il-6 than normal-weight.	after therapy than non-obese ones.	
Gonçalves et al., 2014	Serum Leptin; Adiponectin	BoP (%); PD (mm); CAL (mm).	Interventional: Obese with CP (18); Non-obese with CP (21).	> 30 % of the sites with concomitant PD and CAL ≥ 4 mm and at least six teeth distributed in the different quadrants presenting at least one site with PD and CAL ≥ 5 mm and BoP at baseline.	BMI: Obesity ≥30; WHR: ≥0.9 males; ≥0.8 for females	Obese: 48.8; Non-obese: 48.4.	03 and 06 months	Non-surgical therapy: OHI+ scaling and root planning	Highest levels of leptin at any time in obese. No differences between adiponectin. Non-surgical periodontal therapy did not reduce serum leptin and adiponectin.	Periodontal therapy significantly improved clinical parameters in obese and non-obese. Non-obese subjects presented better response at 06 months, with lower PD mean and greater PD reduction.	Included in meta-analysis. For meta-analysis, only the 06 months data were considered.
Suvan et al., 2014	-	BoP (%); PD (mm); CAL (mm).	Interventional: Obese with CP (55); Overweight with DP (93); Non-obese with CP (112).	PD>5mm; marginal alveolar bone loss of > 30% with > 50% of the teeth affected	BMI: Overweight 25-29.99; Obesity ≥30	Obese: 46.3; Overweight: 47.3; Non-obese: 46.6	02 months	Non-surgical therapy: OHI+ scaling and root planning	-	Obese subjects presented worse clinical parameters at any time of follow-up. The response to periodontal therapy was poorer in obese than in non-obese and overweight, with greater PI, BOP	Clinical data presented in a graph.

										and PD.	
Zuza et al., 2011	Serum IL-1β, IL-6, TNF-α, INF-ɣ	BoP (%); PD (mm); CAL (mm).	Interventional: Obese with CP (27); Non-obese with CP (25).	≥2 teeth with PD ≥5mm; CAL sites: shallow: 0-3mm; mild-to-moderate: 4-6mm; deep: ≥7mm.	BMI: Obesity ≥30; WHR: ≥0.9 males; ≥0.8 for females; WC: >102 males; >88 females; BF: ≥25% males; ≥33% females.	Obese: 45.1; Non-obese: 42.9	03 months	Non-surgical: scaling and root planning	Highest levels of IL-1β, IL-6, TNF-α: obese subjects. Non-surgical periodontal therapy significantly reduced all cytokines in both groups; after treatment, IL-6, TNF-α were significantly higher among obese subjects.	Periodontal therapy was effective to improve clinical parameters in obese and non-obese. No differences observed between obese and non-obese post-therapy.	Authors stated that the original dataset was not available. Clinical data presented in percentages of sites with PD ≤3; PD 4-6; PD ≥7; CAL≤3; CAL 4-6; CAL ≥7. Data regarding BoP was included in the meta-analysis.

IL-1β: Interleukin-1beta; IL-6: Interleukin-6; TNF-α: Tumor Necrosis Factor-alpha; INF-ɣ: Interferon-gamma; CRP: C-reactive protein; PI: Plaque index; BoP: Bleeding on Probing; PD: Probing Depth; CAL: Clinical attachment level; CP: Chronic Periodontitis; BMI: Body Mass Index; WC: Waist Circumference; WHR: Waist-hip ratio; OHI: Oral hygiene instruction

Artigo de Revisão publicado no periódico *Journal of Clinical Periodontology*

J Clin Periodontol 2015; doi: 10.1111/jcpe.12417

Journal of Clinical Periodontology

Systematic Review

Is weight gain associated with the incidence of periodontitis? A systematic review and meta-analysis

Gustavo G. Nascimento[1,2], Fábio R.M. Leite[1,2], Loc G. Do[2], Karen G. Peres[2], Marcos B. Correa[1], Flávio F. Demarco[1,3] and Marco A. Peres[2]

[1]Postgraduate Program in Dentistry, Federal University of Pelotas, Pelotas, Brazil; [2]Australian Research Centre for Population Oral Health, School of Dentistry, The University of Adelaide, Adelaide, SA, Australia; [3]Postgraduate Program in Epidemiology, Federal University of Pelotas, Pelotas, Brazil

Nascimento GG, Leite FRM, Do LG, Peres KG, Correa MB, Demarco FF, Peres MA. Is weight gain associated with the incidence of periodontitis? A systematic review and meta-analysis. J Clin Periodontol 2015; doi:10.1111/jcpe.12417.

Abstract

Aim: This study aimed to conduct a systematic review assessing the effects of weight gain on the incidence of periodontitis in adults.

Methods: Electronic searches in four databases were performed up to and including February 2015. Only prospective longitudinal studies assessing the association between weight gain and the incidence of periodontitis in adults were eligible to be included in this study. All studies should state a clear description of nutritional status (Body Mass Index; Waist Circumference) as well as the case definition of periodontitis. Pooled relative risks (RR) for becoming overweight and obese on the incidence of periodontitis were estimated by meta-analysis. Quality was assessed with the Newcastle–Ottawa scale for cohort studies.

Results: Five articles were included in this review and meta-analysis with 42,198 subjects enrolled. Subjects who became overweight and obese presented higher risk to develop new cases of periodontitis (RR 1.13; 95%CI 1.06–1.20 and RR 1.33 95%CI 1.21–1.47 respectively) compared with counterparts who stayed in normal weight.

Conclusions: A clear positive association between weight gain and new cases of periodontitis was found. However, these results are originated from limited evidence. Thus, more studies with longitudinal prospective design are needed.

Key words: incidence; longitudinal studies; meta-analysis; nutritional status; obesity; overweight; periodontal disease; periodontitis; systematic review; weight gain

Accepted for publication 3 May 2015

Body weight tends to remain stable in most adult individuals for long periods of time (Jequier & Tappy 1999). In this context, it is possible to assume that regulatory processes coordinate the dietary fuel supply with energy requirements with the intention of maintaining a stable body mass and adipose reservoir (Schwartz et al. 1999). However, when an unbalance between calorific intake and energy expenditure occurs, the body may excessively accumulate fat leading to overweight and further to obesity (Martinez et al. 2014). According to the World Health Organization recommendation, subjects whose Body Mass Index (BMI) is between 25 and 29.9 are considered overweight, whereas those whose BMI is equal or greater than 30 are considered obese (WHO 2000).

Obesity can be defined as a systemic disease characterized by excessive body fat accumulation that can lead to adverse impacts on health conditions (Kopelman 2000, WHO 2000). Its prevalence has risen not only in high-income but also in medium- and low-income countries, consuming large amounts of health care resources (WHO 2000, Specchia et al. 2014). Several reports have

Conflict of interest and source of funding statement
The authors state that there are no potential conflicts of interest. The study was self-funded by the authors and their institution.

demonstrated the adverse effects of obesity on chronic health outcomes, such as diabetes, cardiovascular disease, infectious diseases and cancer (Falagas & Kompoti 2006, Kahn et al. 2006, Van Gaal et al. 2006, Friedman 2009).

Amongst the most prevalent chronic diseases, periodontitis is a destructive condition affecting the supporting structures of the teeth, which develops through an inflammatory process mainly induced by the presence of a microbial biofilm (Van Dyke & van Winkelhoff 2013). It is beyond dispute that besides the role played by periodontopathogens, the quality of the host immune response is also responsible for the transition from health to disease (Cekici et al. 2014). The interplay between immune system and periodontal bacteria challenge determines not only the establishment but also the severity of disease progression (Cekici et al. 2014). As periodontitis presents itself in cycles of progression and latency, when an unbalance in this interplay occurs, it is expected a greater susceptibility for active destruction. This, in turn, is affected by other systemic risk factors (Montero et al. 2011).

Previous reports have demonstrated a positive association between fat accumulation and periodontitis (Al-Zahrani et al. 2003, Han et al. 2010). Different mechanisms have been proposed to explain this possible association. Essentially, macrophage infiltration driven by cell apoptosis at the core of the excessive adipose tissue may induce a generalized chronic low-grade inflammation, with those becoming obese and overweight being more susceptible to infectious diseases than their counterparts who are normal weight (Falagas & Kompoti 2006). Considering the infectious nature of periodontitis, it is expected that a similar relationship between obesity and periodontitis may exist, such as found between obesity and other infectious diseases, like respiratory and skin infections (Falagas & Kompoti 2006).

Systematic reviews exploring the association between obesity/overweight and periodontitis have corroborated the positive association between those conditions (Chaffee & Weston 2010, Suvan et al. 2011, Moura-Grec et al. 2014). Nevertheless, even with those reviews the effects of changes in the nutritional status, especially weight gain, on periodontal disease are not evident, leaving a gap in the literature. Furthermore, no information about development of new cases of periodontitis is addressed in those reports, thus, the role of weight gain in the establishment of periodontal disease is not clear. Studying incidence cases is a more appropriate approach to estimate such an association, as prevalence cases could underestimate the magnitude of this association, and result in biased causal effects in variables that change with time (Heaton et al. 2014).

We previously hypothesized that individuals experiencing more weight gain will present with higher risk of developing periodontitis, than those with less or without weight gain on the basis of the evidence from cross-sectional studies reporting relationship between nutritional status and periodontitis and the occurrence of cumulative inflammatory condition caused by fat accumulation (Nascimento et al. 2014). However, the cross-sectional studies suffer with issues of temporality while longitudinal studies are able to address this. Considering the limitations of cross-sectional studies and the lack of conclusive evidence from longitudinal studies on this relationship, this study conducted a systematic review of prospective longitudinal studies assessing the effects of weight gain, with individuals becoming overweight or obese, on the incidence of periodontitis in adults.

Methods

Review questions

1 Is weight gain leading to overweight associated with the incidence of periodontitis in adults?
2 Is weight gain leading to obesity associated with the incidence of periodontitis in adults?

Inclusion and exclusion criteria

Original prospective observational studies which assessed the association between weight gain and incidence of periodontitis in adults aged 18 or older were included in this systematic review. At least two time points for both exposure and outcome were required to fulfil the inclusion criteria. All studies should state a clear description of nutritional status, such as Body Mass Index, Waist Circumference, as well as the case definition for periodontitis. In each study, the case definition for periodontitis determined by the authors was respected. Case–control, cross-sectional studies, longitudinal retrospective studies, animal studies, in-vitro studies, letters to the editor and reviews were excluded.

Search strategy

An electronic search was conducted without initial date restriction up to and including February 2015 in PubMed via Medline, Embase, Web of Knowledge and Scopus to identify studies that prospectively analysed the effect of weight gain during time on the incidence of periodontitis in adults after follow-up. An initial search was conducted on PubMed with the following MeSH and free terms: "("Periodontal diseases" [Mesh] OR "Periodontitis [Mesh]" OR "Chronic Periodontitis" [Mesh]) AND ("Obesity"[Mesh] OR "Overweight"[Mesh] OR "Obesity, Abdominal"[Mesh] OR "Body Fat Distribution"[Mesh] OR "Abdominal Fat"[Mesh] OR "Intra-Abdominal Fat"[Mesh] OR "Waist Circumference"[Mesh]) OR "Waist-Hip Ratio"[Mesh]) OR "Body Mass Index"[Mesh] OR "Weight Gain" [all] OR "Weight Changes" [all] OR "Nutritional Status" [all] OR "Body composition" [all])". The search was conducted in a second time with the inclusion of specific filters for prospective studies in the search strategy. Strategies used for specific databases are detailed in the Appendix S1. No language restrictions were applied in any search.

All references were managed in the software EndNote X7 (Thomson Reuters, New York, NY, USA). Duplicate references were excluded. Titles, abstracts and key words were screened based on the inclusion and exclusion criteria by two reviewers independently (GGN and FRML). Lists were compared and in case of disagreement, a consensus was reached by discussion. Assessment of the full articles

identified in the initial screening was performed by the same two reviewers. In addition to the electronic search, a hand search was performed in the reference list of all included studies by the same reviewers. Predefined data collection worksheets were employed for the assessment of each selected publication. This systematic review followed the PRISMA statements (Moher et al. 2009).

Data extraction and quality assessment

After the first screening, the following data were sought from articles with potential to be included in the review: author's name, country where the study was conducted, sample size and its main characteristics, subjects enrolment, follow-up period, classification criteria for periodontitis, clinical examination data collected, parameters to determine the incidence of periodontitis, definition and assessment of nutritional status, and presence and type of adjustment in the statistical analysis. In addition, to conduct meta-analysis, effect measures (Relative Risk – RR) with respective 95% Confidence Intervals (95%CI) were also recorded. Authors were contacted to clarify any queries on the study methodology or result. Data were extracted by the same two reviewers. Cases of disagreement were discussed until a consensus was reached.

The specific version of the Newcastle–Ottawa scale for cohort studies was used to assess the quality of included studies (Wells et al. 2001). The scale comprises eight items distributed in three dimensions: (a) selection of study groups; (b) comparability of study groups; (c) assessment of outcome and adequacy of follow-up (Appendix S2). Each item scored 1 point, except for one (Comparability dimension) that could score at most 2 points. Thus, total score could range from 0 to 9 points. Studies with 7–9 points (approximately 80% or more of the domains satisfactorily fulfilled) were arbitrarily considered to be of high quality, whereas studies with 5–6 points were classified as moderate quality and studies with less than 5 points were of low-methodological quality (Zangrando et al. 2015). Finally, the overall quality of evidence was estimated according to the GRADE guideline (Guyatt et al. 2008). Papers were evaluated by the same two referees independently and disagreements were decided by consensus after discussion.

Statistical analysis

Two different meta-analyses were conducted considering the review questions: (1) association between becoming overweight and the incidence of periodontitis; (2) association between becoming obese and the incidence of periodontitis. Only adjusted results were included in the analysis, once two reports did not present the crude effect size. For each model, a combined relative risk effect was obtained with fixed- and random-effect models. If heterogeneity was present ($p < 0.05$) the random-effect model was employed (DerSimonian & Laird 1986). One study presented missing data, however, after contacting authors, values to be included in the meta-analysis were provided. As the effect measure presented by the authors was odds ratio, a conversion into relative risk was needed. For this, data were converted according to the formula proposed by Zhang and Yu:

$$\widehat{\mathrm{RR}} = \frac{\text{odds ratio}}{1 - \text{risk}_0 + \text{risk}_0 \times \text{odds ratio}},$$

where, risk_0 is the risk of having a positive outcome in the control or unexposed group (Zhang & Yu 1998). As different relative risk measures were used, a sensitivity analysis was performed to verify the influence of these results in the pooled effect for both exposures. All analyses were conducted using Stata 12.0 software (StataCorp., College Station, TX, USA).

Results

Electronic database search revealed 1,398 articles. From those, 471 were duplicated and subsequently removed. A total of 927 articles were included for title and abstract evaluation. Figure 1 displays the flow chart of studies selection. From those, 12 articles were included for full text review. Further seven of those 12 were excluded after full text appraisal conducted independently by two reviewers. Table 1 presents main reasons for exclusions of those seven papers.

Therefore, five studies fulfilled the criteria to be included in this review and meta-analysis. The study of Morita et al. (2011) was included twice in the analyses, as it presented results stratified by gender. Table 2 displays the main findings of included studies. The samples enrolled in the studies that fulfilled all inclusion criteria totalled 42,198 study participants. According to the Newcastle–Ottawa scale included studies scored as follows: 6 (Ekuni et al. 2014) indicating a moderate methodological quality; 7 (Morita et al. 2011, Jimenez et al. 2012); 8 (Saxlin et al. 2010); and 9 (Gorman et al. 2012b), indicating high methodological quality (Fig. 2). The overall quality of evidence applying the GRADE approach was moderate for both meta-analyses (Table S1).

All studies were conducted in high-income countries, with one in Finland (Saxlin et al. 2010), two in Japan (Morita et al. 2011, Ekuni et al. 2014) and two in the United States of America (Gorman et al. 2012b, Jimenez et al. 2012). One study used self-reported data for periodontal disease (Jimenez et al. 2012), whereas the others used clinical measures: probing depth (Saxlin et al. 2010, Morita et al. 2011, Gorman et al. 2012b, Ekuni et al. 2014), clinical attachment loss and alveolar bone loss (Gorman et al. 2012b) and Community Periodontal Index (Ekuni et al. 2014). For nutritional status assessment, the Body Mass Index was used in all articles, however, one used the self-reported measure (Jimenez et al. 2012). All studies also presented adjusted results for sociodemographic, behavioural and oral health variables.

Meta-analysis considering the effects of weight gain on the incidence of periodontitis showed that subjects who became overweight had greater risk to develop new cases of periodontitis (RR 1.13; 95% CI 1.06–1.20) (Fig. 3) as well as those who became obese (RR 1.33 95% CI 1.21–1.47) compared with counterparts who stayed normal weight for the same period (Fig. 4). In both analyses, heterogeneity was not significant ($p > 0.05$); therefore the fixed-effect model was employed.

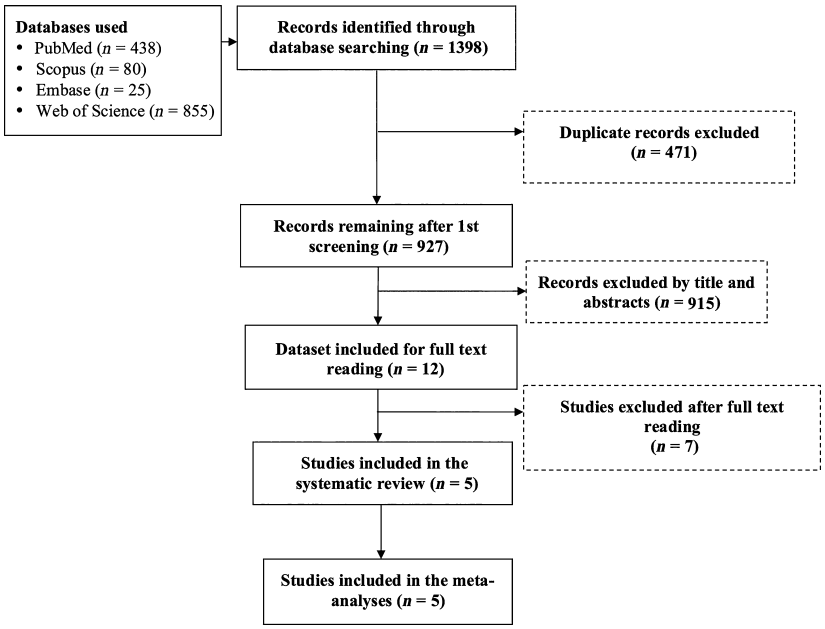


Fig. 1. Flow chart of studies selection for the systematic review according to inclusion and exclusion criteria.

Table 1. Excluded studies and main reason for exclusion

Study	Country	Reason for exclusion
Reeves et al. (2006)	United States of America	Cross-sectional study
Linden et al. (2007)	United Kingdom	Longitudinal Retrospective study
Saxlin et al. (2011)	Finland	Cross-sectional study
de Castilhos et al. (2012)	Brazil	Longitudinal Retrospective study
Östberg et al. (2012)	Sweden	No data regarding periodontal disease
Gorman et al. (2012a)	United States of America	Same sample from a previous study included in this review
Buduneli et al. (2014)	Turkey	Cross-sectional study

The omission of any study would not modify the association for both exposures as indicated by Figs 5 and 6.

Discussion

The present findings demonstrated that individuals who became overweight or obese presented higher risk to develop new cases of periodontitis than those who stayed normal weight in the same period. These findings support our previous hypothesis that fat accumulation could play a role in the development of periodontitis in adults, suggesting that incidence of periodontal disease increases with the rise of body fat accumulation. A positive association between periodontal disease and obesity has been demonstrated across many reports (Al-Zahrani et al. 2003, Dalla Vecchia et al. 2005, Kongstad et al. 2009, Han et al. 2010). Most of them used a cross-sectional design, which prevented establishing temporal relationships between the presumed exposures and outcome. As a consequence, the actual association between those conditions remains unclear. Prospective longitudinal studies are reliable sources of evidence, with temporal inferences able to be determined (de Castilhos et al. 2012). Hence, to the best of authors' knowledge, this is the first systematic review with meta-analysis analysing only prospective longitudinal studies exploring the association between weight gain and its effects on the incidence of periodontitis.

Given the results, some mechanisms linking weight gain with periodontitis could be addressed. First, the white adipose tissue works as an endocrine organ, responsible for secreting different types of specific cytokines: adipocytokines, such as resistin, leptin and adiponectin; as well as non-specific cytokines such as interleukins and tumour necrosis factors (Kershaw & Flier 2004, Tilg & Moschen 2006). Furthermore, as adipose tissue volume expands during weight gain some adipocytes could initiate apoptosis due to hypoxia, caused mainly by the constraint of blood vessels responsible for cellular nutrition (Neels & Olefsky 2006). This situation also leads to recruitment of macrophages especially around dead adipocytes, exacerbating the inflammatory framework in an upregulation feedback (Neels & Olefsky 2006). The combination of these situations promotes a chronic generalized low-grade inflammation that alters the host immune innate response threshold making obese and overweight subjects more susceptible to infectious diseases than normal weight ones (Falagas & Kompoti 2006, Morgan et al. 2010). In addition, it is suggested that lipopolysaccharide (LPS) of gram-negative periodontal bacteria could lead to hepatic dyslipidaemia and insulin resistance (Pischon et al. 2007). As the inflammation framework seems to be exacerbated by the increase in fat accumulation, it is expected that subjects with higher fat accumulation would present worse prognosis facing an infectious challenge, such as periodontitis, compared to those less obese, corroborating our findings.

Evidence suggests that other mechanisms rather than the biologic might play a role in this association. Given that both conditions, obesity/overweight and periodontitis, are chronic diseases, it is expected that they share common risk factors, such as low socioeconomic position (Thomson et al. 2012, Adair et al. 2013). As subjects from a disadvantaged background present higher prevalence rates of obesity and overweight (Adair et al. 2013) and periodontitis, a consistent social pattern is observed. Thomson and colleagues (Thomson et al. 2012) also stated that at least part of the socioeconomic variation in periodontitis could be influenced by this association. This relationship, however, seems to vary during the life-course,

Table 2. Main findings of articles that fulfilled inclusion criteria for this systematic review

Study and country	Sample characteristics	Follow-up period	Definition of Periodontal Disease	Clinical examination for PD	Incidence of PD	Assessment of nutritional status	Main findings	Adjustments	Observations
Saxlin et al. (2010), Finland	396 dentate, healthy subjects (non-diabetics and non-smokers) aged 30–60-yo enrolled in the Health 2000 Survey	Assessment of obesity and PD at baseline and 4 years later	Probing Depth: Healthy <4 mm; PD ≥4 mm	Full-mouth examination; 4 sites per tooth. Five dentists at baseline and one at follow-up	Number of teeth with new >4 mm deepened pockets at follow-up; change in periodontal pocket (no change, increase or decrease)	BMI was classified as follow: eutrophic <25, overweight ≥25 to ≤30; obese >30	Subjects who were PD healthy at baseline, obesity (IRR 1.3; 0.7–2.1) and overweight (IRR 1.2; 0.7–1.8) had no effect on incidence of PD after adjustment; Among subjects who presented PD at baseline, obesity (IRR 1.1; 0.8–1.7) and overweight (IRR 1.0; 0.7–1.4) had no effect on the incidence of PD after adjustment, as well as, in the change in periodontal pockets' depth.	Results adjusted for gender, age (continuous variable), education, presence of dental plaque, dental attendance pattern, toothbrushing frequency, periodontal treatment and number of teeth.	Data regarding only Probing on depth, without any reference to BoP or CAL.

Table 2. (continued)

Study and country	Sample characteristics	Follow-up period	Definition of Periodontal Disease	Clinical examination for PD	Incidence of PD	Assessment of nutritional status	Main findings	Adjustments	Observations
Morita et al. (2011), Japan	3590 (2787 men and 803 women) employed subjects aged 21–69-yo that attended annual statutory health checkups. Only subjects periodontally health at baseline were enrolled in the study.	Assessment of obesity and PD at baseline and 5 years later	Probing Depth: Health <4 mm; PD ≥4 mm	Partial-mouth examination: 10 teeth from 6 sextants; the highest score of the 6 dental sextants was used as the patient's periodontal disease score	Number of new teeth with PD ≥ 4 mm.	BMI was classified as follow: <22; 22–24.9, 25–29.9, and ≥30	Analyses stratified by gender. In men: incidence of PD was associated with BMI 25–30 after adjustments (HR 1,30; 1.11–1.53); in women: incidence of PD was associated with BMI 25–30 (HR 1.70; 1.15–255) and ≥30 (HR 3.24; 1.32–7.94) after adjustments	Results adjusted for age, smoking status, and clinical history of diabetes mellitus	
Gorman et al. (2012b), United States of America	1038 medically healthy, non-Hispanic, white males enrolled in the VA Dental Longitudinal Study since 1969	Baseline assessment of obesity and PD between 1969–1972. (Data regarding CAL were collected only in 1981–1985 assessment). Dental examinations occurred every 3 years.	Alveolar Bone Loss (ABL) ≥40% or PD or CAL ≥5 mm	Full-mouth examination; 6 sites per tooth. ABL: radiographic distance between CEJ and root apex	Two or more teeth advance to PD definition. Lost teeth were considered if tooth presented ABL=20%, >3 CAL/PD <5 at all prior examination	BMI was classified as follow: eutrophic <25, overweight ≥25 to ≤30; obese >30. WC was classified as follow: ≤102; >102. Waist-height ratio: ≤50%; >50%	After adjustment, obesity (BMI>30) was associated with incidence of PD ≥ 5 (HR 1.40; 1.02–1.91); CAL ≥ 5 (1.52; 1.05–2.21) and ABL ≥ 40% (1.60; 1.07–2.38). High WHtR (≥50%) was associated with incidence CAL ≥ 5 (HR 1.41; 1.01–1.97)	All models adjusted for age, cigarette use, education beyond high school, number of decayed or filled surfaces, treatment for periodontal disease in past year, prophylaxis in past year, and diabetes diagnosis	Sample size composed only by men. No information about date when last assessment was conducted

Table 2. (continued)

Study and country	Sample characteristics	Follow-up period	Definition of Periodontal Disease	Clinical examination for PD	Incidence of PD	Assessment of nutritional status	Main findings	Adjustments	Observations
Jimenez et al. (2012), United States of America	36,910 healthy male participants of the Health Professionals Follow-Up Study (HPFS) who were free of periodontal disease at baseline	Baseline: 1986; Last assessment: 2006	Self-reported PD: "Have you been professionally diagnosed with periodontal disease with bone loss?"	–	New cases of self-reported PD	Self-reported weight, height, WC and WHR. BMI was classified as follow: eutrophic <25, overweight ≥25 to ≤30; obese >30. WC >40 and WHR>0.95 were considered elevated	After adjustments, overweight (HR 1.09; 1.01–1.17) and obese (1.30; 1.16–1.45) presented higher incidence of PD. WC was not associated with incidence of PD after adjustments. WHR ≥ 0.99 was associated with incidence of PD (HR 1.24; 1.07–1.43).	BMI: Adjusted for age, smoking, race, physical activity, fruit and vegetable intake, alcohol consumption, dental profession, and diabetes status at baseline and number of teeth. WC and WHR: Adjusted for age, smoking, race, physical activity, fruit and vegetable intake, alcohol consumption, dental profession, and diabetes status at baseline, number of teeth and BMI	Self-reported measures; sample composed only by workers
Ekuni et al. (2014), Japan	224 university students healthy (non-diabetics and non-smokers)	Baseline: 2009; last assessment: 2012	Probing Depth: Healthy <4 mm; PD ≥4 mm	10 indices teeth; 6 sites per tooth	Number of new teeth with PD ≥ 4 mm.	BMI was classified as follow: eutrophic <25, overweight ≥25 to ≤30; obese >30	After adjustment, neither overweight (OR 0.52; 0.05–5.10) nor obese (OR 4.48; 0.44–27.67) presented higher incidence of PD	Adjusted by: Gender, age and oral health behaviours at baseline, and changes in BMI (increase and decrease)	Data provided by the authors after contact. Data converted in RR measures as described in the Methods section

ABL, alveolar bone loss; BMI, Body Mass Index; BoP, bleeding on probing; PD, pocket depth; CAL, clinical attachment loss; HRR, hazard risk ratio; IRR, incidence risk ratio; OR, odds ratio; WC, waist circumference; WHtR, waist-height ratio; WHR, waist-hip ratio.

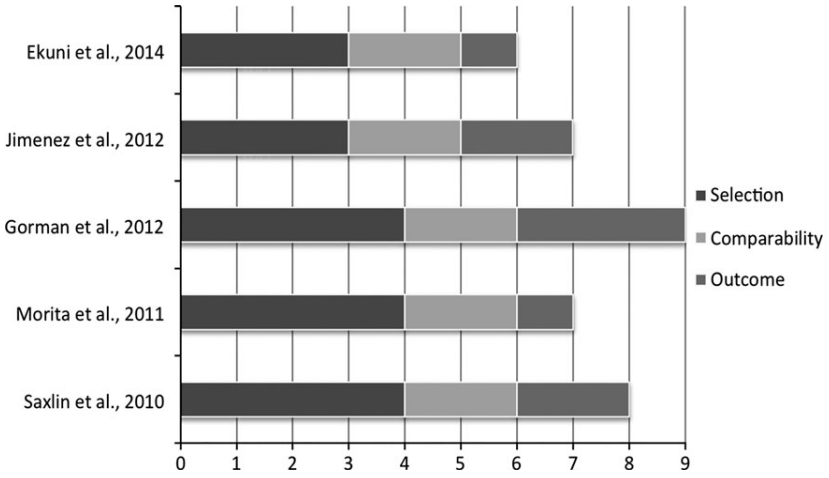


Fig. 2. Methodological quality of included studies according to the NOS-scale for cohort studies.

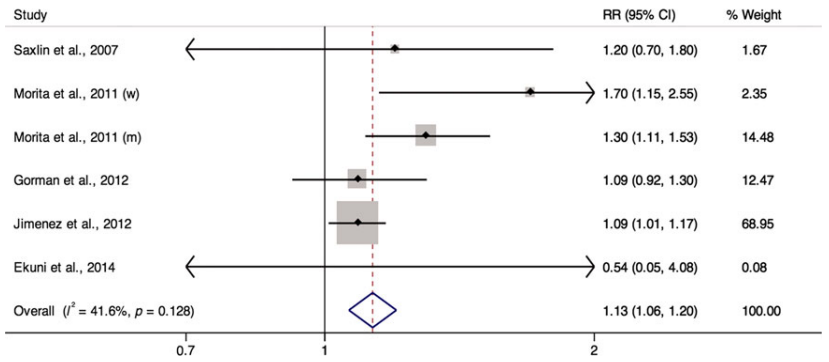


Fig. 3. Pooled effect of becoming overweight on the incidence of periodontitis. Data are presented as relative risk for each study (boxes), 95% CIs (horizontal lines) and summary as relative risk with 95% CI (diamond).

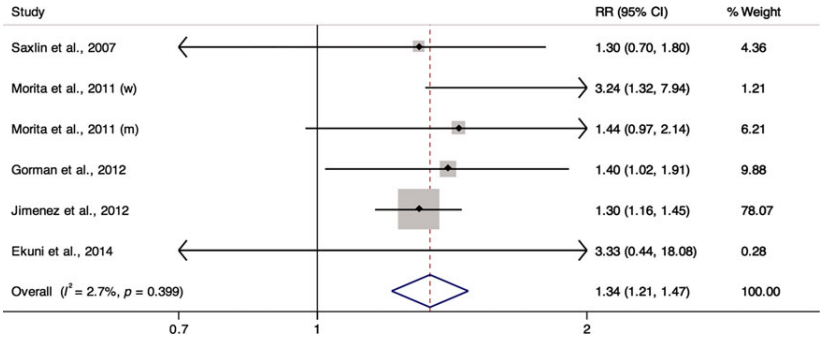


Fig. 4. Pooled effect of becoming obese on the incidence of periodontitis. Data are presented as relative risk for each study (boxes), 95%CI (horizontal lines) and summary as relative risk with 95%CI (diamond).

once prevalence rates of obesity increase since early life, whereas an unfavourable periodontal status is more evident in adulthood. The differences in effects of socioeconomic positions on this association between the high and lower – middle income countries could not be highlighted as all the selected studies were from higher income countries. Furthermore, considering that it is quite evident that the patterns of inequalities are different between these two distinct groups of countries, the effects may vary significantly (Lima-Costa et al. 2012).

Some methodological details should be addressed. Morita et al. (2011) used a different cut-off point of BMI to assess overweight and obesity, modified according to their sample. In the study of Gorman et al. (2012b) just data regarding probing depth were used. Even with the limitations of this measure, it was also used for three studies included in this analysis. All studies considered incidence as the development of disease in sites/teeth that were free of disease at baseline. In three of them (Saxlin et al. 2010, Morita et al. 2011, Jimenez et al. 2012), only periodontally health subjects were included at baseline, whereas in the remaining, subjects with periodontitis at baseline were enrolled; in those, incidence was considered the increment of cases from baseline assessment. The small number of studies that fulfilled the inclusion criteria precluded the statistical and the visual assessments for publication bias. The Egger's test has several limitations when the number of included studies is lower than 20 (Egger & Smith 1998); and the interpretation of a funnel-plot with a small number of studies could misrepresent the actual findings.

Our results however should be considered in the context of some limitations. First, only a few number of studies fulfilled the inclusion criteria defined for this review, and almost all of them presented positive results. Thus, it is not possible to define if longitudinal prospective studies exploring this association have not been conducted, or if studies with negative results have not been published. Second, it was just possible to perform pooled analyses with data regarding probing depth. Even though it is a useful measure to detect periodontal disease, the clinical attachment loss should be preferred, as it is more reliable measure to diagnose disease. Third, one included study (Jimenez et al. 2012) presented only self-reported data for nutritional status so as for periodontal disease with possible recall bias. Even with previous reports validating the self-

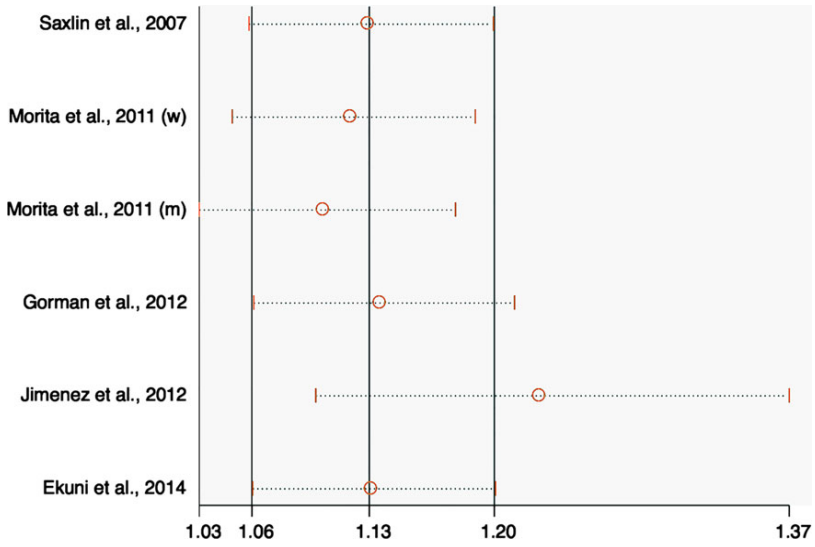


Fig. 5. Sensitivity analysis demonstrating the influence of each study in the pooled effect of becoming overweight on the incidence of periodontitis. Data are presented as new overall relative risk for each study omission (circles) and 95%CI (horizontal lines).

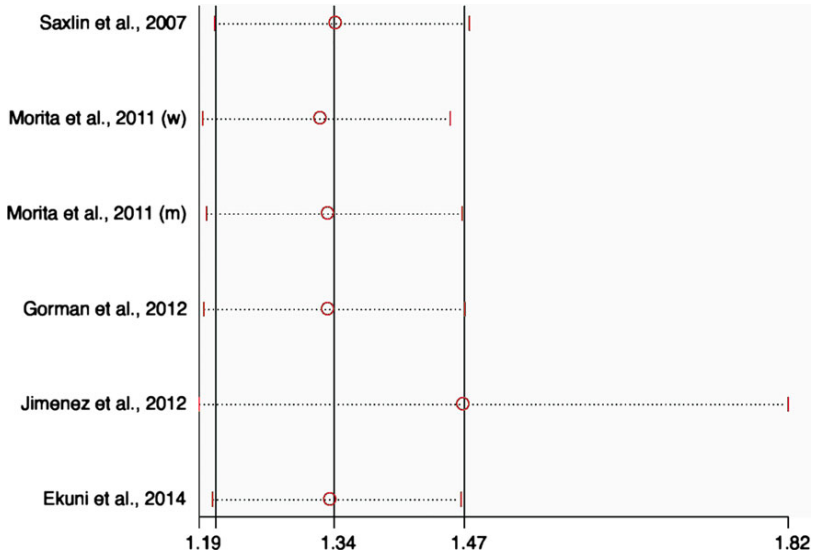


Fig. 6. Sensitivity analysis demonstrating the influence of each study in the pooled effect of becoming obese on the incidence of periodontitis. Data are presented as new overall relative risk for each study omission (circles) and 95%CI (horizontal lines).

reported nutritional status (Rimm et al. 1990) and periodontitis (Joshipura et al. 2002) used by the authors, it is unclear the impact of such measures on the association between both conditions. This fact impacted negatively on the overall quality of the evidence estimated with the GRADE approach. Fourth, one study (Ekuni et al. 2014) evaluated periodontitis using the Community Periodontal Index, which could have misrepresented the incidence of periodontitis. However, after contacting the authors, data regarding probing depth were provided, which allowed us to include this study in the analyses. Last, the young age of participants enrolled in the study of Ekuni et al. (2014) and the considerable short follow-up period of the studies could have underestimated the magnitude of such association, as many cases of periodontitis could have taken longer period until a clinical sign was observed. Also, in a young population, the incidence of periodontitis is low due to the chronicity of this disease.

Regardless of the limitations, it is worth pointing out some strengths of our review. Initially, as only prospective studies were included, the temporal effects of weight gain on the incidence of periodontitis could be observed. As aforementioned, to the best of authors' knowledge, no previous systematic review explored this topic previously, supporting in a very explicit way the actual impact of weight gain on the incidence of periodontal disease. The pooled estimates obtained with the meta-analyses showed a positive association between weight gain and periodontitis development, corroborating the findings of almost all the included studies. Even though some studies did not present a statistically significant association in their individual results, the positive association was achieved in the meta-analyses due to the increased sample size. Second, the use of incident cases as outcomes rather than prevalent ones should also be highlighted, as use of the latter could underestimate the actual association (Heaton et al. 2014). Third, the meta-analyses conducted presented pooled results from high-quality articles totalling more than 40,000 people enrolled. These facts could counterbalance the low number of studies included in the review providing a strong evidence of this association, not only due to the number of subjects but also to the quality of results. Even though the study of Ekuni et al. (2014) was classified as moderate risk of bias, this study presented low weight in the analyses (0.28% in the overweight model and 0.08% in the obesity model), not influencing our results as demonstrated by the sensitivity analyses. Fourth, all combined results were originated from adjusted analyses. These results were controlled by potential confounders and mediators of the relationship between weight gain and periodontitis, such as diabetes and smoking. It may reduce the likelihood of bias providing more solid findings. However, confounders such as medica-

tion intake and other systemic diseases should be considered in future studies, since it remains unclear the role played by those in the relationship between weight gain and periodontitis. Finally, the sensitivity analysis estimated the effect of omitting each study in the combined result, supporting the relevance of our findings. This analysis justifies our methodological option to pool studies with distinct relative risk measures as well as to include the study with self-reported data.

The results of our systematic review and meta-analyses clearly demonstrated the effects of weight gain on the incidence of periodontal disease. However, this evidence is originated from limited studies identified after extensive and careful searches. Our findings also suggest that further studies with prospective design exploring this association are needed with further follow-up periods not only in high-income countries, but especially in those low- and middle-income, where the prevalence of obesity and periodontitis is greater. As those conditions share key risk factors, their prevention should be based on a common risk factor approach (Sheiham & Watt 2000), which seems to be more rationale than focusing on only one specific condition. Also, clinicians should be aware of the role played by weight gain on the development of new cases of periodontitis, as it seems to be a risk factor for the establishment of such condition.

Acknowledgements

The authors are grateful to the Coordination for the Improvement of Higher Education Personnel (CAPES) for the scholarship provided to GGN (#BEX 13810/13-8) and to the National Counsel of Technological and Scientific Development (CNPq) for the scholarship provided to FRML (#BEX 229279/2013-9).

References

Adair, L. S., Fall, C. H., Osmond, C., Stein, A. D., Martorell, R., Ramirez-Zea, M., Sachdev, H. S., Dahly, D. L., Bas, I., Norris, S. A., Micklesfield, L., Hallal, P., Victora, C. G. & group, C., (2013) Associations of linear growth and relative weight gain during early life with adult health and human capital in countries of low and middle income: findings from five birth cohort studies. *Lancet* **382**, 525–534.

Al-Zahrani, M. S., Bissada, N. F. & Borawskit, E. A. (2003) Obesity and periodontal disease in young, middle-aged, and older adults. *Journal of Periodontology* **74**, 610–615.

Buduneli, N., Biyikoglu, B., Ilgenli, T., Buduneli, E., Nalbantsoy, A., Sarac, F. & Kinane, D. F. (2014) Is obesity a possible modifier of periodontal disease as a chronic inflammatory process? A case-control study. *Journal of Periodontal Research* **49**, 465–471.

de Castilhos, E. D., Horta, B. L., Gigante, D. P., Demarco, F. F., Peres, K. G. & Peres, M. A. (2012) Association between obesity and periodontal disease in young adults: a population-based birth cohort. *Journal of Clinical Periodontology* **39**, 717–724.

Cekici, A., Kantarci, A., Hasturk, H. & Van Dyke, T. E. (2014) Inflammatory and immune pathways in the pathogenesis of periodontal disease. *Periodontology 2000* **64**, 57–80.

Chaffee, B. W. & Weston, S. J. (2010) Association between chronic periodontal disease and obesity: a systematic review and meta-analysis. *Journal of Periodontology* **81**, 1708–1724.

Dalla Vecchia, C. F., Susin, C., Rosing, C. K., Oppermann, R. V. & Albandar, J. M. (2005) Overweight and obesity as risk indicators for periodontitis in adults. *Journal of Periodontology* **76**, 1721–1728.

DerSimonian, R. & Laird, N. (1986) Meta-analysis in clinical trials. *Controlled Clinical Trials* **7**, 177–188.

Egger, M. & Smith, G. D. (1998) Bias in location and selection of studies. *BMJ* **316**, 61–66.

Ekuni, D., Mizutani, S., Kojima, A., Tomofuji, T., Irie, K., Azuma, T., Yoneda, T., Furuta, M., Eshima, N., Iwasaki, Y. & Morita, M. (2014) Relationship between increases in BMI and changes in periodontal status: a prospective cohort study. *Journal of Clinical Periodontology* **41**, 772–778.

Falagas, M. E. & Kompoti, M. (2006) Obesity and infection. *The Lancet Infectious Diseases* **6**, 438–446.

Friedman, J. M. (2009) Obesity: Causes and control of excess body fat. *Nature* **459**, 340–342.

Gorman, A., Kaye, E. K., Apovian, C., Fung, T. T., Nunn, M. & Garcia, R. I. (2012b) Overweight and obesity predict time to periodontal disease progression in men. *Journal of Clinical Periodontology* **39**, 107–114.

Gorman, A., Kaye, E. K., Nunn, M. & Garcia, R. I. (2012a) Changes in body weight and adiposity predict periodontitis progression in men. *Journal of Dental Research* **91**, 921–926.

Guyatt, G. H., Oxman, A. D., Vist, G. E., Kunz, R., Falck-Ytter, Y., Alonso-Coello, P. & Schünemann, H. J. & GRADE Working Group (2008) GRADE: an emerging consensus on rating the quality of evidence and strength recommendations. *BMJ* **26**, 924–926.

Han, D. H., Lim, S. Y., Sun, B. C., Paek, D. M. & Kim, H. D. (2010) Visceral fat area-defined obesity and periodontitis among Koreans. *Journal of Clinical Periodontology* **37**, 172–179.

Heaton, B., Applebaum, K. M., Rothman, K. J., Brooks, D. R., Heeren, T., Dietrich, T. & Garcia, R. I. (2014) The influence of prevalent cohort bias in the association between periodontal disease progression and incident coronary heart disease. *Annals of Epidemiology* **24**, 741–746.

Jequier, E. & Tappy, L. (1999) Regulation of body weight in humans. *Physiological Reviews* **79**, 451–480.

Jimenez, M., Hu, F. B., Marino, M., Li, Y. & Joshipura, K. J. (2012) Prospective associations between measures of adiposity and periodontal disease. *Obesity (Silver Spring)* **20**, 1718–1725.

Joshipura, K. J., Pitiphat, W. & Douglass, C. W. (2002) Validation of self-reported periodontal measures among health professionals. *Journal of Public Health Dentistry* **62**, 115–121.

Kahn, S. E., Hull, R. L. & Utzschneider, K. M. (2006) Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature* **444**, 840–846.

Kershaw, E. E. & Flier, J. S. (2004) Adipose tissue as an endocrine organ. *Journal of Clinical Endocrinology and Metabolism* **89**, 2548–2556.

Kongstad, J., Hvidtfeldt, U. A., Gronbaek, M., Stoltze, K. & Holmstrup, P. (2009) The relationship between body mass index and periodontitis in the Copenhagen City Heart Study. *Journal of Periodontology* **80**, 1246–1253.

Kopelman, P. G. (2000) Obesity as a medical problem. *Nature* **404**, 635–643.

Lima-Costa, F., Oliveira, C., Macinko, J. & Marmot, M. (2012) Socioeconomic inequalities in health in older adults in Brazil and England. *American Journal of Public Health* **102**, 1535–1541.

Linden, G., Patterson, C., Evans, A. & Kee, F. (2007) Obesity and periodontitis in 60–70-year-old men. *Journal of Clinical Periodontology* **34**, 461–466.

Martinez, J. A., Navas-Carretero, S., Saris, W. H. & Astrup, A. (2014) Personalized weight loss strategies-the role of macronutrient distribution. *Nature Reviews. Endocrinology* **10**, 749–760.

Moher, D., Liberati, A., Tetzlaff, J. & Altman, D. G. & The PRISMA Group (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine* **6**, e1000097.

Montero, J., Bravo, M., Vicente, M. P., Galindo, M. P., Lopez-Valverde, A., Casals, E., Cortes-Martinicorena, F. J. & Llodra, J. C. (2011) Oral pain and eating problems in Spanish adults and elderly in the Spanish National Survey performed in 2005. *Journal of Orofacial Pain* **25**, 141–152.

Morgan, O. W., Bramley, A., Fowlkes, A., Freedman, D. S., Taylor, T. H., Gargiullo, P., Belay, B., Jain, S., Cox, C., Kamimoto, L., Fiore, A., Finelli, L., Olsen, S. J. & Fry, A. M. (2010) Morbid obesity as a risk factor for hospitalization and death due to 2009 pandemic influenza A(H1N1) disease. *PLoS One* **5**, e9694.

Morita, I., Okamoto, Y., Yoshii, S., Nakagaki, H., Mizuno, K., Sheiham, A. & Sabbah, W. (2011) Five-year incidence of periodontal disease is related to body mass index. *Journal of Dental Research* **90**, 199–202.

Moura-Grec, P. G., Marsicano, J. A., Carvalho, C. A. & Sales-Peres, S. H. (2014) Obesity and periodontitis: systematic review and meta-analysis. *Ciência & Saúde Coletiva* **19**, 1763–1772.

Nascimento, G. G., Leite, F. R., Correa, M. B., Horta, B. L., Peres, M. A. & Demarco, F. F. (2014) Relationship between periodontal disease and obesity: the role of life-course events. *Brazilian Dental Journal* **25**, 87–89.

Neels, J. G. & Olefsky, J. M. (2006) Inflamed fat: what starts the fire? *Journal of Clinical Investigation* **116**, 33–35.

Östberg, A. L., Bengtsson, C., Lissner, L. & Hakeberg, M. (2012) Oral health and obesity indicators. *BMC Oral Health* **12**, 50.

Pischon, N., Heng, N., Bernimoulin, J. P., Kleber, B. M., Willich, S. N. & Pischon, T. (2007) Obesity, inflammation, and periodontal disease. *Journal of Dental Research* **86**, 400–409.

Reeves, A. F., Rees, J. M., Schiff, M. & Hujoel, P. (2006) Total body weight and waist circumference associated with chronic periodontitis among adolescents in the United States. *Archives of Pediatrics and Adolescent Medicine* **160**, 894–899.

Rimm, E. B., Stampfer, M. J., Colditz, G. A., Chute, C. G., Litin, L. B. & Willett, W. C. (1990) Validity of self-reported waist and hip circumferences in men and women. *Epidemiology* **1**, 466–473.

Saxlin, T., Ylostalo, P., Suominen-Taipale, L., Aromaa, A. & Knuuttila, M. (2010) Overweight and obesity weakly predict the development of periodontal infection. *Journal of Clinical Periodontology* **37**, 1059–1067.

Saxlin, T., Ylostalo, P., Suominen-Taipale, L., Mannisto, S. & Knuuttila, M. (2011) Association between periodontal infection and obesity: results of the Health 2000 Survey. *Journal of Clinical Periodontology* **38**, 236–242.

Schwartz, M. W., Baskin, D. G., Kaiyala, K. J. & Woods, S. C. (1999) Model for the regulation of energy balance and adiposity by the central nervous system. *American Journal of Clinical Nutrition* **69**, 584–596.

Sheiham, A. & Watt, R. G. (2000) The common risk factor approach: a rational basis for promoting oral health. *Community Dentistry and Oral Epidemiology* **28**, 399–406.

Specchia, M. L., Veneziano, M. A., Cadeddu, C., Ferriero, A. M., Mancuso, A., Ianuale, C., Parente, P., Capri, S. & Ricciardi, W. (2015) Economic impact of adult obesity on health systems: a systematic review. *European Journal of Public Health* **25**, 255–262.

Suvan, J., D'Aiuto, F., Moles, D. R., Petrie, A. & Donos, N. (2011) Association between overweight/obesity and periodontitis in adults. A systematic review. *Obesity Reviews* **12**, e381–e404.

Thomson, W. M., Sheiham, A. & Spencer, A. J. (2012) Sociobehavioral aspects of periodontal disease. *Periodontology 2000* **60**, 54–63.

Tilg, H. & Moschen, A. R. (2006) Adipocytokines: mediators linking adipose tissue, inflammation and immunity. *Nature Reviews Immunology* **6**, 772–783. doi:10.1038/nri1937.

Van Dyke, T. E. & van Winkelhoff, A. J. (2013) Infection and inflammatory mechanisms. *Journal of Clinical Periodontology* **40** (Suppl 14), S1–S7. doi:10.1111/jcpe.12088.

Van Gaal, L. F., Mertens, I. L. & De Block, C. E. (2006) Mechanisms linking obesity with cardiovascular disease. *Nature* **444**, 875–880. doi:10.1038/nature05487.

Wells, G. A., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M. & Tugwell, P. (2001) The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa. University of Ottawa. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm.

World Health Organization (2000) *Obesity: Preventing and Managing the Global Epidemic. Report of a WHO Consultation World Health Organization Technical Report Series*. 894, i–xii, 1–253, World Health Organization, Geneva.

Zangrando, M. S., Damante, C. A., Sant'Ana, A. C., Rubo de Rezende, M. L., Greghi, S. L. & Chambrone, L. (2015) Long-term evaluation of periodontal parameters and implant outcomes in periodontally compromised patients. a systematic review. *Journal of Periodontology* **86**, 201–221.

Zhang, J. & Yu, K. F. (1998) What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. *JAMA* **280**, 1690–1691.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Search Strategies.
Appendix S2. Newcastle-Ottawa Scale for cohort studies applied in this review.
Table S1. Overall quality of evidence according to the GRADE approach.

Address:
Gustavo G. Nascimento
457 Gonçalves Chaves St, 5th floor
Zip 96015-560
Pelotas, RS
Brazil
E-mail: gustavo.gnascimento@hotmail.com

Clinical Relevance

Scientific rationale for the study: Previous systematic reviews found positive association between obesity and periodontal disease. However, none of them explored the effects of weight gain on the incidence of periodontitis.

Principal findings: A relationship between weight gain and incidence of periodontal disease was demonstrated. Thus, subjects who became obese and overweight presented higher risk than those who were normal weight to develop periodontitis. In addition, those who became obese were at higher risk of having periodontitis than overweight subjects.

Practical implications: Clinicians should be aware of the role played by weight gain on the development of periodontitis.

Artigo Original submetido ao periódico *Journal of Clinical Periodontology*

Estimating the direct effect of overweight/obesity on periodontal outcomes among adults by using Marginal Structural Model (MSM): a population-based cohort study

Running title: Obesity & periodontal disease using MSM

Gustavo G Nascimento[1,2], Karen G Peres[2], Gloria C Mejia[2], Diego A Silva[3], David Gonzalez-Chica[4], Marco A Peres[2]

[1] Postgraduate Program in Dentistry, Federal University of Pelotas, Pelotas, Brazil;

[2] Australian Research Centre for Population Oral Health, School of Dentistry, Faculty of Health Sciences, University of Adelaide, Adelaide, Australia

[3] Postgraduate Program in Physical Education. Postgraduate Program in Public Health. Federal University of Santa Catarina, Florianopolis, Brazil.

[4] School of Population Health, Faculty of Health Sciences, University of Adelaide, Adelaide, Australia.

Corresponding author:

Marco A Peres

Australian Research Centre for Population Oral Health, School of Dentistry, Faculty of Health Sciences, University of Adelaide, Adelaide, Australia

Tel: +61 8 8313 5438 Fax: +61 8 8313 3070
Email: marco.peres@adelaide.edu.au

Conflict of Interest and Source of Funding:

The authors state that there are no potential conflicts of interest.

The 2009 study was supported by the National Counsel of Technological and Scientific Development (CNPq, Brazil), grant number 485327/2007-4. The 2012 wave was supported by the National Counsel of Technological and Scientific Development (CNPq, Brazil), grant number 477061/2010-9.

Abstract

Aim: To estimate the controlled direct effects of overtime changes in obesity/overweight on periodontal outcomes in a cohort of Brazilian adults by comparing conventional regression and Marginal Structured Modelling (MSM) using inverse probability weights.

Methods: Obesity/overweight was assessed in 2009 (n=1,720) and 2012 (n=1,222). Participants with ≥1 episode of obesity/overweight in the follow-up period comprised the comparison category. Periodontal outcomes were: i) Percentage of teeth with bleeding on probing (BOP) and ii) Combination of BOP and Clinical Attachment Loss (CAL). Hypertension and depression were set as mediators. All analyses controlled for baseline confounders.

Results: 1,076 participants presented periodontal data. Central obesity was associated with BOP and CAL in both conventional regression (Rate Ratio-RR 2.17) and MSM (RR 1.85) after adjustment for hypertension and confounders. General and central obesity were associated with BOP and CAL in the conventional regression and MSM (RR 1.86 and RR 2.35 respectively) after adjustment for depression and confounders. General obesity had an effect on the percentage of BOP (RR 1.39 for hypertension as mediator; RR 1.38 for depression as mediator) using conventional regression. No effect was noted using MSM.

Conclusions: Overweight/obesity has a controlled direct effect on unfavorable periodontal outcomes. Conventional regression overestimated these associations.

Key words: Periodontitis; Nutritional Status; Inverse Probability Weighting; Causal Inference; Mediation; Longitudinal Studies; Cohort Studies.

Clinical Significance

Scientific rationale for the study: Previous longitudinal studies investigating the relationship between overweight/obesity and periodontal diseases have not considered the longitudinal design in the analytical approach used thus limiting the inferences drawn.

Principal findings: Overweight/obesity, especially the abdominal one, is associated with unfavorable periodontal outcomes, independently of hypertension and depression. Conventional regression methods overestimated such association in most analyses.

Practical implications: Clinicians and public policy makers should interpret with caution the results from previous studies. Researchers are encouraged to use current epidemiologic methods for causal inference.

Introduction

Obesity has been associated with adverse effects on chronic health conditions, such as type II diabetes, hypertension, depression, infectious diseases and all-cause mortality (Falagas and Kompoti, 2006, Friedman, 2009, Berrington de Gonzalez et al., 2010). Systematic reviews support an association between nutritional status and periodontal disease (Chaffee and Weston, 2010, Suvan et al., 2011).

Mechanisms were proposed to explain the relationship between obesity and periodontal disease. The expansion of adipose tissue during weight gains constraints blood vessels causing macrophage migration into this tissue, which may induce a generalized chronic low-grade inflammation. Other systemic conditions seem to exacerbate this inflammatory load, such as depression and hypertension. The increased blood pressure affects collagen and bone metabolism. It also impacts on the gingival arteriolar wall thickening leading to a precarious local immune response (Tsioufis et al., 2011). When obesity is associated with depression, it increases the levels of pro-inflammatory circulating cytokines and alters the immune response via limbic–hypothalamic–pituitary–adrenal axis and the sympathetic nervous system, exacerbating the inflammation (Warren et al., 2014). Furthermore, depression can influence health-related behaviors, e.g. oral hygiene, impacting on periodontal disease development (Aleksejuniene et al., 2002).

A systematic review focusing on prospective longitudinal studies showed that weight gain increases the incidence of periodontal disease in adults (Nascimento et al., 2015). However, the few included studies suffer from methodological limitations, since they used a similar analytical approach for confounders and mediators in the analysis. Therefore, it might have produced biased results.

Robins and colleagues (2000) proposed a new model to analyze longitudinal data with time varying confounders and mediators (Robins et al., 2000). Marginal structural models (MSM) are a new class of causal models that distinguishes between confounder and mediators in the analysis, reducing the gap left for conventional regression methods to assess mediation (Lange et al., 2014, Nandi et al., 2012). Furthermore, by dealing with potential confounding by measured covariates through weighting rather than conditioning on covariates, MSM allows for the identification of direct effects even in settings in which conventional approaches are biased (Robins et al., 2000). This technique is also considerably relevant for

observational studies when exposures cannot be allocated in a randomized intervention, such as overweight/obesity, because it simulates a randomized controlled trial scenario. Despite these advantages MSMs are starting to make their way into the dental field recently (Chaffee et al., 2014).

This study aimed to investigate the effects of obesity/overweight on periodontal disease, controlled for well-known general chronic diseases mediators, in a population-based cohort of Brazilian adults. We also compared results by using MSM with estimates obtained using conventional regression. Additionally, we estimated the effects of eliminating obesity in the population and in the exposed individuals. We hypothesize that overweight/obesity has a direct effect on periodontal outcomes independently of the mediating factors; and that the estimates obtained from conventional methods undermine the association between overweight/obesity and periodontal disease.

Methods

Study population and sampling

A population-based cohort study of adults residing in Florianópolis, Southern Brazil, began in 2009 when participants were 20 to 59 year-olds. The second wave was carried out three years later in 2012. A clustered sample of 2,016 adults was calculated with detailed information described elsewhere (Peres et al., 2012). Out of 2,016 targeted participants, 1,720 were effectively investigated (participation rate of 85.3%). In the second wave, in 2012, all participants investigated in the baseline study were contacted for a home visit in order to conduct interview, dental exams and anthropometric measurements. This study followed the STROBE checklist.

Eligibility and exclusion criteria

All adult residents in the selected houses were eligible to participate in the baseline study. Amputees, bedridden individuals, those with an arm cast, individuals who could not remain in the proper position for the required measurements, those who were considered unable to answer the questionnaire, pregnant women and those who were within six months from delivery, and edentulous people were excluded from this study.

Data collection - baseline 2009

Interview and anthropometric measures (weight, height, and waist circumference) along with blood pressure were taken. Information on socioeconomic,

demographics, self-reported chronic diseases, self-rated general and oral health, diet, physical activity, tobacco and alcohol consumption were gathered.

Data collection - second wave 2012

In 2012 a second questionnaire was applied gathering information on socioeconomic trajectory and diet. Anthropometric measures (weight and waist circumference) and blood pressure were assessed and dental exams were performed by trained dentists. Periodontal exams included assessment of dental calculus, bleeding on probing, periodontal pocket, and attachment loss in two diagonal quadrants randomly selected according to the identification number of the participants. Six sites per tooth were examined using a ball-ended periodontal probe (CPI probe). Bleeding on probing up to 10s of probing and calculus were recorded (as “present” or “absent”) for each examined tooth. Probing depth was measured as the distance (in mm) from the gingival margin to the base of the gingival sulcus and recorded as sound, shallow (4.0-5.5 mm) and deep (6.0+mm). Clinical attachment loss (CAL) was measured in mm and categorized as: 0.0-3.0 mm; 4.0-5.0 mm; 6.0-8.0 mm; 9.0-11.0 mm; or 12.0+mm. This measure was dichotomized in absence (0-3.0 mm) and presence of CAL (≤4.0mm).

Outcomes

The following outcomes were created:

1. Percentage of teeth with bleeding on probing (BOP): A continuous variable based on the number of examined teeth with the presence of BOP. The ratio between the number of examined teeth with presence of BOP and all examined teeth was calculated.
2. Combination of clinical attachment loss and bleeding on probing: The aforementioned variable, “Percentage of teeth with BOP”, was divided in tertiles and combined with the dichotomous variable regarding the presence or absence of CAL. A composite variable with three different categories was created: (1) no BOP and no CAL; (2) BOP and CAL in different teeth; (3) BOP and CAL in the same tooth. The first category of this variable comprised all participants with absence of BOP (first tertile of percentage of teeth with BOP) and CAL. The second category included participants in the second or third tertiles of the “Percentage of teeth with BOP” variable or those with presence

of CAL. To be included in this category, individuals should present at least one of these conditions in at least one tooth; however, once both conditions were present, they could not be observed in the same tooth. Finally, the last category was composed by individuals with concomitant presence of BOP and CAL in at least one tooth.

Main exposures

The Body Mass Indexes in 2009 and in 2012 were calculated by dividing the weight for the square of the height (Kg/m^2). The cut-off point recommended by the WHO was used: eutrophic (BMI<25 Kg/m^2) and overweight/obese (BMI≥25 Kg/m^2). Considering the lack of agreement of waist circumference cut-offs for Latin-Americans, this variable was categorized in quartiles, and those individuals in the last quartile of waist circumference were considered overweight (Choi et al., 2010). Based on nutrition status in 2009 and 2012, one dichotomous variable was created for each type of excess of weight (general – BMI; central – waist circumference). These variables considered as the reference category those subjects who remained eutrophic for the entire cohort period. Therefore, those presenting at least one episode of excess of weight comprised the comparison category.

Covariates

Baseline Confounders

We considered as baseline confounders the following variables from the 2009 wave: sex, age (20-29; 30-39; 40-49; 50-59-years-old), equalized household income in tertiles (ratio between household income and square root of the residents in the house), smoking status (never smoker, former smoker and current smoker), hazardous and harmful alcohol consumption patterns (Babor et al., 2001). Physical activity during leisure time, fat meat consumption and percentage of dietary energy from sugar consumption were assessed through a questionnaire previously used in the Telephone-based Surveillance of Risk and Protective Factors of Chronic Disease (VIGITEL) in Brazil (Florindo et al., 2009, Mendes et al., 2011). Presence of dental calculus was considered a proxy of dental hygiene and was included as a confounder in the depression-outcome model.

Mediators

Based on the literature we identified three possible mediators of the relationship between excess of weight and periodontal outcomes: diabetes mellitus (Genco and Borgnakke, 2013), depression (Warren et al., 2014) and hypertension (Tsioufis et al., 2011). The three diseases were assessed by the following question: “Have you ever been told by a doctor you have?” followed by the name of the respective disease. Additionally, individuals were asked whether they were using any medication for blood pressure. Wrist systolic and diastolic blood pressures were measured twice during the interview using standardized procedures (Silva et al., 2012). Hypertension was then defined as when the subject had been diagnosed as having hypertension and/or reported being on use of medication for blood pressure control and/or had a systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg (Chobanian et al., 2003, Silva et al., 2012). Due to the low prevalence of diabetes mellitus in this population (3.1%), this variable was not included in our analyses. In order to measure the potential impact of such variable on our findings we performed sensitivity analyses (Supplementary material – S1).

Data quality control was conducted by administering the questionnaire through telephone interview to 15% of the sample (n=248 in 2009; n=183 in 2012). Kappa index and intra-class correlation coefficient ranged from 0.60-0.90 in 2009 and from 0.60-0.95 in 2012. Missing cases were subjects who could not be located after four attempts or refused to participate in the study.

Theoretical causal framework and data analyses

We drew a directed acyclic graph (DAG) (Greenland et al., 1999) in order to establish potential causal pathways between the presumed exposure and outcomes (Figure S2A and S2B).

Our main goal was to estimate the controlled direct effect (CDE) of at least one episode of overweight/obesity on periodontal outcomes that was not mediated neither by depression nor hypertension after adjustment for potential confounders. The CDE is a comparison of the expected outcome conditional on the exposure and the mediator for different values of the exposure while keeping the mediator fixed (Robins and Greenland, 1992). Also, we compared the two approaches for estimating such direct effect: the conventional regression by effect decomposition (Baron and Kenny, 1986) and MSM using the inverse probability weights (Robins et al., 2000). Details regarding the steps used to estimate the direct effect using

conventional regression methods and inverse probability weights were described in the Supplementary Material section (S3).

For the MSM approach, we performed weights for each mediator and exposure accordingly. Weights were estimated using logistic regression for exposures and mediators. Predicted probabilities for the numerator and denominator were assigned and later divided in order to obtain the stabilized weights (Robins et al., 2000). For the composite outcome, the multinomial logistic regression was used, while for the continuous one, the negative binomial regression was employed. We also performed MSM analyses accounting for censored individuals, by calculating stabilized weights of those clinically examined but not included in the previous analyses due to missing data regarding the outcome (Table S1) (Cole and Hernan, 2008). Additionally to those analyses, we calculated i) the population attributable risk (PAR) to quantity the contribution of risk factor (obesity/overweight) to the burden of periodontal outcomes and ii) Etiological fraction (EF) which is the proportion of the cases that the exposure (obesity/overweight) has played a causal role (Table S2). Analyses were performed in Stata 12.0 software with commands for complex samples.

Ethical issues

The Ethics Committee in Human Research of the Federal University of Santa Catarina approved both waves of the study.

Results

Of the 1,222 (71.0%) participants contacted in the second wave, 1,140 were dentally examined and interviewed, and 53 were excluded due to complete tooth loss. Finally, 1,076 participants were assessed for periodontal data (Figure 1).

Presence of BOP and CAL in the same tooth was observed in 14.1% of the participants. The mean percentage of BOP was 13.4%; 57% presented at least one episode of general obesity, whereas 29% presented at least one episode of abdominal obesity. Table 1 presents the characteristics of the total sample at baseline (2009) and in the second wave (2012) and the distribution of the sample according to the dependent variables in 2012.

Estimates of total and direct effects of presenting at least one episode of obesity on periodontal outcomes are shown in Tables 2 and 3. Those who presented at least on episode of general and central obesity in the 3-years period had increased risk for BOP and CAL in different teeth and in the same tooth.

In Table 2, model 2 displays Rate Ratio (RR) estimates after adjustment for baseline confounders and hypertension (mediator). In the presence of confounders and mediator, no direct effect of general obesity on periodontal disease was observed. When central obesity was set as the main dependent variable, higher risk was noted for the presence of BOP and CAL in the same tooth (RR 2.17). Finally, applying MSM, controlled direct effect of central obesity on BOP and CAL in the same tooth was 85% higher compared to eutrophic in the period (RR 1.85) (Table 2).

In Table 3, model 2, it is possible to observe that those individuals who presented at least one episode of general and central obesity had higher risk for BOP and CAL in the same tooth (RR 1.90 and 2.42, respectively) in the presence of confounders and mediator (depression). In Model 3, dental calculus was also included in the model; the effects of general and central obesity on the combination of BOP and CAL in the same tooth were RR 1.86 and RR 2.35 respectively. Model 4 shows the controlled direct effect of obesity/overweight on periodontal outcomes using the MSM approach. General obesity increased the risk for BOP and CAL in different teeth and BOP and CAL in the same tooth (RR 1.39; RR 1.80, respectively); whereas central obesity impacted on BOP and CAL in the same tooth (RR 2.41).

Tables 4 and 5 display the effects of general and central obesity on BOP. The total effect (Model 1) adjusted for baseline confounders reveals that those who experienced general obesity increased the risk for BOP (RR 1.38). After controlling

for confounders and mediators using conventional regression approach (Model 2 in Table 4 and Models 2 and 3 in Table 5), general obesity remained associated with percentage of BOP (RR 1.39 for hypertension as mediator; RR 1.38 for depression as mediator). Finally, the MSM for both mediators (Model 4) did not provide evidence of controlled direct effect of general and central obesity on increased risk for BOP.

Table S1 (Supplementary material) presents MSM results including censored individuals, which did not differ from our original findings. The PAR and EF also revealed that conventional regression approaches overestimated the effects of eliminating excess of weight in the population and only among the exposed (Table S2).

Discussion

The aim of our study was to assess the controlled direct effects of obesity, general and abdominal, on periodontal outcomes; also to compare the conventional regression methods and the MSM approach to estimate such causal relationship. Our findings provided evidence that overweight/obesity, mainly the central one, has a direct effect on unfavorable periodontal outcome in a sample of Brazilian adults, after controlling for confounders and mediators. The comparison between the conventional regression approach and the MSM analysis revealed that the first underestimated the role of the mediators, providing overestimated controlled effects of obesity/overweight on periodontal disease.

Our findings revealed that central overweight/obesity might play a different role from general excess of weight in the association with periodontal outcomes. Body Mass Index does not distinguish between fat mass and lean mass and does not consider the distribution of fat over the body (Snijder et al., 2006). On the other hand, previous reports revealed that abdominal obesity, independent of general obesity, is associated with metabolic disturbances and increased risk for other chronic diseases (Canoy, 2008).

Our study addresses an alternative approach for analyzing longitudinal data. When a consequence of the exposure confounds the association between mediator and outcome, the controlled direct effects cannot be estimated with conventional regression, regardless of controlling for other confounders of such association (VanderWeele, 2009). When factors that confound the association between mediator and outcome are omitted from the regression model, conditioning only on the

mediator may induce a biased estimate due to collider stratification, which means controlling for a common effect of exposure and outcome (Cole and Hernan, 2002). This could explain the overestimation of the direct effects of episodes of overweight/obesity in the conventional regression analyses, even though this type of bias could underestimate the effects. The use of MSM evades this potential confounding. Our findings suggest that the disagreeing results in the literature regarding the association between obesity and periodontal disease might be explained, partially, by biases originated from conventional regression approaches. This is evident in our study when the conventional regression approach is used, the associations between episodes of obesity and percentage of BOP are significant; however, there is a null association when the MSM approach is employed.

Biased results might not be an exclusive concern in the academic field. Policy makers can base their decisions on the available evidence to propose public policies. In order to measure the impact of eliminating obesity on periodontal disease, we calculate PAR and EF. It is clear to see the impact of biased results from a public health perspective; the estimates originated from conventional regression approach also overestimate the impact of eliminating obesity/overweight in the population and especially among the exposed. The EF estimates obtained from conventional regression results overestimated this value in approximately 15% compared to MSM, also explaining the controversial results from previous studies.

The longitudinal prospective design adopted allowed us to establish a causal pathway between exposures and outcomes. It helps to close the gap existing in the literature regarding the potential bidirectional association between obesity and periodontal disease. To the best of the authors' knowledge this is the first study in the field of periodontology to use this type of approach for longitudinal data and causal inference. The MSM approach allowed us to properly deal with confounders and mediators and, consequently, reduce the likelihood of bias, providing more solid findings to clinicians and public health professionals. As some participants were dropped from our analyses due to missing information regarding the outcome, we performed MSM analyses with the censored. In these analyses, no differences in the magnitude were observed (Table S2).

This study is not free of limitations. Firstly, the short follow-up period precluded us to measure the effects of the change in nutritional status, focusing on the effects of weight gain on periodontal outcomes after 3 years. Owing to the chronicity of

obesity, the prevalence of weight gain was low (9.0%) to consider it as a category to be included in the analysis. Therefore, the decision to evaluate in only one category all the subjects who were at least once exposed to obesity during the cohort period did not allow us to estimate a dose-response effect. However, we believe the analytical approach used in our study circumvents other potential biases that could undermine our results. Secondly, we could not consider diabetes as a mediator in our analyses. MSM and inverse-probability weighting require a positivity assumption that the probabilities in weight of the denominator are non-zero (Cole and Hernan, 2008). Consequently, the inclusion of diabetes in the model might have violated this assumption. Even though this variable was not included in the statistical models, we performed a separate sensitivity analyses (Supplementary material – S2) showing no significant influence on our results. Thirdly, the use of a partial mouth protocol for periodontal outcomes assessment could have underestimated the prevalence of the outcome (Eke et al., 2010). This fact would not alter our findings, since the direction of the association would not change; probably a greater magnitude in the effect measure would be observed. Fourthly, the use of inverse probability weights does not address the unmeasured confounding. We attempted to minimize this possible source of bias, including recognized potential confounders in our DAG in order to establish all alternatives pathways. Nonetheless, unmeasured confounders influenced by the exposure might potentially confound the association between mediators and outcomes. Finally, we could address only one mediator at each time in our analyses. In the depression model, the presence of a mediator-outcome confounder influenced by the exposure precluded the inclusion of the two mediators in one single analysis. Despite of the existence of a technique that allows dealing with multiple mediators, the absence of mediator-outcome confounder is required (Lange et al., 2014).

Our results support the hypothesis that at least one episode of overweight/obesity have an effect on periodontal outcomes in adults after 3 years. Our analyses also revealed the differences regarding the analytical approach used. Theories of chronic disease development suggest an underlying causal relationship in which the MSM model would be able to identify the causal effect of presumed interest; whereas the use of conventional regression methods for estimating direct effects would not. Results therefore strongly encourage the employment of alternative methods, including MSM, for analyzing longitudinal data.

Acknowledgements

The authors are grateful to the Coordination for the Improvement of Higher Education Personnel (CAPES) for the scholarship provided to GGN (#BEX 13810/13-8). We also would like to thank the Brazilian Institute of Geography and Statistics (IBGE) and to the Florianópolis Health Authority staff for their useful help with the practical aspects of the study.

References

Aleksejuniene, J., Holst, D., Eriksen, H. M. & Gjermo, P. (2002) Psychosocial stress, lifestyle and periodontal health. *Journal of Clinical Periodontology* **29,** 326-335.

Babor, T. F., Higgins-Bible, J. C., Saunders, J. B. & Monteiro, M. S. (2001) The Alcohol Use Disorders Identification Test: Guidelines for Use in Primary Care, 2nd edition. Geneve.

Baron, R. M. & Kenny, D. A. (1986) The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *Journal of Personality and Social Psychology* **51,** 1173-1182.

Berrington de Gonzalez, A., Hartge, P., Cerhan, J. R., Flint, A. J., Hannan, L., MacInnis, R. J., Moore, S. C., Tobias, G. S., Anton-Culver, H., Freeman, L. B., Beeson, W. L., Clipp, S. L., English, D. R., Folsom, A. R., Freedman, D. M., Giles, G., Hakansson, N., Henderson, K. D., Hoffman-Bolton, J., Hoppin, J. A., Koenig, K. L., Lee, I. M., Linet, M. S., Park, Y., Pocobelli, G., Schatzkin, A., Sesso, H. D., Weiderpass, E., Willcox, B. J., Wolk, A., Zeleniuch-Jacquotte, A., Willett, W. C. & Thun, M. J. (2010) Body-mass index and mortality among 1.46 million white adults. *The New England journal of medicine* **363,** 2211-2219. doi:10.1056/NEJMoa1000367.

Canoy, D. (2008) Distribution of body fat and risk of coronary heart disease in men and women. *Current Opinion in Cardiology* **23,** 591-598. doi:10.1097/HCO.0b013e328313133a.

Chaffee, B. W., Feldens, C. A. & Vitolo, M. R. (2014) Association of long-duration breastfeeding and dental caries estimated with marginal structural models. *Annals of Epidemiology* **24,** 448-454. doi:10.1016/j.annepidem.2014.01.013.

Chaffee, B. W. & Weston, S. J. (2010) Association between chronic periodontal disease and obesity: a systematic review and meta-analysis. *Journal of Periodontology* **81,** 1708-1724. doi:10.1902/jop.2010.100321.

Chobanian, A. V., Bakris, G. L., Black, H. R., Cushman, W. C., Green, L. A., Izzo, J. L., Jr., Jones, D. W., Materson, B. J., Oparil, S., Wright, J. T., Jr., Roccella, E. J., National Heart, L., Blood Institute Joint National Committee on Prevention, D. E., Treatment of High Blood, P. & National High Blood Pressure Education Program Coordinating, C. (2003) The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood

Pressure: the JNC 7 report. *JAMA* **289,** 2560-2572. doi:10.1001/jama.289.19.2560.

Choi, S. Y., Kim, D., Oh, B. H., Kim, M., Park, H. E., Lee, C. H. & Cho, S. H. (2010) General and abdominal obesity and abdominal visceral fat accumulation associated with coronary artery calcification in Korean men. *Atherosclerosis* **213,** 273-278. doi:10.1016/j.atherosclerosis.2010.07.052.

Cole, S. R. & Hernan, M. A. (2002) Fallibility in estimating direct effects. *International Journal of Epidemiology* **31,** 163-165.

Cole, S. R. & Hernan, M. A. (2008) Constructing inverse probability weights for marginal structural models. *American Journal of Epidemiology* **168,** 656-664. doi:10.1093/aje/kwn164.

Eke, P. I., Thornton-Evans, G. O., Wei, L., Borgnakke, W. S. & Dye, B. A. (2010) Accuracy of NHANES periodontal examination protocols. *Journal of Dental Research* **89,** 1208-1213. doi:10.1177/0022034510377793.

Falagas, M. E. & Kompoti, M. (2006) Obesity and infection. *The Lancet. Infectious Diseases* **6,** 438-446. doi:10.1016/S1473-3099(06)70523-0.

Florindo, A. A., Hallal, P. C., Moura, E. C. & Malta, D. C. (2009) Practice of physical activities and associated factors in adults, Brazil, 2006. *Revista de Saude Publica* **43 Suppl 2,** 65-73.

Friedman, J. M. (2009) Obesity: Causes and control of excess body fat. *Nature* **459,** 340-342. doi:10.1038/459340a.

Genco, R. J. & Borgnakke, W. S. (2013) Risk factors for periodontal disease. *Periodontology 2000* **62,** 59-94. doi:10.1111/j.1600-0757.2012.00457.x.

Greenland, S., Pearl, J. & Robins, J. M. (1999) Causal diagrams for epidemiologic research. *Epidemiology* **10,** 37-48.

Lange, T., Rasmussen, M. & Thygesen, L. C. (2014) Assessing natural direct and indirect effects through multiple pathways. *American Journal of Epidemiology* **179,** 513-518. doi:10.1093/aje/kwt270.

Mendes, L. L., Campos, S. F., Malta, D. C., Bernal, R. T., de Sa, N. N. & Velasquez-Melendez, G. (2011) Validity and reliability of foods and beverages intake obtained by telephone survey in Belo Horizonte, Brazil. *Revista Brasileira de Epidemiologia* **14 Suppl 1,** 80-89.

Nandi, A., Glymour, M. M., Kawachi, I. & VanderWeele, T. J. (2012) Using marginal structural models to estimate the direct effect of adverse childhood social

conditions on onset of heart disease, diabetes, and stroke. *Epidemiology* **23,** 223-232. doi:10.1097/EDE.0b013e31824570bd.

Nascimento, G. G., Leite, F. R. M., Do, L. G., Peres, K. G., Correa, M. B., Demarco, F. F. & Peres, M. A. (2015) Is weight gain associated with the incidence of periodontitis? *Journal of Clinical Periodontology,* doi: 10.1111/jcpe.12417.

Peres, M. A., Tsakos, G., Barbato, P. R., Silva, D. A. & Peres, K. G. (2012) Tooth loss is associated with increased blood pressure in adults--a multidisciplinary population-based study. *Journal of Clinical Periodontology* **39,** 824-833. doi:10.1111/j.1600-051X.2012.01916.x.

Robins, J. M. & Greenland, S. (1992) Identifiability and exchangeability for direct and indirect effects. *Epidemiology* **3,** 143-155.

Robins, J. M., Hernan, M. A. & Brumback, B. (2000) Marginal structural models and causal inference in epidemiology. *Epidemiology* **11,** 550-560.

Silva, D. A., Petroski, E. L. & Peres, M. A. (2012) [Prehypertension and hypertension among adults in a metropolitan area in Southern Brazil: population-based study]. *Revista de Saude Publica* **46,** 988-998.

Snijder, M. B., van Dam, R. M., Visser, M. & Seidell, J. C. (2006) What aspects of body fat are particularly hazardous and how do we measure them? *International Journal of Epidemiology* **35,** 83-92. doi:10.1093/ije/dyi253.

Suvan, J., D'Aiuto, F., Moles, D. R., Petrie, A. & Donos, N. (2011) Association between overweight/obesity and periodontitis in adults. A systematic review. *Obesity Reviews* **12,** e381-404. doi:10.1111/j.1467-789X.2010.00808.x.

Tsioufis, C., Kasiakogias, A., Thomopoulos, C. & Stefanadis, C. (2011) Periodontitis and blood pressure: the concept of dental hypertension. *Atherosclerosis* **219,** 1-9. doi:10.1016/j.atherosclerosis.2011.04.030.

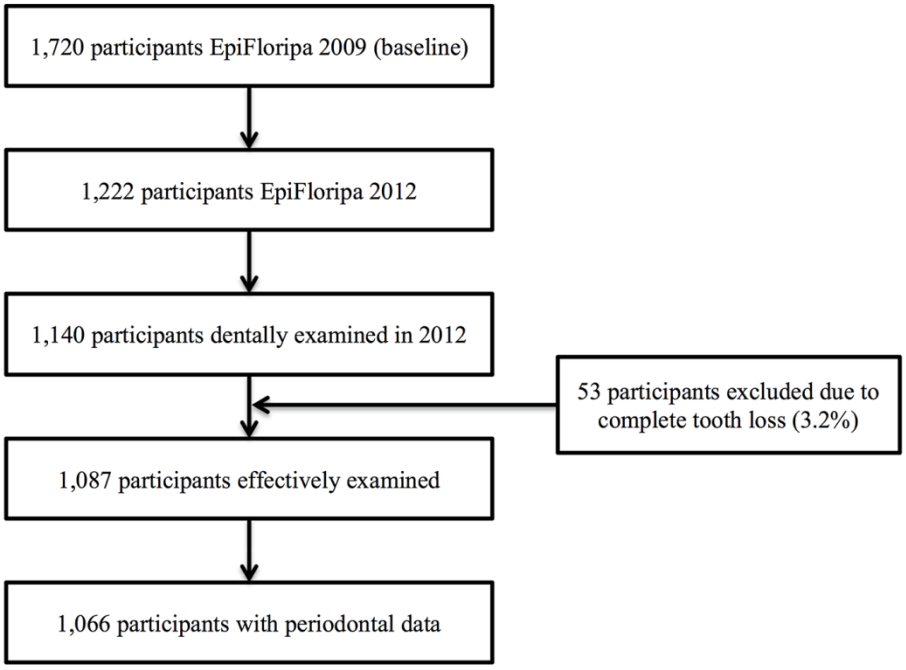
VanderWeele, T. J. (2009) Marginal structural models for the estimation of direct and indirect effects. *Epidemiology* **20,** 18-26. doi:10.1097/EDE.0b013e31818f69ce.

Warren, K. R., Postolache, T. T., Groer, M. E., Pinjari, O., Kelly, D. L. & Reynolds, M. A. (2014) Role of chronic stress and depression in periodontal diseases. *Periodontology 2000* **64,** 127-138. doi:10.1111/prd.12036.

Figure Legends:

Figure 1. Flow chart of the EpiFloripa cohort study.

Figures:



Tables:

Table 1. Sample characteristics in 2009 and 2012 according to periodontal outcomes. Florianópolis, Brazil.

Characteristics	n 2009	% 2009	n 2012	% 2012	No BOP and no CAL (95% CI)*	BOP and CAL in different teeth (95% CI)*	BOP and CAL in the same tooth (95% CI)*	Percentage of BOP Mean and (95% CI)*
Gender								
Male	761	44.9	463	44.3	13.0 (11.1;15.2)	23.6 (21.3;26.1)	7.65 (6.2;9.4)	14.1 (11.7;16.5)
Female	959	55.1	603	55.7	21.8 (19.4;24.5)	27.4 (24.8;30.2)	6.47 (5.2;8.1)	12.8 (10.6;15.0)
Age								
20-29	540	33.4	300	29.6	14.5 (12.0;17.4)	13.9 (11.2;17.0)	1.28 (0.75;2.17)	10.7 (8.45;12.9)
30-39	392	22.9	262	24.9	10.6 (8.6;13.1)	11.8 (9.9;14.0)	2.49 (1.55;3.98)	11.0 (8.2;13.9)
40-49	438	24.3	301	26.8	6.1 (4.6;8.1)	15.9 (13.8;18.2)	4.71 (3.44;6.41)	15.2 (11.9;18.6)
50-59	350	19.4	203	18.7	3.6 (2.5;5.0)	9.4 (7.4;12.0)	5.64 (4.42;7.17)	18.1 (14.4;21.9)
Equalized Income								
3rd Tertile	577	34.2	359	34.7	12.9 (9.8;16.7)	18.5 (14.8;22.8)	3.3 (2.3;4.8)	9.3 (7.2;11.3)
2nd Tertile	549	32.6	359	33.9	11.7 (9.4;14.5)	16.9 (14.4;19.9)	5.2 (4.0;6.9)	14.3 (11.8;16.9)
1st Tertile	559	33.2	335	31.4	10.2 (7.6;13.3)	15.6 (12.5;19.2)	5.6 (4.0;7.8)	16.8 (13.7;19.9)
Smoking								
Never Smoker	926	55.1	584	56.1	21.3 (18.6;24.4)	28.6 (25.8;31.7)	6.1 (4.7;7.9)	11.7 (9.7;13.8)
Former Smoker	449	25.6	285	26.0	8.7 (6.9;11.0)	13.4 (10.9;16.3)	3.9 (2.8;5.6)	13.6 (10.1;17.2)
Current Smoker	336	19.3	191	17.9	4.8 (3.7;6.2)	9.0 (7.4;10.9)	4.1 (3.0;5.4)	17.9 (14.2;21.6)
Physical activity in leisure time								
Inactive	912	53.6	570	54.0	18.9 (16.5;21.5)	25.5 (22.2;29.1)	9.6 (7.6;12.1)	15.6 (13.1;18.1)
Active	806	46.4	494	46.0	16.0 (13.2;19.3)	25.5 (22.5;28.7)	4.5 (3.2;6.2)	10.7 (9.0;12.4)
Alcohol Consumption								
No	1,403	81.3	895	83.7	29.0 (26.3;31.8)	43.1 (40.1;46.2)	11.6 (9.7;13.8)	13.4 (11.7;15.2)
Yes	317	16.7	171	16.3	5.9 (4.4;7.7)	7.9 (6.1;10.1)	2.5 (1.6;4.0)	13.1 (9.1;17.0)
Percentage of calories from sugar consumption								
0%	540	30.5	352	32.3	11.8 (9.7;14.4)	16.4 (13.5;19.9)	4.0 (2.9;5.6)	12.3 (9.2;15.4)
1-10%	796	47.7	478	46.4	16.7 (14.7;19.0)	23.0 (20.4;25.9)	6.6 (5.2;8.3)	12.5 (10.3;14.6)
11% and more	381	21.8	234	21.3	6.3 (4.9;8.0)	11.6 (9.4;14.1)	3.5 (2.3;5.4)	17.0 (13.8;14.6)
Meat Fat consumption								
No	1,196	69.9	766	71.9	26.3 (22.9;30.1)	37.1 (34.1;40.3)	8.4 (6.7;10.5)	11.6 (9.8;13.4)
Yes	524	30.1	300	28.1	8.5 (6.7;10.7)	13.9 (11.3;17.0)	5.7 (4.1;7.7)	17.9 (14.6;21.3)
Hypertension								
No	1,002	59.9	620	59.2	23.2 (20.5;26.1)	28.7 (26.0;31.5)	7.3 (5.8;9.1)	12.3 (10.4;14.3)
Yes	680	40.1	422	40.8	11.5 (9.5;13.9)	22.3 (19.8;25.0)	6.9 (5.39;8.9)	14.7 (12.1;17.2)
Depression								
No	1,425	83.3	891	84.2	29.6 (26.7;32.7)	42.5 (40.0;45.1)	12.1 (10.1;14.4)	12.5 (10.8;14.3)
Yes	295	16.7	174	15.8	5.25 (4.0;6.9)	8.5 (6.9;10.4)	2.1 (1.2;3.4)	17.5 (11.1;23.9)
Presence of dental calculus								
No	-	-	356	33.9	16.4 (14.1;18.9)	15.6 (13.8;17.6)	1.9 (1.2;3.0)	6.2 (4.6;7.7)
Yes	-	-	710	66.1	18.5 (15.8;21.5)	35.4 (32.8;32.1)	12.2 (10.0;14.8)	17.1 (14.9;19.2)
General Obesity								
Always eutrophic	-	-	420	43.0	18.2 (15.8;21.0)	20.8 (18.3;26.3)	3.9 (2.8;5.6)	10.6 (8.6;12.5)
At least one episode of obesity	-	-	589	57.0	17.0 (14.8;19.3)	30.2 (27.2;33.5)	9.8 (7.8;12.2)	14.9 (12.5;17.4)
Central Obesity								
Always eutrophic	-	-	709	70.7	27.3 (24.2;30.6)	35.9 (33.1;38.9)	7.5 (5.8;9.6)	11.9 (10.2;16.3)
At least one episode of obesity	-	-	303	29.3	7.3 (5.7;9.4)	15.3 (13.3;17.7)	6.7 (5.0;8.7)	16.4 (12.9;19.9)

**Weighted values.*

BOP – Bleeding on probing; CAL – Clinical Attachment Loss

Table 2. Conventional regression (crude and adjusted) and MSM results for Periodontal Disease, Hypertension as a Mediator. Florianópolis, Brazil ($n_{\text{general obesity}} = 987$; $n_{\text{central obesity}} = 994$).

Episodes of obesity	**Model 1:** Adjusted by confounders* RR (95%CI)		**Model 2:** Adjusted by mediator and confounders* RR (95%CI)		**Model 4**:** Marginal Structural Model RR (95%CI)	
General Obesity	*BOP + CAL in different teeth*	*CAL + BOP in the same tooth*	*BOP + CAL in different teeth*	*CAL + BOP in the same tooth*	*BOP + CAL in different teeth*	*CAL + BOP in the same tooth*
None	1.00	1.00	1.00	1.00	1.00	1.00
At least one episode	1.32 (0.98;1.77)	1.90 (1.10;3.30)	1.24 (0.90;1.70)	1.74 (0.97;3.11)	1.25 (0.90;1.74)	1.56 (0.95;2.57)
Hypertension						
No	-	-	1.00	1.00	1.00	1.00
Yes	-	-	1.33 (0.97;1.83)	1.39 (0.87;2.24)	1.32 (0.94;1.87)	1.33 (0.82;2.14)
Central Obesity						
None	1.00	1.00	1.00	1.00	1.00	1.00
At least one episode	1.38 (0.96;1.99)	2.35 (1.34;4.13)	1.27 (0.87;1.86)	2.17 (1.20;3.94)	1.14 (0.76;1.70)	1.85 (1.08;3.17)
Hypertension						
No			1.00	1.00	1.00	1.00
Yes			1.32 (0.96;1.82)	1.29 (0.82;2.05)	1.34 (0.95;1.89)	1.29 (0.78;2.15)

** Sex, Age, Equalized family income, Smoking, Alcohol consumption, Physical activity level, Fat consumption, Sugar consumption*
*** Model 3 is omitted for hypertension since no confounder "mediator-outcome" was included.*

Table 3. Conventional regression (crude and adjusted) and MSM results for Periodontal Disease, Depression as a Mediator. Florianópolis, Brazil ($n_{\text{general obesity}} = 991$; $n_{\text{central obesity}} = 980$).

Episodes of obesity	Model 1: Adjusted by baseline confounders* RR (95%CI)		Model 2: Adjusted mediator and confounders* RR (95%CI)		Model 3: Adjusted mediator, baseline confounders and mediator confounders** RR (95%CI)		Model 4: Marginal Structural Model RR (95%CI)	
	BOP + CAL in different teeth	*CAL + BOP in the same tooth*	*BOP + CAL in different teeth*	*CAL + BOP in the same tooth*	*BOP + CAL in different teeth*	*CAL + BOP in the same tooth*	*BOP + CAL in different teeth*	*CAL + BOP in the same tooth*
General Obesity								
None	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
At least one episode	1.32 (0.98;1.77)	1.90 (1.10;3.30)	1.32 (0.98;1.77)	1.90 (1.08;3.33)	1.28 (0.95;1.73)	1.86 (1.04;3.32)	1.39 (1.01;1.92)	1.80 (1.11;1.91)
Depression								
No	-	-	1.00	1.00	1.00	1.00	1.00	1.00
Yes	-	-	1.01 (0.67;1.53)	0.64 (0.34;1.18)	0.99 (0.65;1.48)	0.61 (0.33;1.15)	1.34 (0.86;2.10)	0.85 (0.42;1.72)
Central Obesity								
None	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
At least one episode	1.38 (0.96;1.99)	2.35 (1.34;4.13)	1.38 (0.96;2.00)	2.42 (1.38;4.24)	1.35 (0.91;2.00)	2.38 (1.33;4.27)	1.38 (0.95;2.01)	2.41 (1.50;3.89)
Depression								
No	-	-	1.00	1.00	1.00	1.00	1.00	1.00
Yes	-	-	0.97 (0.64;1.48)	0.56 (0.30;1.05)	0.94 (0.62;1.43)	0.55 (0.29;1.03)	1.21 (0.77;1.89)	0.89 (0.44;1.79)

** Sex, Age, Equalized family income, Smoking, Alcohol consumption, Physical activity level, Fat consumption, Sugar consumption*
*** Variables from Model 2 and presence of dental calculus*

Table 4. Conventional regression (crude and adjusted) and MSM results for Percentage of Bleeding on Probing, Hypertension as a Mediator. Florianópolis, Brazil ($n_{\text{general obesity}} = 974$; $n_{\text{central obesity}} = 985$).

Episodes of obesity	**Model 1:** Adjusted by baseline confounders* RR (95%CI)	**Model 2:** Adjusted mediator and confounders* RR. (95%CI)	**Model 4**:** Marginal Structural Model RR (95%CI)
		Percentage of BOP	*Percentage of BOP*
General Obesity			
None	1.00	1.00	1.00
At least one episode	1.38 (1.08;1.76)	1.39 (1.08;1.79)	1.23 (0.94;1.61)
Hypertension			
No	-	1.0	1.00
Yes	-	1.03 (0.79;1.34)	1.05 (0.82;1.35)
Central Obesity			
None	1.00	1.00	1.00
At least one episode	1.24 (0.96;1.60)	1.23 (0.94;1.59)	1.17 (0.91;1.51)
Hypertension			
No	-	1.00	1.00
Yes	-	1.01 (0.78;1.31)	1.03 (0.80;1.32)

** Sex, Age, Equalized income, Smoking, Alcohol consumption, Physical activity, Fat consumption, Sugar consumption*
*** Model 3 is omitted for hypertension since no confounder "mediator-outcome" was included.*

Table 5. Conventional regression (crude and adjusted) and MSM results for Percentage of Bleeding on Probing, Depression as a Mediator. Florianópolis, Brazil ($n_{\text{general obesity}} = 991$; $n_{\text{central obesity}} = 980$).

Episodes of obesity	**Model 1:** Adjusted by baseline confounders* RR (95%CI)	**Model 2:** Adjusted mediator and confounders* RR. (95%CI)	**Model 3:** Adjusted mediator, baseline confounders and mediator confounders** RR. (95%CI)	**Model 4:** Marginal Structural Model RR. (95%CI)
	Percentage of BOP	*Percentage of BOP*	*Percentage of BOP*	*Percentage of BOP*
General Obesity				
None	1.00	1.00	1.00	1.00
At least one episode	1.38 (1.08;1.76)	1.38 (1.07;1.75)	1.32 (1.04;1.69)	1.25 (0.96;1.63)
Depression				
No		1.00	1.00	1.00
Yes		1.22 (0.87;1.71)	1.17 (0.85;1.62)	1.35 (0.94;1.91)
Central Obesity				
None	1.00	1.00	1.00	1.00
At least one episode	1.24 (0.96;1.60)	1.24 (0.96;1.60)	1.25 (0.96;1.62)	1.26 (0.98;1.61)
Depression				
No		-	1.00	1.00
Yes		-	1.15 (0.83;1.60)	1.38 (0.98;1.95)

** Sex, Age, Equalized income, Smoking, Alcohol consumption, Physical activity, Fat consumption, Sugar consumption*
*** Variables from Model 2 and presence of dental calculus*

Supplementary Material

S1 - Sensitivity Analyses for Diabetes

General Obesity

```
. episens cron5 obes_geral_dic, dpexp(c(0.03)) dpunexp (c(0.0053)) drrcd(c(4.35)) dorce(c
> (1.44))

Pr(c=1|e=1): Constant(.03)
Pr(c=1|e=0): Constant(.0053)
RR_cd      : Constant(4.35)
OR_ce      : Constant(1.44)

Observed Odds Ratio [95% Conf. Interval]= 4.31 [1.65, 11.22]

Deterministic sensitivity analysis for unmeasured confounding
   External adjusted Odds Ratio = 4.27
   Percent bias =   1%



. episens cron5 obes_geral_dic, dpexp(c(0.03)) dpunexp (c(0.0053)) drrcd(c(4.35)) dorce(c
> (4.28))

Pr(c=1|e=1): Constant(.03)
Pr(c=1|e=0): Constant(.0053)
RR_cd      : Constant(4.35)
OR_ce      : Constant(4.28)

Observed Odds Ratio [95% Conf. Interval]= 4.31 [1.65, 11.22]

Deterministic sensitivity analysis for unmeasured confounding
   External adjusted Odds Ratio = 4.08
   Percent bias =   6%
```

Central Obesity

```
. episens cron5 obes_cint_dic, dpexp(c(0.026)) dpunexp (c(0.011)) drrcd(c(5.63)) dorce(c(
> 1.44))

Pr(c=1|e=1): Constant(.026)
Pr(c=1|e=0): Constant(.011)
RR_cd      : Constant(5.63)
OR_ce      : Constant(1.44)

Observed Odds Ratio [95% Conf. Interval]= 5.71 [2.77, 11.75]

Deterministic sensitivity analysis for unmeasured confounding
   External adjusted Odds Ratio = 5.59
   Percent bias =   2%



. episens cron5 obes_cint_dic, dpexp(c(0.026)) dpunexp (c(0.011)) drrcd(c(5.63)) dorce(c(
> 4.28))

Pr(c=1|e=1): Constant(.026)
Pr(c=1|e=0): Constant(.011)
RR_cd      : Constant(5.63)
OR_ce      : Constant(4.28)

Observed Odds Ratio [95% Conf. Interval]= 5.71 [2.77, 11.75]

Deterministic sensitivity analysis for unmeasured confounding
   External adjusted Odds Ratio = 4.95
   Percent bias =  15%
```

S2 - Directed Acyclic Graphs

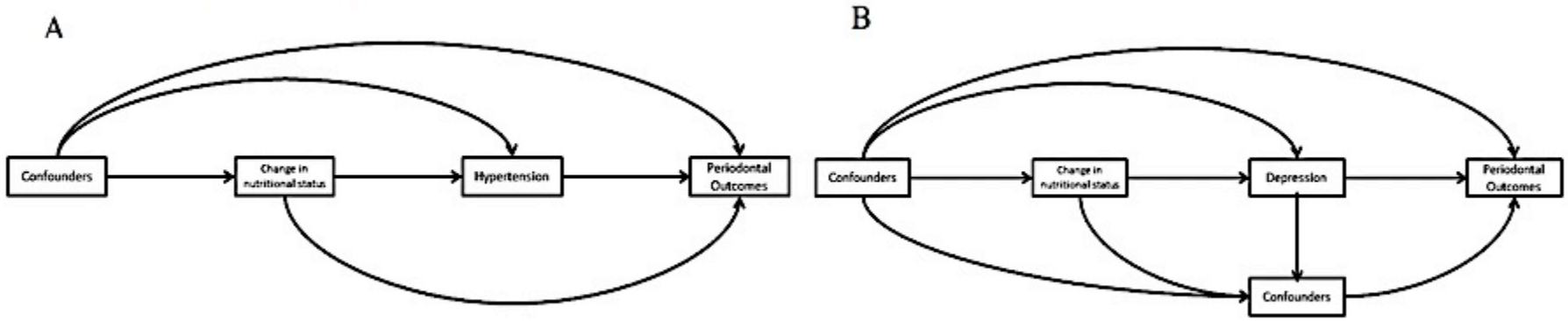


Figure S1. (A) Directed acyclic graph for the hypertension model; (B) Directed acyclic graph for the depression model.

S3 – Steps used for estimating controlled direct effects of obesity/overweight on periodontal outcomes using conventional regression methods and the inverse probability weighting

For the conventional regression approach, we firstly regressed the composite outcome (CAL+BOP) on each main exposure at a time (central excess of weight and general excess of weight) conditional on baseline confounders using multinomial logistic regression. Also, we regressed the continuous variable (percentage of BOP) on the same exposure variables conditional on baseline confounders using negative binomial regression (Model 1). Negative binomial regression model was chosen due to skewed and over dispersion distribution of percentage of BOP. Secondly, we estimated the direct effect of at least one episode on excess of weight on the outcomes using the approach proposed by Baron and Kenny (Baron and Kenny, 1986). In essence, we regressed the exposures on the outcomes, the mediators and the set of baseline confounders by fitting a multinomial logistic regression model for the composite outcome and a negative binomial regression model for the continuous outcome (Model 2). In this model, we tested for interaction between the exposures and the mediators by including cross-product terms. As no evidence of interaction was observed, the cross-product terms were subsequently omitted. Thirdly, when depression was considered a mediator, we included the variable “presence of dental calculus” as a confounder between mediator and outcomes (Model 3). Finally, in the model 4, we estimated the controlled direct effect of at least one episode of excess of weight on our outcomes using a MSM approach with a stabilized inverse probability weight (Robins et al., 2000). Potential baseline confounders and mediator-outcome confounders were accounted for the estimating the stabilized inverse probability weight (W=$W_i^A * W_i^M$) where:

$$W_i^A = \frac{P(A = a_i)}{P(A = a_i | C = c_i)}$$

and

$$W_i^M = \frac{P(M = m_i | A = a_i)}{P(M = m_i | A = a_i, C = c_i, R = r_i)}$$

where A=exposure; M=mediator; C=baseline confounders; R=mediator-outcome confounders; and i=each individual. The “exposure weight” considers for measured confounders of the relation between nutritional status and periodontal outcomes,

whereas the “mediator weight” accounts for the measured confounders between mediators and periodontal outcomes, if any.

S4 - Formulas used for calculation of the inverse probability weights for censored individual

$$W_i^{A,Cens} = \frac{P(Cens = 0|A)}{P(Cens = 0|A, C)}$$

$$W_i^{M,Cens} = \frac{P(Cens = 0|M, A)}{P(Cens = 0|M, A, C, R)}$$

Total weight: $W_i^{A,Cens} * W_i^{A} * W_i^{M,Cens} * W_i^{M}$

Multiplied weights presented the following distribution: mean =1.00, range =0.98;1.10 for hypertension as mediator and general obesity as exposure; mean =1.00, range =0.97;1.08 for depression as mediator and general obesity as outcome; mean =1.00, range =0.97;1.11 for hypertension as mediator and central obesity as exposure; mean =1.00, range =0.98;1.12.

Table S1. MSM results for periodontal outcomes including censored individuals. Florianópolis, Brazil.

Episodes of obesity	**Marginal Structural Model:** Hypertension RR (95%CI)			**Marginal Structural Model:** Depression RR (95%CI)		
General Obesity	*BOP + CAL in different teeth*	*CAL + BOP in the same tooth*	*Percentage of BOP*	*BOP + CAL in different teeth*	*CAL + BOP in the same tooth*	*Percentage of BOP*
None	1.00	1.00	1.00	1.00	1.00	1.00
At least one episode	1.28 (0.93;1.78)	1.58 (0.96;2.61)	1.23 (0.95;1.61)	1.42 (1.03;1.96)	1.86 (1.14;3.01)	1.26 (0.97;1.64)
Hypertension						
No	1.00	1.00	1.00	1.00	1.00	1.00
Yes	1.34 (0.95;1.89)	1.35 (0.85–2.18)	1.05 (0.82;1.36)	1.35 (0.86;2.12)	0.83 (0.41;1.68)	1.32 (0.92;1.89)
Central Obesity						
None	1.00	1.00	1.00	1.00	1.00	1.00
At least one episode	1.16 (0.78;1.83)	2.17 (1.20;3.94)	1.18 (0.92;1.51)	1.40 (0.96;2.03)	2.45 (1.53;2.93)	1.27 (1.00;1.62)
Hypertension						
No	1.00	1.00	1.00	1.00	1.00	1.00
Yes	1.36 (0.96;1.92)	1.29 (0.82;2.05)	1.03 (0.80;1.33)	1.20 (0.77;1.88)	0.86 (0.43;1.70)	1.36 (0.96;1.92)

Table S2. Attributable Fraction for the entire population and among exposed considering the conventional regression approach and the MSM approach.

	Attributable Fraction Population*				Attributable Fraction Exposed**			
	BOP + CAL in different teeth		BOP + CAL in the same tooth		BOP + CAL in different teeth		BOP + CAL in the same tooth	
	Conventional regression	MSM	Conventional regression	MSM	Conventional regression	MSM	Conventional regression	MSM
General Obesity – Hypertension	5%	6%	4%	3%	20%	20%	42%	36%
General Obesity – Depression	8%	6%	4%	4%	22%	28%	46%	44%
Central Obesity – Hypertension	3%	2%	4%	3%	21%	12%	54%	46%
Central Obesity – Depression	4%	4%	4%	4%	26%	27%	58%	58%

*Calculated using the formula $AF_p = \frac{P_c(RR-1)}{RR}$, where P_c =exposure prevalence among cases, and RR =rate ratio (Porta, 2008).

**Calculated using the formula $AF_e = \frac{RR-1}{RR}$ (Porta, 2008).

References

Baron, R. M. & Kenny, D. A. (1986) The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol* **51,** 1173-1182.

Robins, J. M., Hernan, M. A. & Brumback, B. (2000) Marginal structural models and causal inference in epidemiology. *Epidemiology* **11,** 550-560.

Porta, M. (2008) A dictionary of Epidemiology. 5th edition, Oxford University Press. New York.

Title: Does the increase of overweight and obesity impact on periodontitis risk? An application of the parametric g-formula in the 1982 Pelotas birth cohort.

Authors: Gustavo G. Nascimento[1,2], Marco A. Peres[2], Murthy N. Mittinty[3], Karen G. Peres[2], Loc G. Do[2], Mark Bartold[4], Bernardo L. Horta[5], Denise P. Gigante[5], Marcos B. Corrêa[1], Flávio F. Demarco[1,5]

[1]Postgraduate Program in Dentistry, Federal University of Pelotas, Pelotas, Brazil
[2]Australian Research Centre for Population Oral Health (ARCPOH), University of Adelaide, Adelaide, Australia
[3]School of Population Health, University of Adelaide, Adelaide, Australia
[4] Colgate Australian Clinical Dental Research Centre, School of Dentistry, University of Adelaide, Adelaide, Australia
[5]Postgraduate Program in Epidemiology, Federal University of Pelotas, Pelotas, Brazil

Corresponding author:

Prof Flávio F. Demarco,
457, Gonçalves Chaves St., room 506
Pelotas, RS, Brazil
ZIP: 96015-380
Email: ffdemarco@gmail.com

Abstract

Background: Overweight and obesity have been associated with increased periodontitis risk; however uncertainty persists regarding the causal relationship of such conditions. Thus, we estimated independent and joint hypothetical interventions on overweight/obesity and other unhealthy habits (smoking, alcohol consumption and fat and carbohydrates consumption) on the risk of any periodontitis, moderate/severe periodontitis and the combination of bleeding on probing and clinical attachment loss (BOP+CAL) in adults aged 31-years-old from the 1982 Pelotas Birth Cohort, Brazil.

Methods: We used the parametric g-formula to estimate the 31-year periodontitis risk in the following scenarios: under no intervention; setting the BMI to overweight; setting the BMI to obesity; smoking, having high consumption of alcohol and consuming high amount of fat and carbohydrates. Interventions were set independently to each risk factor and in joint interventions with overweight and obesity on the entire population.

Results: 539 participants had oral examinations. The 31-year risk under no intervention was 33.3%, 14.3% and 14.7% for any periodontitis, moderate/severe periodontitis and BOP+CAL, respectively. Overweight and obesity increased the risk of all outcomes: 11% (overweight) and 22% (obesity) higher risk of periodontitis; 12% (overweight) and 27% (obesity) greater risk of moderate and severe periodontitis; 21% (overweight) and 57% (obesity) higher risk of CAL+BOP. When combined with other unhealthy habits, the risk was even greater, suggesting a cluster effect.

Conclusions: Increase of overweight and obesity increased the risk for unfavorable periodontal outcomes in this population of Brazilian adults. This effect was even greater when a combination of excess of weight and unhealthy habits existed.

Key-words: g-formula; Periodontal Diseases; Nutritional Status; Interventions; Obesity; Overweight; Smoking; Alcohol; Diet; Cohort Studies.

Introduction

Amongst the most prevalent chronic diseases, periodontitis is an inflammatory condition induced by specific bacteria that affect the supporting tissue of teeth[1]. Besides the infectious component, the establishment and progression of such disease also depend on the quality of the host immune response, which is impacted by unhealthy habits and systemic conditions such as type II diabetes and obesity[1-7]. Between 1990 and 2010 periodontitis was ranked as the 6th most prevalent chronic disease worldwide[8, 9]. Furthermore, given the combination of high population growth with a greater life expectance and a significant reduction in tooth loss, it is expected an increase in the prevalence of periodontitis is expected[8]. It is a major concern for health professionals and policy makers, since periodontitis has been identified as a risk factor to other chronic inflammation-related conditions such cardiovascular diseases[10-12].

Overweight and obesity can be defined as diseases in which body fat has excessively been accumulated adversely affecting health conditions[13]. It is an emerging chronic disease associated with relevant morbidity and mortality, not only in high-income but also in medium- and low-income countries[14, 15]. In the 1982 Pelotas birth cohort, the prevalence of overweight and obesity has increased over the time following the world tendency. In 1986, when participants were aged 4, only 7% of the cohort was considered with excess of weight, whereas in 2012, when participants were aged 30, this rate has risen to about 60%[16]. This condition has been associated with adverse effects on many systemic diseases, such as type II diabetes, hypertension, cardiovascular disease, infectious diseases and cancer[17, 18].

The association between obesity and periodontal disease has been supported by systematic reviews[19, 20]. However, their findings showed that few studies adopted longitudinal designs. Thus, the source of such findings is originated from cross-sectional studies. Even though a positive association between weight gain and incidence of periodontitis has been observed, no causal inference between obesity development and periodontitis occurrence could be established[21].

Some mechanisms have been proposed to explain the complex relationship between obesity and periodontitis[19, 20]. The excessive adipose tissue by downgrading adiponectin levels creates a reservoir of circulating pro-inflammatory mediators inducing a chronic inflammatory condition[22]. This systemic low-grade inflammation is

responsible to increase the susceptibility of obese subjects to infectious challenges by down-regulating the local immune response[17, 23]. Also, obese and overweight subjects tend to present more detrimental health related behaviors such as smoking, physical inactivity, and unhealthy diet, with higher consumption of fat, carbohydrates and sugar, which have been associated with unfavorable periodontal outcomes as well[2-5]. Thus, it is possible to assume that obesity and periodontitis share common risk factors. Also, the impact of the simultaneous occurrence of several risk factors on health indicators are greater than the isolated effect of a single factor, suggesting a clustering effect[24]. The literature has provided useful information regarding the identification of such clustered behaviors, but little is known about the effects of intervening on them since large randomized trials are needed. Another difficulty lays on the fact that some exposures, such as obesity, cannot be allocated in a randomized intervention.

In the medical and dental fields, the studies investigating the effects of life-course obesity on systemic chronic conditions in later life have not considered the cumulative effects of obesity during life-course. Additionally, they have not employed causal analytical approaches not accounting for the time-varying confounders neither distinguishing between confounders and mediators[25]. This might have leaded to biased and controversial findings[26].

Statistical methods have been proposed for estimation of causal effects in observational studies[27]. Amongst these methods, the inverse-probability-of-treatment-weighting is the most frequently used in epidemiology[28]; however, experts have pointed out the statistical inefficiency of such estimator in some specific scenarios, like in the presence of time-dependent variables[29]. In this context, G-computation can be used as an alternative analytic technique, especially when the explanatory variables are measured at several different points in time on each subject[30, 31]. This specific approach also allows estimating the population risk of a disease under hypothetical interventions, providing useful information for health professionals and policy makers[32].

Given the aforementioned, it is clear that no research studied the cumulative effects of life-course obesity on periodontitis in adulthood. In addition, no studies explored the clustering effects of potential risk factors in the underlying relationship between obesity and periodontal disease. Therefore, considering the rising rates of overweight and obesity observed worldwide and in this cohort, this study aimed to

answer the following research question: “Does the increase of overweight and obesity impact on the burden of periodontitis?” Furthermore, we intended to estimate the effect of unhealthy habits combined with overweight and obesity on periodontitis by simulating hypothetical interventions using the parametric g-formula. We hypothesize that if individuals were obese during life-course they would present a higher risk for periodontal disease development followed by those overweight [33]. Additionally, we expect that the greater the number of combined risk factors during life-course, the higher the risk of periodontal disease in adulthood.

Methods

The 1982 Pelotas Birth Cohort

In 1982, the three maternity hospitals in Pelotas, a southern medium-size Brazilian city, were visited daily, and 7,392 births were identified. Those children whose parents lived in the urban area of the city (N=5,914) were examined and the mothers were interviewed[16]. Since then, those individuals have been followed on several occasions during life-course. In 2012, all individuals aged 30 were contacted for interview and health examination, including anthropometric measurements, carotid intima media thickness and blood tests (N=3,701). The interviews covered issues related to socioeconomic condition, dietary habits, smoking, alcohol consumption and health conditions. Details about this cohort are found elsewhere[16].

In 1997, when the participants were aged 15 years, 900 individuals were randomly selected as sample for the Oral Health Study (OHS-97). In 2006, when those individuals were 24-years-old, 888 subjects investigated in the OHS-97 (98.7%) were contacted for new assessment comprised of interviews and oral health exams. From those, 720 were clinically examined. In 2013, individuals were assessed for oral examination. In the OHS-2013, the same 888 individuals investigated in the OHS-97 were contacted for new assessment. All teeth were examined for the presence of periodontal disease (bleeding on probing, probing depth and gingival margin), dental caries and other dental and oral conditions. Oral examination was performed at home by six dentists previously trained and calibrated. Examiners underwent theoretical and practical training. Practical training was

performed on 20 individuals, and reproducibility assessment was performed on 20 individuals with similar age but not enrolled in the 1982 Pelotas birth cohort. The lowest intra-class correlation coefficient for probing depth and gingival margin was 0.85. In order to assure the quality of the study, 15% of all interviews were repeated. Methodological aspects of the OHSs in the 1982 Pelotas birth cohort study are discussed in depth elsewhere[34].

Outcomes

The outcomes of this study were periodontal disease and bleeding on probing at age 31. Periodontal examinations comprised a full-mouth probing at six sites per tooth using a PCP2 probe. Two different criteria were adopted for this study:

1. American Academy of Periodontology and the Center for Diseases Control and Prevention (AAP/CDC): Individuals were classified into four categories: healthy, mild periodontitis, moderate periodontitis and severe periodontitis[35]. Following that, two different dichotomous variables were created: the first included all individuals with any periodontitis compared to those considered healthy; the second grouped only the individuals with moderate and severe periodontitis in the comparison category; thus, those healthy and with mild periodontitis comprised the reference category.
2. Baelum and Lopez [36]: Individuals with at least one site with simultaneous occurrence of Clinical Attachment Loss (CAL) ≥4mm and Bleeding on Probing (BOP) were classified as having periodontitis.

Nutritional Status Assessment

In each visit, subjects were weighted and their height was assessed. We used four different episodes of obesity during life-course to estimate the cumulative effects of obesity on periodontitis: at ages 4, 15, 23 and 30. Obesity at age 4 was defined according to the following cut-off: eutrophic (*Z* score for age and sex ≤2 SD); overweight (*Z* score for age and sex >2 SD and ≤3SD); obese (*Z* score for age and sex >3 SD)[37, 38]. At the age of 15 years, the following cut-off was adopted: eutrophic (*Z* score for age and sex ≤1 SD); overweight (*Z* score for age and sex >1 SD and

≤2SD); obese (*Z* score for age and sex >2 SD)[39]. At ages 23 and 30, the Body Mass Index (BMI) was calculated by the ratio between the weight and the square of the height (Kg/m^2). Subjects were classified accordingly: eutrophic (BMI<25 Kg/m^2); overweight (BMI≥25 and <30 Kg/m^2); obese (BMI≥30 Kg/m^2) [14]. For all follow-ups conducted from childhood to adulthood, we used portable scales and anthropometers to assess weight and height, respectively. Those measures were obtained using the techniques proposed by Lohman, Roche [40] and the interviewers were trained according to the techniques. Quality control measures included scale calibration and repetition of 5% of interviews. Further methodological details are found elsewhere[41].

Covariates

Baseline Covariates

We set as baseline confounders the following variables collected in 1982: sex, maternal schooling at birth (0-8 years; ≥9 years) and household income at birth (categorized in tertiles and converted in a dichotomous variable where the first and the second tertiles were grouped)[42].

Time-varying variables

Potential pathways to periodontal disease were identified through the Directed Acyclic Graph (DAG)[43]. Based on the literature, we decided to include a set of time-varying covariates in the analyses: smoking status (current or former/never smoker), type II diabetes (≥126mg/dl), hypertension (systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg). Alcohol consumption was collected in grams per day. Percentage of dietary energy from fat and carbohydrate consumption was assessed through a semi-quantitative, interviewer-administered FFQ[44]. The variables “alcohol consumption” and “fat and carbohydrate consumption” were categorized in tertiles, and the first and the second tertiles were grouped in one category. Figure 1 displays a simplified DAG demonstrating possible causal relationship between the variables. A more detailed figure is available in the Supplemental Material section.

Hypothetical Interventions

Based on the literature from randomized controlled trials and observational studies, we defined different hypothetical interventions on the time-varying variables to analyze their potential effects on periodontitis on the entire population: being overweight, being obese, smoking, having high consumption of alcohol and having high consumption of fat and carbohydrates. We excluded diabetes and hypertension from the hypothetical interventions since those conditions are indirectly modified by the other specified risk factors.

Data analyses

The parametric g-formula, a generalization of standardization for time-varying exposures and confounders, was used to estimate the standardized risk of periodontal disease under hypothetical interventions in this population. This standardized risk comprises a weighted average of the risks conditional on the specified exposure history and the observed confounders with the probability density functions of the time-varying confounders as weights. This analytical approach has been previously employed to estimate the effects of hypothetical interventions on different outcomes such as cardiovascular disease[45] and diabetes[46].

Briefly, the parametric g-formula estimates the risk as follows: initially regression models are fitted for all potential confounders and for the outcome using data on the entire study population. After that, these fitted models are used to simulate the risk of the outcome under hypothetical interventions in five steps:

(a) Obtain the observed joint distribution of covariates at baseline;

(b) Estimate the joint distribution of time-varying covariates at the next time-point using the parametric models;

(c) Hypothetically intervene by setting the values of chosen covariates in order to simulate the interventions;

(d) Estimate the predicted probability of the outcome using those new covariate values;

(e) Repeat steps “b” through “d” for the follow-up duration in order to estimate the predicted risk of disease under the determined interventions. A detailed description can be found elsewhere [32].

We performed a Monte Carlo simulation of 10,000 individuals. Baseline covariates were assigned by using the empirical distribution. The values of time-

varying covariates for each time interval were drawn from the distribution estimated via regression models after setting obesity and other risk factors to the values specified by each specific intervention. As some time-varying covariates were not measured in all visits, only the most recent measurement was used, and an interaction term between the most recent measurement and the time since that measurement was included in the model. The models included the following baseline confounders: sex, household income at birth and maternal schooling at birth (Table 1).

For each model, we estimated the outcome risk associated with respective hypothetical intervention. Additionally, we set the risk under no intervention as the reference category, and estimated the population risk ratio for each selected intervention. If the assumptions of no unmeasured confounding, no model misspecification, and no measurement error hold, our results can be interpreted as arising from a randomized experiment in which individuals were randomly assigned and adhered the specified interventions. In order to obtain the 95% confidence intervals, we used nonparametric bootstraps with 1,000 samples. We examined the possibility of effect modification by conducting specific analyses in the subsets of the study population defined at baseline according to sex, household income and maternal schooling experience. Also, we tested effect modification on the outcome and exposure relationship taking the most recent measure of the time-varying covariates. All analyses were conducted using SAS 9.4 (Cary, NC, USA). We employed the g-formula SAS macro implemented by Taubman, Robins [32] available at http://www.hsph.harvard.edu/causal/software. The codes used for this study are available in the Supplemental Material.

Ethical Issues

All phases of this study were approved by the Ethics Committee of the Federal University of Pelotas, Faculty of Medicine. Written informed consent was obtained from all enrolled individuals or from their parents or legal guardians.

Results

In total, 539 31-years-old individuals were examined (61% of OHS-97). The observed risk of having mild, moderate and severe periodontitis at aged 31 was 20%, 13% and 1%, respectively. The observed risk of having at least one site with the combination of CAL+BOP was 15%. Table 2 describes the sample according to sociodemographic characteristics and nutritional status during life-course. Information regarding the other health related characteristics is described in Table S1 (Supplemental Material).

The simulated risks under no intervention on any type of periodontitis, moderate and severe periodontitis and the combination of CAL and BOP was 33%, 14%, 15% respectively. Table 3 describes the effects of hypothetical interventions on periodontitis. Overall, it is possible to note that both overweight and obesity increased the risk of any periodontitis (RR 1.11 and RR1.22, respectively). Other risk factors also increased the risk of periodontitis, except alcohol consumption. When hypothetical interventions combined overweight and obesity with any other risk factor, the risk of periodontitis increased. Those participants who were overweight, smokers, with high consumption of fat and carbohydrates and physically inactive presented 44% higher risk of periodontitis, whereas those obese had almost 62% higher risk of periodontitis compared to those under no intervention.

Table 4 shows the risk of moderate and severe periodontitis. Those overweight and those obese presented greater risk of moderate/severe periodontitis (RR 1.12 and RR 1.27, respectively). Smoking also increased the risk (RR 1.18), whereas diet had no influence and alcohol consumption slightly reduced the risk. The combination of overweight with smoking increased the risk of moderate/severe periodontitis in 32%; when obesity was associated with smoking, the risk was even greater (RR 1.48). Compared with no intervention, the risk ratio for being overweight, smoker and consuming high amount of fat and carbohydrates was 1.35 and for being obese 1.52. Alcohol consumption lowered the risk in all hypothetical interventions.

Overweight and obesity also increased the risk of CAL+BOP (Table 5). Individuals who were overweight had 21% higher risk than those under no intervention, while those obese had 50% increase in risk. Smokers had 11% greater risk for CAL and BOP, whilst diet did not change materially the risk. High consumption of alcohol lowered the risk of CAL and BOP (RR 0.88). The risk ratio for

overweight and smoking was 1.50, and for obesity and smoking was 2.01. When unhealthy diet was hypothetically intervened on, those individuals overweight and smokers presented 57% greater chance for CAL and BOP, and those obese more than twice the risk (RR 2.09). In the combined interventions, alcohol consumption did not change materially the risk.

We replicated our analyses under random order of covariates in the model. The risk under no intervention and the other parameters were not substantially altered, thus indicating the robustness of our models.

Discussion

The present findings suggest a causal relationship between being overweight or obese during life-course and the occurrence of periodontitis in adulthood. Also, that a combination of detrimental health behaviors and overweight/obesity increases the risk for periodontitis in this population. These findings support our hypothesis, since those obese and with higher number of risk factor presented the greatest risk of all types of periodontitis. A positive association between obesity and overweight has been demonstrated by many observational studies, so as by systematic reviews. The majority of them presented cross-sectional design which suffers with issues from temporality. The longitudinal studies that have investigated such topic also presented limitations, especially regarding to the analytical approach employed. Besides that, only two studies used information from early life to predict periodontal disease in adulthood. However, those also present a different perspective from our study; while one used self-reported BMI at age 21 to predict periodontal disease at age 60[47], the other explored the number of episodes of obesity from adolescence to young adult life to investigate the presence of gingival bleeding, dental calculus and periodontal pocket at age 24[48]. In both of them, no association between early obesity with the later periodontal disease was observed. Nevertheless, both have not considered either the childhood obesity or the cumulative effects of obesity during life-course on periodontitis in later life. Obesity developed in early life could be a result of unhealthy behaviors that are set in this younger age and might have repercussions later in life. Also, obesity and overweight can have effects on general health and oral health, including the periodontal health[49] that could have detrimental effects on the periodontal health in latter ages.

Our findings also suggest that the combination of multiple detrimental health behaviors impacts on the risk of periodontitis. Those behaviors are well-known risk factors to cardiovascular disease, cancer and premature mortality[50]. Individuals that accumulated unhealthy behaviors presented higher risk for periodontitis, indicating that this oral condition is similarly influenced by systemic factors as other chronic diseases. Previous reports have demonstrated the combined effect of multiple risk factors is greater than individual ones, suggesting a cluster effect[50]. It is beyond dispute the importance of such findings in the public health perspective, since these poor lifestyle choices frequently coexist. Besides that, our analytical approach

allowed us to establish a causal relationship between those potential behaviors and periodontitis, strengthening our results. To the best of the authors' knowledge, this is the first study to simulate the effects of overweight and obesity in combination with other detrimental habits on the risk of periodontitis.

Previous reports could not address the causal effects of overweight and obesity on periodontitis since a bidirectional association between those conditions could exist. Our results clearly showed the cumulative effects of both, overweight and obesity, on periodontitis in later life. It has been hypothesized that the white adipose tissue (WAT) is responsible for secreting inflammatory cytokines in the blood stream, affecting the general and the local immune response. Moreover, the recruitment of macrophages to the core of the WAT, caused by adipocytes expansion, exacerbates the previous inflammatory process. This low-grade inflammation alters significantly the immune response threshold, making obese and overweight individuals more susceptible to infectious diseases than normal weight ones[17, 51].

In addition to that, poor health behaviors also play a role in this relationship. Since obese individuals are more likely to present neglected health care, the coexistence of poor health behaviors is expected, increasing the risk of periodontitis. Smoking, diet, and alcohol consumption are also closely related to obesity and periodontitis. Smoking has been identified as a risk factor for chronic periodontitis in adults[52]. Authors suggest that smoking has a cumulative effect on periodontal attachment loss, thus, it is expected the older the individual the higher the effect. Given the age of the individuals enrolled in this cohort, this fact could explain a reduced effect of smoking on periodontitis in our study. Also, the decreasing prevalence of smoking in this population corroborates our findings. The effects of fat and carbohydrate consumption on periodontal disease have been pointed out by different authors. Excessive carbohydrate and fat ingestion may lead to increased inflammatory framework and oxidative stress inducing a hyperinflammatory state, which has been associated with periodontitis and obesity[53, 54]. In our results, the effects of high consumption of fat and carbohydrates varied according to the outcome. When the presence of periodontitis was set as the outcome, diet increased in 10% the risk of periodontitis. Nevertheless, it had no isolated effect on the risk of CAL and BOP, but contributed to the cluster effect when combined with other risk factors.

The association between alcohol consumption and periodontal disease, however, is not conclusive. A systematic review presented inconclusive results regard such association, indicating a need for more studies investigating the topic[55, 56]. Studies revealed that alcohol can have both, protective and detrimental, effects on periodontal tissues depending on the dose it is consumed. In our study, the isolated consumption of alcohol lowered the risk of periodontitis; conversely, it did not influence the estimates when combined with other risk factors. Our results could be attributed to the considerable low-consumption of alcohol in this specific population. Even the ones included in the last tertile of alcohol consumption presented a moderate daily consumption, which has been proved to have beneficial effects on periodontitis and other chronic diseases. Periodontal tissue breakdown requests an inflammatory host response, but light to moderate alcohol intake reduces the monocyte production of circulating pro-inflammatory cytokines and the levels of C-reactive protein[57, 58]. Furthermore, alcohol consumption might present an antimicrobial effect in dental biofilm [59].

Our study presents several strengths that should be highlighted. First of all, the prospective longitudinal data originated from a population-based birth cohort provide robust information since early-life. It allowed us to estimate the cumulative effect of obesity since childhood on a chronic disease established in adulthood. Even though a possibility of attrition bias could exist, analytical methods employed circumvented this possible caveat. The use of repeated measures for exposure and risk factors also supported the robustness of our findings. Moreover, the employment of the parametric g-formula allowed us to appropriately adjust our analyses for time-varying confounders; besides to estimate the effects of joint interventions, what makes it directly relevant for policy makers and clinicians[30, 60]. Our study, however, has a major difference from previous studies using the parametric g-formula: while the later set hypothetical interventions to decrease the risk of outcomes, ours went in the opposite direction. Our methodological choice was based on the rising prevalence of excess of weight. As aforementioned, in this cohort, the prevalence of overweight/obesity increased 100% from 1986 to 2012, suggesting an ascending pattern of such condition. Furthermore, the similarity between the simulated risks for the different outcomes with the corresponding observed risks is a condition for no model misspecification in the calculation of estimates using the parametric g-formula. Finally, we should emphasize the reliability of our measures since data were

obtained from clinical examinations by trained and calibrated examiners. Additionally, the use of renowned classification for periodontitis also corroborates the robustness of our findings.

This study is not free of limitations. Firstly, we only obtained measures of alcohol consumption and diet from early adulthood. As some detrimental habits start in adolescence, this could underestimate the effects of such habits in the hypothetical interventions. We used BMI to classify the nutritional status of the individuals. This index does not distinguish between fat mass and lean mass and does not consider the distribution of fat over the body. Additionally, previous studies have demonstrated that waist circumference is a more reliable measurement for obesity, since abdominal obesity, independent of general obesity, is associated with metabolic disturbances and increased risk for chronic diseases, such as periodontitis[61, 62]. Thus, abdominal obesity should be preferred in future studies. Nevertheless, even with the limitations of BMI, a strong effect of both, overweight and obesity, on periodontitis could be demonstrated using the hypothetical interventions. Our estimates may not be extrapolated to other populations with different distribution of risk factors, since the g-formula standardizes the risk to the distribution of risk factors in this particular population under study. Also, the validity of our findings relies on the usual assumptions for all analyses of observational data: no unmeasured confounding, no measurement error and no model misspecification. However, a possibility of residual confounding cannot be logically excluded; also, a certain degree of measurement error is expected, what might have contributed as a source of bias.

Regardless of the limitations, our study demonstrated the impact of increasing overweight and obesity on periodontitis in adults from a Brazilian birth cohort. As periodontitis is ranked amongst the 10th most prevalent chronic conditions in the global burden of diseases, the increase of obesity will further add to the burden of periodontitis. Additionally, the combination of obesity with other risk factors may increase the risk of periodontitis development. Thus, a common risk approach seems to be more rationale to prevent periodontal disease development and progression than intervening on each specific risk factor[63].

Acknowledgements:

This article is based on data from the study "Pelotas Birth Cohort, 1982" conducted by Postgraduate Program in Epidemiology at Universidade Federal de Pelotas with the collaboration of the Brazilian Public Health Association (ABRASCO). The authors are grateful to the Coordination for the Improvement of Higher Education Personnel (CAPES) and to the Rio Grande do Sul State Research Support Foundation (FAPERGS) for the scholarships provided to GGN (#BEX 13810/13-8).

Funding:

The Oral Health Study-2013 (OHS-13) was supported by the National Counsel of Technological and Scientific Development (CNPq) (#403257/2012-3-FFP and #475979/2013-3-MBC).

References

1. Van Dyke TE, van Winkelhoff AJ. Infection and inflammatory mechanisms. *J Clin Periodontol* 2013; 40 Suppl 14: S1-7.

2. Al-Zahrani MS, Bissada NF, Borawskit EA. Obesity and periodontal disease in young, middle-aged, and older adults. *J Periodontol* 2003; 74: 610-5.

3. Franchini R, Petri A, Migliario M, Rimondini L. Poor oral hygiene and gingivitis are associated with obesity and overweight status in paediatric subjects. *J Clin Periodontol* 2011; 38: 1021-8.

4. Silva DA, Peres KG, Boing AF, Gonzalez-Chica DA, Peres MA. Clustering of risk behaviors for chronic noncommunicable diseases: a population-based study in southern Brazil. *Prev Med* 2013; 56: 20-4.

5. Lula EC, Ribeiro CC, Hugo FN, Alves CM, Silva AA. Added sugars and periodontal disease in young adults: an analysis of NHANES III data. *Am J Clin Nutr* 2014; 100: 1182-7.

6. Cekici A, Kantarci A, Hasturk H, Van Dyke TE. Inflammatory and immune pathways in the pathogenesis of periodontal disease. *Periodontol 2000* 2014; 64: 57-80.

7. Nascimento GG, Leite FR, Do LG, et al. Is weight gain associated with the incidence of periodontitis? A systematic review and meta-analysis. *J Clin Periodontol* 2015.

8. Kassebaum NJ, Bernabe E, Dahiya M, Bhandari B, Murray CJ, Marcenes W. Global Burden of Severe Periodontitis in 1990-2010: A Systematic Review and Meta-regression. *J Dent Res* 2014; Nov;93(11):1045-53.

9. Marcenes W, Kassebaum NJ, Bernabe E, et al. Global burden of oral conditions in 1990-2010: a systematic analysis. *J Dent Res* 2013; 92: 592-7.

10. Mealey BL, Ocampo GL. Diabetes mellitus and periodontal disease. *Periodontol 2000* 2007; 44: 127-53.

11. Tsioufis C, Kasiakogias A, Thomopoulos C, Stefanadis C. Periodontitis and blood pressure: the concept of dental hypertension. *Atherosclerosis* 2011; 219: 1-9.

12. Cullinan MP, Seymour GJ. Periodontal disease and systemic illness: will the evidence ever be enough? *Periodontol 2000* 2013; 62: 271-86.

13. Kopelman PG. Obesity as a medical problem. *Nature* 2000; 404: 635-43.

14. World Health Organization. Obesity: Preventing and Managing the Global Epidemic. In: Series WTR, editor. Geneva; 2000.

15. Haslam DW, James WP. Obesity. *Lancet* 2005; 366: 1197-209.

16. Horta BL, Gigante DP, Goncalves H, et al. Cohort Profile Update: The 1982 Pelotas (Brazil) Birth Cohort Study. *Int J Epidemiol* 2015.

17. Falagas ME, Kompoti M. Obesity and infection. *Lancet Infect Dis* 2006; 6: 438-46.

18. Chrysant SG, Chrysant GS. New insights into the true nature of the obesity paradox and the lower cardiovascular risk. *J Am Soc Hypertens* 2013; 7: 85-94.

19. Chaffee BW, Weston SJ. Association between chronic periodontal disease and obesity: a systematic review and meta-analysis. *J Periodontol* 2010; 81: 1708-24.

20. Suvan J, D'Aiuto F, Moles DR, Petrie A, Donos N. Association between overweight/obesity and periodontitis in adults. A systematic review. *Obes Rev* 2011; 12: e381-404.

21. Nascimento GG, Leite FRM, Do LG, et al. Is weight gain associated with the incidence of periodontitis? *J Clin Periodontol* 2015; Accepted Article.

22. Genco RJ, Grossi SG, Ho A, Nishimura F, Murayama Y. A proposed model linking inflammation to obesity, diabetes, and periodontal infections. *J Periodontol* 2005; 76: 2075-84.

23. Ghigliotti G, Barisione C, Garibaldi S, et al. Adipose tissue immune response: novel triggers and consequences for chronic inflammatory conditions. *Inflammation* 2014; 37: 1337-53.

24. Poortinga W. The prevalence and clustering of four major lifestyle risk factors in an English adult population. *Prev Med* 2007; 44: 124-8.

25. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000; 11: 550-60.

26. Murray ET, Hardy R, Hughes A, et al. Overweight across the life course and adipokines, inflammatory and endothelial markers at age 60-64 years: Evidence from the 1946 birth cohort. *Int J Obes (Lond)* 2015.

27. Snowden JM, Rose S, Mortimer KM. Implementation of G-computation on a simulated data set: demonstration of a causal inference technique. *Am J Epidemiol* 2011; 173: 731-8.

28. Cole SR, Hernan MA, Anastos K, Jamieson BD, Robins JM. Determining the effect of highly active antiretroviral therapy on changes in human immunodeficiency virus type 1 RNA viral load using a marginal structural left-censored mean model. *Am J Epidemiol* 2007; 166: 219-27.

29. Ertefaie A, Stephens DA. Comparing approaches to causal inference for longitudinal data: inverse probability weighting versus propensity scores. *The international journal of biostatistics* 2010; 6: Article 14.

30. Robins JM. A new approach to causal inference in mortality studies with a sustained exposure period—application to control of the healthy worker survivor effect. *Mathe Model* 1986; 7: 1393–512.

31. Daniel RM, De Stavola BL, Cousens SN. gformula: Estimating causal effects in the presence of time-varying confounding or mediation using the g-computation formula. *Stata J* 2011; 11: 479-517.

32. Taubman SL, Robins JM, Mittleman MA, Hernan MA. Intervening on risk factors for coronary heart disease: an application of the parametric g-formula. *Int J Epidemiol* 2009; 38: 1599-611.

33. Nascimento GG, Leite FR, Correa MB, Horta BL, Peres MA, Demarco FF. Relationship between periodontal disease and obesity: the role of life-course events. *Braz Dent J* 2014; 25: 87-9.

34. Peres KG, Peres MA, Demarco FF, Tarquinio SB, Horta BL, Gigante DP. Oral health studies in the 1982 Pelotas (Brazil) birth cohort: methodology and principal results at 15 and 24 years of age. *Cad Saude Publica* 2011; 27: 1569-80.

35. Eke PI, Page RC, Wei L, Thornton-Evans G, Genco RJ. Update of the case definitions for population-based surveillance of periodontitis. *J Periodontol* 2012; 83: 1449-54.

36. Baelum V, Lopez R. Defining a periodontitis case: analysis of a never-treated adult population. *J Clin Periodontol* 2012; 39: 10-9.

37. Rolland-Cachera MF. Childhood obesity: current definitions and recommendations for their use. *Int J Pediatr Obes* 2011; 6: 325-31.

38. World Health Organization (WHO). Reliability of anthropometric measurements in the WHO Multicentre Growth Reference Study. *Acta Paediatr* 2006; **450**: 38-46.

39. World Health Organization (WHO). *Growth reference 5-19 years* 2007 [cited 2015 February 11]; Available from: http://www.who.int/growthref/who2007_bmi_for_age/en/index.html

40. Lohman TG, Roche AF, Martorell R. *Anthropometric Standardization Reference Manual.* Champaign, IL, USA; 1988.

41. Gigante DP, Victora CG, Matijasevich A, Horta BL, Barros FC. Association of family income with BMI from childhood to adult life: a birth cohort study. *Public Health Nutr* 2013; 16: 233-9.

42. Peres MA, Peres KG, de Barros AJ, Victora CG. The relation between family socioeconomic trajectories from childhood to adolescence and dental caries and associated oral behaviours. *J Epidemiol Community Health* 2007; 61: 141-5.

43. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology* 1999; 10: 37-48.

44. Olinto MT, Willett WC, Gigante DP, Victora CG. Sociodemographic and lifestyle characteristics in relation to dietary patterns among young Brazilian adults. *Public Health Nutrition* 2011; 14: 150-9.

45. Lajous M, Willett WC, Robins J, et al. Changes in fish consumption in midlife and the risk of coronary heart disease in men and women. *Am J Epidemiol* 2013; 178: 382-91.

46. Danaei G, Pan A, Hu FB, Hernan MA. Hypothetical midlife interventions in women and risk of type 2 diabetes. *Epidemiology* 2013; 24: 122-8.

47. Linden G, Patterson C, Evans A, Kee F. Obesity and periodontitis in 60-70-year-old men. *J Clin Periodontol* 2007; 34: 461-6.

48. de Castilhos ED, Horta BL, Gigante DP, Demarco FF, Peres KG, Peres MA. Association between obesity and periodontal disease in young adults: a population-based birth cohort. *J Clin Periodontol* 2012; 39: 717-24.

49. Nascimento GG, Seerig LM, Vargas-Ferreira F, Correa FO, Leite FR, Demarco FF. Are obesity and overweight associated with gingivitis occurrence in Brazilian schoolchildren? *J Clin Periodontol* 2013; 40: 1072-8.

50. Kvaavik E, Batty GD, Ursin G, Huxley R, Gale CR. Influence of individual and combined health behaviors on total and cause-specific mortality in men and women: the United Kingdom health and lifestyle survey. *Arch Intern Med* 2010; 170: 711-8.

51. Morgan OW, Bramley A, Fowlkes A, et al. Morbid obesity as a risk factor for hospitalization and death due to 2009 pandemic influenza A(H1N1) disease. *PLoS One* 2010; 5: e9694.

52. Zeng J, Williams SM, Fletcher DJ, et al. Reexamining the association between smoking and periodontitis in the dunedin study with an enhanced analytical approach. *J Periodontol* 2014; 85: 1390-7.

53. D'Aiuto F, Nibali L, Parkar M, Patel K, Suvan J, Donos N. Oxidative stress, systemic inflammation, and severe periodontitis. *J Dent Res* 2010; 89: 1241-6.

54. O'Keefe JH, Gheewala NM, O'Keefe JO. Dietary strategies for improving post-prandial glucose, lipids, inflammation, and cardiovascular health. *J Am Coll Cardiol* 2008; 51: 249-55.

55. Amaral Cda S, Vettore MV, Leao A. The relationship of alcohol dependence and alcohol consumption with periodontitis: a systematic review. *J Dent* 2009; 37: 643-51.

56. Dye BA. The relationship between periodontitis and alcohol use is not clear. *J Evid Based Dent Pract* 2010; 10: 225-7.

57. Szabo G, Mandrekar P, Girouard L, Catalano D. Regulation of human monocyte functions by acute ethanol treatment: decreased tumor necrosis factor-alpha, interleukin-1 beta and elevated interleukin-10, and transforming growth factor-beta production. *Alcohol Clin Exp Res* 1996; 20: 900-7.

58. Imhof A, Woodward M, Doering A, et al. Overall alcohol intake, beer, wine, and systemic markers of inflammation in western Europe: results from three MONICA samples (Augsburg, Glasgow, Lille). *Eur Heart J* 2004; 25: 2092-100.

59. Nishida N, Tanaka M, Hayashi N, et al. Association of ALDH(2) genotypes and alcohol consumption with periodontitis. *J Dent Res* 2004; 83: 161-5.

60. Garcia-Aymerich J, Varraso R, Danaei G, Camargo CA, Jr., Hernan MA. Incidence of adult-onset asthma after hypothetical interventions on body mass index and physical activity: an application of the parametric g-formula. *Am J Epidemiol* 2014; 179: 20-6.

61. Snijder MB, van Dam RM, Visser M, Seidell JC. What aspects of body fat are particularly hazardous and how do we measure them? *Int J Epidemiol* 2006; 35: 83-92.

62. Canoy D. Distribution of body fat and risk of coronary heart disease in men and women. *Curr Opin Cardiol* 2008; 23: 591-8.

63. Sheiham A, Watt RG. The common risk factor approach: a rational basis for promoting oral health. *Community Dent Oral Epidemiol* 2000; 28: 399-406.

Figures

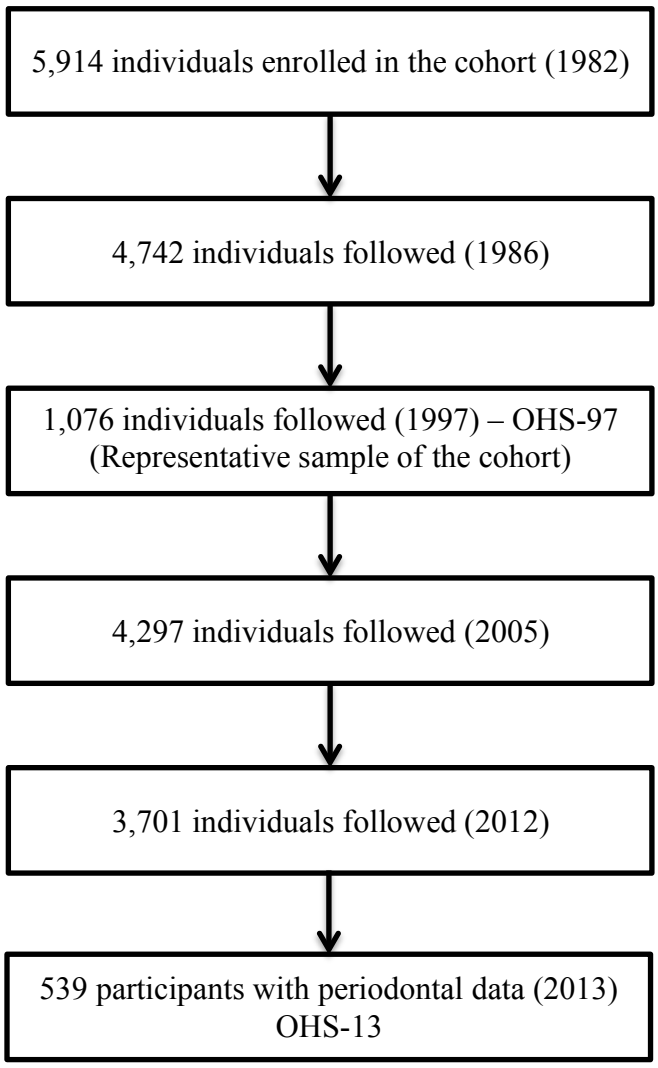


Figure 1. Flow chart of the 1982 Pelotas Birth Cohort and the Oral Health Studies

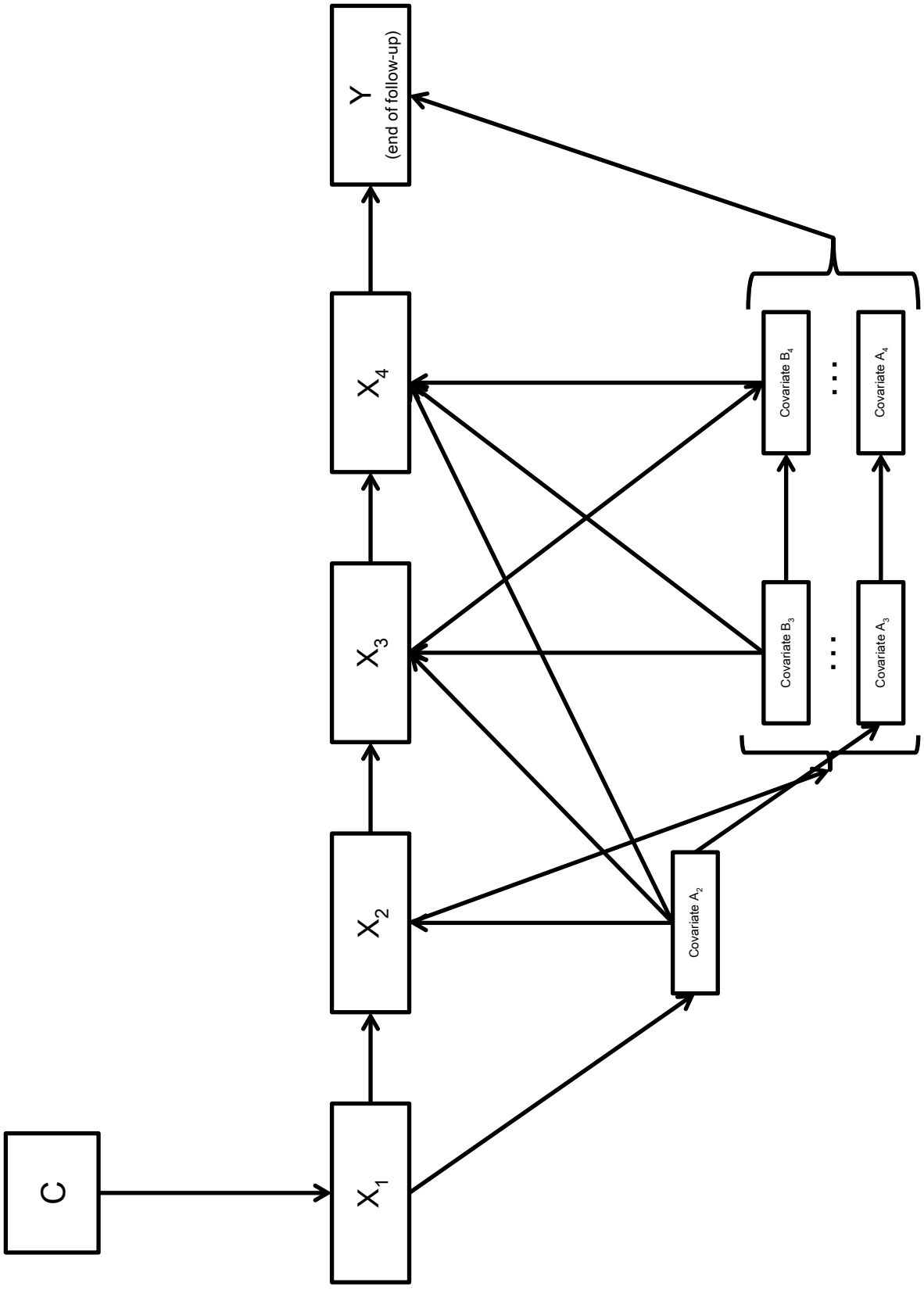


Figure 2. Simplified causal directed acyclic graph to depict the relationship between time-varying exposure (obesity), outcomes (periodontal disease) and time-varying covariates

Table 1. Covariates used to model incidence of periodontitis in the 1982 Pelotas Birth Cohort (1982-2013), Pelotas, Brazil.

Variables	Years assessed	Type of model when used as dependent variable	Functional form when used as predictor
Non-modifiable			
Time period	-	Not predicted	Period indicators
Sex	1982	Not predicted	Indicator
Household income	1982	Not predicted	Indicator
Maternal Schooling	1982	Not predicted	Indicator
Experience			
Modifiable			
BMI	1986, 1997, 2005, 2012	Nested Logistic	Three categories*
Smoking	1997, 2005, 2012	Logistic	Indicator
Alcohol	2005, 2012	Logistic	Indicator
Diet	2005, 2012	Logistic	Indicator
Indirectly Modifiable			
Hypertension	2005, 2012	Logistic to failure	Indicator
Diabetes	2005, 2012	Logistic to failure	Indicator

* Categories were: eutrophic, overweight and obese.

Table 2. Sociodemographic and anthropometric characteristics of the sample in 1982, 2012 and OHS-13 according to periodontal outcomes. Pelotas, Brazil.

	Total sample (1982)	Total sample (2012)	OHS-13 (2013)	Any Periodontitis (2013)	Moderate and severe Periodontitis (2013)	Clinical Attachment Loss and Bleeding on Probing (2013)
Baseline Covariates						
Sex						
Male	51.36	53.0	50.65	58.21	69.94	60.0
Female	48.64	47.0	49.35	41.79	35.06	40.0
Household Income						
1st and 2nd tertiles	69.28	69.39	69.70	73.13	76.62	70.0
3rd tertile	30.72	30.61	30.30	26.87	23.38	30.0
Maternal Schooling Experience						
0-8 years	74.71	75.14	77.32	77.50	77.92	72.86
9 years or more	25.29	24.86	22.68	22.50	22.08	27.14
Time-varying Exposure						
Body Mass Index (1986)						
Eutrophic	-	92.46	92.53	91.49	94.44	96.92
Overweight	-	6.06	5.89	7.45	5.56	1.54
Obese	-	1.49	1.57	1.06	0	1.54
Body Mass Index (1997)						
Eutrophic	-	75.79	74.81	69.19	68.83	71.43
Overweight	-	17.05	16.54	22.22	24.68	21.43
Obese	-	7.17	8.65	8.59	6.49	7.14
Body Mass Index (2005)						
Eutrophic	-	71.67	68.02	62.50	62.86	60.32
Overweight	-	20.23	23.48	27.17	28.57	33.33
Obese	-	8.10	8.50	10.33	8.57	6.35
Body Mass Index (2012)						
Eutrophic	-	41.88	40.30	31.64	27.14	20.0
Overweight	-	34.74	35.02	42.94	47.14	53.85
Obese	-	23.38	24.68	25.42	25.71	26.15

Table 3. Periodontitis Risk Under Hypothetical Interventions, 1982 Pelotas Birth Cohort, 1982–2013, Pelotas, Brazil.

Intervention	31-year risk of Periodontitis (%) (95% CI)[a]	Population risk ratio (95% CI)	Population risk difference (%) (95% CI)	Number needed to intervene
(0) No intervention[b]	33.29 (26.99;40.25)	1.00	0	-
(1) Overweight	36.93 (30.30;44.04)	1.11 (0.94;1.35)	3.64 (-2.44;10.77)	27
(2) Obesity	40.72 (27.98;46.63)	1.22 (1.01;1.67)	7.44 (-4.66;22.21)	13
(3) Smoking	35.84 (25.31;48.82)	1.08 (0.80;1.39)	2.56 (-6.31;12.42)	39
(4) Diet	36.58 (28.49;46.20)	1.10 (0.83;1.49)	3.29 (-6.50;15.15)	30
(5) Alcohol	31.80 (22.33;42.46)	0.96 (0.72;1.27)	-1.48 (-9.89;8.37)	NA
(6) Overweight and smoking	39.60 (27.76;52.58)	1.19 (0.88;1.67)	6.31 (-4.25;19.94)	16
(7) Overweight and diet	42.42 (33.76;52.48)	1.27 (0.93;1.72)	9.14 (-2.48;20.58)	11
(8) Overweight and alcohol	35.39 (26.44;44.45)	1.06 (0.77;1.46)	2.10 (-0.88;2.76)	48
(9) 1, 3, 4 combined	45.09 (32.07;59.33)	1.35 (0.92;1.99)	11.80 (-3.03;26.95)	8
(10) 1, 3, 4, 5 combined	47.95 (33.59;62.10)	1.44 (0.98;2.13)	14.66 (-0.58;31.07)	7
(11) Obesity and smoking	43.44 (28.46;61.90)	1.30 (0.84;2.00)	10.15 (-5.80;30.22)	10
(12) Obesity and diet	48.47 (33.47;62.53)	1.46 (0.92;2.07)	15.18 (-2.84;31.17)	7
(13) Obesity and alcohol	39.13 (28.63;50.83)	1.18 (0.78;1.74)	5.85 (-8.37;20.70)	17
(14) 2, 3, 4 combined	51.06 (33.49;68.16)	1.53 (0.97;1.40)	17.77 (-0.89;38.78)	6
(15) 2, 3, 4, 5 combined	53.85 (36.51;70.87)	1.62 (1.04;2.45)	20.56 (1.36;41.21)	5

[a] The observed risk was 33.39%.
[b] Reference category.

Table 4. Moderate and Severe Periodontitis Risk Under Hypothetical Interventions, 1982 Pelotas Birth Cohort, 1982–2013, Pelotas, Brazil.

Intervention	31-year risk of Periodontitis (%) (95% CI)[a]	Population risk ratio (95% CI)	Population risk difference (%) (95% CI)	Number needed to intervene
(0) No intervention[b]	14.30 (9.59;18.56)	1.00	0	-
(1) Overweight	16.16 (11.17;20.75)	1.12 (0.84;1.50)	1.86 (-2.44;6.19)	56
(2) Obesity	18.28 (10.99;28.99)	1.27 (0.76;2.14)	3.98 (-4.44;14.08)	26
(3) Smoking	16.96 (8.76;26.70)	1.18 (0.67;2.08)	2.66 (-5.69;11.50)	39
(4) Diet	14.80 (7.67;25.09)	1.03 (0.59;1.65)	0.50 (-7.42;9.66)	235
(5) Alcohol	13.55 (7.75;20.27)	0.94 (0.63;1.38)	-0.75 (-5.80;4.84)	NA
(6) Overweight and smoking	18.94 (10.58;29.32)	1.32 (0.69;2.50)	4.64 (-4.84;16.22)	22
(7) Overweight and diet	16.62 (9.00;26.22)	1.16 (0.59;1.98)	2.32 (-7.16;11.54)	45
(8) Overweight and alcohol	15.27 (9.36;22.15)	1.06 (0.67;1.75)	0.97 (-5.64;7.70)	111
(9) 1, 3, 4 combined	19.46 (9.16;32.24)	1.35 (0.55;2.80)	5.16 (-7.66;19.61)	20
(10) 1, 3, 4, 5 combined	18.44 (8.25;33.56)	1.28 (0.47;3.00)	4.14 (-8.88;21.04)	25
(11) Obesity and smoking	21.24 (11.84;33.13)	1.48 (0.66;3.27)	6.94 (-5.51;21.64)	15
(12) Obesity and diet	18.77 (9.59;30.80)	1.31 (0.59;2.40)	4.47 (-7.55;17.03)	23
(13) Obesity and alcohol	17.32 (9.99;27.67)	1.21 (0.65;2.26)	3.02 (-6.39;13.03)	34
(14) 2, 3, 4 combined	21.79 (10.31;37.85)	1.52 (0.57;3.36)	7.49 (-7.28;24.98)	13
(15) 2, 3, 4, 5 combined	20.71 (8.89;38.14)	1.44 (0.52;3.28)	6.41 (-8.89;25.57)	16

[a] The observed risk was 14.31%.
[b] Reference category.

Table 5. Clinical Attachment Loss and Bleeding on Probing Risk Under Hypothetical Interventions, 1982 Pelotas Birth Cohort, 1982–2013, Pelotas, Brazil.

Intervention	31-year risk of Periodontitis (%) (95% CI)[a]	Population risk ratio (95% CI)	Population risk difference (%) (95% CI)	Number needed to intervene
(0) No intervention[b]	14.70 (9.36;19.19)	1.00	0	-
(1) Overweight	17.78 (10.82;24.72)	1.21 (0.83;1.63)	3.08 (-2.42;8.63)	32
(2) Obesity	21.97 (11.07;34.84)	1.50 (0.73;2.58)	7.27 (-3.95;21.53)	14
(3) Smoking	16.24 (3.43;31.37)	1.11 (0.23;2.64)	1.54 (-12.60;18.87)	64
(4) Diet	14.39 (7.56;22.37)	0.99 (0.52;1.61)	-0.31 (-7.01;7.15)	NA
(5) Alcohol	12.80 (6.28;22.84)	0.88 (0.49;1.52)	-1.90 (-8.53;6.96)	NA
(6) Overweight and smoking	21.96 (7.54;38.58)	1.50 (0.54;3.01)	7.26 (-7.33;25.92)	14
(7) Overweight and diet	17.45 (9.20;26.95)	1.19 (0.65;2.15)	2.75 (-5.80;11.95)	36
(8) Overweight and alcohol	16.86 (89.71;25.65)	1.15 (0.72;1.82)	2.16 (-4.57;10.10)	46
(9) 1, 3, 4 combined	22.99 (7.25;44.69)	1.57 (0.53;3.31)	8.29 (-6.54;24.93)	12
(10) 1, 3, 4, 5 combined	21.82 (8.05;43.23)	1.49 (0.57;3.22)	7.12 (-5.71;26.80)	14
(11) Obesity and smoking	29.44 (7.49;57.23)	2.01 (0.54;4.65)	14.74 (-6.98;43.19)	7
(12) Obesity and diet	21.59 (10.46;37.61)	1.47 (0.67;3.28)	6.89 (-5.45;24.17)	14
(13) Obesity and alcohol	22.29 (8.60;38.32)	1.52 (0.72;1.82)	7.59 (-5.65;25.23)	13
(14) 2, 3, 4 combined	30.63 (9.33;68.01)	2.09 (0.66;5.01)	15.93 (-5.05;33.80)	6
(15) 2, 3, 4, 5 combined	30.84 (10.74;64.90)	2.10 (0.79;4.79)	16.14 (-2.92;49.20)	6

[a] The observed risk was 15.15%.
[b] Reference category.

Supplementary Material

Table S1. Information regarding the participants of the 1982 Pelotas birth cohort at ages 15, 23 and 30. Pelotas, Brazil.

	Number of participants	%
Age 15		
Smoking	166	12.5
Age 23		
Smoking	1,103	25.7
Diet	971	21.7
Alcohol	1,431	33.3
Hypertension	474	11.0
Diabetes	170	4.6
Age 30		
Smoking	861	23.6
Diet	1,616	44.3
Alcohol	1,143	31.3
Hypertension	425	11.7
Diabetes	127	3.6

S2. Codes used for the analyses

```
options linesize=88 pagesize=54;
options nonotes;
%include "gformula1.sas";

**INTERVENTION Calls;


%let interv1=
intno =1, intlabel = 'Episodes of overweight', nintvar =1,
intvar1 =bmi, inttype1 =1, intvalue1 =1, inttimes1 = 1 2 3 4;

%let interv2=
intno =2, intlabel = 'Episodes of obesity', nintvar =1,
intvar1 =bmi, inttype1 =1, intvalue1 =2, inttimes1 = 1 2 3 4;

%let interv3=
intno =3, intlabel = 'Alcohol', nintvar =1,
intvar1 =alc, inttype1 =1, intvalue1 =1, inttimes1 =  3 4;

%let interv4=
intno =4, intlabel = 'Diet', nintvar =1,
intvar1 =gorddic, inttype1 =1, intvalue1 =1, inttimes1 = 3 4;

%let interv5=
intno =5, intlabel = 'Smoking', nintvar =1,
intvar1 =smk, inttype1 =1, intvalue1 =1, inttimes1 = 2 3 4;

%let interv6=
intno =6, intlabel = 'Overweight and smk', nintvar =2,
intvar1 =bmi, inttype1 =1, intvalue1 =1, inttimes1 = 1 2 3 4,
intvar2 =smk, inttype2 =1, intvalue2 =1, inttimes2 = 2 3 4;


%let interv7=
intno =7, intlabel = 'Obesity and smk', nintvar =2,
intvar1 =bmi, inttype1 =1, intvalue1 =2, inttimes1 = 1 2 3 4,
intvar2 =smk, inttype2 =1, intvalue2 =1, inttimes2 = 2 3 4;

%let interv8=
intno =8, intlabel = 'Ovw and Alcohol', nintvar =2,
intvar1 =bmi, inttype1 =1, intvalue1 =1, inttimes1 = 1 2 3 4,
intvar2 =alc, inttype2 =1, intvalue2 =1, inttimes2 = 3 4;

%let interv9=
intno =9, intlabel = 'Obesity and Alcohol', nintvar =2,
intvar1 =bmi, inttype1 =1, intvalue1 =2, inttimes1 = 1 2 3 4,
intvar2 =alc, inttype2 =1, intvalue2 =1, inttimes2 = 3 4;

%let interv10=
intno =10, intlabel = 'Ovw and diet', nintvar =2,
intvar1 =bmi, inttype1 =1, intvalue1 =1, inttimes1 = 1 2 3 4,
intvar2 =diet, inttype2 =1, intvalue2 =1, inttimes2 = 3 4;

%let interv11=
intno =11, intlabel = 'Obesity and diet', nintvar =2,
intvar1 =bmi, inttype1 =1, intvalue1 =2, inttimes1 = 1 2 3 4,
intvar2 =diet, inttype2 =1, intvalue2 =1, inttimes2 = 3 4;

%let interv12=
intno =12, intlabel = 'Ovw, diet and smk', nintvar =3,
intvar1 =bmi, inttype1 =1, intvalue1 =1, inttimes1 = 1 2 3 4,
intvar2 =diet, inttype2 =1, intvalue2 =1, inttimes2 = 3 4,
intvar3 =smk, inttype3 =1, intvalue3 =1, inttimes3 = 2 3 4;

%let interv13=
intno =13, intlabel = 'Obesity, diet and smk', nintvar =3,
intvar1 =bmi, inttype1 =1, intvalue1 =2, inttimes1 = 1 2 3 4,
intvar2 =diet, inttype2 =1, intvalue2 =1, inttimes2 = 3 4,
intvar3 =smk, inttype3 =1, intvalue3 =1, inttimes3 = 2 3 4;


%let interv14=
intno =14, intlabel = 'Ovw, diet, smk and Alcohol', nintvar =4,
intvar1 =bmi, inttype1 =1, intvalue1 =1, inttimes1 = 1 2 3 4,
intvar2 =diet, inttype2 =1, intvalue2 =1, inttimes2 = 3 4,
intvar3 =smk, inttype3 =1, intvalue3 =1, inttimes3 = 2 3 4,
intvar4 =alc, inttype4 =1, intvalue4 =1, inttimes4 = 3 4;


%let interv15=
intno =15, intlabel = 'Obesity, diet, smk and Alcohol', nintvar =4,
intvar1 =bmi, inttype1 =1, intvalue1 =2, inttimes1 = 1 2 3 4,
intvar2 =diet, inttype2 =1, intvalue2 =1, inttimes2 = 3 4,
intvar3 =smk, inttype3 =1, intvalue3 =1, inttimes3 = 2 3 4,
intvar4 =alc, inttype4 =1, intvalue4 =1, inttimes4 = 3 4;
```

```
**GFORMULA Call;
title 'GFORMULA OBESITY';
%gformula(
data=dataset,
id=id,
time=time, timepoints= 4,
outc=cal_bop, outctype= bineofu,
fixedcov = psex incomedic matschool,
ncov= 7,

cov1 =time, cov1otype = 0, cov1ptype= concat, cov1inc= 1, cov1knots= 0 1 2 3, cov1lev= 4,
cov2 =bmi, cov2otype = 5, cov2ptype= lag1cat, cov2lev= 2,
cov3 =hyp, cov3otype = 2, cov3ptype = lag2bin,
cov4 =pdm, cov4otype = 2, cov4ptype = lag2bin,
cov5 =smk, cov5otype = 1, cov5ptype = lag3bin,
cov6 =alc, cov6otype =1, cov6ptype= skpbin, cov6skip = 2,
cov7 =diet, cov7otype =1, cov7ptype= skpbin, cov7skip = 2,



seed= 7348,
nsimul= 10000,
nsamples= 1000,
numint= 15
);
```

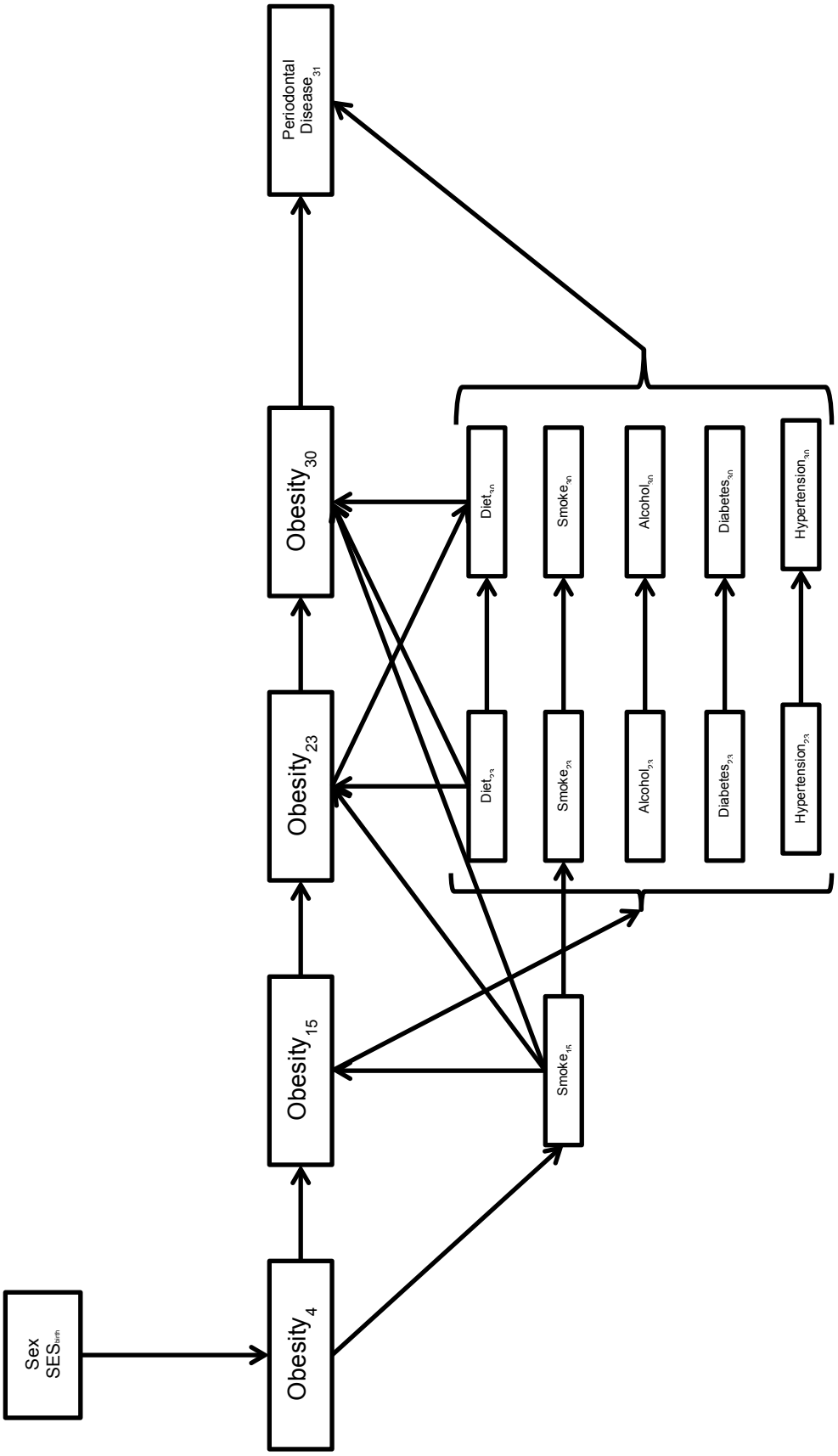


Figure S3. Causal directed acyclic graph to depict the relationship between time-varying exposure (obesity), outcomes (periodontal disease) and time-varying covariates.

Considerações Finais

Os resultados dos diferentes estudos desta tese evidenciam a associação entre excesso de peso e doença periodontal nas diferentes fases da vida. Os achados ainda sugerem a existência de uma relação causal entre sobrepeso/obesidade e doença periodontal em adultos. Assim, é evidente a importância e a necessidade de estudos que investiguem o impacto de condições sistêmicas sobre desfechos de saúde bucal.

Os resultados evidenciados pelos artigos que compõem este volume têm impacto direto sobre a prática clínica não apenas do cirurgião-dentista, mas também dos demais profissionais de saúde. Estes resultados sugerem que a obesidade e o sobrepeso devem ser considerados importantes fatores de risco às doenças periodontais. Ainda, as intervenções hipotéticas simuladas no último artigo analítico desta tese demonstram que o efeito do sobrepeso e da obesidade sobre o risco à periodontite, nesta população, são equivalentes ou superiores aos efeitos de conhecidos fatores de risco à doença periodontal, como o fumo. Assim, faz-se necessária a mudança nos atuais paradigmas de prevenção e tratamento das doenças periodontais.

Os achados desta tese também devem ser considerados no contexto da saúde pública. Durante os anos de 1990 a 2010, a forma severa de periodontite ocupou a sexta posição no ranking das doenças crônicas mais prevalentes mundialmente. Na coorte de Pelotas de 1982, aproximadamente 30% dos participantes apresentam algum tipo de periodontite aos 31 anos. Diante do aumento da expectativa de vida e da diminuição das perdas dentárias espera-se que a prevalência desta condição seja ainda maior em um futuro próximo. Associado a isto, a prevalência de sobrepeso e de obesidade também tem aumentado de forma significativa mundialmente. Assim, a abordagem de risco comum deve ser amplamente reforçada para prevenção e tratamento de doenças crônicas, como a obesidade e a doença periodontal, tendo em vista seus fatores de risco comuns e seus potenciais efeitos sobre outras condições de saúde. Isto implica uma organização dos serviços de saúde evidenciando a necessidade de um cuidado integral e abrangente.

Futuros estudos longitudinais prospectivos de base populacional se fazem necessários para corroborar estes achados. Neste cenário, métodos analíticos causais devem ser preferidos, e medidas mais precisas da composição corporal devem ser empregadas sempre que possível.

Referências

ADAIR, L. S.; FALL, C. H.; OSMOND, C.; STEIN, A. D.; MARTORELL, R.; RAMIREZ-ZEA, M.; SACHDEV, H. S.; DAHLY, D. L.; BAS, I.; NORRIS, S. A.; MICKLESFIELD, L.; HALLAL, P.; VICTORA, C. G.; GROUP, C. Associations of linear growth and relative weight gain during early life with adult health and human capital in countries of low and middle income: findings from five birth cohort studies. **Lancet,** v. 382, n. 9891, p. 525-534, 2013.

ADRIAENS, P. A.; ADRIAENS, L. M. Effects of nonsurgical periodontal therapy on hard and soft tissues. **Periodontology 2000,** v. 36, p. 121-145, 2004.

AINAMO, J.; BAY, I. Problems and proposals for recording gingivitis and plaque. **International Dental Journal,** v. 25, n. 4, p. 229-235, 1975.

AKMAN, P. T.; FENTOGLU, O.; YILMAZ, G.; ARPAK, N. Serum plasminogen activator inhibitor-1 and tumor necrosis factor-alpha levels in obesity and periodontal disease. **Journal of Periodontology,** v. 83, n. 8, p. 1057-1062, 2012.

AL-ZAHRANI, M. S.; ALGHAMDI, H. S. Effect of periodontal treatment on serum C-reactive protein level in obese and normal-weight women affected with chronic periodontitis. **Saudi Medical Journal,** v. 33, n. 3, p. 309-314, 2012.

AL-ZAHRANI, M. S.; BISSADA, N. F.; BORAWSKIT, E. A. Obesity and periodontal disease in young, middle-aged, and older adults. **Journal of Periodontology,** v. 74, n. 5, p. 610-615, 2003.

ALBANDAR, J. M.; BRUNELLE, J. A.; KINGMAN, A. Destructive periodontal disease in adults 30 years of age and older in the United States, 1988-1994. **Journal of Periodontology,** v. 70, n. 1, p. 13-29, 1999.

ALBERTI, K. G.; ECKEL, R. H.; GRUNDY, S. M.; ZIMMET, P. Z.; CLEEMAN, J. I.; DONATO, K. A.; FRUCHART, J. C.; JAMES, W. P.; LORIA, C. M.; SMITH, S. C., JR.; INTERNATIONAL DIABETES FEDERATION TASK FORCE ON, E.; PREVENTION; HATIONAL HEART, L.; BLOOD, I.; AMERICAN HEART, A.; WORLD HEART, F.; INTERNATIONAL ATHEROSCLEROSIS, S.; INTERNATIONAL ASSOCIATION FOR THE STUDY OF, O. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. **Circulation,** v. 120, n. 16, p. 1640-1645, 2009.

ALEKSEJUNIENE, J.; HOLST, D.; ERIKSEN, H. M.; GJERMO, P. Psychosocial stress, lifestyle and periodontal health. **Journal of Clinical Periodontology,** v. 29, n. 4, p. 326-335, 2002.

ALTAY, U.; GURGAN, C. A.; AGBAHT, K. Changes in inflammatory and metabolic parameters after periodontal treatment in patients with and without obesity. **Journal of Periodontology,** v. 84, n. 1, p. 13-23, 2013.

ALVES, L. S.; SUSIN, C.; DAME-TEIXEIRA, N.; MALTZ, M. Overweight and obesity are not associated with dental caries among 12-year-old South Brazilian schoolchildren. **Community Dentistry and Oral Epidemiology,** v. 41, n. 3, p. 224-231, 2013.

AMARAL CDA, S.; VETTORE, M. V.; LEAO, A. The relationship of alcohol dependence and alcohol consumption with periodontitis: a systematic review. **Journal of Dentistry,** v. 37, n. 9, p. 643-651, 2009.

AMUNA, P.; ZOTOR, F. B. Epidemiological and nutrition transition in developing countries: impact on human health and development. **Proceedings of the Nutrition Society,** v. 67, n. 1, p. 82-90, 2008.

ANDRUKHOV, O.; HARIRIAN, H.; BERTL, K.; RAUSCH, W. D.; BANTLEON, H. P.; MORITZ, A.; RAUSCH-FAN, X. Nitric oxide production, systemic inflammation and lipid metabolism in periodontitis patients: possible gender aspect. **Journal of Clinical Periodontology,** v. 40, n. 10, p. 916-923, 2013.

ARBES, S. J., JR.; AGUSTSDOTTIR, H.; SLADE, G. D. Environmental tobacco smoke and periodontal disease in the United States. **American Journal of Public Health,** v. 91, n. 2, p. 253-257, 2001.

BABOR, T. F.; HIGGINS-BIBLE, J. C.; SAUNDERS, J. B.; MONTEIRO, M. S. The Alcohol Use Disorders Identification Test: Guidelines for Use in Primary Care, 2nd edition, 2001, Geneva.

BAELUM, V.; LOPEZ, R. Defining a periodontitis case: analysis of a never-treated adult population. **Journal of Clinical Periodontology,** v. 39, n. 1, p. 10-19, 2012.

BARKER, D. J. P. **Foetal and infant origin of adult disease.** London: BMJ Publishing Group, 1992.

BARON, R. M.; KENNY, D. A. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. **Journal of Personality and Social Psychology,** v. 51, n. 6, p. 1173-1182, 1986.

BENER, A.; YOUSAFZAI, M. T.; DARWISH, S.; AL-HAMAQ, A. O.; NASRALLA, E. A.; ABDUL-GHANI, M. Obesity index that better predict metabolic syndrome: body mass index, waist circumference, waist hip ratio, or waist height ratio. **Journal of Obesity,** v. 2013, p. 269038, 2013.

BENGUIGUI, C.; BONGARD, V.; RUIDAVETS, J. B.; SIXOU, M.; CHAMONTIN, B.; FERRIERES, J.; AMAR, J. Evaluation of oral health related to body mass index. **Oral Diseases,** v. 18, n. 8, p. 748-755, 2012.

BERRINGTON DE GONZALEZ, A.; HARTGE, P.; CERHAN, J. R.; FLINT, A. J.; HANNAN, L.; MACINNIS, R. J.; MOORE, S. C.; TOBIAS, G. S.; ANTON-CULVER, H.; FREEMAN, L. B.; BEESON, W. L.; CLIPP, S. L.; ENGLISH, D. R.; FOLSOM, A. R.; FREEDMAN, D. M.; GILES, G.; HAKANSSON, N.; HENDERSON, K. D.; HOFFMAN-BOLTON, J.; HOPPIN, J. A.; KOENIG, K. L.; LEE, I. M.; LINET, M. S.; PARK, Y.;

POCOBELLI, G.; SCHATZKIN, A.; SESSO, H. D.; WEIDERPASS, E.; WILLCOX, B. J.; WOLK, A.; ZELENIUCH-JACQUOTTE, A.; WILLETT, W. C.; THUN, M. J. Body-mass index and mortality among 1.46 million white adults. **New England Journal of Medicine,** v. 363, n. 23, p. 2211-2219, 2010.

BORRELL, L. N.; PAPAPANOU, P. N. Analytical epidemiology of periodontitis. **Journal of Clinical Periodontology,** v. 32 Suppl 6, p. 132-158, 2005.

BRASIL. **SB Brasil 2010. Pesquisa Nacional de Saúde Bucal - Resultados Principais**. 2011. 92f. Ministério da Saúde, Brasília.

BRASIL. **Dados da Pesquisa de Vigilância de Fatores de Risco e de Proteção para Doenças Crônicas por Inquérito Telefônico (VIGITEL)**. 2013. Ministério da Saúde, Brasília.

BUCHWALD, S.; KOCHER, T.; BIFFAR, R.; HARB, A.; HOLTFRETER, B.; MEISEL, P. Tooth loss and periodontitis by socio-economic status and inflammation in a longitudinal population-based study. **Journal of Clinical Periodontology,** v. 40, n. 3, p. 203-211, 2013.

BUDUNELI, N.; BIYIKOGLU, B.; ILGENLI, T.; BUDUNELI, E.; NALBANTSOY, A.; SARAC, F.; KINANE, D. F. Is obesity a possible modifier of periodontal disease as a chronic inflammatory process? A case-control study. **Journal of Periodontal Research,** v. 49, n. 4, p. 465-471, 2014.

BUETTNER, R.; SCHOLMERICH, J.; BOLLHEIMER, L. C. High-fat diets: modeling the metabolic disorders of human obesity in rodents. **Obesity (Silver Spring),** v. 15, n. 4, p. 798-808, 2007.

BULLO, M.; GARCIA-LORDA, P.; MEGIAS, I.; SALAS-SALVADO, J. Systemic inflammation, adipose tissue tumor necrosis factor, and leptin expression. **Obesity Research,** v. 11, n. 4, p. 525-531, 2003.

CANCELLO, R.; CLEMENT, K. Is obesity an inflammatory illness? Role of low-grade inflammation and macrophage infiltration in human white adipose tissue. **BJOG: An International Journal of Obstetrics and Gynaecology,** v. 113, n. 10, p. 1141-1147, 2006.

CANOY, D. Distribution of body fat and risk of coronary heart disease in men and women. **Current Opinion in Cardiology,** v. 23, n. 6, p. 591-598, 2008.

CEKICI, A.; KANTARCI, A.; HASTURK, H.; VAN DYKE, T. E. Inflammatory and immune pathways in the pathogenesis of periodontal disease. **Periodontology 2000,** v. 64, n. 1, p. 57-80, 2014.

CHAFFEE, B. W.; FELDENS, C. A.; VITOLO, M. R. Association of long-duration breastfeeding and dental caries estimated with marginal structural models. **Annals of Epidemiology,** v. 24, n. 6, p. 448-454, 2014.

CHAFFEE, B. W.; WESTON, S. J. Association between chronic periodontal disease and obesity: a systematic review and meta-analysis. **Journal of Periodontology,** v. 81, n. 12, p. 1708-1724, 2010.

CHIAPINOTTO, F. A.; VARGAS-FERREIRA, F.; DEMARCO, F. F.; CORREA, F. O.; MASOTTI, A. S. Risk factors for gingivitis in a group of Brazilian schoolchildren. **Journal of Public Health Dentistry,** v. 73, n. 1, p. 9-17, 2013.

CHOBANIAN, A. V.; BAKRIS, G. L.; BLACK, H. R.; CUSHMAN, W. C.; GREEN, L. A.; IZZO, J. L., JR.; JONES, D. W.; MATERSON, B. J.; OPARIL, S.; WRIGHT, J. T., JR.; ROCCELLA, E. J.; NATIONAL HEART, L.; BLOOD INSTITUTE JOINT NATIONAL COMMITTEE ON PREVENTION, D. E.; TREATMENT OF HIGH BLOOD, P.; NATIONAL HIGH BLOOD PRESSURE EDUCATION PROGRAM COORDINATING, C. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. **JAMA,** v. 289, n. 19, p. 2560-2572, 2003.

CHOI, S. Y.; KIM, D.; OH, B. H.; KIM, M.; PARK, H. E.; LEE, C. H.; CHO, S. H. General and abdominal obesity and abdominal visceral fat accumulation associated with coronary artery calcification in Korean men. **Atherosclerosis,** v. 213, n. 1, p. 273-278, 2010.

CHRYSANT, S. G.; CHRYSANT, G. S. New insights into the true nature of the obesity paradox and the lower cardiovascular risk. **Journal of the American Society of Hypertension,** v. 7, n. 1, p. 85-94, 2013.

COLE, S. R.; HERNAN, M. A. Fallibility in estimating direct effects. **International Journal of Epidemiology,** v. 31, n. 1, p. 163-165, 2002.

COLE, S. R.; HERNAN, M. A. Constructing inverse probability weights for marginal structural models. **American Journal of Epidemiology,** v. 168, n. 6, p. 656-664, 2008.

COLE, S. R.; HERNAN, M. A.; ANASTOS, K.; JAMIESON, B. D.; ROBINS, J. M. Determining the effect of highly active antiretroviral therapy on changes in human immunodeficiency virus type 1 RNA viral load using a marginal structural left-censored mean model. **American Journal of Epidemiology,** v. 166, n. 2, p. 219-227, 2007.

COLE, T. J.; BELLIZZI, M. C.; FLEGAL, K. M.; DIETZ, W. H. Establishing a standard definition for child overweight and obesity worldwide: international survey. **BMJ,** v. 320, n. 7244, p. 1240-1243, 2000.

CORREA, F. O.; GONCALVES, D.; FIGUEREDO, C. M.; BASTOS, A. S.; GUSTAFSSON, A.; ORRICO, S. R. Effect of periodontal treatment on metabolic control, systemic inflammation and cytokines in patients with type 2 diabetes. **Journal of Clinical Periodontology,** v. 37, n. 1, p. 53-58, 2010.

CULLINAN, M. P.; SEYMOUR, G. J. Periodontal disease and systemic illness: will the evidence ever be enough? **Periodontology 2000,** v. 62, n. 1, p. 271-286, 2013.

D'AIUTO, F.; NIBALI, L.; PARKAR, M.; PATEL, K.; SUVAN, J.; DONOS, N. Oxidative stress, systemic inflammation, and severe periodontitis. **Journal of Dental Research,** v. 89, n. 11, p. 1241-1246, 2010.

DALLA VECCHIA, C. F.; SUSIN, C.; ROSING, C. K.; OPPERMANN, R. V.; ALBANDAR, J. M. Overweight and obesity as risk indicators for periodontitis in adults. **Journal of Periodontology,** v. 76, n. 10, p. 1721-1728, 2005.

DANAEI, G.; PAN, A.; HU, F. B.; HERNAN, M. A. Hypothetical midlife interventions in women and risk of type 2 diabetes. **Epidemiology,** v. 24, n. 1, p. 122-128, 2013.

DANESH, J.; WHEELER, J. G.; HIRSCHFIELD, G. M.; EDA, S.; EIRIKSDOTTIR, G.; RUMLEY, A.; LOWE, G. D.; PEPYS, M. B.; GUDNASON, V. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. **New England Journal of Medicine,** v. 350, n. 14, p. 1387-1397, 2004.

DANIEL, R. M.; DE STAVOLA, B. L.; COUSENS, S. N. gformula: Estimating causal effects in the presence of time-varying confounding or mediation using the g-computation formula. **Stata Journal,** v. 11, n. 4, p. 479-517, 2011.

DASU, M. R.; DEVARAJ, S.; DU CLOS, T. W.; JIALAL, I. The biological effects of CRP are not attributable to endotoxin contamination: evidence from TLR4 knockdown human aortic endothelial cells. **Journal of Lipid Research,** v. 48, n. 3, p. 509-512, 2007.

DEMARCO, F. F.; PERES, K. G.; PERES, M. A. Life course epidemiology and its implication for oral health. **Brazilian Oral Research,** v. 28, n. 1, 2014.

DERSIMONIAN, R.; LAIRD, N. Meta-analysis in clinical trials. **Controlled Clinical Trials,** v. 7, n. 3, p. 177-188, 1986.

DESCHNER, J.; EICK, S.; DAMANAKI, A.; NOKHBEHSAIM, M. The Role of Adipokines in Periodontal Infection and Healing. **Molecular Oral Microbiology**, v. 29, n. 6, p. 258-269, 2014.

DICKIE DE CASTILHOS, E.; HORTA, B. L.; GIGANTE, D. P.; DEMARCO, F. F.; PERES, K. G.; PERES, M. A. Association between obesity and periodontal disease in young adults: a population-based birth cohort. **Journal of Clinical Periodontology,** v. 39, n. 8, p. 717-724, 2012.

DOWNS, S. H.; BLACK, N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. **Journal of Epidemiology and Community Health,** v. 52, n. 6, p. 377-384, 1998.

DYE, B. A. The relationship between periodontitis and alcohol use is not clear. **Journal of Evidence-Based Dental Practice,** v. 10, n. 4, p. 225-227, 2010.

EGGER, G.; DIXON, J. Inflammatory effects of nutritional stimuli: further support for the need for a big picture approach to tackling obesity and chronic disease. **Obesity Reviews,** v. 11, n. 2, p. 137-149, 2010.

EKE, P. I.; PAGE, R. C.; WEI, L.; THORNTON-EVANS, G.; GENCO, R. J. Update of the case definitions for population-based surveillance of periodontitis. **Journal of Periodontology,** v. 83, n. 12, p. 1449-1454, 2012.

EKE, P. I.; THORNTON-EVANS, G. O.; WEI, L.; BORGNAKKE, W. S.; DYE, B. A. Accuracy of NHANES periodontal examination protocols. **Journal of Dental Research,** v. 89, n. 11, p. 1208-1213, 2010.

EKSTRAND, K. R.; BRUUN, G.; BRUUN, M. Plaque and gingival status as indicators for caries progression on approximal surfaces. **Caries Research,** v. 32, n. 1, p. 41-45, 1998.

EKUNI, D.; MIZUTANI, S.; KOJIMA, A.; TOMOFUJI, T.; IRIE, K.; AZUMA, T.; YONEDA, T.; FURUTA, M.; ESHIMA, N.; IWASAKI, Y.; MORITA, M. Relationship between increases in BMI and changes in periodontal status: a prospective cohort study. **Journal of Clinical Periodontology,** v. 41, n. 8, p. 772-778, 2014.

ERTEFAIE, A.; STEPHENS, D. A. Comparing approaches to causal inference for longitudinal data: inverse probability weighting versus propensity scores. **Int J Biostat,** v. 6, n. 2, p. Article 14, 2010.

FADEL, H. T.; PLIAKI, A.; GRONOWITZ, E.; MARILD, S.; RAMBERG, P.; DAHLEN, G.; YUCEL-LINDBERG, T.; HEIJL, L.; BIRKHED, D. Clinical and biological indicators of dental caries and periodontal disease in adolescents with or without obesity. **Clinical Oral Investigations**, v. 18, n. 2, p. 359-368, 2014.

FALAGAS, M. E.; KOMPOTI, M. Obesity and infection. **Lancet Infectious Diseases,** v. 6, n. 7, p. 438-446, 2006.

FLORINDO, A. A.; HALLAL, P. C.; MOURA, E. C.; MALTA, D. C. Practice of physical activities and associated factors in adults, Brazil, 2006. **Revista de Saúde Publica,** v. 43 Suppl 2, p. 65-73, 2009.

FRANCHINI, R.; PETRI, A.; MIGLIARIO, M.; RIMONDINI, L. Poor oral hygiene and gingivitis are associated with obesity and overweight status in paediatric subjects. **Journal of Clinical Periodontology,** v. 38, n. 11, p. 1021-1028, 2011.

FRIEDMAN, J. M. Obesity: Causes and control of excess body fat. **Nature,** v. 459, n. 7245, p. 340-342, 2009.

FURUTA, M.; SHIMAZAKI, Y.; TAKESHITA, T.; SHIBATA, Y.; AKIFUSA, S.; ESHIMA, N.; KIYOHARA, Y.; NINOMIYA, T.; HIRAKAWA, Y.; MUKAI, N.; NAGATA, M.; YAMASHITA, Y. Gender differences in the association between metabolic syndrome and periodontal disease: the Hisayama Study. **Journal of Clinical Periodontology,** v. 40, n. 8, p. 743-752, 2013.

GALOBARDES, B.; LYNCH, J. W.; DAVEY SMITH, G. Childhood socioeconomic circumstances and cause-specific mortality in adulthood: systematic review and interpretation. **Epidemiologic Reviews,** v. 26, p. 7-21, 2004.

GARCIA-AYMERICH, J.; VARRASO, R.; DANAEI, G.; CAMARGO, C. A., JR.; HERNAN, M. A. Incidence of adult-onset asthma after hypothetical interventions on body mass index and physical activity: an application of the parametric g-formula. **American Journal of Epidemiology,** v. 179, n. 1, p. 20-26, 2014.

GENCO, R. J.; BORGNAKKE, W. S. Risk factors for periodontal disease. **Periodontology 2000,** v. 62, n. 1, p. 59-94, 2013.

GENCO, R. J.; GROSSI, S. G.; HO, A.; NISHIMURA, F.; MURAYAMA, Y. A proposed model linking inflammation to obesity, diabetes, and periodontal infections. **Journal of Periodontology,** v. 76, n. 11 Suppl, p. 2075-2084, 2005.

GHIGLIOTTI, G.; BARISIONE, C.; GARIBALDI, S.; FABBI, P.; BRUNELLI, C.; SPALLAROSSA, P.; ALTIERI, P.; ROSA, G.; SPINELLA, G.; PALOMBO, D.; ARSENESCU, R.; ARSENESCU, V. Adipose tissue immune response: novel triggers and consequences for chronic inflammatory conditions. **Inflammation,** v. 37, n. 4, p. 1337-1353, 2014.

GIBBS, B. G.; FORSTE, R. Socioeconomic status, infant feeding practices and early childhood obesity. **Pediatric Obesity**, 2013.

GIGANTE, D. P.; VICTORA, C. G.; MATIJASEVICH, A.; HORTA, B. L.; BARROS, F. C. Association of family income with BMI from childhood to adult life: a birth cohort study. **Public Health Nutrition,** v. 16, n. 2, p. 233-239, 2013.

GOETTEMS, M. L.; CORREA, M. B.; VARGAS-FERREIRA, F.; TORRIANI, D. D.; MARQUES, M.; DOMINGUES, M. R.; HALLAL, P. C.; DEMARCO, F. F. Methods and logistics of a multidisciplinary survey of schoolchildren from Pelotas, in the Southern Region of Brazil. **Cadernos de Saúde Publica,** v. 29, n. 5, p. 867-878, 2013.

GONCALVES, T. E.; FERES, M.; ZIMMERMANN, G. S.; FAVERI, M.; FIGUEIREDO, L. C.; BRAGA, P. G.; DUARTE, P. M. Effects of scaling and root planing on clinical response and serum levels of adipocytokines in patients with obesity and chronic periodontitis. **Journal of Periodontology,** v. 86, n. 1, p. 53-61, 2015.

GONZÁLEZ CHICA, D. A. **Efeito de condições sociodemográficas e do crescimento precoce sobre a obesidade abdominal em adultos jovens: resultados da coorte de Pelotas de 1982**. 2009. (Doutorado) - Universidade Federal de Pelotas, Pelotas.

GORMAN, A.; KAYE, E. K.; APOVIAN, C.; FUNG, T. T.; NUNN, M.; GARCIA, R. I. Overweight and obesity predict time to periodontal disease progression in men. **Journal of Clinical Periodontology,** v. 39, n. 2, p. 107-114, 2012.

GRAZIANI, F.; LAURELL, L.; TONETTI, M.; GOTTLOW, J.; BERGLUNDH, T. Periodontal wound healing following GTR therapy of dehiscence-type defects in the

monkey: short-, medium- and long-term healing. **Journal of Clinical Periodontology,** v. 32, n. 8, p. 905-914, 2005.

GREENLAND, S.; PEARL, J.; ROBINS, J. M. Causal diagrams for epidemiologic research. **Epidemiology,** v. 10, n. 1, p. 37-48, 1999.

GUYATT, G. H.; OXMAN, A. D.; VIST, G. E.; KUNZ, R.; FALCK-YTTER, Y.; ALONSO-COELLO, P.; SCHUNEMANN, H. J.; GROUP, G. W. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. **BMJ,** v. 336, n. 7650, p. 924-926, 2008.

HAN, D. H.; LIM, S. Y.; SUN, B. C.; PAEK, D. M.; KIM, H. D. Visceral fat area-defined obesity and periodontitis among Koreans. **Journal of Clinical Periodontology,** v. 37, n. 2, p. 172-179, 2010.

HASLAM, D. W.; JAMES, W. P. Obesity. **Lancet,** v. 366, n. 9492, p. 1197-1209, 2005.

HEATON, B.; APPLEBAUM, K. M.; ROTHMAN, K. J.; BROOKS, D. R.; HEEREN, T.; DIETRICH, T.; GARCIA, R. I. The influence of prevalent cohort bias in the association between periodontal disease progression and incident coronary heart disease. **Annals of Epidemiology,** v. 24, n. 10, p. 741-746, 2014.

HONNE, T.; PENTAPATI, K.; KUMAR, N.; ACHARYA, S. Relationship between obesity/overweight status, sugar consumption and dental caries among adolescents in South India. **International Journal of Dental Hygiene,** v. 10, n. 4, p. 240-244, 2012.

HORTA, B. L.; GIGANTE, D. P.; GONCALVES, H.; DOS SANTOS MOTTA, J.; LORET DE MOLA, C.; OLIVEIRA, I. O.; BARROS, F. C.; VICTORA, C. G. Cohort Profile Update: The 1982 Pelotas (Brazil) Birth Cohort Study. **International Journal of Epidemiology**, 2015.

HOTAMISLIGIL, G. S. Inflammation and metabolic disorders. **Nature,** v. 444, n. 7121, p. 860-867, 2006.

HSIEH, S. D.; YOSHINAGA, H. Waist/height ratio as a simple and useful predictor of coronary heart disease risk factors in women. **Internal Medicine,** v. 34, n. 12, p. 1147-1152, 1995.

HUJOEL, P. P.; CUNHA-CRUZ, J.; KRESSIN, N. R. Spurious associations in oral epidemiological research: the case of dental flossing and obesity. **Journal of Clinical Periodontology,** v. 33, n. 8, p. 520-523, 2006.

IMHOF, A.; WOODWARD, M.; DOERING, A.; HELBECQUE, N.; LOEWEL, H.; AMOUYEL, P.; LOWE, G. D.; KOENIG, W. Overall alcohol intake, beer, wine, and systemic markers of inflammation in western Europe: results from three MONICA samples (Augsburg, Glasgow, Lille). **European Heart Journal,** v. 25, n. 23, p. 2092-2100, 2004.

JEQUIER, E.; TAPPY, L. Regulation of body weight in humans. **Physiological Reviews,** v. 79, n. 2, p. 451-480, 1999.

JIMENEZ, M.; HU, F. B.; MARINO, M.; LI, Y.; JOSHIPURA, K. J. Prospective associations between measures of adiposity and periodontal disease. **Obesity (Silver Spring),** v. 20, n. 8, p. 1718-1725, 2012.

JOKOVIC, A.; LOCKER, D.; STEPHENS, M.; KENNY, D.; TOMPSON, B.; GUYATT, G. Validity and reliability of a questionnaire for measuring child oral-health-related quality of life. **Journal of Dental Research,** v. 81, n. 7, p. 459-463, 2002.

JOSHIPURA, K. J.; PITIPHAT, W.; DOUGLASS, C. W. Validation of self-reported periodontal measures among health professionals. **Journal of Public Health Dentistry,** v. 62, n. 2, p. 115-121, 2002.

KA, K.; ROUSSEAU, M. C.; LAMBERT, M.; TREMBLAY, A.; TRAN, S. D.; HENDERSON, M.; NICOLAU, B. Metabolic syndrome and gingival inflammation in Caucasian children with a family history of obesity. **Journal of Clinical Periodontology,** v. 40, n. 11, p. 986-993, 2013.

KAHN, S. E.; HULL, R. L.; UTZSCHNEIDER, K. M. Mechanisms linking obesity to insulin resistance and type 2 diabetes. **Nature,** v. 444, n. 7121, p. 840-846, 2006.

KARLSSON, E. A.; BECK, M. A. The burden of obesity on infectious disease. **Experimental Biology and Medicine (Maywood, N.J.),** v. 235, n. 12, p. 1412-1424, 2010.

KASSEBAUM, N. J.; BERNABE, E.; DAHIYA, M.; BHANDARI, B.; MURRAY, C. J.; MARCENES, W. Global Burden of Severe Periodontitis in 1990-2010: A Systematic Review and Meta-regression. **Journal of Dental Research**, 2014.

KAZEMNEJAD, A.; ZAYERI, F.; ROKN, A. R.; KHARAZIFARD, M. J. Prevalence and risk indicators of periodontal disease among high-school students in Tehran. **East Mediterranean Health Journal,** v. 14, n. 1, p. 119-125, 2008.

KELLER, A.; ROHDE, J. F.; RAYMOND, K.; HEITMANN, B. L. Association between periodontal disease and overweight and obesity: a systematic review. **Journal of Periodontology,** v. 86, n. 6, p. 766-776, 2015.

KERSHAW, E. E.; FLIER, J. S. Adipose tissue as an endocrine organ. **Journal of Clinical Endocrinology and Metabolism,** v. 89, n. 6, p. 2548-2556, 2004.

KHADER, Y. S.; BAWADI, H. A.; HAROUN, T. F.; ALOMARI, M.; TAYYEM, R. F. The association between periodontal disease and obesity among adults in Jordan. **Journal of Clinical Periodontology,** v. 36, n. 1, p. 18-24, 2009.

KINGMAN, A.; ALBANDAR, J. M. Methodological aspects of epidemiological studies of periodontal diseases. **Periodontology 2000,** v. 29, p. 11-30, 2002.

KONGSTAD, J.; HVIDTFELDT, U. A.; GRONBAEK, M.; STOLTZE, K.; HOLMSTRUP, P. The relationship between body mass index and periodontitis in the Copenhagen City Heart Study. **Journal of Periodontology,** v. 80, n. 8, p. 1246-1253, 2009.

KOPELMAN, P. G. Obesity as a medical problem. **Nature,** v. 404, n. 6778, p. 635-643, 2000.

KUH, D.; BEN-SHLMO, Y. **The life course approach to chronic epidemiology**. 2 ed. Oxford: Oxford University Press, 2004.

KUMAR, M.; MISHRA, L.; MOHANTY, R.; NAYAK, R. "Diabetes and gum disease: The diabolic duo". **Diabetes & Metabolic Syndrome,** v. 8, n. 4, p. 255-258, 2014.

KVAAVIK, E.; BATTY, G. D.; URSIN, G.; HUXLEY, R.; GALE, C. R. Influence of individual and combined health behaviors on total and cause-specific mortality in men and women: the United Kingdom health and lifestyle survey. **Archives of Internal Medicine,** v. 170, n. 8, p. 711-718, 2010.

KWON, Y. E.; HA, J. E.; PAIK, D. I.; JIN, B. H.; BAE, K. H. The relationship between periodontitis and metabolic syndrome among a Korean nationally representative sample of adults. **Journal of Clinical Periodontology,** v. 38, n. 9, p. 781-786, 2011.

LAINE, M. L.; MOUSTAKIS, V.; KOUMAKIS, L.; POTAMIAS, G.; LOOS, B. G. Modeling susceptibility to periodontitis. **Journal of Dental Research,** v. 92, n. 1, p. 45-50, 2013.

LAJOUS, M.; WILLETT, W. C.; ROBINS, J.; YOUNG, J. G.; RIMM, E.; MOZAFFARIAN, D.; HERNAN, M. A. Changes in fish consumption in midlife and the risk of coronary heart disease in men and women. **American Journal of Epidemiology,** v. 178, n. 3, p. 382-391, 2013.

LAKKIS, D.; BISSADA, N. F.; SABER, A.; KHAITAN, L.; PALOMO, L.; NARENDRAN, S.; AL-ZAHRANI, M. S. Response to periodontal therapy in patients who had weight loss after bariatric surgery and obese counterparts: a pilot study. **Journal of Periodontology,** v. 83, n. 6, p. 684-689, 2012.

LANGE, T.; RASMUSSEN, M.; THYGESEN, L. C. Assessing natural direct and indirect effects through multiple pathways. **American Journal of Epidemiology,** v. 179, n. 4, p. 513-518, 2014.

LEAN, M. E.; HAN, T. S.; MORRISON, C. E. Waist circumference as a measure for indicating need for weight management. **BMJ,** v. 311, n. 6998, p. 158-161, 1995.

LEITE, L. D.; ROCHA, E. D. M.; BRANDÃO-NETO, J. Obesidade: uma doença inflamatória. **Revista Ciência e Saúde**, v. 2, n. 2, p. 85-95, 2009.

LEVY-COSTA, R. B.; SICHIERI, R.; PONTES NDOS, S.; MONTEIRO, C. A. [Household food availability in Brazil: distribution and trends (1974-2003)]. **Revista de Saúde Publica,** v. 39, n. 4, p. 530-540, 2005.

LIMA-COSTA, M. F.; DE OLIVEIRA, C.; MACINKO, J.; MARMOT, M. Socioeconomic inequalities in health in older adults in Brazil and England. **American Journal of Public Health,** v. 102, n. 8, p. 1535-1541, 2012.

LINDEN, G.; PATTERSON, C.; EVANS, A.; KEE, F. Obesity and periodontitis in 60-70-year-old men. **Journal of Clinical Periodontology,** v. 34, n. 6, p. 461-466, 2007.

LINDHE, Jan et al. **Tratato de Periodontia Clínica e Implantologia Oral**. 4 ed. Rio de Janeiro: Guanabara Koogan, 2005. 1013p.

LINDHE, J.; NYMAN, S. The effect of plaque control and surgical pocket elimination on the establishment and maintenance of periodontal health. A longitudinal study of periodontal therapy in cases of advanced disease. **Journal of Clinical Periodontology,** v. 2, n. 2, p. 67-79, 1975.

LINHARES RDA, S.; HORTA, B. L.; GIGANTE, D. P.; DIAS-DA-COSTA, J. S.; OLINTO, M. T. [Distribution of general and abdominal obesity in adults in a city in southern Brazil]. **Cadernos de Saúde Publica,** v. 28, n. 3, p. 438-447, 2012.

LINTSI, M.; KAARMA, H.; KULL, I. Comparison of hand-to-hand bioimpedance and anthropometry equations versus dual-energy X-ray absorptiometry for the assessment of body fat percentage in 17-18-year-old conscripts. **Clinical Physiology and Functional Imaging,** v. 24, n. 2, p. 85-90, 2004.

LOCKER, D.; LEAKE, J. L. Risk indicators and risk markers for periodontal disease experience in older adults living independently in Ontario, Canada. **Journal of Dental Research,** v. 72, n. 1, p. 9-17, 1993.

LOCKHART, P. B.; BOLGER, A. F.; PAPAPANOU, P. N.; OSINBOWALE, O.; TREVISAN, M.; LEVISON, M. E.; TAUBERT, K. A.; NEWBURGER, J. W.; GORNIK, H. L.; GEWITZ, M. H.; WILSON, W. R.; SMITH, S. C., JR.; BADDOUR, L. M. Periodontal disease and atherosclerotic vascular disease: does the evidence support an independent association?: a scientific statement from the American Heart Association. **Circulation,** v. 125, n. 20, p. 2520-2544, 2012.

LOLMEDE, K.; DURAND DE SAINT FRONT, V.; GALITZKY, J.; LAFONTAN, M.; BOULOUMIE, A. Effects of hypoxia on the expression of proangiogenic factors in differentiated 3T3-F442A adipocytes. **International Journal of Obesity and Related Metabolic Disorders,** v. 27, n. 10, p. 1187-1195, 2003.

LOPEZ, R.; FERNANDEZ, O.; BAELUM, V. Social gradients in periodontal diseases among adolescents. **Community Dentistry and Oral Epidemiology,** v. 34, n. 3, p. 184-196, 2006.

LULA, E. C.; RIBEIRO, C. C.; HUGO, F. N.; ALVES, C. M.; SILVA, A. A. Added sugars and periodontal disease in young adults: an analysis of NHANES III data. **American Journal of Clinical Nutrition,** v. 100, n. 4, p. 1182-1187, 2014.

MARCENES, W.; KASSEBAUM, N. J.; BERNABE, E.; FLAXMAN, A.; NAGHAVI, M.; LOPEZ, A.; MURRAY, C. J. Global burden of oral conditions in 1990-2010: a systematic analysis. **Journal of Dental Research,** v. 92, n. 7, p. 592-597, 2013.

MARIOTTI, A. Dental plaque-induced gingival diseases. **Annals of Periodontology,** v. 4, n. 1, p. 7-19, 1999.

MARTINEZ-PABON, M. C.; DUQUE-AGUDELO, L.; DIAZ-GIL, J. D.; ISAZA-GUZMAN, D. M.; TOBON-ARROYAVE, S. I. Comparison of the effect of two sugar-substituted chewing gums on different caries- and gingivitis-related variables: a double-blind, randomized, controlled clinical trial. **Clinical Oral Investigations**, 2013.

MARTINEZ, J. A.; NAVAS-CARRETERO, S.; SARIS, W. H.; ASTRUP, A. Personalized weight loss strategies-the role of macronutrient distribution. **Nature Reviews: Endocrinology,** v. 10, n. 12, p. 749-760, 2014.

MEALEY, B. L.; OCAMPO, G. L. Diabetes mellitus and periodontal disease. **Periodontology 2000,** v. 44, p. 127-153, 2007.

MEDZHITOV, R. Origin and physiological roles of inflammation. **Nature,** v. 454, n. 7203, p. 428-435, 2008.

MELLIN, A. E.; NEUMARK-SZTAINER, D.; STORY, M.; IRELAND, M.; RESNICK, M. D. Unhealthy behaviors and psychosocial difficulties among overweight adolescents: the potential impact of familial factors. **Journal of Adolescent Health,** v. 31, n. 2, p. 145-153, 2002.

MENDES, L. L.; CAMPOS, S. F.; MALTA, D. C.; BERNAL, R. T.; DE SA, N. N.; VELASQUEZ-MELENDEZ, G. Validity and reliability of foods and beverages intake obtained by telephone survey in Belo Horizonte, Brazil. **Revista Brasileira de Epidemiologia,** v. 14 Suppl 1, p. 80-89, 2011.

MOHAN, V.; DEEPA, R.; VELMURUGAN, K.; PREMALATHA, G. Association of C-reactive protein with body fat, diabetes and coronary artery disease in Asian Indians: the Chennai Urban Rural Epidemiology Study (CURES-6). **Diabetic Medicine,** v. 22, n. 7, p. 863-870, 2005.

MOHER, D.; LIBERATI, A.; TETZLAFF, J.; ALTMAN, D. G.; GROUP, P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. **PLoS Medicine,** v. 6, n. 7, p. e1000097, 2009.

MONTEIRO, C. A.; LEVY, R. B.; CLARO, R. M.; DE CASTRO, I. R.; CANNON, G. Increasing consumption of ultra-processed foods and likely impact on human health: evidence from Brazil. **Public Health Nutrition,** v. 14, n. 1, p. 5-13, 2011.

MONTERO, J.; BRAVO, M.; VICENTE, M. P.; GALINDO, M. P.; LOPEZ-VALVERDE, A.; CASALS, E.; CORTES-MARTINICORENA, F. J.; LLODRA, J. C. Oral pain and eating problems in Spanish adults and elderly in the Spanish National Survey performed in 2005. **Journal of Orofacial Pain,** v. 25, n. 2, p. 141-152, 2011.

MORGAN, O. W.; BRAMLEY, A.; FOWLKES, A.; FREEDMAN, D. S.; TAYLOR, T. H.; GARGIULLO, P.; BELAY, B.; JAIN, S.; COX, C.; KAMIMOTO, L.; FIORE, A.; FINELLI, L.; OLSEN, S. J.; FRY, A. M. Morbid obesity as a risk factor for hospitalization and death due to 2009 pandemic influenza A(H1N1) disease. **PloS One,** v. 5, n. 3, p. e9694, 2010.

MORITA, I.; OKAMOTO, Y.; YOSHII, S.; NAKAGAKI, H.; MIZUNO, K.; SHEIHAM, A.; SABBAH, W. Five-year incidence of periodontal disease is related to body mass index. **Journal of Dental Research,** v. 90, n. 2, p. 199-202, 2011.

MOURA-GREC, P. G.; MARSICANO, J. A.; CARVALHO, C. A.; SALES-PERES, S. H. Obesity and periodontitis: systematic review and meta-analysis. **Ciência e Saúde Coletiva,** v. 19, n. 6, p. 1763-1772, 2014.

MURRAY, E. T.; HARDY, R.; HUGHES, A.; WILLS, A.; SATTAR, N.; DEANFIELD, J.; KUH, D.; WHINCUP, P. Overweight across the life course and adipokines, inflammatory and endothelial markers at age 60-64 years: Evidence from the 1946 birth cohort. **International Journal of Obesity (2005)**, 2015.

NANDI, A.; GLYMOUR, M. M.; KAWACHI, I.; VANDERWEELE, T. J. Using marginal structural models to estimate the direct effect of adverse childhood social conditions on onset of heart disease, diabetes, and stroke. **Epidemiology,** v. 23, n. 2, p. 223-232, 2012.

NASCIMENTO, G. G.; LEITE, F. R.; CORREA, M. B.; HORTA, B. L.; PERES, M. A.; DEMARCO, F. F. Relationship between periodontal disease and obesity: the role of life-course events. **Brazilian Dental Journal,** v. 25, n. 2, p. 87-89, 2014.

NASCIMENTO, G. G.; LEITE, F. R.; DO, L. G.; PERES, K. G.; CORREA, M. B.; DEMARCO, F. F.; PERES, M. A. Is weight gain associated with the incidence of periodontitis? A systematic review and meta-analysis. **Journal of Clinical Periodontology**, 2015.

NASCIMENTO, G. G.; SEERIG, L. M.; VARGAS-FERREIRA, F.; CORREA, F. O.; LEITE, F. R.; DEMARCO, F. F. Are obesity and overweight associated with gingivitis occurrence in Brazilian schoolchildren? **Journal of Clinical Periodontology,** v. 40, n. 12, p. 1072-1078, 2013.

NAZMI, A.; OLIVEIRA, I. O.; HORTA, B. L.; GIGANTE, D. P.; VICTORA, C. G. Lifecourse socioeconomic trajectories and C-reactive protein levels in young adults: findings from a Brazilian birth cohort. **Social Science and Medicine,** v. 70, n. 8, p. 1229-1236, 2010.

NEELS, J. G.; OLEFSKY, J. M. Inflamed fat: what starts the fire? **Journal of Clinical Investigation,** v. 116, n. 1, p. 33-35, 2006.

NICOLAU, B.; THOMSON, W. M.; STEELE, J. G.; ALLISON, P. J. Life-course epidemiology: concepts and theoretical models and its relevance to chronic oral conditions. **Community Dentistry and Oral Epidemiology,** v. 35, n. 4, p. 241-249, 2007.

NISHIDA, N.; TANAKA, M.; HAYASHI, N.; NAGATA, H.; TAKESHITA, T.; NAKAYAMA, K.; MORIMOTO, K.; SHIZUKUISHI, S. Association of ALDH(2) genotypes and alcohol consumption with periodontitis. **Journal of Dental Research,** v. 83, n. 2, p. 161-165, 2004.

NOKHBEHSAIM, M.; KESER, S.; JAGER, A.; JEPSEN, S.; DESCHNER, J. Regulation of regenerative periodontal healing by NAMPT. **Mediators of Inflammation,** v. 2013, p. 202530, 2013.

NOKHBEHSAIM, M.; KESER, S.; NOGUEIRA, A. V.; CIRELLI, J. A.; JEPSEN, S.; JAGER, A.; EICK, S.; DESCHNER, J. Beneficial Effects of Adiponectin on Periodontal Ligament Cells under Normal and Regenerative Conditions. **Journal od Diabetes Research,** v. 2014, p. 796565, 2014.

O'KEEFE, J. H.; GHEEWALA, N. M.; O'KEEFE, J. O. Dietary strategies for improving post-prandial glucose, lipids, inflammation, and cardiovascular health. **Journal of the American College of Cardiology,** v. 51, n. 3, p. 249-255, 2008.

OLINTO, M. T.; WILLETT, W. C.; GIGANTE, D. P.; VICTORA, C. G. Sociodemographic and lifestyle characteristics in relation to dietary patterns among young Brazilian adults. **Public Health Nutrition**, v.14, n.1, p. 150-159, 2011.

OLIVEIRA, L. J.; CORREA, M. B.; NASCIMENTO, G. G.; GOETTEMS, M. L.; TARQUINIO, S. B.; TORRIANI, D. D.; DEMARCO, F. F. [Inequalities in oral health: are schoolchildren receiving the Bolsa Familia more vulnerable?]. **Revista de Saúde Publica,** v. 47, n. 6, p. 1039-1047, 2013.

OSTBERG, A. L.; BENGTSSON, C.; LISSNER, L.; HAKEBERG, M. Oral health and obesity indicators. **BMC Oral Health,** v. 12, p. 50, 2012.

PAPAGEORGIOU, S. N.; REICHERT, C.; JAGER, A.; DESCHNER, J. Effect of overweight/obesity on response to periodontal treatment: systematic review and a meta-analysis. **Journal of Clinical Periodontology,** v. 42, n. 3, p. 247-261, 2015.

PATARO, A. L.; COSTA, F. O.; CORTELLI, S. C.; CORTELLI, J. R.; DUPIM SOUZA, A. C.; NOGUEIRA GUIMARAES ABREU, M. H.; GIRUNDI, M. G.; COSTA, J. E. Influence of obesity and bariatric surgery on the periodontal condition. **Journal of Periodontology,** v. 83, n. 3, p. 257-266, 2012.

PEARSON, T. A.; MENSAH, G. A.; ALEXANDER, R. W.; ANDERSON, J. L.; CANNON, R. O., 3RD; CRIQUI, M.; FADL, Y. Y.; FORTMANN, S. P.; HONG, Y.; MYERS, G. L.; RIFAI, N.; SMITH, S. C., JR.; TAUBERT, K.; TRACY, R. P.; VINICOR, F.; CENTERS FOR DISEASE, C.; PREVENTION; AMERICAN HEART, A. 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,** v. 107, n. 3, p. 499-511, 2003.

PERES, K. G.; PERES, M. A.; DEMARCO, F. F.; TARQUINIO, S. B.; HORTA, B. L.; GIGANTE, D. P. Oral health studies in the 1982 Pelotas (Brazil) birth cohort: methodology and principal results at 15 and 24 years of age. **Cadernos de Saúde Publica,** v. 27, n. 8, p. 1569-1580, 2011.

PERES, M. A.; BARROS, A. J.; PERES, K. G.; ARAUJO, C. L.; MENEZES, A. M. Life course dental caries determinants and predictors in children aged 12 years: a population-based birth cohort. **Community Dentistry and Oral Epidemiology,** v. 37, n. 2, p. 123-133, 2009.

PERES, M. A.; PERES, K. G.; CASCAES, A. M.; CORREA, M. B.; DEMARCO, F. F.; HALLAL, P. C.; HORTA, B. L.; GIGANTE, D. P.; MENEZES, A. B. Validity of partial protocols to assess the prevalence of periodontal outcomes and associated sociodemographic and behavior factors in adolescents and young adults. **Journal of Periodontology,** v. 83, n. 3, p. 369-378, 2012.

PERES, M. A.; PERES, K. G.; DE BARROS, A. J.; VICTORA, C. G. The relation between family socioeconomic trajectories from childhood to adolescence and dental caries and associated oral behaviours. **Journal of Epidemiology and Community Health,** v. 61, n. 2, p. 141-145, 2007.

PERES, M. A.; PERES, K. G.; THOMSON, W. M.; BROADBENT, J. M.; GIGANTE, D. P.; HORTA, B. L. The influence of family income trajectories from birth to adulthood on adult oral health: findings from the 1982 Pelotas birth cohort. **American Journal of Public Health,** v. 101, n. 4, p. 730-736, 2011.

PERES, M. A.; TRAEBERT, J.; MARCENES, W. [Calibration of examiners for dental caries epidemiologic studies]. **Cadernos de Saúde Publica,** v. 17, n. 1, p. 153-159, 2001.

PERES, M. A.; TSAKOS, G.; BARBATO, P. R.; SILVA, D. A.; PERES, K. G. Tooth loss is associated with increased blood pressure in adults--a multidisciplinary population-based study. **Journal of Clinical Periodontology,** v. 39, n. 9, p. 824-833, 2012.

PETERSEN, P. E.; OGAWA, H. The global burden of periodontal disease: towards integration with chronic disease prevention and control. **Periodontology 2000,** v. 60, n. 1, p. 15-39, 2012.

PISCHON, N.; HENG, N.; BERNIMOULIN, J. P.; KLEBER, B. M.; WILLICH, S. N.; PISCHON, T. Obesity, inflammation, and periodontal disease. **Journal of Dental Research,** v. 86, n. 5, p. 400-409, 2007.

POORTINGA, W. The prevalence and clustering of four major lifestyle risk factors in an English adult population. **Preventive Medicine,** v. 44, n. 2, p. 124-128, 2007.

POPKIN, B. M. Global nutrition dynamics: the world is shifting rapidly toward a diet linked with noncommunicable diseases. **American Journal of Clinical Nutrition,** v. 84, n. 2, p. 289-298, 2006.

PRADEEP, A. R.; KUMARI, M.; KALRA, N.; PRIYANKA, N. Correlation of MCP-4 and high-sensitivity C-reactive protein as a marker of inflammation in obesity and chronic periodontitis. **Cytokine,** v. 61, n. 3, p. 772-777, 2013.

PRADEEP, A. R.; PRIYANKA, N.; PRASAD, M. V.; KALRA, N.; KUMARI, M. Association of progranulin and high sensitivity CRP concentrations in gingival crevicular fluid and serum in chronic periodontitis subjects with and without obesity. **Disease Markers,** v. 33, n. 4, p. 207-213, 2012.

PRESHAW, P. M.; TAYLOR, J. J. How has research into cytokine interactions and their role in driving immune responses impacted our understanding of periodontitis? **Journal of Clinical Periodontology,** v. 38 Suppl 11, p. 60-84, 2011.

RANGE, H.; POITOU, C.; BOILLOT, A.; CIANGURA, C.; KATSAHIAN, S.; LACORTE, J. M.; CZERNICHOW, S.; MEILHAC, O.; BOUCHARD, P.; CHAUSSAIN, C. Orosomucoid, a new biomarker in the association between obesity and periodontitis. **PloS One,** v. 8, n. 3, p. e57645, 2013.

REEVES, A. F.; REES, J. M.; SCHIFF, M.; HUJOEL, P. Total body weight and waist circumference associated with chronic periodontitis among adolescents in the United States. **Archives of Pediatrics and Adolescent Medicine,** v. 160, n. 9, p. 894-899, 2006.

REYNOLDS, M. A. Modifiable risk factors in periodontitis: at the intersection of aging and disease. **Periodontology 2000,** v. 64, n. 1, p. 7-19, 2014.

RIMM, E. B.; STAMPFER, M. J.; COLDITZ, G. A.; CHUTE, C. G.; LITIN, L. B.; WILLETT, W. C. Validity of self-reported waist and hip circumferences in men and women. **Epidemiology,** v. 1, n. 6, p. 466-473, 1990.

ROBINS, J. M. 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,** v. 7, n. 9-12, p. 1393–1512, 1986.

ROBINS, J. M.; HERNAN, M. A.; BRUMBACK, B. Marginal structural models and causal inference in epidemiology. **Epidemiology,** v. 11, n. 5, p. 550-560, 2000.

ROLLAND-CACHERA, M. F. Childhood obesity: current definitions and recommendations for their use. **International Journal of Pediatric Obesity,** v. 6, n. 5-6, p. 325-331, 2011.

SAITO, T.; YAMAGUCHI, N.; SHIMAZAKI, Y.; HAYASHIDA, H.; YONEMOTO, K.; DOI, Y.; KIYOHARA, Y.; IIDA, M.; YAMASHITA, Y. Serum levels of resistin and adiponectin in women with periodontitis: the Hisayama study. **Journal of Dental Research,** v. 87, n. 4, p. 319-322, 2008.

SAXLIN, T.; SUOMINEN-TAIPALE, L.; KATTAINEN, A.; MARNIEMI, J.; KNUUTTILA, M.; YLOSTALO, P. Association between serum lipid levels and periodontal infection. **Journal of Clinical Periodontology,** v. 35, n. 12, p. 1040-1047, 2008.

SAXLIN, T.; YLOSTALO, P.; SUOMINEN-TAIPALE, L.; AROMAA, A.; KNUUTTILA, M. Overweight and obesity weakly predict the development of periodontal infection. **Journal of Clinical Periodontology,** v. 37, n. 12, p. 1059-1067, 2010.

SAXLIN, T.; YLOSTALO, P.; SUOMINEN-TAIPALE, L.; MANNISTO, S.; KNUUTTILA, M. Association between periodontal infection and obesity: results of the Health 2000 Survey. **Journal of Clinical Periodontology,** v. 38, n. 3, p. 236-242, 2011.

SCHMIDT, M. I.; DUNCAN, B. B.; AZEVEDO E SILVA, G.; MENEZES, A. M.; MONTEIRO, C. A.; BARRETO, S. M.; CHOR, D.; MENEZES, P. R. Chronic non-communicable diseases in Brazil: burden and current challenges. **Lancet,** v. 377, n. 9781, p. 1949-1961, 2011.

SCHROEDER, H. E.; LINDHE, J. Conversion of stable established gingivitis in the dog into destructive periodontitis. **Archives of Oral Biology,** v. 20, n. 12, p. 775-782, 1975.

SCHWARTZ, M. W.; BASKIN, D. G.; KAIYALA, K. J.; WOODS, S. C. Model for the regulation of energy balance and adiposity by the central nervous system. **American Journal of Clinical Nutrition,** v. 69, n. 4, p. 584-596, 1999.

SHEARER, D. M.; THOMSON, W. M.; CASPI, A.; MOFFITT, T. E.; BROADBENT, J. M.; POULTON, R. Inter-generational continuity in periodontal health: findings from the Dunedin family history study. **Journal of Clinical Periodontology,** v. 38, n. 4, p. 301-309, 2011.

SHEIHAM, A.; ALEXANDER, D.; COHEN, L.; MARINHO, V.; MOYSES, S.; PETERSEN, P. E.; SPENCER, J.; WATT, R. G.; WEYANT, R. Global oral health inequalities: task group--implementation and delivery of oral health strategies. **Advances in Dental Research,** v. 23, n. 2, p. 259-267, 2011.

SHEIHAM, A.; WATT, R. G. The common risk factor approach: a rational basis for promoting oral health. **Community Dentistry and Oral Epidemiology,** v. 28, n. 6, p. 399-406, 2000.

SHIBLI, R.; RUBIN, L.; AKONS, H.; SHAOUL, R. Morbidity of overweight (>or=85th percentile) in the first 2 years of life. **Pediatrics,** v. 122, n. 2, p. 267-272, 2008.

SILVA, D. A.; PERES, K. G.; BOING, A. F.; GONZALEZ-CHICA, D. A.; PERES, M. A. Clustering of risk behaviors for chronic noncommunicable diseases: a population-based study in southern Brazil. **Preventive Medicine,** v. 56, n. 1, p. 20-24, 2013.

SILVA, D. A.; PETROSKI, E. L.; PERES, M. A. [Prehypertension and hypertension among adults in a metropolitan area in Southern Brazil: population-based study]. **Revista de Saúde Publica,** v. 46, n. 6, p. 988-998, 2012.

SNIJDER, M. B.; VAN DAM, R. M.; VISSER, M.; SEIDELL, J. C. What aspects of body fat are particularly hazardous and how do we measure them? **International Journal of Epidemiology,** v. 35, n. 1, p. 83-92, 2006.

SNOWDEN, J. M.; ROSE, S.; MORTIMER, K. M. Implementation of G-computation on a simulated data set: demonstration of a causal inference technique. **American Journal of Epidemiology,** v. 173, n. 7, p. 731-738, 2011.

SPECCHIA, M. L.; VENEZIANO, M. A.; CADEDDU, C.; FERRIERO, A. M.; MANCUSO, A.; IANUALE, C.; PARENTE, P.; CAPRI, S.; RICCIARDI, W. Economic impact of adult obesity on health systems: a systematic review. **European Journal of Public Health**, 2014.

STEFAN, N.; STUMVOLL, M. Adiponectin--its role in metabolism and beyond. **Hormone and Metabolic Research,** v. 34, n. 9, p. 469-474, 2002.

SUK, S. H.; SACCO, R. L.; BODEN-ALBALA, B.; CHEUN, J. F.; PITTMAN, J. G.; ELKIND, M. S.; PAIK, M. C.; NORTHERN MANHATTAN STROKE, S. Abdominal obesity and risk of ischemic stroke: the Northern Manhattan Stroke Study. **Stroke,** v. 34, n. 7, p. 1586-1592, 2003.

SUSIN, C.; HAAS, A. N.; VALLE, P. M.; OPPERMANN, R. V.; ALBANDAR, J. M. Prevalence and risk indicators for chronic periodontitis in adolescents and young adults in south Brazil. **Journal of Clinical Periodontology,** v. 38, n. 4, p. 326-333, 2011.

SUSIN, C.; KINGMAN, A.; ALBANDAR, J. M. Effect of partial recording protocols on estimates of prevalence of periodontal disease. **Journal of Periodontology,** v. 76, n. 2, p. 262-267, 2005.

SUVAN, J.; D'AIUTO, F.; MOLES, D. R.; PETRIE, A.; DONOS, N. Association between overweight/obesity and periodontitis in adults. A systematic review. **Obesity Reviews,** v. 12, n. 5, p. e381-404, 2011.

SUVAN, J.; PETRIE, A.; MOLES, D. R.; NIBALI, L.; PATEL, K.; DARBAR, U.; DONOS, N.; TONETTI, M.; D'AIUTO, F. Body mass index as a predictive factor of periodontal therapy outcomes. **Journal of Dental Research,** v. 93, n. 1, p. 49-54, 2014.

SZABO, G.; MANDREKAR, P.; GIROUARD, L.; CATALANO, D. Regulation of human monocyte functions by acute ethanol treatment: decreased tumor necrosis factor-alpha, interleukin-1 beta and elevated interleukin-10, and transforming growth factor-beta production. **Alcoholism, Clinical and Experimental Research,** v. 20, n. 5, p. 900-907, 1996.

TAN, L.; WANG, M. J.; MODINI, M.; JOYCE, S.; MYKLETUN, A.; CHRISTENSEN, H.; HARVEY, S. B. Preventing the development of depression at work: a systematic review and meta-analysis of universal interventions in the workplace. **BMC Medicine,** v. 12, p. 74, 2014.

TAUBMAN, S. L.; ROBINS, J. M.; MITTLEMAN, M. A.; HERNAN, M. A. Intervening on risk factors for coronary heart disease: an application of the parametric g-formula. **International Journal of Epidemiology,** v. 38, n. 6, p. 1599-1611, 2009.

THOMSON, W. M. Social inequality in oral health. **Community Dentistry and Oral Epidemiology,** v. 40 Suppl 2, p. 28-32, 2012.

THOMSON, W. M.; BROADBENT, J. M.; POULTON, R.; BECK, J. D. Changes in periodontal disease experience from 26 to 32 years of age in a birth cohort. **Journal of Periodontology,** v. 77, n. 6, p. 947-954, 2006.

THOMSON, W. M.; SHEIHAM, A.; SPENCER, A. J. Sociobehavioral aspects of periodontal disease. **Periodontology 2000,** v. 60, n. 1, p. 54-63, 2012.

TILG, H.; MOSCHEN, A. R. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. **Nature Reviews: Immunology,** v. 6, n. 10, p. 772-783, 2006.

TSIOUFIS, C.; KASIAKOGIAS, A.; THOMOPOULOS, C.; STEFANADIS, C. Periodontitis and blood pressure: the concept of dental hypertension. **Atherosclerosis,** v. 219, n. 1, p. 1-9, 2011.

VAN DER WEIJDEN, F.; SLOT, D. E. Oral hygiene in the prevention of periodontal diseases: the evidence. **Periodontology 2000,** v. 55, n. 1, p. 104-123, 2011.

VAN DYKE, T. E.; VAN WINKELHOFF, A. J. Infection and inflammatory mechanisms. **Journal of Clinical Periodontology,** v. 40 Suppl 14, p. S1-7, 2013.

VAN GAAL, L. F.; MERTENS, I. L.; DE BLOCK, C. E. Mechanisms linking obesity with cardiovascular disease. **Nature,** v. 444, n. 7121, p. 875-880, 2006.

VANDERWEELE, T. J. Marginal structural models for the estimation of direct and indirect effects. **Epidemiology,** v. 20, n. 1, p. 18-26, 2009.

VICTORA, C. G.; BARROS, F. C. Cohort profile: the 1982 Pelotas (Brazil) birth cohort study. **International Journal of Epidemiology,** v. 35, n. 2, p. 237-242, 2006.

WANG, Y.; BEYDOUN, M. A. The obesity epidemic in the United States--gender, age, socioeconomic, racial/ethnic, and geographic characteristics: a systematic review and meta-regression analysis. **Epidemiologic Reviews,** v. 29, p. 6-28, 2007.

WARREN, K. R.; POSTOLACHE, T. T.; GROER, M. E.; PINJARI, O.; KELLY, D. L.; REYNOLDS, M. A. Role of chronic stress and depression in periodontal diseases. **Periodontology 2000,** v. 64, n. 1, p. 127-138, 2014.

WELLS, G. A.; SHEA, B.; O'CONNEL, D.; PETERSON, J.; WELCH, V.; LOSOS, M.; TUGWELL, P. **The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses.** Ottawa. University of Ottawa. Disponível em: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm

WORLD HEALTH ORGANIZATION. **Obesity: Preventing and Managing the Global Epidemic**. WHO Techincal Report Series. 2000. Geneva.

WORLD HEALTH ORGANIZATION. **Preventing chronic diseases: a vital investment**. World Health Organization. 2005. Geneva.

WORLD HEALTH ORGANIZATION. **Growth reference 5–19 years.** Disponível em: http://www.who.int/growthref/who2007_bmi_for_ age/en/index.html (último acesso em 20 de maio de 2013).

WORLD HEALTH ORGANIZATION. **Oral Health Survey: Basic Methods.** Report from a WHO consultation. World Health Organization. 1997. Geneva.

WORLD HEALTH ORGANIZATION. Reliability of anthropometric measurements in the WHO Multicentre Growth Reference Study. **Acta Paediatrica**, v. 450, p. 38-46, 2006.

WU, T.; TREVISAN, M.; GENCO, R. J.; FALKNER, K. L.; DORN, J. P.; SEMPOS, C. T. Examination of the relation between periodontal health status and cardiovascular risk factors: serum total and high density lipoprotein cholesterol, C-reactive protein, and plasma fibrinogen. **American Journal of Epidemiology,** v. 151, n. 3, p. 273-282, 2000.

XU, H.; BARNES, G. T.; YANG, Q.; TAN, G.; YANG, D.; CHOU, C. J.; SOLE, J.; NICHOLS, A.; ROSS, J. S.; TARTAGLIA, L. A.; CHEN, H. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. **Journal of Clinical Investigation,** v. 112, n. 12, p. 1821-1830, 2003.

ZANGRANDO, M. S.; DAMANTE, C. A.; SANT'ANA, A. C.; RUBO DE REZENDE, M. L.; GREGHI, S. L.; CHAMBRONE, L. Long-term evaluation of periodontal parameters and implant outcomes in periodontally compromised patients: a systematic review. **Journal of Periodontology,** v. 86, n. 2, p. 201-221, 2015.

ZENG, J.; WILLIAMS, S. M.; FLETCHER, D. J.; CAMERON, C. M.; BROADBENT, J. M.; SHEARER, D. M.; THOMSON, W. M. Reexamining the association between smoking and periodontitis in the dunedin study with an enhanced analytical approach. **Journal of Periodontology,** v. 85, n. 10, p. 1390-1397, 2014.

ZHANG, J.; YU, K. F. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. **JAMA,** v. 280, n. 19, p. 1690-1691, 1998.

ZIMMERMANN, G. S.; BASTOS, M. F.; DIAS GONCALVES, T. E.; CHAMBRONE, L.; DUARTE, P. M. Local and circulating levels of adipocytokines in obese and normal weight individuals with chronic periodontitis. **Journal of Periodontology,** v. 84, n. 5, p. 624-633, 2013.

ZUZA, E. P.; BARROSO, E. M.; CARRARETO, A. L.; PIRES, J. R.; CARLOS, I. Z.; THEODORO, L. H.; TOLEDO, B. E. The role of obesity as a modifying factor in patients undergoing non-surgical periodontal therapy. **Journal of Periodontology,** v. 82, n. 5, p. 676-682, 2011.