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Association of periodontitis with handgrip strength and skeletal muscle mass in middle-aged U.S. adults from NHANES 2013–2014

Dissertation

zur Erlangung des Grades eines Doktors der Zahnmedizin
an der Medizinischen Fakultät der Universität Hamburg.

vorgelegt von:

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Hamburg 2023

Angenommen von der
Medizinischen Fakultät der Universität Hamburg am: 11.04.2024

Veröffentlicht mit Genehmigung der
Medizinischen Fakultät der Universität Hamburg.

Prüfungsausschuss, der/die Vorsitzende: Prof. Dr. Hans-Helmut König

Prüfungsausschuss, zweite/r Gutachter/in: Prof. Dr. Antonia Zapf

TABLE OF CONTENTS

1. Published Article

Aging Clinical and Experimental Research
https://doi.org/10.1007/s40520-023-02471-2

ORIGINAL ARTICLE

Association of periodontitis with handgrip strength and skeletal muscle mass in middle-aged US adults from NHANES 2013–2014

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Received: 21 March 2023 / Accepted: 5 June 2023

Abstract

Objectives The relationship between periodontitis and sarcopenia parameters in middle-aged adults is largely unexplored. This study investigated the association between periodontitis and combined handgrip strength and skeletal muscle mass in middle-aged adults.

Materials and methods A sub-cohort of 1912 individuals with complete periodontal and whole-body dual X-ray absorptiometry examinations from the 2013–2014 wave of the National Health and Nutrition Examination Survey ($n = 10{,}175$) were analyzed using fully adjusted multiple linear regression models for associations between periodontitis and skeletal muscle mass index (kg/m^2) and combined handgrip strength (kg).

Results The mean age of the study cohort was 43 (± 8.4) years and 49.4% of the participants were male. In total, 612 participants (32%) were determined to have periodontitis, of which 513 (26.8%) had non-severe (mild or moderate) periodontitis, and 99 (5.2%) had severe periodontitis. In unadjusted regression models, both non-severe and severe periodontitis were associated with SMMI ($\beta_{\text{non-severe}} = 1.01$, 95% CI 0.50; 1.52 and $\beta_{\text{severe}} = 1.42$, 95% CI 0.59; 2.25) but not with cHGS. After adjusting for age, sex, education, body mass index, bone mineral density, diabetic status, education, total energy intake, total protein intake, and serum vitamin D2 + D3, periodontitis was associated with cHGS ($\beta_{\text{non-severe}} = -2.81$, 95% CI − 4.7; − 1.15 and $\beta_{\text{severe}} = -2.73$, 95% CI − 6.31; 0.83). The association between periodontitis and SMMI remained for non-severe periodontitis ($\beta_{\text{non-severe}} = 0.07$, 95% CI − 0.26; 0.40 and $\beta_{\text{severe}} = 0.22$, 95% CI − 0.34; 0.78).

Conclusion The present study highlights the need of further prospective research to investigate the nature and direction of the relationship between periodontitis and sarcopenia indicators**.** Future studies can support the screening, prevention and clinical management of sarcopenia and periodontitis, and emphasize the interdisciplinary and complementary approach between the disciplines of geriatric medicine and periodontology.

Keywords Periodontitis · Sarcopenia · Frailty · Skeletal muscle mass · Handgrip strength · Epidemiology

Introduction

Periodontitis is a chronic inflammatory disease of the tooth-supporting tissues caused by an oral dysbiosis that, if left untreated, leads to tissue breakdown and tooth loss. It is a major cause of tooth loss in adults and is associated with reduced oral health-related quality of life [1]. Periodontitis has been shown to be an independent risk factor for various non-communicable diseases, such as cardiovascular diseases [2], diabetes mellitus [3], hypertension [4], and chronic kidney disease [5]. Periodontitis has been linked to the manifestation or exacerbation of these conditions through a variety of mechanisms, including increased low-grade systemic chronic inflammation due to periodontal inflammation and infiltration

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Published online: 30 June 2023

of periodontal pathogens into the circulatory system, resulting in *alio loco* tissue reactions [6].

Sarcopenia is a muscle disorder associated with frailty, decreased mobility, and increased risk of mortality due to loss of muscle mass and function in adults [7–9]. Metabolic complications and the risk of fall injuries increase in sarcopenia patients, causing relevant disability, malnutrition, reduced health-related quality of life, and even mortality [7]. Systemic diseases that increase chronic low-grade systemic inflammation, such as diabetes [8], obesity [10], and metabolic syndrome [11], were associated with sarcopenia, reducing the overall health-related quality of life. A reduction of muscle mass and strength in sarcopenia patients is widely associated with a reduction in anabolic metabolic function, a decline in immune system functions, and increased inflammation [12].

Chronic and inflammation-based diseases and conditions that considerably reduce the quality of life are associated with common risk factors, such as smoking, obesity, a sedentary lifestyle, and low socioeconomic status [13]. Since both periodontitis and sarcopenia are chronic diseases that are associated with common risk factors, we hypothesized that the two conditions could be interrelated. In recent years, an increasing number of studies have reported clear associations between sarcopenia indicators, such as handgrip strength, masticatory functions, and muscle mass, and reduced oral health and oral hypofunction [14]. The number of remaining teeth and higher masticatory function showed negative associations with handgrip strength in older adults in Japan [15]. Edentulism and poor oral health also showed relevant associations with frailty in older adults in Mexico [16]. In addition, tooth loss and masticatory problems were suggested to contribute to a poorer diet and nutritional status, resulting in frailty and sarcopenia [17]. In this context, difficulty eating, having fewer teeth, and edentulism showed considerable associations with frailty in older British men in a nationally representative study [18]. Handgrip strength was recently associated with periodontitis in 30-year-old or older Korean adults [19]. However, the majority of studies relating to the associations between periodontitis and sarcopenia indicators were conducted on older adults aged over 65. There remains a clear gap in the literature regarding associations of sarcopenia indicators and periodontitis in younger adults and in different populations.

In the present study, we will investigate the associations between periodontitis and with handgrip strength or skeletal muscle mass index in a subset of a representatively sampled U.S. population.

Materials and methods

Study population

A cross-sectional study was conducted on the adult participants of the 2013–2014 National Health and Nutrition Examination Survey (NHANES). NHANES examines the health and nutritional status of a representative group of children and adults in the USA by conducting household interviews, laboratory and physical examinations. The NHANES datasets are publicly available, and the participants have consented to the use of their data for research purposes. The design and methods of NHANES 2013–2014 have been described elsewhere [20]. The 2013–2014 wave of NHANES was selected because it included both complete periodontal examinations and whole-body dual-energy X-ray absorptiometry (DXA) examinations. Both examinations were available for the cohort that were aged between 30 and 59 years. The reasons for excluding participants from the DXA examination included pregnancy, a history of barium use in the previous 7 days, weight above 204 kg (450 lbs), and height above 198 cm (6′ 5″) [21]. The exclusion criteria for periodontal examination were having less than one natural tooth and any requirement for antibiotic prophylaxis prior to periodontal probing [22]. A more detailed description of the NHANES 2013–2014 cohort can be found in the study published by Eke et al. [23]. In the present study, adults with certain medical conditions were excluded due to their strong association with sarcopenia. The exclusion criteria of the present study included the following: (1) adults with cancer or malignancies (self-reported, $n = 91$) [24], (2) chronic kidney disease (estimated glomerular filtration rate < 30 mL/min, $n = 0$) [25], (3) heart disease (self-reported heart failure, coronary heart disease, coronary heart attack, angina pectoris, ischemic heart disease, and stroke, $n = 163$) [26], and (4) those who were undergoing treatment with systemic corticosteroids (self-reported, $n = 0$) [27]. Data flowchart is presented in Fig. 1.

Periodontal examination and classification

Gingival recessions (mm) from the cemento-enamel junction and probing pocket depths (PPD, mm) were recorded by licensed dentists at six sites (disto-facial, mid-facial, mesio-facial, disto-oral, oral, and mesio-oral) for each permanent tooth, excluding third molars according to the NHANES protocol [28]. Clinical attachment loss (CAL, mm) was calculated based on the sum of gingival recession and probing pocket depth at each examination site for each tooth, and gingiva height was recorded as a negative value, 0, or a positive value, depending on the position of the gingival margin relative to the CEJ [28]. Periodontitis was classified according to the updated Centers for Disease Control and Prevention/American Academy of Periodontology (CDC/AAP) criteria for periodontitis case definitions [29]. Inter-examiner and intra-examiner calibration data for periodontal parameters in NHANES

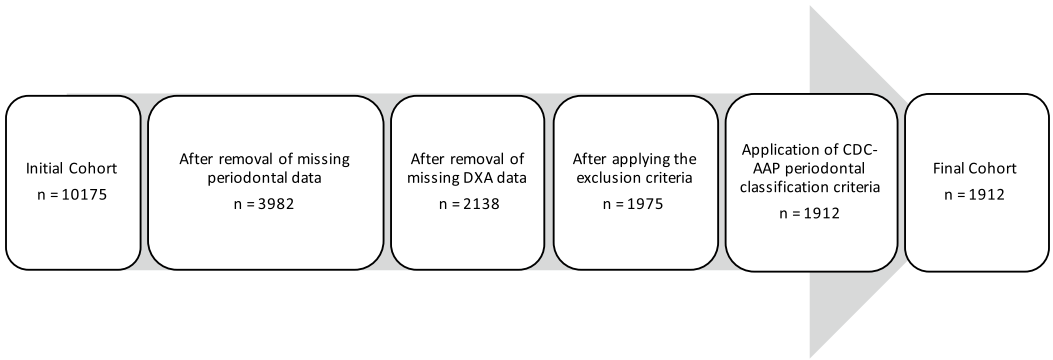

Fig. 1 Data selection flowchart diagram

III have previously been published by Dye et al. [30]. All participants that met the CDC-AAP criteria were classified as "no periodontitis", "non-severe periodontitis (mild or moderate)" or "severe periodontitis" ($n = 1912$).

Determination of skeletal muscle mass

The whole-body dual X-ray absorptiometry scans were acquired by trained and certified radiology technicians at the NHANES center using the Hologic Discovery model A densitometer (Hologic, Inc., Bedford, Massachusetts) and assessed using Apex 3.2 software according to the published NHANES protocol [31]. Data on total lean mass without bone mineral content were available in the database and were divided by the value of height squared to allow comparisons between individuals. This calculation was included in the analysis as the skeletal muscle mass index (SMMI). Low SMMI was defined as below 5.5 kg/m^2 for women and below 7.0 kg/m^2 for men according to the previously published case definitions for sarcopenia [8].

Determination of muscle strength

The muscle strength was measured by way of an isometric handgrip test using a dynamometer (Takei Digital Grip Strength Dynamometer, Model T.K.K.5401) in a standing position and involved exhaling while squeezing the dynamometer to avoid increasing intra-thoracic pressure [20]. The test was repeated three times on each hand. The combined handgrip strength (cHGS, kg) was the sum of the largest reading from each hand. Further details about the protocol can be found on the NHANES website [20]. Low cHGS was defined as 16 kg and/or below for women and 27 kg and/or below for men in accordance with the previously published case definitions of sarcopenia [8].

Covariates

Potential associations with skeletal muscle mass, handgrip strength, and/or periodontitis were considered when selecting covariates. Age (continuous), sex assigned at birth (female, male), total daily energy intake (continuous, kcal/day), daily protein intake (continuous, g/day), and education level (low: 12th grade with no diploma and/or below; medium: high school graduate and/or equivalent and/or some level of higher education; or high: completed college degree and/or above) were self-reported by the participants (for details see https://www.cdc.gov/nchs/NHANES/). Smoking status could not be included in the analysis due to more than 60% missing data of the variable. Body measurements were recorded by trained health technicians, and the body mass index (BMI, kg/m^2) was calculated based on the weight and standing height of the participants recorded at the NHANES examination center. From laboratory HbA1c results, the diabetes mellitus type II status was included as a categorical variable [HbA1c (%)], non-diabetes: < 5.7; prediabetes: 5.7–6.5; diabetes: > 6.5]. Body mass index (BMI) was categorized according to the World Health Organization (WHO) obesity classification for participant characteristics but was included as a continuous variable in the regression analysis. Bone mineral density (BMD, g/cm^2) and total serum vitamin D2 and D3 (nmol/L) were reported in the NHANES dataset and were included as continuous variables. An estimated glomerular filtration rate (eGFR) was calculated from standardized serum creatinine using a previously validated equation for the study population [32]. Chronic kidney disease was classified according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative eGFR reference values [33].

Statistical analyses

All continuous variables are reported as mean with standard deviation, while categorical variables are reported as values and percentages. All analyses were predicated on investigating the association between periodontitis and its severity as independent variables and SMMI or cHGS as dependent variables using multiple linear regression models. Unadjusted and adjusted associations were reported as regression coefficients with corresponding two-sided 95% confidence intervals (95% CI). Adjusted associations were estimated while accounting for confounding variables that were identified a priori based on biological plausibility and evidence. Interaction terms were included in the models to account for potential effect modifications. In the analyses, a stepwise approach was avoided, and all covariates that were identified a priori were included. In all regression analyses, the complex survey design of NHANES was considered and survey weights, primary sampling units, and strata were included in the survey design using the *survey* package in R. All statistical analyses were performed exploratively in R version 4.0.3.

Results

Participant characteristics

A subset of 1912 individuals with the periodontal classification and a whole-body dual X-ray absorptiometry examination from the 2013 to 2014 main cohort were included in the analysis. The mean age of the study cohort was 43.4 (± 8.4) years and 49.4% of the participants were male. Detailed participant characteristics are presented in Table 1. Low handgrip strength and low skeletal muscle mass index were not observed in the study cohort; thus, a classification of sarcopenia was omitted. The SMMI and cHGS were included as continuous variables in the analysis. Overall, 612 (32%) of the participants were determined to have periodontitis, of whom 513 (26.8%) had non-severe (mild or moderate) and 99 (5.2%) had severe periodontitis.

Results of unadjusted and fully adjusted multiple linear regression analyses of association between periodontitis and SMMI or cHGS

In unadjusted regression models, non-severe or severe periodontitis were not associated with SMMI ($\beta = 1.01$, 95% CI 0.50; 1.52 and $\beta = 1.42$, 95% CI 0.59; 2.25, respectively) but with cHGS by tendency ($\beta = 1.83$, 95% CI − 0.38; 4.05 and $\beta = 2.03$, 95% CI − 4.64; 8.69 and, respectively). The results of the unadjusted analyses are presented in Table 2.

After adjusting for age, sex, education, BMI, BMD, diabetic status, education, total energy intake, total protein intake, and serum vitamin D2 + D3, periodontitis showed relevant associations with cHGS ($\beta_{\text{non-severe}} = -2.81$, 95% CI − 4.7; − 1.15 and $\beta_{\text{severe}} = -2.73$, 95% CI − 6.31; 0.83 with severe periodontitis). The fully adjusted regression analysis of the association of SMMI with periodontitis resulted in $\beta_{\text{non-severe}} = 0.07$, 95% CI − 0.26; 0.40 and $\beta_{\text{severe}} = 0.22$, 95% CI − 0.34; 0.78. The detailed results of the adjusted regression analyses of combined handgrip strength and skeletal muscle mass index are presented in Table 3. Further predictors and coefficients of the models are presented in the supplementary tables (Supplementary Tables 1 and 2).

Discussion

In the present study, we investigated the association between periodontitis and sarcopenia indicators (cHGS and SMMI), without using tooth loss as a proxy and taking common risk factors and demographic characteristics into consideration. The results indicated that periodontitis was associated with cHGS but not with SMMI in adults below 60 years of age, after adjusting for covariates that were associates of muscle function and muscle metabolism as well as common risk factors of sarcopenia and periodontitis, such as diabetes mellitus and BMI.

A possible explanation for the association between the cHGS and periodontitis could be the reduced oral function and worsened nutrition as a result of tooth loss. Although the reasons of tooth loss are often unspecified in most studies in the literature, periodontitis is a leading cause of tooth loss in adults [34]. Adults with tooth loss are at greater risk of malnutrition [35], an important risk factor for sarcopenia and frailty [36]. Tooth mobility in periodontitis patients has been associated with a reduced bite force [37]. The reduced mechanoreceptive activity in the periodontal ligament can result in reduced periodontal support, which impairs the regulation of masticatory forces [38]. Function is an important predictor of muscle strength and skeletal and masticatory muscle endurance capacity [39]. Thus, reduced masticatory function due to periodontitis can contribute to oral hypofunction and sarcopenia [40]. A recent study reported that oral hypofunction was significantly associated with frailty [41]. In a study of a nationally representative cohort, participants with fewer than nine teeth showed significant associations with lower handgrip strength in Korean men (OR: 1.39, 95% CI 1.03; 1.88, mean age 72.9 ± 0.1) after adjusting for covariates [42]. In a study of 2,089 adult men and women between the ages of 30 and 90 in northern Germany, higher clinical attachment loss was associated with lower handgrip strength [43]. In sarcopenic Korean adults, periodontitis prevalence

Table 1 Participant characteristics stratified by periodontal status

	No periodontitis ($n=1300$)	Non-severe periodontitis ($n=513$)	Severe periodontitis ($n=99$)	p Value
Age (in years)	42.69 (±8.22)	44.20 (±8.51)	48.13 (±7.99)	<0.001
Sex at birth				<0.001
Female	714 (73.8%)	220 (22.7%)	34 (3.5%)	
Male	586 (62.1%)	293 (31.0%)	65 (6.9%)	
Education level				<0.001
Low	152 (11.7%)	151 (29.4%)	31 (31.3%)	
Medium	636 (48.9%)	293 (57.1%)	58 (58.6%)	
High	512 (39.4%)	69 (13.5%)	10 (10.1%)	
Type II diabetes mellitus				<0.001
No diabetes	1011 (77.8%)	357 (69.6%)	60 (60.6%)	
Pre-diabetes	172 (13.2%)	92 (17.9%)	25 (25.3%)	
Diabetes	89 (6.9%)	53 (10.3%)	12 (12.1%)	
Missing	28 (2.2%)	11 (2.1%)	2 (2.0%)	
Body mass index (kg/m^2)				0.3
≤24.9	377 (29.0%)	131 (25.5%)	21 (21.2%)	
25–29.9	438 (33.7%)	178 (34.7%)	33 (33.3%)	
≥30	483 (37.2%)	203 (39.6%)	44 (44.4%)	
Missing	2 (0.2%)	1 (0.2%)	1 (1.0%)	
Skeletal muscle mass index				<0.001
Mean (SD)	18.09 (±3.35)	18.70 (±3.30)	19.22 (±2.94)	<0.001
Missing	1 (0.1%)	1 (0.2%)	1 (1.0%)	
Combined handgrip strength (kg)				0.4
Mean (SD)	76.22 (±21.71)	77.26 (±21.68)	78.59 (±20.75)	
Missing	52 (4%)	28 (5.5%)	4 (4.0%)	
Bone mineral density (g/cm^2)				0.6
Mean (SD)	1.12 (±0.11)	1.11 (±0.12)	1.12 (±0.11)	
Missing	12 (0.9%)	4 (0.8%)	0 (0%)	
Total energy intake (kcal/day)				0.1
Mean (SD)	201.66 (±983.26)	2310.81 (±1108.61)	2353.13 (±1123.12)	
Missing	60 (4.6%)	38 (7.4%)	9 (9.1%)	
Total protein intake (g/day)				0.1
Mean (SD)	86.67 (±43.79)	91.55 (±48.48)	85.53 (±41.90)	
Missing	60 (4.6%)	38 (7.4%)	9 (9.1%)	
Vitamin D2 and D3 (nmol/L)				<0.001
Mean (SD)	62.0 (47.0–77.2)	54.6 (39.0–69.9)	53.6 (37.4–67.6)	

All continuous variables are reported with mean and standard deviation, $\bar{x}$ (±SD), while categorical variables are reported in percentages, no (%)

Table 2 Unadjusted results of linear regression analyses of association between periodontitis and SMMI or cHGS

Predictors	SMMI			cHGS		
	Estimates	95% CI	p value	Estimates	95% CI	p Value
Intercept	18.06	17.80–18.33	**<0.001**	77.56	76.02–79.10	**<0.001**
Non-severe periodontitis	1.01	0.50–1.52	**0.001**	1.83	− 0.38 to 4.05	0.098
Severe periodontitis	1.42	0.59–2.25	**0.003**	2.03	− 4.64 to 8.69	0.523

Reference group no periodontitis, *SMMI* skeletal muscle mass index, *cHGS* combined handgrip strength

Bold values are significant if $p < 0.05$

Table 3 Fully adjusted results of linear regression analyses of association between periodontitis and SMMI or cHGS

Predictors	SMMI			cHGS		
	Estimates	95% CI	*p* value	Estimates	95% CI	*p* value
Intercept	4.30	1.85 – 6.76	**0.017**	62.32	51.29 – 73.35	**< 0.001**
Non-severe periodontitis	0.07	− 0.26 to 0.40	0.451	− 2.81	− 4.47 to − 1.15	**0.005**
Severe periodontitis	0.22	− 0.34 to 0.78	0.231	− 2.73	− 6.31 to 0.83	**0.154**

Reference group no periodontitis, *SMMI* skeletal muscle mass index, *cHGS* combined handgrip strength
Bold values are significant if $p < 0.05$

was significantly higher compared to non-sarcopenic adults (30.3% vs. 18.3% in males, 45.9% vs. 17.4% in females, $p < 0.001$) [44]. The same study reported that having fewer than 20 teeth was associated with a higher incidence of sarcopenia in adults aged 65 years and older (OR 1.92, 95% CI 1.49; 2.66 in men and OR 2.63, 95% CI 2.25; 3.64 in women) [44].

Not only epidemiological studies but also in vivo experiments suggest that periodontitis may possibly be associated with muscle strength and mass. In an experimental ligature-induced periodontitis model, reduced strength, reduced number of capillaries, and increased number of inflammatory cells and fibroblasts in skeletal striated muscles were detected in immobilized Wistar rats with periodontitis compared to those without periodontitis, suggesting that periodontitis could possibly contribute to muscle atrophy [45]. In mice, the injection of the lipopolysaccharide of *Porphyromonas (P.) gingivalis*, a major periodontal pathogen, into the masseter and tibialis anterior muscles decreased muscle weight and increased fibrotic area and myocyte apoptosis eightfold in the masseter muscle, mediated in part by the activation of the toll-like receptor 4 (TLR4)/extracellular signal-regulated kinase (ERK) pathway [46]. Oral administration of *P. gingivalis* also altered glucose uptake signaling and gene expression in soleus muscle tissue in mice, resulting in increased mRNA expression of tumor necrosis factor alpha (*Tnfa),* interleukin-6 *(Il6)*, C-C motif chemokine 2 (*Ccl2*), and myogenin (*Myog*) compared to administration of saline [47]. Approximately, 79% of periodontitis patients may harbor *P. gingivalis* [48], a highly virulent pathogen that can also invade peripheral tissues, e.g., atherosclerotic plaques [49] and synovial fluids [50], and contribute to the pathogenesis of cardiovascular and rheumatic diseases.

This study has several limitations. First, there were relatively fewer participants in the severe periodontitis group compared to non-severe periodontitis group, which may have influenced the results. Second, a causal relationship between periodontitis and cHGS or SMMI cannot be inferred from this cross-sectional analysis. In addition, the sub-cohort included in the present study lacked participants with low SSMI or low cHGS, because it included only dentate U.S. adults below 60 years of age, who underwent both a clinical periodontal examination and a whole-body DXA scan. Therefore, our results are only representative for the studied sub-cohort ($n = 1912$), but not for the entire NHANES 2013–2014 cohort (n = 10,683). This affects the generalization of the results and introduces selection bias. In older ages, the association between muscle mass and muscle strength becomes more prominent than at younger ages; hence, this may result in a disparity in the association estimates of SMMI and cHGS with periodontitis. Finally, a number of independent factors influence muscle strength and mass, such as physical activity, genetics and hormones, which could not be accounted for in the present study. However, our results align with previous studies conducted in different populations and age groups that investigated the association between periodontitis proxies, i.e., tooth loss, and sarcopenia indicators, i.e., handgrip strength, despite these limitations.

Conclusions

The findings of the current study indicate that periodontitis and sarcopenia indicators may be interrelated. Further observational studies are needed to clarify the nature and direction of an association. Future studies can contribute to findings that support the screening, prevention and clinical management of sarcopenia and periodontitis, and emphasize the interdisciplinary and complementary approach between the disciplines of geriatric medicine and periodontology.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40520-023-02471-2.

Acknowledgements The authors would like to thank Michael Nolde, Katrin Borof, Ghazal Aarabi and Thomas Beikler for their comments and support.

Author contributions KB contributed to the conceptualization and design of the study, performed the data analysis, wrote the main manuscript and critically revised and edited the manuscript. GB, AJ-C, and TE, contributed to the conceptualization and design of the study, and critically revised and edited the manuscript. CW and AZ contributed to the statistical analysis of the manuscript and critically revised and edited the manuscript.

Funding Open Access funding enabled and organized by Projekt DEAL. This study has not received any external funding or sponsorship.

Availability of data and materials The data used in this study is publicly available under the following link: https://www.cdc.gov/nchs/NHANES/.

Declarations

Conflict of interest The authors declare no competing interests financial or otherwise.

Ethical approval The NHANES 2013–2014 has been approved by the National Center for Health Statistics Research Ethics Review Board (continuation of Protocol #2011–17, ERB).

Statement of human and animal rights This study does not include any animal studies conducted by the authors and adheres to the guidelines for conducting research involving human participants.

Informed consent Informed consent statement of NHANES 2013-2014 can be found under the following link: https://www.cdc.gov/nchs/nhanes/genetics/genetic_participants.htm

References

1. Peres MA, Macpherson LMD, Weyant RJ et al (2019) Oral diseases: a global public health challenge. Lancet 394:249–260
2. Sanz M, Marco Del Castillo A, Jepsen S et al (2020) Periodontitis and cardiovascular diseases: Consensus report. J Clin Periodontol 47:268–288
3. Lalla E, Papapanou PN (2011) Diabetes mellitus and periodontitis: a tale of two common interrelated diseases. Nat Rev Endocrinol 7:738–748
4. Czesnikiewicz-Guzik M, Osmenda G, Siedlinski M et al (2019) Causal association between periodontitis and hypertension: evidence from Mendelian randomization and a randomized controlled trial of non-surgical periodontal therapy. Eur Heart J 40:3459–3470
5. Kapellas K, Singh A, Bertotti M et al (2019) Periodontal and chronic kidney disease association: a systematic review and meta-analysis. Nephrology (Carlton) 24:202–212
6. Hasturk H, Kantarci A (2015) Activation and resolution of periodontal inflammation and its systemic impact. Periodontol 2000 69:255–273
7. Cruz-Jentoft AJ, Sayer AA (2019) Sarcopenia. Lancet 393:2636–2646
8. Cruz-Jentoft AJ, Bahat G, Bauer J et al (2019) Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 48:601
9. Bhasin S, Travison TG, Manini TM et al (2020) Sarcopenia definition: the position statements of the sarcopenia definition and outcomes consortium. J Am Geriatr Soc 68:1410–1418
10. Batsis JA, Mackenzie TA, Jones JD et al (2016) Sarcopenia, sarcopenic obesity and inflammation: results from the 1999–2004 National Health and Nutrition Examination Survey. Clin Nutr 35:1472–1483
11. Zhang H, Lin S, Gao T et al (2018) Association between sarcopenia and metabolic syndrome in middle-aged and older non-obese adults: a systematic review and meta-analysis. Nutrients 10:364
12. Tuttle CSL, Thang LAN, Maier AB (2020) Markers of inflammation and their association with muscle strength and mass: a systematic review and meta-analysis. Ageing Res Rev 64:101185
13. Watt RG, Petersen PE (2012) Periodontal health through public health—the case for oral health promotion. Periodontol 2000 60:147–155
14. Hatta K, Ikebe K (2021) Association between oral health and sarcopenia: a literature review. J Prosthodont Res 65:131–136
15. Abe T, Tominaga K, Ando Y et al (2021) Number of teeth and masticatory function are associated with sarcopenia and diabetes mellitus status among community-dwelling older adults: a Shimane CoHRE study. PLoS ONE 16:e0252625
16. Velázquez-Olmedo LB, Borges-Yáñez SA, Andrade Palos P et al (2021) Oral health condition and development of frailty over a 12-month period in community-dwelling older adults. BMC Oral Health 21:355
17. Azzolino D, Passarelli PC, De Angelis P et al (2019) Poor oral health as a determinant of malnutrition and sarcopenia. Nutrients 11:2898
18. Ramsay SE, Papachristou E, Watt RG et al (2018) Influence of poor oral health on physical frailty: a population-based cohort study of older British men. J Am Geriatr Soc 66:473–479
19. An HR, Choi JS (2022) Association between handgrip strength and periodontitis in korean adults aged ≥30 years: data from the Korea National Health and Nutrition Examination Survey (2014–2015). Int J Environ Res Public Health 19:10598
20. CDC, N (2013) Muscle strength manual. Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey data. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. 30 November 2020]. https://wwwn.cdc.gov/nchs/data/nhanes/2013-2014/manuals/muscle_strength_2013.pdf. Accessed 21 May 2022
21. CDC, N (2020) National Health and Nutrition Examination Survey 2013–2014 data documentation, codebook, and frequencies dual-energy X-ray absorptiometry—whole body (DXX_H). https://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/DXX_H.htm#Eligible_Sample. Accessed 21 May 2022
22. CDC, N (2016) National Health and Nutrition Examination Survey 2013–2014 data documentation, codebook, and frequencies oral health—periodontal (OHXPER_H). https://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/OHXPER_H.htm#Eligible_Sample. Accessed 21 May 2022
23. Eke PI, Thornton-Evans GO, Wei L et al (2018) Periodontitis in US adults: National Health and Nutrition Examination Survey 2009–2014. J Am Dent Assoc 149:576-588.e6
24. Colloca G, Di Capua B, Bellieni A et al (2019) Muscoloskeletal aging, sarcopenia and cancer. J Geriatr Oncol 10:504–509
25. Souza VA, Oliveira D, Barbosa SR et al (2017) Sarcopenia in patients with chronic kidney disease not yet on dialysis: analysis of the prevalence and associated factors. PLoS ONE 12:e0176230

26. Sasaki KI, Kakuma T, Sasaki M et al (2020) The prevalence of sarcopenia and subtypes in cardiovascular diseases, and a new diagnostic approach. J Cardiol 76:266–272
27. Klein GL (2015) The effect of glucocorticoids on bone and muscle. Osteoporos Sarcopenia 1:39–45
28. CDC, N (2013) Oral health examination manual. Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey data, Hyattsville, State of Maryland, U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. 2013 [30 November 2020]. https://wwwn.cdc.gov/nchs/data/nhanes/2013-2014/manuals/Oral_Health_Examiners.pdf. Accessed 21 May 2022
29. Eke PI, Page RC, Wei L et al (2012) Update of the case definitions for population-based surveillance of periodontitis. J Periodontol 83:1449–1454
30. Dye BA, Afful J, Thornton-Evans G et al (2019) Overview and quality assurance for the oral health component of the National Health and Nutrition Examination Survey (NHANES), 2011–2014. BMC Oral Health 19:95
31. CDC, N (2013) Body composition DXA manual. Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. 2013 [30 November 2020]. https://wwwn.cdc.gov/nchs/data/nhanes/2013-2014/manuals/2013_Body_Composition_DXA.pdf. Accessed 21 May 2022
32. Levey AS, Stevens LA, Schmid CH et al (2009) A new equation to estimate glomerular filtration rate. Ann Intern Med 150:604–612
33. Foundation NK (2002) K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 39:S1-266
34. Frencken JE, Sharma P, Stenhouse L et al (2017) Global epidemiology of dental caries and severe periodontitis—a comprehensive review. J Clin Periodontol 44:S94-s105
35. Zelig R, Goldstein S, Touger-Decker R et al (2022) Tooth loss and nutritional status in older adults: a systematic review and meta-analysis. JDR Clin Trans Res 7:4–15
36. Cruz-Jentoft AJ, Kiesswetter E, Drey M et al (2017) Nutrition, frailty, and sarcopenia. Aging Clin Exp Res 29:43–48
37. Palinkas M, Borges TF, Junior MT et al (2019) Alterations in masticatory cycle efficiency and bite force in individuals with periodontitis. Int J Health Sci (Qassim) 13:25–29
38. Johansson AS, Svensson KG, Trulsson M (2006) Impaired masticatory behavior in subjects with reduced periodontal tissue support. J Periodontol 77:1491–1497
39. Raj IS, Bird SR, Shield AJ (2010) Aging and the force–velocity relationship of muscles. Exp Gerontol 45:81–90
40. Xia X, Xu Z, Hu F et al (2022) Nutrition mediates the relationship between number of teeth and sarcopenia: a pathway analysis. BMC Geriatr 22:649
41. Nakamura M, Hamada T, Tanaka A et al (2021) Association of oral hypofunction with frailty, sarcopenia, and mild cognitive impairment: a cross-sectional study of community-dwelling Japanese older adults. J Clin Med 10:1626
42. Yun J, Lee Y (2020) Association between oral health status and handgrip strength in older Korean adults. Eur Geriatr Med 11:459–464
43. Eremenko M, Pink C, Biffar R et al (2016) Cross-sectional association between physical strength, obesity, periodontitis and number of teeth in a general population. J Clin Periodontol 43:401–407
44. Han CH, Chung JH (2018) Association between sarcopenia and tooth loss. Ann Geriatr Med Res 22:145–150
45. Leite MA, de Mattia TM, Kakihata CMM et al (2017) Experimental periodontitis in the potentialization of the effects of immobilism in the skeletal striated muscle. Inflammation 40:2000–2011
46. Kawamura N, Ohnuki Y, Matsuo I et al (2019) Effects of chronic *Porphyromonas gingivalis* lipopolysaccharide infusion on skeletal muscles in mice. J Physiol Sci 69:503–511
47. Watanabe K, Katagiri S, Takahashi H et al (2021) Porphyromonas gingivalis impairs glucose uptake in skeletal muscle associated with altering gut microbiota. FASEB J 35:e21171
48. Griffen AL, Becker MR, Lyons SR et al (1998) Prevalence of *Porphyromonas gingivalis* and periodontal health status. J Clin Microbiol 36:3239–3242
49. Velsko IM, Chukkapalli SS, Rivera MF et al (2014) Active invasion of oral and aortic tissues by Porphyromonas gingivalis in mice causally links periodontitis and atherosclerosis. PLoS ONE 9:e97811
50. Martinez-Martinez RE, Abud-Mendoza C, Patiño-Marin N et al (2009) Detection of periodontal bacterial DNA in serum and synovial fluid in refractory rheumatoid arthritis patients. J Clin Periodontol 36:1004–1010

1.1. Supplementary Table 1

Results of fully adjusted linear regression model of association between combined handgrip strength and periodontitis

	cHGS		
Predictors	***Estimates***	***CI***	***p***
Intercept	62.32	51.29 – 73.35	**<0.001**
Periodontitis [Non-severe periodontitis]	-2.81	-4.47 – -1.15	**0.005**
Periodontitis [Severe periodontitis]	-2.73	-6.31 – 0.83	**0.154**
Sex at birth [Women]	-37.34	-43.42 – -31.27	**<0.001**
Age (in years)	-0.32	-0.46 – -0.19	**<0.001**
BMD, g/cm^2	30.04	22.96 – 37.11	**<0.001**
BMI, kg/m2	0.39	0.28 – 0.49	**<0.001**
Type II Diabetes status [Diabetes]	-1.57	-4.59 – 1.41	0.316
Type II Diabetes status [Prediabetes]	-0.04	-2.12 – 2.02	0.968
Education level [Low]	-0.22	-2.65 –2.21	0.861
Education level [Medium]	0.53	-0.57 – 1.64	0.361
Age (in years) * Sex at birth [Women]	0.08	-0.05 – 0.21	**0.265**
Total energy intake (kcal/day)	0.00	-0.00 – 0.00	0.577
Total protein intake (g/day)	-0.01	-0.03 – 0.02	0.564
Vit D2 and D3 (nmol/l)	0.04	0.01 – 0.06	**0.022**
Number of observations	1676		
R^2	0.725		

cHGS: combined handgrip strength, CI: 95% confidence interval, SMMI: skeletal muscle mass index, BMD: bone mineral density, BMI: body-mass index, Vit D2 and D3: total serum vitamin D2 and D3. Reference categories: No periodontitis, Male, No diabetes, High education.

1.2. Supplementary Table 2

Results of fully adjusted linear regression model of association between skeletal muscle mass index and periodontitis

	SMMI		
Predictors	***Estimates***	***CI***	***p***
Intercept	4.30	1.85 – 6.76	**0.017**
Periodontitis [Non-severe periodontitis]	0.07	-0.26 – 0.40	0.451
Periodontitis [Severe periodontitis]	0.22	-0.34 – 0.78	0.231
Sex at birth [Women]	-3.02	-3.34 – -2.69	**0.001**
Age (in years)	-0.01	-0.03 – 0.00	0.072
BMD, g/cm^2	3.14	1.91 – 4.36	**0.008**
BMI, kg/m2	0.42	0.38 – 0.45	**<0.001**
Type II Diabetes status [Diabetes]	0.51	-0.11 – 1.13	0.070
Type II Diabetes status [Prediabetes]	0.31	-0.12 – 0.74	0.090
Education level [Low]	0.04	-0.40 – 0.49	0.708

Education level [Medium]	-0.08	-0.45 – 0.28	0.429
Total energy intake (kcal/day)	0.00	-0.00 – 0.00	0.319
Total protein intake (g/day)	0.00	-0.00 – 0.01	0.530
Vit D2 and D3 (nmol/l)	0.00	-0.00 – 0.01	0.168
Number of observations	1742		
R^2	0.710		

CI: 95% confidence interval, SMMI: skeletal muscle mass index, BMD: bone mineral density, BMI: body-mass index, Vit D2 and D3: total serum vitamin D2 and D3. Reference categories: No periodontitis, Male, No diabetes, High education.

1.3. R Code

```
library(SASxport)
library(tidyverse)
library(survey)
library(broom)
library(gt)
library(labelled)
library(gtsummary)
library(Gmisc)
library(sjPlot)
library(sjmisc)
library(sjlabelled)

lookup.xport("/Users/kubrabunte/Desktop/NHANES/oral.xpt")
lookup.xport("/Users/kubrabunte/Desktop/NHANES/dx.xpt")
lookup.xport("/Users/kubrabunte/Desktop/NHANES/musclegripdata.xpt")
lookup.xport("/Users/kubrabunte/Desktop/NHANES/bodymeasuresdata.xpt")
lookup.xport("/Users/kubrabunte/Desktop/NHANES/demographicsdata.xpt")
lookup.xport("/Users/kubrabunte/Desktop/NHANES/glycohemoglobindata.xpt")
lookup.xport("/Users/kubrabunte/Desktop/NHANES/nutrientintakedata.xpt")
lookup.xport("/Users/kubrabunte/Desktop/NHANES/vitddata.xpt")
lookup.xport("/Users/kubrabunte/Desktop/NHANES/cotinine.xpt")
lookup.xport("/Users/kubrabunte/Desktop/NHANES/cbcdata.xpt")
lookup.xport("/Users/kubrabunte/Desktop/NHANES/biochemdata.xpt")
lookup.xport("/Users/kubrabunte/Desktop/NHANES/diabetesquestionnairedata.xpt")
lookup.xport("/Users/kubrabunte/Desktop/NHANES/physicalactivityquestdata.xpt")
lookup.xport("/Users/kubrabunte/Desktop/NHANES/disabilitydata.xpt")
lookup.xport("/Users/kubrabunte/Desktop/NHANES/smokingdata.xpt")
lookup.xport("/Users/kubrabunte/Desktop/NHANES/medicalcondata.xpt")
lookup.xport("/Users/kubrabunte/Desktop/NHANES/bpdata.xpt")
lookup.xport("/Users/kubrabunte/Desktop/NHANES/prescriptiondata.xpt")

oraldata <- read.xport ("/Users/kubrabunte/Desktop/NHANES/oral.xpt")
dxdata <- read.xport("/Users/kubrabunte/Desktop/NHANES/dx.xpt")
gripdata <- read.xport("/Users/kubrabunte/Desktop/NHANES/musclegripdata.xpt")
bodydata <- read.xport("/Users/kubrabunte/Desktop/NHANES/bodymeasuresdata.xpt")
demogdata <- read.xport("/Users/kubrabunte/Desktop/NHANES/demographicsdata.xpt")
hbA1cdata <- read.xport("/Users/kubrabunte/Desktop/NHANES/glycohemoglobindata.xpt")
nutrientdata <-
read.xport("/Users/kubrabunte/Desktop/NHANES/nutrientintakedata.xpt")
vitddata <- read.xport("/Users/kubrabunte/Desktop/NHANES/vitddata.xpt")
nicotinedata <- read.xport("/Users/kubrabunte/Desktop/NHANES/cotinine.xpt")
cbcdata <- read.xport("/Users/kubrabunte/Desktop/NHANES/cbcdata.xpt")
biochemdata <- read.xport("/Users/kubrabunte/Desktop/NHANES/biochemdata.xpt")
```

```
diabquestdata <-
read.xport("/Users/kubrabunte/Desktop/NHANES/diabetesquestionnairedata.xpt")
physicalactquestdata <-
read.xport("/Users/kubrabunte/Desktop/NHANES/physicalactivityquestdata.xpt")
disabilitydata <- read.xport("/Users/kubrabunte/Desktop/NHANES/disabilitydata.xpt")
smokingdata <- read.xport("/Users/kubrabunte/Desktop/NHANES/smokingdata.xpt")
medicalcondata <- read.xport("/Users/kubrabunte/Desktop/NHANES/medicalcondata.xpt")
bpdata <- read.xport("/Users/kubrabunte/Desktop/NHANES/bpdata.xpt")
prescrdata <- read.xport("/Users/kubrabunte/Desktop/NHANES/prescriptiondata.xpt")

mydata <- merge(demogdata, oraldata, by= "SEQN",all = TRUE)
mydata <- merge(mydata, gripdata, by="SEQN",all = TRUE)
mydata <- merge(mydata, bodydata, by="SEQN",all = TRUE)
mydata <- merge(mydata, dxdata, by="SEQN", all.x=TRUE, all.y=TRUE)
mydata <- merge(mydata, hbA1cdata, by="SEQN",all = TRUE)
mydata <- merge(mydata, nutrientdata, by="SEQN",all = TRUE)
mydata <- merge(mydata, vitddata, by="SEQN",all = TRUE)
mydata <- merge(mydata, nicotinedata, by="SEQN",all = TRUE)
mydata <- merge(mydata, cbcdata, by="SEQN",all = TRUE)
mydata <- merge(mydata, biochemdata, by="SEQN",all = TRUE)
mydata <- merge(mydata, diabquestdata, by="SEQN",all = TRUE)
mydata <- merge(mydata, physicalactquestdata, by="SEQN",all = TRUE)
mydata <- merge(mydata, disabilitydata, by="SEQN",all = TRUE)
mydata <- merge(mydata, smokingdata, by="SEQN",all = TRUE)
mydata <- merge(mydata, medicalcondata, by="SEQN",all = TRUE)
mydata <- merge(mydata, bpdata, by="SEQN",all = TRUE)

# Removing participants with missing data from periodontal examinations
mydata <- mydata[!mydata$OHDPDSTS == 2, ]
mydata <- mydata[!mydata$OHDPDSTS == 3, ]
mydata <- mydata[!is.na(mydata$OHDPDSTS),]

# Removing participants with missing dual x-ray absorptiometry data
mydata<- mydata[mydata$DXAEXSTS ==1, ]
mydata <- mydata[!is.na(mydata$DXDTOLE),]

##### Application of Exclusion Criteria #####

# 1.Exclude medical conditions

# MCQ160B(heart failure)
mydata <- mydata[mydata$MCQ160B != 1,]
# MCQ160C(coronary heart disease),
mydata <- mydata[mydata$MCQ160C != 1,]
# MCQ160D (angina pectoris),
mydata <- mydata[mydata$MCQ160D != 1,]
# MCQ160E (heart attack),
mydata <- mydata[mydata$MCQ160E != 1,]
# MCQ160F (stroke),
mydata <- mydata[mydata$MCQ160F != 1,]
# MCQ220 (cancer/malignancy)
mydata <- mydata[mydata$MCQ220 != 1,]

# 2. Exclude corticosteroid use:
#d00254-hydrocortisone, d00206-dexamethasone,
#d00608-fluodrocortisone, d00609-cortisone
drugs <- c("d00254", "d00206", "d00608", "d00609")
mydata <- mydata[!(mydata %in% drugs), ]
```

```
##### Periodontal Classification #####

# 1. Buildung up vectors for the probes to check (names of the teeth according to
American system)
n_mesio <- c(2:15, 18:31)
n_distal <- c(3:14, 19:30)
neighbor_mesio <- c(replicate(7, 1), replicate(7, -1), replicate(7, 1),
replicate(7, -1))
neighbor_distal <- c(replicate(6, -1), replicate(6, 1), replicate(6, -1),
replicate(6, 1))

# 2. Column names for interproximal AL probes
al_cn_self <- c(sprintf("OHX%02dLAD", n_distal),sprintf("OHX%02dLAP",
n_distal),sprintf("OHX%02dLAS", n_mesio),sprintf("OHX%02dLAA", n_mesio))

# 3. Column names for neighboring AL probes to check if they exist
al_cn_test <- c(sprintf("OHX%02dLAS", n_distal +
neighbor_distal),sprintf("OHX%02dLAA", n_distal +
neighbor_distal),sprintf("OHX%02dLAD", n_mesio +
neighbor_mesio),sprintf("OHX%02dLAP", n_mesio + neighbor_mesio))

# 4. Column names for interproximal PD probes
pd_cn_self <- c(sprintf("OHX%02dPCD", n_distal),sprintf("OHX%02dPCP",
n_distal),sprintf("OHX%02dPCS", n_mesio),sprintf("OHX%02dPCA", n_mesio))

# 5. Column names for neighboring PD probes to check if they exist
pd_cn_test <- c(sprintf("OHX%02dPCS", n_distal +
neighbor_distal),sprintf("OHX%02dPCA", n_distal +
neighbor_distal),sprintf("OHX%02dPCD", n_mesio +
neighbor_mesio),sprintf("OHX%02dPCP", n_mesio + neighbor_mesio))

all_pds <- c(sprintf("OHX%02dPCD", n_mesio), sprintf("OHX%02dPCP", n_mesio),
sprintf("OHX%02dPCM", n_mesio),sprintf("OHX%02dPCL", n_mesio),sprintf("OHX%02dPCS",
n_mesio),sprintf("OHX%02dPCA", n_mesio))

all_als <- c(sprintf("OHX%02dLAD", n_mesio),sprintf("OHX%02dLAP",
n_mesio),sprintf("OHX%02dLAM", n_mesio),sprintf("OHX%02dLAL",
n_mesio),sprintf("OHX%02dLAS", n_mesio),sprintf("OHX%02dLAA", n_mesio))

# 6. Function to execute for each row to build up a list of columns of
interproximal columns
getInterproximalColNames <- function(x, cn_self, cn_test) {
  v <- c()
  for (i in 1:length(cn_self)) {
    v <- c(v, ifelse(x[cn_self[i]] < 99 & x[cn_test[i]] < 99, cn_self[i], ""))
  }
  v <- v[!v %in% ""]
  c(v, use.names = FALSE)
}

# 7. Executing the function and remove patients that have no interproximal AL
probes
mydata$interp_al_names <- unname(apply(mydata, 1, getInterproximalColNames,
al_cn_self, al_cn_test))
mydata <- mydata[lengths(mydata$interp_al_names) > 0, ]
mydata$interp_pd_names <- unname(apply(mydata, 1, getInterproximalColNames,
pd_cn_self, pd_cn_test))
mydata <- mydata[lengths(mydata$interp_pd_names) > 0, ]
```

```
# 8. Function to calculate how many columns have an value equal or greater than a
certain value
calcNumGt <- function(x, col.name, min_value) {sum(unlist(x[x[[col.name]]]) >=
min_value)}

calcNumTeethGt <- function(x, col.name, min_value) {
  tooth <- as.numeric(substr(x[[col.name]], 4, 5))
  d <- data.frame(probe=x[[col.name]], tooth=tooth, pd=unlist(x[x[[col.name]]]))
  max_pd_per_tooth <- aggregate(d$pd, list(d$tooth), max)
  sum(max_pd_per_tooth[2] >= min_value)}

calcMaxPd <- function(x, col.names) {pds <- unlist(x[col.names])max(pds[pds !=
99])}

calcMeanValue <- function(x, col.names) {values <- unlist(x[col.names])
  mean(values[values != 99])}

# 9. Apply function for 3mm, 4mm and 6mm AL
mydata$num_al_3mm <- apply(mydata, 1, calcNumGt, "interp_al_names", 3)
mydata$num_teeth_al_4mm <- apply(mydata, 1, calcNumTeethGt, "interp_al_names", 4)
mydata$num_teeth_al_6mm <- apply(mydata, 1, calcNumTeethGt, "interp_al_names", 6)

# 10. Apply function for 4mm and 5mm AL
mydata$num_teeth_pd_4mm <- apply(mydata, 1, calcNumTeethGt, "interp_pd_names", 4)
mydata$num_teeth_pd_5mm <- apply(mydata, 1, calcNumTeethGt, "interp_pd_names", 5)

# 11. Maximum PD for this patient
mydata$max_pd <- apply(mydata, 1, calcMaxPd, all_pds)

# 12. Classify periodontitis in 4 categories
classifyPerio <- function(x) {if (x$num_teeth_al_6mm >= 2 & x$num_teeth_pd_5mm >=
1) {return("Severe")} else if (x$num_teeth_al_4mm >= 2 | x$num_teeth_pd_5mm >= 2)
{return("Moderate")} else if (x$num_al_3mm >= 2 & (x$num_teeth_pd_4mm >= 2 |
x$max_pd >= 5)) {return("Mild")} else {return("No")}}

###### Periodontal Classification after applying all exclusion criteria #######
mydata$periocat4 <- apply(mydata, 1, classifyPerio)
mydata$perioStatus <- mydata$periocat4 != "No"

# Classification as no, Non-Severe and Severe periodontitis
mydata$periocat3 <- ifelse(mydata$periocat4 == "Mild" | mydata$periocat4 ==
"Moderate", "Non-Severe", mydata$periocat4)
mydata$periocat3 <- ifelse(mydata$periocat4 == "Severe", "Severe",
mydata$periocat3)
mydata$periocat3 <- ifelse(mydata$periocat4 == "No", "No", mydata$periocat3)
mydata$periocat3 <- factor(mydata$periocat3)
mydata$periocat3 <- relevel(mydata$periocat3, ref = "No")

# Skeletal muscle mass index
summary(mydata$DXDTOLE, exclude=NULL)
summary(mydata$BMXHT, exclude=NULL)
mydata$heightinmeters <- as.numeric(mydata$BMXHT)/100
summary(mydata$heightinmeters)
mydata$musclemassinkg <- mydata$DXDTOLE/1000
summary(mydata$musclemassinkg)
mydata$HASMM <-
as.numeric(mydata$musclemassinkg)/(as.numeric(mydata$heightinmeters)^2)
summary(mydata$HASMM, exclude=NULL)
```

```
#Sex at birth
mydata$RIAGENDR <- as.factor(mydata$RIAGENDR)
levels(mydata$RIAGENDR)[levels(mydata$RIAGENDR)==1] <- "Men"
levels(mydata$RIAGENDR)[levels(mydata$RIAGENDR)==2] <- "Women"

# Education
mydata$education <- ifelse(mydata$DMDEDUC2 %in% c("1","2"), "low", mydata$DMDEDUC2)
mydata$education <- ifelse(mydata$DMDEDUC2 %in% c("3","4"), "medium",
mydata$education)
mydata$education <- ifelse(mydata$DMDEDUC2 == 5, "high", mydata$education)

#BMI
mydata$BMIcat <- ifelse(mydata$BMXBMI <= 24.9, "<=24.9",mydata$BMXBMI)
mydata$BMIcat <- ifelse(mydata$BMXBMI >= 25 & mydata$BMXBMI <= 29.9, "25-29.9",
mydata$BMIcat)
mydata$BMIcat <- ifelse(mydata$BMXBMI >= 30,  "30>=", mydata$BMIcat)

#HbA1c
table(mydata$LBXGH)
mydata$diabcat <- ifelse(mydata$LBXGH >= 6.5 , "Diabetes", mydata$LBXGH)
mydata$diabcat <- ifelse(mydata$LBXGH < 6.5 & mydata$LBXGH > 5.7 , "Prediabetes",
mydata$diabcat)
mydata$diabcat <- ifelse(mydata$LBXGH <= 5.7 , "Non-diabetes", mydata$diabcat)
mydata$diabcat <- as.factor(mydata$diabcat)
mydata$diabcat <- relevel(mydata$diabcat, ref = "Non-diabetes")
table(mydata$diabcat)

### RESULTS ###

# 1. Participant characteristics

getTable1Stats <- function(x, digits = 2, ...){
  getDescriptionStatsBy (x = x, by = mydata$periocat3, digits = digits,
continuous_fn = describeMean, prop_fn = describeProp, header_count =
TRUE,statistics = TRUE, missing_value = "-",...)}

table1 <- list()
table1[["Age"]] <-getTable1Stats(mydata$RIDAGEYR)
table1[["Sex at birth"]] <-getTable1Stats(mydata$RIAGENDR)
table1[["Education"]] <-getTable1Stats(mydata$education)
table1[["Diabetes Mellitus"]] <- getTable1Stats(mydata$diabcat)
table1[["BMI"]] <- getTable1Stats(mydata$BMIcat)
table1[["SMMI"]] <-getTable1Stats(mydata$HASMM)
table1[["Handgrip strength"]] <-getTable1Stats(mydata$MGDCGSZ)
table1[["Bone mineral Density"]] <- getTable1Stats(mydata$DXDTOBMD)
table1[["Total Daily Energy Intake"]] <-getTable1Stats(mydata$DR1TKCAL)
table1[["Total Daily Protein Intake"]] <- getTable1Stats(mydata$DR1TPROT)
table1[["Vitamin D2 and D3"]] <- getTable1Stats(mydata$LBXVIDMS)

mergeDesc(table1,
          getTable1Stats(mydata$periocat3)) %>%
  htmlTable(caption  = "Participant characteristics stratified by periodontitis",
            tfoot = c("All continuous variables are reported with mean and standard
deviation, x̄ (± SD), while categorical variables are reported in percentages, no
(%) "),
            ctable = TRUE)
table1 <- data.frame(table1)
```

```
# 2. Survey design
mydata <- subset(mydata , !is.na(WTMEC2YR))
mydata <- subset(mydata , !is.na(SDMVPSU))

nhanesDesign <- svydesign (id= ~SDMVPSU,strata  = ~SDMVSTRA,weights = ~WTMEC2YR,
nest=TRUE, data=mydata)
nhanesDesign

ageDesign <- subset(nhanesDesign, RIDAGEYR > 29 & RIDAGEYR < 60)

# 3. Unadjusted models
smmi <- svyglm (HASMM ~ periocat3,family = gaussian(),data   = nhanesDesign, design
= ageDesign)
summary(smmi)
plot(smmi)
tab_model(smmi)

hgs <- svyglm (MGDCGSZ ~ periocat3, family = gaussian(),data   = nhanesDesign,
design = ageDesign)
summary(hgs)
plot(hgs)
tab_model(hgs)

# 4. Fully adjusted models
adjustedsmmi <- svyglm (HASMM ~ periocat3 + RIAGENDR + RIDAGEYR + DXDTOBMD + BMXBMI
+diabcat + education + DR1TKCAL + DR1TPROT + LBXVIDMS, family = gaussian(),data   =
nhanesDesign, design = ageDesign)
summary(adjustedsmmi)
plot(adjustedsmmi)
tab_model(adjustedsmmi)

adjustedhgs <- svyglm (HASMM ~ periocat3 + RIAGENDR + RIDAGEYR + DXDTOBMD + BMXBMI
+ diabcat + education + DR1TKCAL + DR1TPROT + LBXVIDMS, family = gaussian(),data
= nhanesDesign, design = ageDesign)
summary(adjustedhgs)
plot(adjustedhgs)
tab_model(adjustedhgs)
```

2. Presentation of the publication with bibliography

2.1. Periodontitis

Periodontitis is caused by oral dysbiosis, a chronic inflammatory condition of the tooth-supporting tissues that, if left untreated, promotes tissue disintegration and tooth loss. It is responsible for the majority of adult tooth loss [1]. Periodontitis raises the risk of cardiovascular disease, diabetes, hypertension, and chronic renal disease on its own [2-5]. By infiltrating periodontal germs into the circulatory system, periodontitis induces alio loco tissue reactions [6]. The symbiotic microbiota and homeostatic immunity both contribute to maintaining periodontal health. A dysbiotic multi-microbial community, where multiple organisms play separate and synergistic functions that foster damaging inflammation, is linked to periodontitis. Keystone pathogens initially weaken host defenses, which results in the development of

dysbiotic microbiota, which occurs when commensal- pathobionts excessively activate the inflammatory process and result in tissue destruction [1]. Keystone pathogens are assisted by accessory pathogens by virtue of nutrition and/or colonization support. Through the supply of resources for the bacteria (resulting from tissue breakdown products, such as peptides of collagen and heme-containing substances), inflammation can further aggravate dysbiosis. As a result, dysbiosis and inflammation are mutually reinforced, creating a positive feedback loop. This self-sustaining cycle, whose growth necessitates a vulnerable host, may be the cause of the chronic nature of periodontitis. The existence of germs that interfere with the immune system's response, systemic illness, smoking, age, eating a high-fat diet, and immunological deficiencies are risk factors, among others [6]. These elements could contribute to dysbiosis either alone or more potently when combined. Periodontitis is clinically diagnosed by probing depth (PD), clinical attachment level (CAL), radiographic pattern and degree of alveolar bone loss, gingival inflammation as evaluated by bleeding on probing, or a combination of these markers.

2.2. Sarcopenia

A disorder known as sarcopenia is characterized by a decrease of both the mass and function of skeletal muscle. Despite the fact that sarcopenia is largely a disease of older people, its occurrence may be accompanied with diseases that are not solely found in older people, such as inactivity, malnutrition, and cachexia. This condition can also be found in younger people, such as those who suffer from inflammatory disorders. Sarcopenia is a condition that is defined by gradual and pervasive decrease in skeletal muscle mass and strength, and it is tightly connected with physical impairment, poor quality of life, and ultimately mortality [7]. Age, gender, and amount of physical activity are all characteristics that can play a role in the development of sarcopenia [8]. Lean body mass is reduced whereas fat mass may be kept or even grown in situations such as malignant tumors, rheumatoid arthritis, and the natural aging process. In adulthood, sarcopenia causes frailty and mobility problems [7-9]. Sarcopenia patients experience metabolic difficulties as well as falls, which can result in incapacity, malnutrition, and death [7]. Sarcopenia has a negative impact on health-related quality of life [8, 10, 11]. Sarcopenia patients' loss of muscle mass and strength impairs anabolic metabolic activity, immune system function, and inflammation [12].

The muscle mass as well as its function, i.e., strength belong to the assessment criteria of sarcopenia. The mass, the strength, and the physical performance are the factors that are measured for its diagnosis when possible. Computed tomography (CT scan), magnetic

resonance imaging (MRI), and dual energy X-ray absorptiometry (DXA) are the three imaging methods that have been utilized in the process of determining lean body mass or muscle mass. These technologies are regarded to be the gold standard for measuring muscle mass in research because of their ability to differentiate between fat and other soft tissues of the body, which is why CT and MRI are considered to be exceptionally precise imaging systems. The use of these whole-body imaging technologies in ordinary clinical practice is restricted due to factors such as the high cost, restricted access to equipment at certain locations, and concerns around radiation exposure. When it comes to research as well as therapeutic applications, DXA is an appealing alternative technology that can differentiate between fat, bone mineral, and lean tissues. The patient will be exposed to a low level of radiation during this whole-body scan.

2.3. Periodontitis-Sarcopenia Link and Hypothesis

Local inflammatory disruption has a number of disease-related consequences. This might happen as a result of periodontitis-related inflammatory cascades: locally generated pro-inflammatory mediators reach systemic circulation, allowing them to impact distant organs and destabilize inflammatory state equilibria [6]. Patients with periodontitis, as compared to healthy participants, have greater levels of circulating white blood cells as well as other systemic inflammatory indicators such as C-reactive protein (CRP), a protein generated by the liver in reaction to external stress [2]. As a result, we may claim that periodontitis-associated local inflammation can become systemic, altering organismal inflammatory burdens, and that systemic inflammation can influence periodontal health. The association between myocardial infarction and periodontitis has also been studied in terms of oxidative stress and molecular mechanisms of inflammation [2, 4]. Along similar lines, it has been shown that low-grade inflammation (LGI) is present in the majority of prevalent chronic illnesses such as diabetes, obesity, cardiovascular and neurological disorders [6]. LGI has been connected to Parkinson's disease in some circumstances. Causality, on the other hand, is not yet shown with high level of evidence. As a result, it has been proposed that periodontal inflammation is directly connected to the development and progression of chronic systemic illnesses through a process of LGI induction, which is thought to be a hidden risk factor for many of them.

In this context, there is clinical evidence linking periodontitis to the etiology of systemic inflammation. A cause-and-effect link, however, has yet to be established. Some studies have found a drop in systemic inflammatory biomarkers following periodontal treatments, with the potential advantage of lowering cardiovascular risk as endothelial dysfunction [2]. However,

evidence of its long-term effects on cardiovascular events is still limited, and there is no evidence that they prevent or affect the outcomes of atherosclerotic vascular disease, thus more research is needed. In addition, periodontal therapy has been linked to a slight decrease in glycated hemoglobin (HbA1c) in type 2 diabetes patients [4]. However, there is little confidence in the result due to a paucity of large-scale multicenter trials. Similarly, it has not been feasible to evaluate if periodontal therapy benefits women at risk of obstetric problems; nonetheless, it appears to be a good practice to implement preventative efforts in women with periodontitis.

Tobacco use, obesity, sedentary lifestyles, and poor socioeconomic position are all risk factors for chronic and inflammatory illnesses, which diminish quality of life [13]. We suspected a link between periodontitis and sarcopenia, two chronic illnesses with similar risk factors. Sarcopenia markers such as handgrip strength, masticatory ability, and muscle mass have been associated to poor dental health and hypofunction in recent research [14]. Handgrips were weaker in Japanese seniors with fewer teeth and lower mastication strength [15]. Mexican seniors with edentulism and poor oral health were frail [16]. Frailty and sarcopenia may result from tooth loss and masticatory issues. Older British males with eating disorders, fewer teeth, or edentulism were frailer in a nationally representative sample [18]. In a Korean study, 30-year-olds with periodontitis had weaker grips compared to those without periodontitis [19]. The majority of periodontitis and sarcopenia investigations recruited people over the age of 65. Sarcopenia indices and periodontitis in younger and more varied populations have received less attention. Thus, this study investigates the association between periodontitis and handgrip strength or skeletal muscle mass index in a subgroup of U.S. population.

2.4. Methods

The 2013–2014 NHANES adult participants were studied cross-sectionally. NHANES uses home interviews, laboratory, and physical exams to assess the health and nutrition of a representative population of US children and adults. NHANES datasets are publicly available, and individuals have consented to study use. NHANES 2013-2014 design and techniques are explained elsewhere [20]. The 2013–2014 NHANES wave was chosen since it contained full-body DXA and periodontal exams. The 30-59-year-old cohort had both exams. Pregnancy, barium usage in the last 7 days, weight over 204 kg (450 lbs), and height above 198 cm (6’5”) excluded participants from the DXA [21]. Having fewer than one natural tooth and needing antibiotic prophylaxis before periodontal probing were exclusion criteria [22]. Eke et al. [23] describe the NHANES 2013-2014 cohort in further depth. Sarcopenia-associated medical

problems eliminated people from this research. Present research exclusion criteria: 1) adults with cancer or malignancies (self-reported, n=91) [24], 2) chronic kidney disease (estimated glomerular filtration rate < 30 mL/min, n=0) [25], 3) heart disease (self-reported heart failure, coronary heart disease, coronary heart attack, angina pectoris, ischemic heart disease, and stroke, n=163) [26], and 4) those receiving systemic corticosteroids (n=0) [27]. Figure 1 shows data flowchart.

According to the NHANES protocol, licensed dentists recorded gingival recessions (mm) from the cemento-enamel junction and probing pocket depths (PPD, mm) at six sites (disto-facial, mid-facial, mesio-facial, disto-oral, oral, and mesio-oral) for each permanent tooth, excluding third molars [28]. Clinical attachment loss (CAL, mm) was calculated by adding gingival recession and probing pocket depth at each examination site for each tooth, and gingiva height was recorded as negative, 0, or positive depending on the gingival margin's position relative to the CEJ [28]. The new CDC/AAP periodontitis case definitions were used [29]. Dye et al. provided NHANES III inter- and intra-examiner calibration data for periodontal parameters [30]. All individuals who satisfied CDC-AAP criteria were categorized as "no periodontitis," "non-severe (mild or moderate)," or "severe" (n=1,912). According to the NHANES protocol, trained and certified radiology technicians at the NHANES center used the Hologic Discovery model A densitometer (Hologic, Inc., Bedford, Massachusetts) to acquire whole-body dual x-ray absorptiometry scans and assessed them using Apex 3.2 software [31]. To compare individuals, total lean mass without bone mineral content was divided by height squared in the database. Skeletal muscle mass index (SMMI) was calculated from this. Sarcopenia case criteria established low SMMI as below 5.5 kg/m2 for women and below 7.0 kg/m2 for males [8]. An isometric handgrip test with a dynamometer (Takei Digital Grip Strength Dynamometer, Model T.K.K.5401) in a standing position assessed muscular strength [20]. Exhaling while squeezing the dynamometer prevented intra-thoracic pressure from rising. Each hand was tested three times. The combined handgrip strength (cHGS, kg) was the highest reading from each hand. The NHANES website has protocol details [20]. According to sarcopenia case criteria, low cHGS was 16 kg or less for women and 27 kg or less for males at least in one hand [8].

Selecting variables considered skeletal muscle mass, handgrip strength, and periodontitis. Participants self-reported their age (continuous), sex assigned at birth (female, male), total daily energy intake (continuous, kcal/day), daily protein intake (continuous, g/day), and education

level (low: 12th grade with no diploma and/or below; medium: high school graduate and/or equivalent and/or some level of higher education; or high: completed college degree and/or above). Smoking status was excluded from analysis due to over 60% missing data. The NHANES assessment center's health professionals measured participants' weight and standing height to compute their body mass index (BMI, kg/m2). The diabetes mellitus type II status was categorical [HbA1c (%)], non-diabetes: < 5.7; prediabetes: 5.7–6.5; diabetes: > 6.5]. The regression analysis included BMI as a continuous variable, but participant characteristics were grouped by WHO obesity classification. BMD (g/cm2) and vitamin D2 and D3 (nmol/l) were continuous variables in the NHANES dataset. A validated algorithm for the study population was used to compute eGFR from standardized blood creatinine [32]. National Kidney Foundation Kidney Disease Outcomes Quality Initiative eGFR reference levels defined chronic kidney disease [33]. All continuous data are provided as mean with standard deviation, whereas categorical variables are values and percentages. All studies used multiple linear regression models to examine the relationship between periodontitis severity and SMMI or cHGS. Regression coefficients with two-sided 95% CIs were presented for unadjusted and adjusted relationships. Biological plausibility and evidence were used to identify confounding factors and estimate adjusted relationships. Models incorporated interaction terms for effect changes. The analyses avoided a stepwise approach and incorporated all predetermined factors. The sophisticated NHANES survey design was included in all regression models, and the survey package in R contained survey weights, main sample units, and strata. All statistical analyses were performed in R 4.0.3.

2.5. Results

There was a subset of 1,912 participants who satisfied the requirements for the periodontal categorization and had a whole-body dual x-ray absorptiometry test within the main cohort that was collected in 2013–2014. This subgroup was analyzed separately from the main cohort. The analysis did consider these particular individuals. The participants in the study group had an average age of 43.4 years (with a standard deviation of 8.4 years), and male participants accounted for 49.4% of the total. The individuals' individual characteristics are presented in detail in Table 1. The individuals in the study were not categorized as having sarcopenia since none of them had a low hand-grip strength or a low skeletal muscle mass index. As a result, a classification of sarcopenia could not be carried out. Throughout the entirety of the study, both the SMMI and the cHGS were regarded as being continuous variables in the analyses. It was determined that 612 of the participants, or 32%, had periodontitis, with 513 (26.8%) of those

persons having non-severe (mild or moderate) periodontitis and 99 (5.2%) of those individuals having severe periodontitis.

In unadjusted regression models, non-severe or severe periodontitis were associated with SMMI ($ß_{non\text{-}severe}$ = 1.01, 95% CI 0.50; 1.52 and $ß_{severe}$ = 1.42, 95% CI 0.59; 2.25), and cHGS ($ß_{non\text{-}severe}$ = 1.83, 95% CI -0.38; 4.05 and $ß_{severe}$ = 2.03, 95% CI -4.64; 8.69). After accounting for age, gender, education, body mass index (BMI), bone mineral density (BMD), diabetic status, education, total energy intake, total protein intake, and serum vitamin D2+D3, periodontitis was found to have strong associations with cHGS ($ß_{non\text{-}severe}$ = -2.81, 95% confidence interval [CI] = -4.7; -1.15 and $ß_{severe}$ = -2.73, 95% confidence interval [CI] = -6.31; 0.83. The findings of the fully adjusted regression analysis of the relationship between SMMI and periodontitis were as follows: $ß_{non\text{-}severe}$ = 0.07, with a 95% confidence interval ranging from -0.26 to 0.40, and $ß_{severe}$ = 0.22, with a 95% confidence interval ranging from -0.34 to 0.78. The outcomes of the thorough adjusted regression analyses of combined handgrip strength and skeletal muscle mass index are presented in Table 3.

2.6. Discussion

This study investigated the association between periodontitis and sarcopenia markers, specifically grip strength (cHGS) and skeletal muscle mass index (SMMI), while excluding tooth loss as a surrogate measure and considering shared risk factors and demographic characteristics. After accounting for covariates related to muscle function, metabolism, and risk factors for sarcopenia such as diabetes mellitus and BMI, periodontitis was found to be associated with grip strength but not skeletal muscle mass index (SMMI) in adults below the age of 60.

Tooth loss and inadequate dietary habits may account for the association between chronic generalized severe periodontitis (cHGS) and its underlying causes. Periodontitis is a leading cause of adult tooth loss [34]. Malnutrition is associated with an increased risk of developing sarcopenia and frailty [35]. Periodontitis diminishes biting force by inducing tooth displacement [37]. The activity of mechanoreceptors in the periodontal ligament decreases, leading to a decline in periodontal support and the ability to control masticatory force [38]. The function is capable of predicting the endurance and strength of skeletal and masticatory muscles [39]. Periodontitis-induced masticatory dysfunction may lead to oral hypofunction and sarcopenia [40]. Oral hypofunction was significantly associated with frailty [41]. In a cohort

that represents the entire nation, Korean males with less than nine teeth exhibited poorer handgrip strength (odds ratio: 1.39, 95% confidence interval 1.03; 1.88, mean age 72.9 ± 0.1) after accounting for various factors [42]. Clinical attachment loss was associated with reduced handgrip strength in a sample of 2,089 adult individuals (both men and women) aged 30 to 90 years in northern Germany [43]. Sarcopenic Korean adults exhibited significantly higher prevalence of periodontitis compared to non-sarcopenic individuals, with rates of 30.3% in males (vs. 18.3%) and 45.9% in females (vs. 17.4%), respectively ($p<0.001$) [44]. Having less than 20 teeth was associated with a higher risk of sarcopenia in 65-year-old individuals, with odds ratios of 1.92 (95% confidence interval: 1.49-2.66) in males and 2.63 (95% confidence interval: 2.25-3.64) in females [44].

Periodontitis has been associated with muscular strength and mass based on epidemiological and in vivo studies. In a ligature-induced periodontitis model experiment, Wistar rats with immobilization and periodontitis exhibited diminished muscular strength, decreased capillary density, and elevated levels of inflammatory cells and fibroblasts within skeletal striated muscles. These findings suggest a potential association between periodontitis and muscle atrophy [45]. The lipopolysaccharide (LPS) of *Porphyromonas (P.) gingivalis*, a prominent pathogen in periodontal disease, was administered to mice by injecting it into the masseter and tibialis anterior muscles. This resulted in a reduction in muscle weight, along with an eight-fold increase in fibrotic area and myocyte apoptosis specifically in the masseter muscle [46]. Oral *P. gingivalis* modified glucose uptake signaling and gene expression in soleus muscle tissue in mice, resulting in elevated mRNA expression of tumor necrosis factor alpha (*Tnfa*), interleukin-6 (Il6), C-C motif chemokine 2 (Ccl2), and myogenin (*Myog*) in comparison to the saline control [47]. *P. gingivalis*, a highly virulent bacterium, can infect peripheral tissues such as atherosclerotic plaques and synovial fluids, potentially leading to cardiovascular and rheumatic disorders in a significant proportion of individuals with periodontitis (79%) [48][49].

The scope of this study is restricted. The imbalance in number of participants between severe periodontitis and non-severe cases may have influenced the outcomes. Furthermore, this cross-sectional study does not establish a causal relationship between periodontitis and low cHGS or SMMI. The study sub-cohort consisted solely of dentate individuals under the age of 60 from the United States, who underwent both a clinical periodontal examination and a whole-body DXA scan. As a result, none of the participants in this sub-cohort exhibited low skeletal muscle mass index (SSMI) or combined handgrip strength (cHGS). The findings presented here pertain

exclusively to the subset of individuals studied (n = 1,912), and should not be generalized to the entire NHANES 2013-2014 population (n = 10,683). Thus, there is a selection bias and generalizability of findings are impacted. The relationship between muscle mass and muscle strength becomes more pronounced with increasing age, potentially accounting for the disparity observed in estimates of periodontitis between SMMI and cHGS. Also, the present study did not consider the influence of physical activity, genetics, and hormones on muscular strength and mass. Notwithstanding these limitations, our findings align with prior studies conducted on various populations and age cohorts, which investigated the correlation between indicators of periodontitis (e.g., tooth loss) and markers of sarcopenia (e.g., handgrip strength).

2.7. Conclusion

Recent studies indicate a potential association between periodontitis and sarcopenia. Additional observational studies are required to ascertain the direction of an association. Further research could contribute to the identification, mitigation, and management of sarcopenia and periodontitis and strengthen interdisciplinary collaborations.

3. Summary in German

Der Zusammenhang zwischen Parodontitis und Sarkopenieparametern bei Erwachsenen mittleren Alters ist weitgehend unerforscht. In dieser Studie wird der Zusammenhang zwischen Parodontitis und kombinierter Handgriffstärke und Skelettmuskelmasse bei Erwachsenen mittleren Alters untersucht.

Eine Teilkohorte von 1.912 Personen mit vollständigen Parodontal- und Ganzkörper-Doppelröntgenabsorptionsuntersuchungen aus der Welle 2013-2014 des National Health and Nutrition Examination Survey (n = 10.175) wurde mithilfe vollständig angepasster multipler linearer Regressionsmodelle auf Assoziationen zwischen Parodontitis und Skelettmuskel-Massenindex (kg/m2) und kombinierter Handgriffstärke (kg) analysiert.

Das Durchschnittsalter der Studienkohorte betrug 43 (±8,4) Jahre und 49,4 % der Teilnehmer waren männlich. Insgesamt wurde bei 612 Teilnehmern (32 %) eine Parodontitis festgestellt, von denen 513 (26,8 %) eine nicht schwere (leichte oder mittelschwere) Parodontitis und 99 (5,2 %) eine schwere Parodontitis aufwiesen. In unbereinigten Regressionsmodellen waren sowohl die nicht-schwere als auch die schwere Parodontitis mit dem SMMI assoziiert ($ß_{nicht-schwer}$ = 1,01, 95% CI 0,50; 1,52 und $ß_{schwer}$ = 1,42, 95% CI 0,59 ; 2,25), jedoch nicht mit dem

cHGS ($ß_{nicht\text{-}schwer}$ = 1.83, 95% CI -0.38 ; 4.05 and $ß_{schwer}$ = 2.03, 95% CI -4.64 ; 8.69). Nach Adjustierung für Alter, Geschlecht, Bildung, Body-Mass-Index, Knochenmineraldichte, Diabetes-Status, Gesamtenergieaufnahme, Gesamtproteinaufnahme und Serum-Vitamin D2+D3 war Parodontitis mit cHGS assoziiert ($ß_{nicht\text{-}schwer}$ = -2,81, 95% CI -4,7 ; -1,15 und $ß_{schwer}$ = -2,73, 95% CI -6,31 ; 0,83).

Die vorliegende Studie unterstreicht die Notwendigkeit weiterer prospektiver Forschung, um die Art und Richtung der Beziehung zwischen Parodontitis und Sarkopenie-Indikatoren zu untersuchen. Künftige Studien können das Screening, die Prävention und das klinische Management von Sarkopenie und Parodontitis unterstützen und den interdisziplinären und komplementären Ansatz zwischen den zwischen den Disziplinen Altersmedizin und Parodontologie.

4. Summary in English

The relationship between periodontitis and sarcopenia parameters in middle-aged adults is largely unexplored. This study investigated the association between periodontitis and combined handgrip strength and skeletal muscle mass in middle-aged adults.

A sub-cohort of 1,912 individuals with complete periodontal and whole-body dual x-ray absorptiometry examinations from the 2013–2014 wave of the National Health and Nutrition Examination Survey (n = 10,175) were analyzed using fully adjusted multiple linear regression models for associations between periodontitis and skeletal muscle mass index (kg/m^2) and combined handgrip strength (kg).

The mean age of the study cohort was 43 (±8.4) years and 49.4% of the participants were male. In total, 612 participants (32%) were determined to have periodontitis, of which 513 (26.8%) had non-severe (mild or moderate) periodontitis, and 99 (5.2%) had severe periodontitis. In unadjusted regression models, both non-severe and severe periodontitis were associated with SMMI ($ß_{non\text{-}severe}$ = 1.01, 95% CI 0.5; 1.52 and $ß_{severe}$ = 1.42, 95% CI 0.59; 2.25) but not with cHGS ($ß_{non\text{-}severe}$ = 1.83, 95% CI -0.38; 4.05 and $ß_{severe}$ = 2.03, 95% CI -4.64 ; 8.69). After adjusting for age, sex, education, body mass index, bone mineral density, diabetic status, education, total energy intake, total protein intake, and serum vitamin D2+D3, periodontitis

was associated with cHGS ($ß_{non-severe}$ = -2.81, 95% CI -4.7; -1.15 and $ß_{severe}$ = -2.73, 95% CI -6.31; 0.83).

The present study highlights the need of further prospective research to investigate the nature and direction of the relationship between periodontitis and sarcopenia indicators**.** Future studies can support the screening, prevention and clinical management of sarcopenia and periodontitis, and emphasize the interdisciplinary and complementary approach between the disciplines of geriatric medicine and periodontology.

5. References

1. Peres, M.A., et al., *Oral diseases: a global public health challenge.* Lancet, 2019. **394**(10194): p. 249-260.
2. Sanz, M., et al., *Periodontitis and cardiovascular diseases: Consensus report.* J Clin Periodontol, 2020. **47**(3): p. 268-288.
3. Lalla, E. and P.N. Papapanou, *Diabetes mellitus and periodontitis: a tale of two common interrelated diseases.* Nat Rev Endocrinol, 2011. **7**(12): p. 738-48.
4. Czesnikiewicz-Guzik, M., et al., *Causal association between periodontitis and hypertension: evidence from Mendelian randomization and a randomized controlled trial of non-surgical periodontal therapy.* Eur Heart J, 2019. **40**(42): p. 3459-3470.
5. Kapellas, K., et al., *Periodontal and chronic kidney disease association: A systematic review and meta-analysis.* Nephrology (Carlton), 2019. **24**(2): p. 202-212.
6. Hasturk, H. and A. Kantarci, *Activation and resolution of periodontal inflammation and its systemic impact.* Periodontol 2000, 2015. **69**(1): p. 255-73.
7. Cruz-Jentoft, A.J. and A.A. Sayer, *Sarcopenia.* Lancet, 2019. **393**(10191): p. 2636-2646.
8. Cruz-Jentoft, A.J., et al., *Sarcopenia: revised European consensus on definition and diagnosis.* Age Ageing, 2019. **48**(4): p. 601.
9. Bhasin, S., et al., *Sarcopenia Definition: The Position Statements of the Sarcopenia Definition and Outcomes Consortium.* J Am Geriatr Soc, 2020. **68**(7): p. 1410-1418.
10. Batsis, J.A., et al., *Sarcopenia, sarcopenic obesity and inflammation: Results from the 1999-2004 National Health and Nutrition Examination Survey.* Clin Nutr, 2016. **35**(6): p. 1472-1483.
11. Zhang, H., et al., *Association between Sarcopenia and Metabolic Syndrome in Middle-Aged and Older Non-Obese Adults: A Systematic Review and Meta-Analysis.* Nutrients, 2018. **10**(3).
12. Tuttle, C.S.L., L.A.N. Thang, and A.B. Maier, *Markers of inflammation and their association with muscle strength and mass: A systematic review and meta-analysis.* Ageing Res Rev, 2020. **64**: p. 101185.
13. Watt, R.G. and P.E. Petersen, *Periodontal health through public health--the case for oral health promotion.* Periodontol 2000, 2012. **60**(1): p. 147-55.
14. Hatta, K. and K. Ikebe, *Association between oral health and sarcopenia: A literature review.* J Prosthodont Res, 2021. **65**(2): p. 131-136.
15. Abe, T., et al., *Number of teeth and masticatory function are associated with sarcopenia and diabetes mellitus status among community-dwelling older adults: A Shimane CoHRE study.* PLoS One, 2021. **16**(6): p. e0252625.
16. Velázquez-Olmedo, L.B., et al., *Oral health condition and development of frailty over a 12-month period in community-dwelling older adults.* BMC Oral Health, 2021. **21**(1): p. 355.
17. Azzolino, D., et al., *Poor Oral Health as a Determinant of Malnutrition and Sarcopenia.* Nutrients, 2019. **11**(12).

18. Ramsay, S.E., et al., *Influence of Poor Oral Health on Physical Frailty: A Population-Based Cohort Study of Older British Men.* J Am Geriatr Soc, 2018. **66**(3): p. 473-479.
19. An, H.R. and J.S. Choi, *Association between Handgrip Strength and Periodontitis in Korean Adults Aged ≥30 Years: Data from the Korea National Health and Nutrition Examination Survey (2014-2015).* Int J Environ Res Public Health, 2022. **19**(17).
20. CDC, N. *Muscle Strength Manual. Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention.* 2013 30 November 2020]; Available from: https://wwwn.cdc.gov/nchs/data/nhanes/2013-2014/manuals/muscle_strength_2013.pdf.
21. CDC, N. *National Health and Nutrition Examination Survey 2013-2014 Data Documentation, Codebook, and Frequencies Dual-Energy X-ray Absorptiometry - Whole Body (DXX_H)*. 2020; Available from: https://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/DXX_H.htm#Eligible_Sample.
22. CDC, N. *National Health and Nutrition Examination Survey 2013-2014 Data Documentation, Codebook, and Frequencies Oral Health - Periodontal (OHXPER_H)*. 2016; Available from: https://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/OHXPER_H.htm#Eligible_Sample.
23. Eke, P.I., et al., *Periodontitis in US Adults: National Health and Nutrition Examination Survey 2009-2014.* J Am Dent Assoc, 2018. **149**(7): p. 576-588.e6.
24. Colloca, G., et al., *Muscoloskeletal aging, sarcopenia and cancer.* J Geriatr Oncol, 2019. **10**(3): p. 504-509.
25. Souza, V.A., et al., *Sarcopenia in patients with chronic kidney disease not yet on dialysis: Analysis of the prevalence and associated factors.* PLoS One, 2017. **12**(4): p. e0176230.
26. Sasaki, K.I., et al., *The prevalence of sarcopenia and subtypes in cardiovascular diseases, and a new diagnostic approach.* J Cardiol, 2020. **76**(3): p. 266-272.
27. Klein, G.L., *THE EFFECT OF GLUCOCORTICOIDS ON BONE AND MUSCLE.* Osteoporos Sarcopenia, 2015. **1**(1): p. 39-45.
28. CDC, N. *Oral Health Examination Manual. Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data, Hyattsville, State of Maryland, U.S. Department of Health and Human Services, Centers for Disease Control and Prevention*. 2013 30 November 2020]; Available from: https://wwwn.cdc.gov/nchs/data/nhanes/2013-2014/manuals/Oral_Health_Examiners.pdf.
29. Eke, P.I., et al., *Update of the case definitions for population-based surveillance of periodontitis.* J Periodontol, 2012. **83**(12): p. 1449-54.
30. Dye, B.A., et al., *Overview and quality assurance for the oral health component of the National Health and Nutrition Examination Survey (NHANES), 2011-2014.* BMC Oral Health, 2019. **19**(1): p. 95.
31. CDC, N. *Body Composition DXA Manual. Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention*. 2013 30 November 2020]; Available from: https://wwwn.cdc.gov/nchs/data/nhanes/2013-2014/manuals/2013_Body_Composition_DXA.pdf.
32. Levey, A.S., et al., *A new equation to estimate glomerular filtration rate.* Ann Intern Med, 2009. **150**(9): p. 604-12.
33. Foundation, N.K., *K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification.* Am J Kidney Dis, 2002. **39**(2 Suppl 1): p. S1-266.
34. Frencken, J.E., et al., *Global epidemiology of dental caries and severe periodontitis - a comprehensive review.* J Clin Periodontol, 2017. **44 Suppl 18**: p. S94-s105.
35. Zelig, R., et al., *Tooth Loss and Nutritional Status in Older Adults: A Systematic Review and Meta-analysis.* JDR Clin Trans Res, 2022. **7**(1): p. 4-15.
36. Cruz-Jentoft, A.J., et al., *Nutrition, frailty, and sarcopenia.* Aging Clin Exp Res, 2017. **29**(1): p. 43-48.

37. Palinkas, M., et al., *Alterations in masticatory cycle efficiency and bite force in individuals with periodontitis.* Int J Health Sci (Qassim), 2019. **13**(1): p. 25-29.
38. Johansson, A.S., K.G. Svensson, and M. Trulsson, *Impaired masticatory behavior in subjects with reduced periodontal tissue support.* J Periodontol, 2006. **77**(9): p. 1491-7.
39. Raj, I.S., S.R. Bird, and A.J. Shield, *Aging and the force–velocity relationship of muscles.* Experimental Gerontology, 2010. **45**(2): p. 81-90.
40. Xia, X., et al., *Nutrition mediates the relationship between number of teeth and sarcopenia: a pathway analysis.* BMC Geriatr, 2022. **22**(1): p. 649.
41. Nakamura, M., et al., *Association of Oral Hypofunction with Frailty, Sarcopenia, and Mild Cognitive Impairment: A Cross-Sectional Study of Community-Dwelling Japanese Older Adults.* J Clin Med, 2021. **10**(8).
42. Yun, J. and Y. Lee, *Association between oral health status and handgrip strength in older Korean adults.* Eur Geriatr Med, 2020. **11**(3): p. 459-464.
43. Eremenko, M., et al., *Cross-sectional association between physical strength, obesity, periodontitis and number of teeth in a general population.* J Clin Periodontol, 2016. **43**(5): p. 401-7.
44. Han, C.H. and J.H. Chung, *Association Between Sarcopenia and Tooth Loss.* Ann Geriatr Med Res, 2018. **22**(3): p. 145-150.
45. Leite, M.A., et al., *Experimental Periodontitis in the Potentialization of the Effects of Immobilism in the Skeletal Striated Muscle.* Inflammation, 2017. **40**(6): p. 2000-2011.
46. Kawamura, N., et al., *Effects of chronic Porphyromonas gingivalis lipopolysaccharide infusion on skeletal muscles in mice.* J Physiol Sci, 2019. **69**(3): p. 503-511.
47. Watanabe, K., et al., *Porphyromonas gingivalis impairs glucose uptake in skeletal muscle associated with altering gut microbiota.* Faseb j, 2021. **35**(2): p. e21171.
48. Velsko, I.M., et al., *Active invasion of oral and aortic tissues by Porphyromonas gingivalis in mice causally links periodontitis and atherosclerosis.* PLoS One, 2014. **9**(5): p. e97811.
49. Martinez-Martinez, R.E., et al., *Detection of periodontal bacterial DNA in serum and synovial fluid in refractory rheumatoid arthritis patients.* J Clin Periodontol, 2009. **36**(12): p. 1004-10.

5. Declaration of Own Contribution

I, Kübra Tuncel, hereby affirm that the sections on conceptualization, methodology (data acquisition from the NHANES database, data organization and statistical processing) and results (coefficients, confidence intervals, figures, and tables), and original manuscript drafting and editing are exclusively my responsibility and contribution.

Furthermore, I declare that I have correctly marked all of the data, the analyses, and the conclusions generated from data obtained in collaboration with other authors, and that I have correctly marked my own contribution and the contributions of other authors.

I declare that the current submitted and accepted publication complies with the guidelines of the ICMJE (International Committee of Medical Journal Editors; www.icmje.org) on authorship. In addition, I declare that I comply with the regulations of University Medical Center Hamburg-Eppendorf on ensuring good scientific practice.

6. Acknowledgements

First and foremost, I would like to express my greatest gratitude to Prof. Dr. Antonia Zapf for her tremendous support and belief in me, as well as Dr. Christian Wiessner for his insightful guidance and great support in the analysis and revision of my work. I also thank Prof. Dr. Alfonso J. Cruz-Jentoft, Prof. Dr. Gülistan Bahat and Dr. Tugba Erdogan for sharing their expertise in the conceptualization of the study from the geriatric medicine perspective.

I also would like to acknowledge the comments of Prof. Dr. Thomas Beikler, Dr. Ghazal Aarabi, Ms. Katrin Borof and Dr. Michael Nolde.

Finally, I thank myself for staying strong, for being dedicated and resilient, for not giving up despite the barriers and challenges occurred on my path towards receiving this degree.

Lebenslauf aus datenschutzrechtlichen Gründen nicht enthalten

8. Affidavit

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe.

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Unterschrift: