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Periodontitis Is Related to Exercise Capacity: Two Cross-sectional Studies

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Abstract

Although a potential link between periodontitis and cardiorespiratory fitness might provide a reasonable explanation for effects of tooth-related alterations seen on cardiometabolic diseases, evidence is currently limited. Thus, we investigated the association between clinically assessed periodontitis and cardiopulmonary exercise testing (CPET). Data from 2 independent cross-sectional population-based studies (5-y follow-up of the Study of Health in Pomerania [SHIP-1; *N* = 1,639] and SHIP-Trend-0 [*N* = 2,439]) were analyzed. Participants received a half-mouth periodontal examination, and teeth were counted. CPET was based on symptom limited-exercise tests on a bicycle ergometer. Associations of periodontitis parameters with CPET parameters were analyzed by confounder-adjusted multivariable linear regression. In the total sample, mean pocket probing depth (PPD), mean clinical attachment levels, and number of teeth were consistently associated with peak oxygen uptake (peakVO_2) and exercise duration in both studies, even after restriction to cardiorespiratory healthy participants. Statistically significant associations with oxygen uptake at anaerobic threshold (VO_2@AT), slope of the efficiency of ventilation in removing carbon dioxide, and peak oxygen pulse (V$\dot{E}$/VCO_2 slope) occurred. Further, interactions with age were identified, such that mainly older individuals with higher levels of periodontal disease severity were associated with lower peakVO_2. Restricted to never smokers, associations with mean clinical attachment levels and the number of teeth mostly diminished, while associations of mean PPD with peakVO_2, VO_2@AT, V$\dot{E}$/VCO_2 slope, and exercise duration in SHIP-1 and SHIP-Trend-0 were confirmed. In SHIP-1, mean peakVO_2 was 1,895 mL/min in participants with a mean PPD of 1.6 mm and 1,809 mL/min in participants with a mean PPD of 3.7 mm. To conclude, only mean PPD reflecting current disease severity was consistently linked to cardiorespiratory fitness in 2 cross-sectional samples of the general population. If confirmed in well-designed large-scale longitudinal studies, the association between periodontitis and cardiorespiratory fitness might provide a biologically plausible mechanism linking periodontitis with cardiometabolic diseases.

Keywords: chronic periodontitis, cardiopulmonary exercise testing, CPET, cross-sectional study, cardiorespiratory fitness, tooth loss

Introduction

Chronic periodontitis is a highly prevalent disease of tooth-supporting tissues (Kassebaum et al. 2014), leading to alveolar bone loss and, finally, tooth loss, if left untreated. It is also associated with low-grade systemic inflammation (Schenkein and Loos 2013) that is either directly induced via dislocation of periopathogenic bacteria into the bloodstream (Tomas et al. 2012), thereby provoking an immune response, or indirectly via increased levels of locally produced proinflammatory mediators (Hajishengallis 2015).

Cardiorespiratory fitness is defined as the ability of the cardiovascular and pulmonary system to deliver oxygen to sustain musculoskeletal function during exercise. Previous studies suggested that reduced levels of systemic inflammation markers are linked to improved cardiorespiratory fitness (Kuo et al. 2007; Lehnert et al. 2019). A potentially causal association between periodontitis and cardiorespiratory fitness would be of special interest, because it would also provide a possible mechanism linking periodontitis with cardiovascular diseases (Dietrich et al. 2017) and cardiovascular and all-cause mortality (Qi et al. 2020).

However, to our knowledge, there are only few studies assessing associations between periodontitis and cardiorespiratory fitness. One population-based cross-sectional study reported

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no relation of clinically assessed periodontal disease severity with maximum oxygen uptake (Thai et al. 2014). Few small-scaled studies used highly selected samples with limited validity and generalizability, reporting rather selective and inconclusive results (Akhter et al. 2008; Gay-Escoda et al. 2010; Oliveira et al. 2010; Eberhard et al. 2014; Hoppe et al. 2016). Because of this large evidence gap, well-designed large-scale population-based studies are needed.

We investigated the association of periodontal disease severity and the number of teeth with cardiopulmonary exercise capacity in 2 cross-sectional studies of the Studies of Health in Pomerania (SHIP-1 and SHIP-Trend-0). Importantly, this is the first study providing comprehensive data to characterize periodontal disease severity and cardiopulmonary fitness assessed through exercise testing.

Materials and Methods

Study Design

Analyses are based on data from 2 independent studies of the SHIP, conducted in northeast Germany. In the first study (SHIP-0), 6,267 eligible people were selected from population registries (John et al. 2001). Of those, 4,308 individuals were examined between 1997 and 2001 (68.8%). Between 2002 and 2006, all participants were reinvited for an examination follow-up (SHIP-1), in which 3,300 people took part (1,589 men and 1,711 women; 83.5% of all eligible people). Of those, 1,708 participants volunteered for cardiopulmonary exercise testing (CPET) (52.0%) (Koch et al. 2011).

For the second study (SHIP-Trend-0), a stratified random sample of 10,000 adults aged 20 to 79 y was randomly drawn from population registries (Volzke et al. 2011). Of 8,826 eligible people, 4,420 individuals participated (response 50.3%) between 2008 and 2012. In SHIP-Trend-0, 2,678 participants volunteered for CPET (60.6%).

Of 1,708 SHIP-1 participants and 2,678 SHIP-Trend-0 participants who underwent CPET, we excluded those with missing data in any of the variables considered, resulting in study population of 1,639 SHIP-1 participants and 2,439 SHIP-Trend-0 participants (see Appendix Fig. 1). For analyses of mean pocket probing depth (PPD), the study population was further reduced to 1,476 in SHIP-1 and 2,273 in SHIP-Trend-0. For analyses of mean clinical attachment levels (CALs), 1,411 SHIP-1 and 2,145 SHIP-Trend-0 participants were included.

All participants gave written informed consent, and both studies followed the recommendations of the Declaration of Helsinki and were approved by the Ethics Committee of the University of Greifswald (registration numbers III-UV-73/01 and BB-39/08a). The study was conducted and reported in accordance with STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.

Cardiopulmonary Exercise Testing

CPET was performed using a calibrated electromagnetically braked cycle ergometer. The following parameters were assessed: peak oxygen uptake (peakVO_2), oxygen uptake at anaerobic threshold (VO_2@AT), the minute ventilation changes as a function of the pulmonary carbon dioxide output ($V\dot{E}/VCO_2$ slope), peak oxygen pulse (O_2HRmax), and exercise duration (Glaser et al. 2010). Reference values for CPET parameters were reported in detail elsewhere (Koch et al. 2009). In short, in the reference population, CPET parameters varied widely and were dependent on age, sex, and body mass index (BMI). PeakVO_2 values were lower with higher age and higher BMI, and they were lower for females than for males, with 5th and 95th percentiles ranging broadly between 17 and 50 mL/min/kg. For VO_2@AT, the 95th percentile declined in an age-dependent manner, while the 5th percentile was neither dependent on age nor on sex or BMI. The 5th and 95th percentiles ranged between 9 and 32 mL/min/kg across all age groups. For detailed information on CPET measurements, as well as on covariate assessments and periodontal measurements, see the Appendix.

Statistical Analyses

Characteristics of the study population are expressed as median, 25th percentile, and 75th percentile (continuous data) or as absolute numbers and percentages (categorical data) stratified by study population. Distributional differences between SHIP-1 and SHIP-Trend-0 were analyses using χ^2 or Mann-Whitney *U* tests.

Multivariable analyses were performed separately for each study. Mean PPD, mean CAL, and number of teeth were associated with CPET parameters by using linear regression models with adjusting for age, sex, smoking status, alcohol consumption, physical activity, self-reported general health, type 2 diabetes, BMI, equivalent income, and time between the basic and the CPET examination (complementary examination with separate appointment).

Participants and nonparticipants of CPET differed regarding mean CAL, number of teeth, age, BMI, physical activity, and current smoking. To account for these differences, we applied inverse probability weights (IPWs). This procedure gives individuals from groups that are more likely to drop out a stronger weight in the analyses compared to individuals from groups with less dropouts. To calculate these weights, we applied 2 logistic regression models using SHIP-1 and SHIP-Trend-0 data with participation at CPET (yes/no) as the outcome and age, sex, education, smoking status, income, alcohol consumption, BMI, type 2 diabetes, hypertension, and history of cancer as explanatory variables. The inverse of the individual predictions derived from these models was used for weighting.

To account for possible nonlinear relationships between periodontal variable levels or any of the confounders with the respective outcome, multivariable fractional polynomials were tested (Royston and Sauerbrei 2008). Results were reported by adjusting means for specific quantiles of exposure variables (taken from SHIP-1) and *P* values. Interactions of the exposure variables with age were tested for the outcome peakVO_2.

In addition, sensitivity analyses were performed excluding 1) former and current smokers and 2) individuals with

Table 1. Characteristics of the 2 Cross-sectional Study Populations.

Characteristic	SHIP-1 ($n = 1,639$)	SHIP-Trend-0 ($n = 2,439$)	*P* Value
Age, y	57 (46, 68)	53 (41, 64)	<0.001
Males, yes	796 (48.6)	1,228 (50.4)	<0.001
Smoking status			<0.001
Never smokers	720 (43.9)	924 (37.9)	
Former smokers	528 (32.2)	969 (39.7)	
Current smokers	391 (23.9)	546 (22.4)	
Alcohol consumption, g/d	4.6 (1.3, 13.4)	3.9 (1.0, 11.4)	0.053
Physically active, yes[a]	—	1,781 (73.0)	
Physical activity according to Baecke score[a]	0 (0, 2.6)	—	
Body mass index, kg/m^2	27.3 (24.3, 30.7)	27.5 (24.6, 30.7)	0.35
Type 2 diabetes mellitus, yes	179 (10.9)	288 (11.0)	0.67
High-sensitive C-reactive protein, mg/L ($n = 1,634$/$n = 2,353$)	1.26 (0.62, 2.77)	1.22 (0.63, 2.61)	0.39
Self-reported diagnosed lung disease, yes	57 (3.5)	115 (4.7)	0.052
Myocardial infarction, yes	52 (3.2)	71 (2.9)	0.63
Heart surgery, yes	29 (1.8)	37 (1.5)	0.53
Arrhythmias of the heart, yes	250 (15.3)	305 (12.5)	0.001
Self-reported general health			0.10
Excellent	49 (3.0)	59 (2.4)	
Very good	322 (19.7)	535 (21.9)	
Good	1,051 (64.1)	1,492 (61.2)	
Less good	197 (12.0)	331 (13.6)	
Bad	20 (1.2)	22 (0.9)	
Equivalent income, €	1,184 (895, 1,550)	1,450 (1,025, 1,803)	<0.001
Mean pocket probing depth, mm	2.1 (1.8, 2.6)	2.4 (2.1, 2.8)	<0.001
Mean clinical attachment level, mm	1.9 (0.8, 3.1)	2.1 (1.3, 3.4)	<0.001
Number of teeth	22 (15, 26)	24 (18, 27)	<0.001
Time between basic examination and CPET, wk	2.6 (0.0, 10.7)	9.2 (7.3, 11.6)	0.003
peakVO_2, mL/min	1,857 (1,513, 2,346)	1,900 (1,500, 2,400)	0.17
peakVO_2, mL/min/kg	24.5 (20.4, 29.2)	23.9 (19.5, 29.0)	0.010
VO_2@AT, mL/min	1,050 (900, 1,280)	950 (800, 1,200)	<0.001
VÉ/VCO_2 slope	25 (22, 28)	27 (25, 30)	<0.001
O_2HRmax, mL/beat	12.9 (10.5, 15.7)	12.6 (10.3, 15.5)	0.36
Exercise duration, min	8.5 (7.0, 11.1)	9.2 (7.3, 11.6)	0.001

Data are presented as median (25th, 75th quantile) for continuous measurements and as absolute numbers (percentages) for categorical measurements; *P* values were retrieved from χ^2 or Mann-Whitney *U* tests.
CPET, cardiopulmonary exercise testing; O_2HRmax, peak oxygen pulse; PeakVO_2, peak oxygen uptake; SHIP, Study of Health in Pomerania; VÉ/VCO_2 slope, slope of the efficiency of ventilation in removing carbon dioxide; VO_2@AT, oxygen uptake at anaerobic threshold.
[a]Expressed continuously as Baecke score in SHIP-1 and categorical in SHIP-Trend-0.

self-reported diagnosed lung disease, previous myocardial infarction, heart surgery, or arrhythmias of the heart.

To assess a potential mediation of effects of mean PPD on CPET parameters by low-grade systemic inflammation, high-sensitive C-reactive protein (hsCRP) levels were added to fully adjusted models using the never-smoker subsample.

A $P < .05$ was considered statistically significant. All analyses were carried out using Stata/SE 16.0 (StataCorp).

Results

Participant Characteristics

SHIP-1 participants were on average 4 y older than SHIP-Trend-0 participants (Table 1). Mean PPD and number of teeth were slightly higher in SHIP-Trend-0 than in SHIP-1. CPET parameters were comparable between SHIP-1 and SHIP-Trend-0 except for exercise duration, which was on average half a minute longer in SHIP-Trend-0.

Associations with Pocket Probing Depth

In multivariable linear regression, mean PPD was inversely associated with peakVO_2, VO_2@AT, and exercise duration in SHIP-1 and SHIP-Trend-0 (Table 2 and Appendix Fig. 2). Specifically, mean peakVO_2 was highest (2,052 mL/min and 2,031 mL/min) in participants with a mean PPD of 1.6 mm (5th quantile) and lowest (1,892 mL/min and 1,927 mL/min) in participants with a mean PPD of 3.7 mm (95th quantile) in SHIP-1 and SHIP-Trend-0. Mean exercise duration was highest (9.4 min and 9.9 min) in participants with a mean PPD of 1.6 mm (5th quantile) and lowest (8.7 min and 9.2 min) in participants with a mean PPD of 3.7 mm (95th quantile) using SHIP-1 and SHIP-Trend-0. An association of mean PPD with

Table 2. Cross-sectional Associations between Mean Pocket Probing Depth and Parameters from the Cardiopulmonary Exercise Testing Using Data from SHIP-1 and SHIP-Trend-0.

	Mean Pocket Probing Depth, mm						
Characteristic	1.6 (Q5)	1.8 (Q25)	2.1 (Q50)	2.6 (Q75)	3.2 (Q90)	3.7 (Q95)	*P* Value
$PeakVO_2$, mL/min							
SHIP-1	2,052 (2,016, 2,087)	2,011 (1,987, 2,034)	1,969 (1,951, 1,988)	1,930 (1,906, 1,953)	1,905 (1,874, 1,935)	1,892 (1,858, 1,926)	<0.001
SHIP-Trend-0	2,031 (2,002, 2,060)	2,021 (1,996, 2,047)	2,006 (1,986, 2,027)	1,982 (1,965, 1,998)	1,952 (1,931, 1,973)	1,927 (1,897, 1,957)	<0.001
$PeakVO_2$, mL/min/kg							
SHIP-1	26.4 (25.9, 26.9)	25.8 (25.5, 26.1)	25.1 (24.9, 25.4)	24.5 (24.2, 24.8)	24.1 (23.7, 24.5)	23.9 (23.5, 24.3)	<0.001
SHIP-Trend-0	25.6 (25.2, 26.0)	25.4 (25.1, 25.8)	25.2 (24.9, 25.5)	24.8 (24.6, 25.0)	24.3 (24.0, 24.6)	23.9 (23.5, 24.3)	<0.001
VO_2@AT, mL/min							
SHIP-1	1,124 (1,106, 1,141)	1,120 (1,104, 1,135)	1,114 (1,101, 1,127)	1,105 (1,092, 1,117)	1,093 (1,076, 1,111)	1,084 (1,060, 1,108)	0.02
SHIP-Trend-0	1,015 (1,000, 1,031)	1,012 (999, 1,026)	1,008 (997, 1,019)	1,001 (992, 1,010)	992 (980, 1,003)	985 (968, 1,001)	0.02
VÉ/VCO_2 slope							
SHIP-1	25.30 (25.01, 25.59)	25.34 (25.09, 25.59)	25.39 (25.18, 25.61)	25.49 (25.27, 25.71)	25.60 (25.27, 25.92)	25.69 (25.25, 26.13)	0.20
SHIP-Trend-0	26.88 (26.62, 27.13)	26.94 (26.72, 27.16)	27.03 (26.86, 27.21)	27.19 (27.04, 27.33)	27.37 (27.17, 27.57)	27.53 (27.24, 27.81)	0.006
O_2HRmax, mL/beat							
SHIP-1	13.41 (13.22, 13.60)	13.38 (13.21, 13.54)	13.32 (13.19, 13.46)	13.24 (13.11, 13.37)	13.14 (12.94, 13.33)	13.05 (12.78, 13.32)	0.07
SHIP-Trend-0	13.16 (12.97, 13.34)	13.12 (12.95, 13.28)	13.05 (12.92, 13.18)	12.95 (12.85, 13.05)	12.83 (12.69, 12.97)	12.73 (12.53, 12.92)	0.009
Exercise duration, min							
SHIP-1	9.4 (9.2, 9.5)	9.2 (9.1, 9.3)	9.0 (8.9, 9.1)	8.8 (8.7, 9.0)	8.7 (8.6, 8.9)	8.7 (8.5, 8.9)	<0.001
SHIP-Trend-0	9.9 (9.7, 10.0)	9.8 (9.7, 9.9)	9.7 (9.6, 9.8)	9.6 (9.5, 9.6)	9.4 (9.3, 9.5)	9.2 (9.1, 9.4)	<0.001

Data are expressed as adjusted means with 95% confidence intervals derived from multivariable linear regression models adjusted for age, sex, smoking status, alcohol consumption, physical activity, self-reported general health, type 2 diabetes mellitus, body mass index, equivalent income, and time between basic and spiroergometry examinations.
O_2HRmax, peak oxygen pulse; $PeakVO_2$, peak oxygen uptake; Q, quantile; SHIP, Study of Health in Pomerania; VÉ/VCO_2 slope, slope of the efficiency of ventilation in removing carbon dioxide; VO_2@AT, oxygen uptake at anaerobic threshold.

VÉ/VCO_2 slope and O_2HRmax was only detected in SHIP-Trend-0.

Associations with Clinical Attachment Levels

Mean CAL was inversely associated with $peakVO_2$ and exercise duration in both studies (Table 3). Associations with VO_2@AT and O_2HRmax occurred only in SHIP-1.

Associations with the Number of Teeth

The number of teeth was positively associated with $peakVO_2$ and exercise duration in both studies (Table 4). Only in SHIP-1, the number of teeth was associated with VO_2@AT and VÉ/VCO_2 slope.

Interactions with Age

In SHIP-Trend-0, but not in SHIP-1, we detected a significant interaction of mean PPD ($P = .03$) and mean CAL ($P < .001$) with age on $peakVO_2$ (Fig.). While in participants younger than 50 y, no statistically significant associations of mean PPD or mean CAL with $peakVO_2$ were observed, participants older than 50 y had lower $peakVO_2$ values with increasing mean PPD. In SHIP-1, we found a statistically significant interaction of number of teeth and age on $peakVO_2$ ($P = .007$), which was not detected in SHIP-Trend-0 ($P = .50$). According to the interaction in SHIP-1, the number of teeth was positively associated with $peakVO_2$ only in participants aged >60 y.

Sensitivity Analyses

The results for a restriction to never smokers are shown in Appendix Tables 2–5. Focusing on effect estimates (Appendix Table 5), associations of mean PPD with $peakVO_2$ (without and with consideration of weight), VO_2@AT, VÉ/VCO_2 slope, and exercise duration in SHIP-1 and SHIP-Trend-0 were consistent, although some effect estimates were reduced and partly associations turned insignificant. For instance, in SHIP-1, mean $peakVO_2$ was 1,895 mL/min in participants with a mean

Table 3. Cross-sectional Associations between Mean Clinical Attachment Levels and Parameters from the Cardiopulmonary Exercise Testing Using Data from SHIP-1 and SHIP-Trend-0.

	Mean Clinical Attachment Level, mm						
Characteristic	0.1 (Q5)	0.8 (Q25)	1.9 (Q50)	3.1 (Q75)	4.6 (Q90)	5.5 (Q95)	*P* Value
$PeakVO_2$, mL/min							
SHIP-1	2,045 (2,010, 2,080)	2,025 (1,998, 2,053)	1,995 (1,975, 2,014)	1,961 (1,940, 1,982)	1,919 (1,884, 1,955)	1,894 (1,848, 1,941)	<0.001
SHIP-Trend-0	2,033 (2,012, 2,055)	2,032 (2,011, 2,053)	2,023 (2,004, 2,042)	2,007 (1,990, 2,024)	1,974 (1,952, 1,998)	1,950 (1,917, 1,982)	<0.001
$PeakVO_2$, mL/min/kg							
SHIP-1	26.1 (25.6, 26.5)	25.8 (25.4, 26.1)	25.4 (25.1, 25.7)	25.0 (24.7, 25.2)	24.4 (24.1, 24.9)	24.1 (23.6, 24.7)	<0.001
SHIP-Trend-0	25.6 (25.2, 26.1)	25.5 (25.1, 25.9)	25.3 (25.0, 25.5)	25.0 (24.8, 25.3)	24.7 (24.3, 25.2)	24.6 (24.0, 25.1)	0.018
VO_2@AT, mL/min							
SHIP-1	1,135 (1,111, 1,159)	1,129 (1,110, 1,148)	1,119 (1,106, 1,132)	1,108 (1,094, 1,123)	1,095 (1,071, 1,119)	1,087 (1,056, 1,118)	0.049
SHIP-Trend-0	1,013 (994, 1,032)	1,012 (997, 1,027)	1,010 (1,000, 1,020)	1,008 (998, 1,018)	1,006 (989, 1,023)	1,004 (982, 1,027)	0.64
$VÉ/VCO_2$ slope							
SHIP-1	25.02 (24.65, 25.40)	25.12 (24.82, 25.42)	25.27 (25.06, 25.48)	25.44 (25.19, 25.68)	25.64 (25.24, 26.05)	25.76 (25.24, 26.29)	0.07
SHIP-Trend-0	26.81 (26.51, 27.11)	26.88 (26.64, 27.12)	27.00 (26.84, 27.16)	27.12 (26.96, 27.28)	27.28 (27.00, 27.55)	27.37 (27.01, 27.73)	0.07
O_2HRmax, mL/beat							
SHIP-1	13.52 (13.28, 13.77)	13.45 (13.25, 13.64)	13.33 (13.20, 13.47)	13.21 (13.08, 13.34)	13.05 (12.83, 13.28)	12.96 (12.67, 13.25)	0.02
SHIP-Trend-0	13.14 (12.92, 13.37)	13.11 (12.93, 13.28)	13.05 (12.93, 13.16)	12.98 (12.86, 13.10)	12.90 (12.69, 13.10)	12.85 (12.58, 13.11)	0.20
Exercise duration, min							
SHIP-1	9.3 (9.2, 9.5)	9.3 (9.1, 9.4)	9.1 (9.0, 9.2)	9.0 (8.9, 9.1)	8.8 (8.7, 9.0)	8.7 (8.5, 8.9)	<0.001
SHIP-Trend-0	10.1 (9.9, 10.2)	10.0 (9.8, 10.1)	9.8 (9.7, 9.9)	9.6 (9.5, 9.7)	9.4 (9.2, 9.5)	9.2 (9.1, 9.4)	<0.001

Data are expressed as adjusted means + confidence interval derived from multivariable linear regression models adjusted for age, sex, smoking status, alcohol consumption, physical activity, self-reported general health, type 2 diabetes mellitus, body mass index, equivalent income, and time between basic and spiroergometry examinations.
O_2HRmax, peak oxygen pulse; $PeakVO_2$, peak oxygen uptake; Q, quantile; SHIP, Study of Health in Pomerania; $VÉ/VCO_2$ slope, slope of the efficiency of ventilation in removing carbon dioxide; VO_2@AT, oxygen uptake at anaerobic threshold.

PPD of 1.6 mm (5th quantile) and 1,809 mL/min in participants with a mean PPD of 3.5 mm (95th quantile). Analogously, mean exercise duration was 8.9 min in participants with a mean PPD of 1.6 mm and 8.3 min in participants with a mean PPD of 3.5 mm. Associations with mean CAL and the number of teeth mostly diminished.

Furthermore, we excluded 338 SHIP-1 participants and 459 SHIP-Trend-0 participants with self-reported diagnosed lung disease, previous myocardial infarction, heart surgery, or cardiac arrhythmias (Appendix Tables 6–9). Results did not change essentially for the outcomes of $peakVO_2$, $VÉ/VCO_2$ slope, and exercise duration in comparison to the findings of the main analyses, with even stronger effects found in SHIP-Trend-0. For VO_2@AT and O_2HRmax, effect estimates were in most cases lower than in main analyses and insignificant. In contrast to the main analyses, mean CAL was positively associated with $VÉ/VCO_2$ slope in the healthy subpopulation of SHIP-1.

Mediation via Low-Grade Systemic Inflammation

We included hs-CRP in fully adjusted models using the never-smoker subsamples. Effect estimates for mean PPD on $peakVO_2$ and exercise duration were not attenuated after inclusion of hsCRP levels (Appendix Table 10).

Discussion

In the 2 cross-sectional population-based studies of SHIP-1 and SHIP-Trend-0, only mean PPD reflecting current periodontal disease severity was consistently linked to cardiorespiratory fitness across main and sensitivity analyses. Although mean PPD, mean CAL, and the number of teeth were consistently associated with $peakVO_2$, $VÉ/VCO_2$ slope, and exercise duration in both studies in the total sample and in cardiorespiratory healthy participants, associations with $peakVO_2$ and exercise duration were only confirmed for mean PPD using

Table 4. Cross-sectional Associations between Number of Teeth and Parameters from the Cardiopulmonary Exercise Testing Using Data from SHIP-1 and SHIP-Trend-0.

	Number of Teeth						
Characteristic	0 (Minimum)	5 (Q12.5)	15 (Q25)	22 (Q50)	26 (Q75)	28 (Maximum)	*P* Value
$PeakVO_2$, mL/min							
SHIP-1	1,845 (1,799, 1,892)	1,863 (1,827, 1,899)	1,898 (1,880, 1,917)	1,923 (1,904, 1,943)	1,937 (1,912, 1,963)	1,945 (1,915, 1,974)	0.004
SHIP-Trend-0	1,904 (1,855, 1,953)	1,919 (1,880, 1,957)	1,947 (1,927, 1,967)	1,967 (1,951, 1,984)	1,979 (1,959, 1,999)	1,985 (1,961, 2,008)	0.01
$PeakVO_2$, mL/min/kg							
SHIP-1	23.4 (22.8, 24.0)	23.6 (23.2, 24.1)	24.2 (24.0, 24.4)	24.6 (24.3, 24.8)	24.8 (24.5, 25.1)	24.9 (24.5, 25.3)	0.001
SHIP-Trend-0	23.9 (23.4, 24.5)	24.1 (23.6, 24.5)	24.3 (24.1, 24.6)	24.5 (24.3, 24.7)	24.6 (24.4, 24.9)	24.7 (24.4, 25.0)	0.047
VO_2@AT, mL/min							
SHIP-1	1,061 (1,032, 1,090)	1,069 (1,047, 1,091)	1,085 (1,073, 1,097)	1,096 (1,083, 1,109)	1,103 (1,086, 1,120)	1,106 (1,087, 1,125)	0.04
SHIP-Trend-0	986 (960, 1,013)	989 (968, 1,010)	994 (984, 1,005)	998 (989, 1,007)	1,000 (989, 1,011)	1,001 (988, 1,014)	0.41
$VÉ/VCO_2$ slope							
SHIP-1	26.47 (25.84, 27.11)	26.27 (25.79, 26.75)	25.86 (25.63, 26.09)	25.58 (25.35, 25.80)	25.41 (25.11, 25.72)	25.33 (24.98, 25.69)	0.01
SHIP-Trend-0	27.71 (27.24, 28.18)	27.61 (27.24, 27.97)	27.41 (27.22, 27.59)	27.26 (27.12, 27.41)	27.18 (27.00, 27.37)	27.14 (26.93, 27.36)	0.07
O_2HRmax, mL/beat							
SHIP-1	13.20 (12.79, 13.60)	13.19 (12.89, 13.50)	13.19 (13.05, 13.33)	13.19 (13.05, 13.33)	13.19 (12.99, 13.39)	13.19 (12.95, 13.42)	0.98
SHIP-Trend-0	13.04 (12.70, 13.38)	13.03 (12.76, 13.29)	13.00 (12.87, 13.13)	12.98 (12.87, 13.08)	12.97 (12.83, 13.11)	12.96 (12.80, 13.13)	0.74
Exercise duration, min							
SHIP-1	8.3 (8.1, 8.5)	8.4 (8.2, 8.6)	8.6 (8.5, 8.7)	8.7 (8.6, 8.8)	8.8 (8.7, 8.9)	8.8 (8.7, 9.0)	0.001
SHIP-Trend-0	8.9 (8.7, 9.2)	9.0 (8.9, 9.2)	9.3 (9.2, 9.4)	9.5 (9.4, 9.5)	9.6 (9.5, 9.7)	9.6 (9.5, 9.7)	<0.001

Data are expressed as adjusted means + confidence interval derived from multivariable linear regression models adjusted for age, sex, smoking status, alcohol consumption, physical activity, self-reported general health, type 2 diabetes mellitus, body mass index, equivalent income and time between basic and spiroergometry examinations.

O_2HRmax, peak oxygen pulse; $PeakVO_2$, peak oxygen uptake; Q, quantile; SHIP, Study of Health in Pomerania; $VÉ/VCO_2$ slope, slope of the efficiency of ventilation in removing carbon dioxide; VO_2@AT, oxygen uptake at anaerobic threshold.

data from never smokers of SHIP-1. For never smokers of SHIP-Trend-0, effect estimates were considerably diluted, turning results completely insignificant.

We conducted several sensitivity analyses restricting participants to either never smokers (completely ruling out residual confounding by smoking as the major confounder) or cardiorespiratory healthy participants, thereby (theoretically) increasing homogeneity and validity (Rothman et al. 2008). In line with this expectation, effect estimates in most cases indicated stronger effects in cardiorespiratory healthy participants of SHIP-Trend-0, while in SHIP-1, effects were slightly diluted (but still statistically significant). Contrary to that expectation, effect estimates in never smokers were mostly diluted, and only in SHIP-1, for which selection bias cannot be ruled out completely (despite application of IPWs), associations of $peakVO_2$ and exercise duration with mean PPD remained statistically significant with effect estimates comparable to analyses in the total sample. Obviously, restriction to certain subgroups did not necessarily result in clearer effects. However, the fact that in never smokers statistically significant effects were restricted to those of mean PPD might be discussed in favor of the overall hypothesis. In contrast to CAL and the number of teeth, which reflect periodontal disease history, PPD reflects soft tissue changes and periodontal inflammation and is thus a measure of current disease severity. In a previous study using SHIP data (Gocke et al. 2014), mean PPD showed stronger long-term associations with markers of systemic inflammation (fibrinogen and leukocyte counts) than mean CAL; systemic inflammation might be considered a potential pathway linking periodontitis with cardiorespiratory fitness. Thus, it seems to be plausible that in this homogeneous subgroup of never smokers, associations with cardiorespiratory variables were restricted to those with mean PPD. Notwithstanding, results should be cautiously interpreted, and definitive conclusions in favor of an association with cardiorespiratory fitness cannot be made.

At first glance, the current (although very limited) literature did not seem to support a relationship between periodontitis and cardiopulmonary fitness (Akhter et al. 2008; Gay-Escoda et al. 2010; Oliveira et al. 2010; Eberhard et al. 2014; Thai et al. 2014; Hoppe et al. 2016). Thai et al. (2014) used data from the National Health and Nutrition Examination Survey

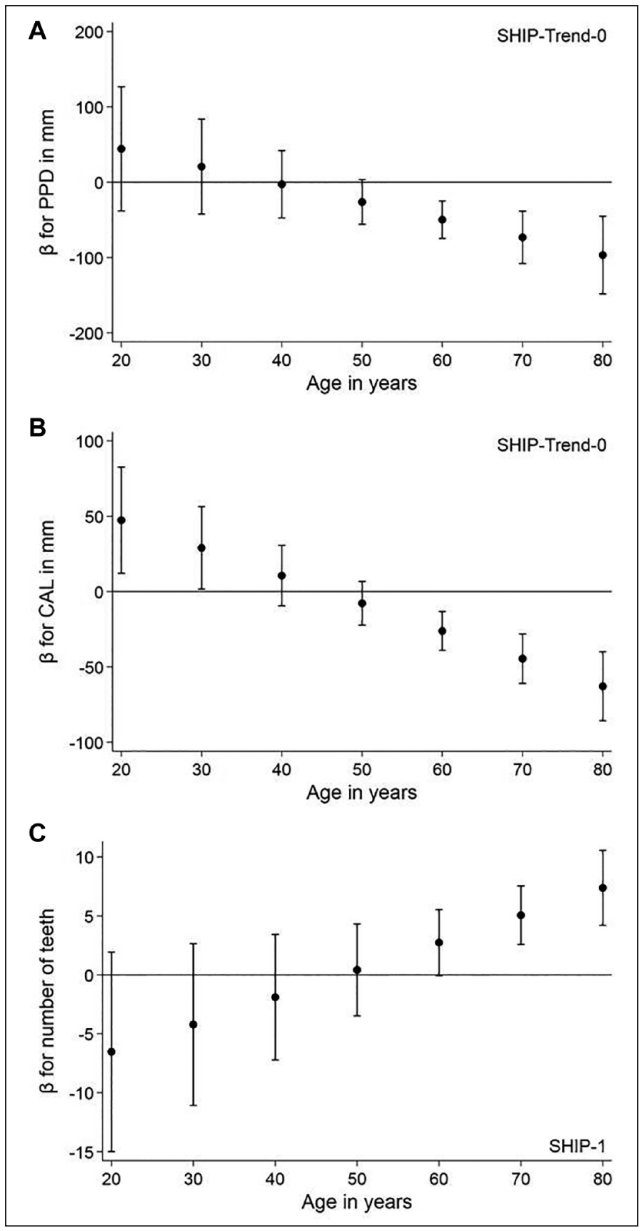

Figure. Statistically significant interactions of periodontal variables with age on peakVO_2. Dots represent β estimates for associations of the respective periodontal variables with peakVO_2 for different ages derived from the interaction model.

(NHANES) 1999 to 2004, reporting that periodontitis was not related to estimated VO_2max in a sample of generally healthy adults. While for participants with moderate/severe periodontitis (defined according to Center for Disease Control and Prevention/American Academy of Periodontology criteria), the odds of reduced eVO_2 max was halved compared to healthy participants (odds ratio = 0.48; 95% confidence interval: 0.23–0.98), no statistically significant associations with eVO_2max were observed for continuous and quantile parameterizations of mean CAL and mean PPD. However, due to implementation of a half-mouth protocol with 2 or 3 sites being probed, classification bias might have occurred when identifying periodontally diseased participants, and estimated effects were potentially biased toward the null (Akinkugbe et al. 2015). Furthermore, restriction to younger persons (20–49 y) might have obfuscated any relations. Indeed, in our study, associations with peakVO_2 were partly more pronounced in participants older than 50 y. Eberhard et al. (2014) included 72 otherwise healthy men aged 45 to 65 y being physically inactive and working in a medical institution, representing a selected sample. A full-mouth recording protocol was applied for periodontal examinations, thereby reducing classification bias for periodontitis. However, only 1 single periodontitis case definition was correlated to peakVO_2, using prediction models rather than etiological models. Thus, various methodological issues comprising inappropriate confounder adjustment, small sample sizes, disuse of extent or severity estimates of periodontitis, and study design issues complicate well-founded conclusions. At least partially, these constrictions also apply to the remaining studies (Akhter et al. 2008; Gay-Escoda et al. 2010; Oliveira et al. 2010; Hoppe et al. 2016). In summary, evidence from previous studies is very limited and inconclusive.

Overall, associations with mean PPD were most convincing for VO_2peak and exercise duration. This might be explained by the fact that assessments of VO_2peak and exercise duration are observer independent, resulting in high measurement accuracy and validity. Nevertheless, exercise duration is highly dependent on the chosen examination protocol. Inconsistent results for remaining CPET parameters might be explained by 1) high observer variabilities (Kaczmarek et al. 2019); 2) the fact that they were derived from other parameters, each presenting with potentially high variability themselves; and 3) the fact that all of them are affected by multiple risk factors (Glaser et al. 2010; Roman et al. 2016). Scattered differences in sizes of effect estimates between SHIP-1 and SHIP-Trend-0 might also be explained by different definitions of confounders (i.e., Baecke score in SHIP-1 versus physically active in SHIP-Trend-0) or varying impacts of residual confounding on effect estimates within both studies. Furthermore, SHIP-1 participants were older, were more often never smokers, had a lower periodontal disease severity, and had partly worse CPET levels compared to SHIP-Trend-0 participants. Also, sample size was considerably lower in SHIP-1, thereby reducing statistical power. However, nonsignificant results were evenly distributed to both studies, making explanations unfeasible.

Although we showed consistent cross-sectional associations of mean PPD with peakVO_2 and exercise duration in total and subgroup samples, effects were probably not clinically relevant. Variation in peakVO_2 across levels of periodontal measures was low, with mean differences in peakVO_2 between participants with highest versus lowest levels of periodontal disease equaling about 2.0 mL/min/kg. However, an increase in peakVO_2 of at least 3.5 mL/min/kg (equaling 1 metabolic equivalent of task [MET]) is needed to decrease all-cause mortality by 12% to 17% (Myers et al. 2002; Gulati et al. 2003). Thus, it is also unclear whether periodontal therapy would have clinically meaningful effects on cardiopulmonary function.

Nevertheless, it has already been shown that periodontal therapy has beneficial effects on systemic inflammation (Demmer et al. 2013), various biomarkers of vascular health,

and surrogate measures of cardiovascular diseases (Orlandi et al. 2020). Thus, current evidence supports the notion that it would be useful to perform large-scaled randomized controlled trials investigating the effect of periodontal treatment on cardiorespiratory function. In particular, considering that periodontal therapy is cost-effective and, in most cases, involves only nonsurgical treatment and improvement of oral hygiene at home, evidence on systemic effects of periodontal treatments should be extended.

A further aspect deserves consideration. We detected statistically significant interactions of periodontitis variables with age on peakVO_2, such that associations with peakVO_2 were only seen in elderly SHIP-Trend-0 participants. Here, the concept of "immunosenescence" (Hajishengallis 2010) provides a plausible explanation. Aging leads to an alteration of several immune functions, modulating not only bone healing but also inflammation, resulting in higher systemic levels of inflammation markers (Hajishengallis 2010). These, in turn, might mediate effects on CPET.

Causal pathways linking periodontal infections with cardiorespiratory fitness may involve low-grade systemic inflammation (Kuo et al. 2007; Schenkein and Loos 2013; Lehnert et al. 2019). Using SHIP data (Lehnert et al. 2019), an inverse association between resting inflammatory status and cardiorespiratory fitness was already reported. Alongside, systemic inflammation has been linked to spirometric lung volumes (Rasmussen et al. 2009), which are in turn associated with decreased exercise capacity (Benck et al. 2017). When we added hsCRP to fully adjusted models of mean PPD using never-smoker subsamples (Appendix Table 10), changes in effect estimates were negligible, implicating a minor role of hsCRP as a mediator of the associations with peakVO_2 and exercise duration. Thus, mediating contributions of hsCRP to associations between mean PPD and CPET parameters might, if present, not be consistently detectable in this study. However, it should also be noted that CRP is an unspecific inflammation marker as it is increased in various infectious and noninfectious diseases. Thus, CRP might as well be a proxy for various processes associated with inflammation, such as nutrition, body fat composition, and also smoking intensity. These biological and behavioral factors might be considered potential confounders of the association between periodontitis and cardiorespiratory fitness. Thus, fully adjusted models including hsCRP might be also be discussed as better approximating "true" and unbiased effect estimates. In this case, associations of mean PPD with peakVO_2 and exercise duration were consistent in effect size after adjustment for hsCRP.

The following strengths of our study merit special consideration. First, SHIP has a population-based setting with a large number of individuals in both sexes and a wide age range (25–88 y in SHIP-1 and 20–83 y in SHIP-Trend-0). Second, all examination methods are well standardized, and dental examiners were thoroughly trained and certified. These comprehensive quality control measures resulted in high to moderate intra- and interrater correlations. Third, use of masks for CPET appears to be a further strength (Glaser et al. 2013).

The following limitations deserve consideration. First, as cause and effect cannot be addressed by cross-sectional studies, any inferences about causality cannot be made. To suggest a cause-and-effect relationship, large-scaled longitudinal studies are needed. Second, the partial recording protocol probably led to an underestimation of periodontal disease severity estimates, thereby resulting in the dilution of effect estimates toward the null (Akinkugbe et al. 2015). Third, selection bias might have been a relevant issue for analyses in SHIP-1, that is, CPET participants might differ from respective nonparticipants with regard to certain subject characteristics affecting either the exposure or the outcome. In this regard, IPWs provided a valuable tool to adequately handle selection bias.

In summary, comprehensive analyses, including restrictions to never smokers and to cardiorespiratory healthy participants, indicated consistent associations of mean PPD with decreased cardiorespiratory fitness in 2 general populations. Nevertheless, well-designed large-scaled prospective studies are demanded.

Author Contributions

B. Holtfreter, contributed to data analysis and interpretation, drafted the manuscript; B. Stubbe, J. Trabandt, contributed to data interpretation, critically revised the manuscript; S. Gläser, contributed to design and data interpretation, critically revised the manuscript; H. Völzke, contributed to design and data acquisition, critically revised the manuscript; R. Ewert, T. Kocher, contributed to conception, design, and data acquisition, critically revised the manuscript; T. Ittermann, contributed to design, data analysis, and interpretation, drafted and critically revised the manuscript; C. Schäper, contributed to design, critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

Declaration of Conflicting Interests

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