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Periodontitis is related to lung volumes and airflow limitation: a cross-sectional study

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ABSTRACT This study aimed to assess the potential association of periodontal diseases with lung volumes and airflow limitation in a general adult population.

Based on a representative population sample of the Study of Health in Pomerania (SHIP), 1463 subjects aged 25–86 years were included. Periodontal status was assessed by clinical attachment loss (CAL), probing depth and number of missing teeth. Lung function was measured using spirometry, body plethysmography and diffusing capacity of the lung for carbon monoxide. Linear regression models using fractional polynomials were used to assess associations between periodontal disease and lung function. Fibrinogen and high-sensitivity C-reactive protein (hs-CRP) were evaluated as potential intermediate factors.

After full adjustment for potential confounders mean CAL was significantly associated with variables of mobile dynamic and static lung volumes, airflow limitation and hyperinflation ($p<0.05$). Including fibrinogen and hs-CRP did not change coefficients of mean CAL; associations remained statistically significant. Mean CAL was not associated with total lung capacity and diffusing capacity of the lung for carbon monoxide. Associations were confirmed for mean probing depth, extent measures of CAL/probing depth and number of missing teeth.

Periodontal disease was significantly associated with reduced lung volumes and airflow limitation in this general adult population sample. Systemic inflammation did not provide a mechanism linking both diseases.

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Introduction

Periodontitis is one of the most prevalent human infections. The majority of adults suffer from some degree of periodontitis, with 15–20% of the adult population having severe periodontal disease [1, 2]. Periodontitis is an oral bacterial infection that results in gingival inflammation, breakdown of the supporting connective tissue, pocket formation between the gingiva and the tooth, destruction of alveolar bone and eventually exfoliation of teeth [3]. While probing depth reflects current disease status, clinical attachment loss (CAL) equals the reduction in the supporting connective tissue of the tooth and reflects cumulative disease experience.

To date, few studies have investigated the relationship between periodontitis [4–14] or oral hygiene [12, 13, 15] and respiratory diseases, although common causes might exist. Both diseases have been related to systemic inflammation [16–20]. Individuals with airflow limitation demonstrate airway and systemic inflammation, depending on the severity of lung disease, physical fitness and potential comorbidities [17–19]. Besides smoking [21] and obesity [22], risk factors for lung function decline and airflow limitation are ageing and pulmonary diseases, such as chronic obstructive pulmonary disease (COPD) [23].

Merely on the basis of a few spirometry parameters, some cross-sectional and case–control studies reported significant associations of periodontal disease with history of COPD and lung function decline [4–8, 12]. Furthermore, periodontal disease has been related to the longitudinal decline in spirometric lung volumes [9, 10, 14]. If periodontal disease causally contributed to a declining lung function as an independent risk factor, it would provide a rationale to consider periodontal prevention and treatment as therapeutic option to target a decreasing lung function, or at least to support dedicated treatments of pneumological diseases. However, the mechanisms behind these observations still remain unclear and controversial.

One theoretical pathway linking both diseases comprehends the aspiration of saliva harbouring oral bacteria into the lung [24]. Another pathway may be upregulated inflammation in the lungs by systemic low-grade inflammation induced by periodontal diseases [16]. Systemic inflammation markers have also been associated with reduced spirometric lung volumes [17–20]. So far, the interrelationship between periodontal disease, inflammation and lung function remains poorly understood.

Thus, the major aim of this study was to further clarify the association between periodontal disease and airflow limitation, lung volumes and diffusing capacity, based on a highly standardised setting of comprehensive lung function test parameters within the population-based Study of Health in Pomerania (SHIP). We further evaluated 1) the strength of confounding by smoking, height and educational status and 2) the role of systemic inflammation as an intermediate factor.

Material and methods

Study population

SHIP is a prospective cohort study in the northeast of Germany. The study was approved by the local institutional review board by the ethics committee. Details of the study design are given elsewhere [25, 26]. Of 7008 randomly selected adults aged 20–79 years with German citizenship, 6262 were invited to participate. Of those, 4308 (68.8%) individuals participated in the baseline study (SHIP-0, 1997–2001). Follow-up examinations (SHIP-1) were performed 5 years later, including 3300 subjects aged 25–85 years [27]. Of these, 1809 subjects (885 males and 924 females) participated in a substudy including body plethysmography, spirometry, helium dilution and diffusing capacity of the lung for carbon monoxide (T_{LCO}) (fig. 1). The median (interquartile range) time interval between core examination of SHIP-1 and lung function examination was 18 (0–74) days. We excluded those with missing lung function data (n=9), missing dental examinations (n=8), regular intake of nonsteroidal antirheumatics or steroids (n=274), high-sensitivity C-reactive protein (hs-CRP) >10 $mg \cdot L^{-1}$ (n=42) indicating acute and active infection, systemic inflammatory processes or physical trauma [28], or missing confounder data (n=13). For the remaining 1463 individuals with complete data, the number of missing teeth was available in all subjects, probing depth data were recorded in 1327 subjects and attachment loss data were available in 1268 subjects (fig. 1). In total, data from 1268 participants were evaluated for our main analyses.

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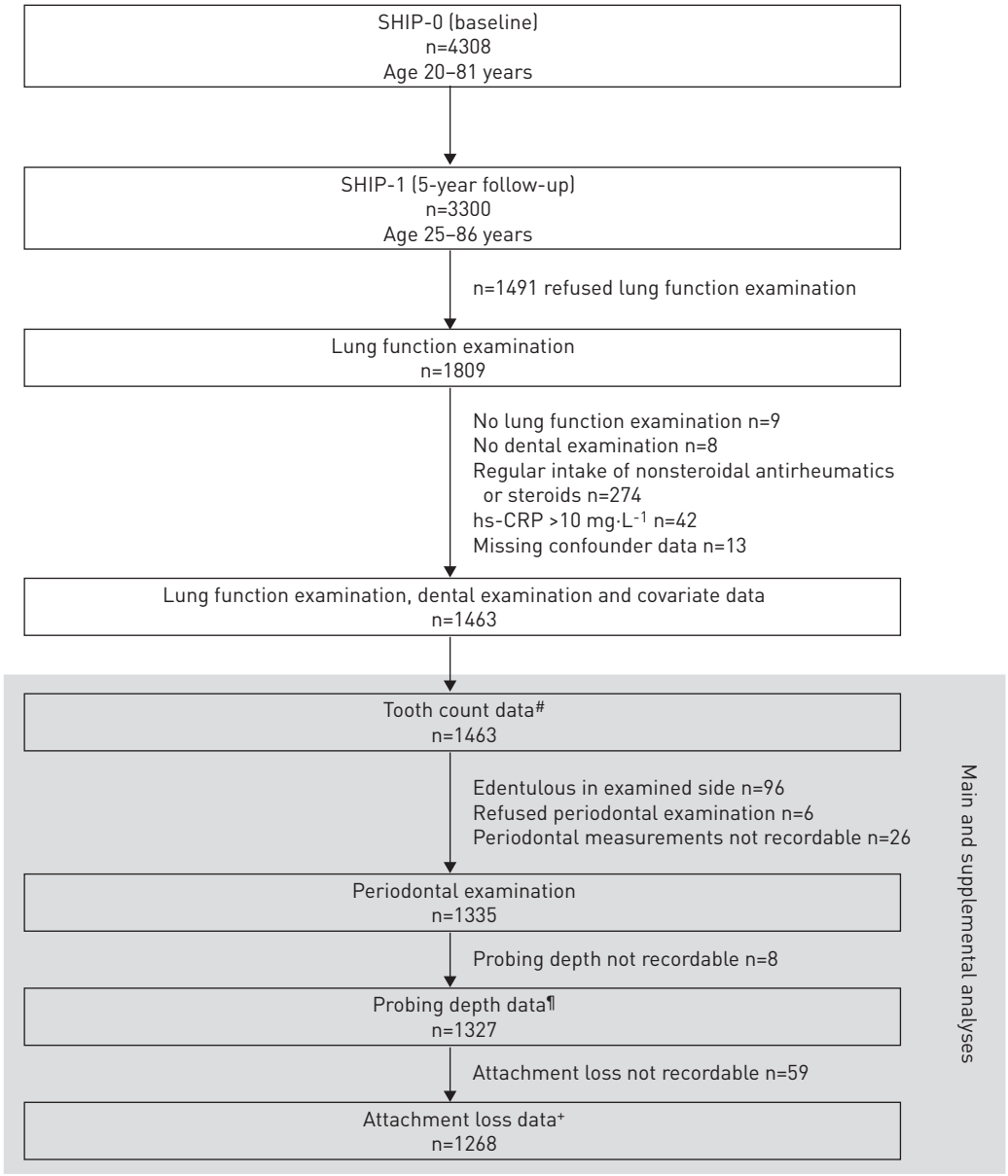

FIGURE 1 Flow chart describing the derivation of the study sample. SHIP: Study of Health in Pomerania; hs-CRP: high-sensitivity C-reactive protein. #: see online supplementary table S1; ¶: see online supplementary table S2; +: see tables 1–3.

Periodontal variables

Periodontal disease was assessed by probing depth and CAL. Measurements were assessed at mesiobuccal, midbuccal, distobuccal and midpalatinal/midlingual tooth sites for all teeth except third molars, according to the half-mouth method; that is the first and fourth quadrants (right side) or the second and third quadrants (left side) were examined, alternating in each subject. A manual periodontal probe was used (PCP2; Hu-Friedy, Chicago, IL, USA). Probing depth (severity of current disease) equals the distance from the free gingival margin to the bottom of the periodontal pocket. CAL (severity of cumulative disease) equals the distance from the cemento-enamel junction to the pocket base. CAL was not recorded when cemento-enamel junction determination was indistinct (*e.g.* wedge-shaped defects, fillings and crown margins). Measurements were rounded to the closest millimetre. Mean CAL/probing depth over all measurement sites and the percentage of sites with CAL/probing depth $\geqslant$4 mm was calculated. The number of missing teeth excluding third molars was determined.

Dental examinations were conducted by calibrated and licenced dentists. Biannual calibration exercises on subjects not connected to the study yielded intraclass correlations of 0.70–0.89 per examiner and an inter-rater correlation of 0.90 for attachment level measurements.

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Lung function variables

Details of lung function examinations that have been used in this study are given elsewhere [20]. In brief, lung function examinations were performed using a body plethysmograph equipped with a pneumotachograph (MasterScreen Body/Diff; Jaeger, Hoechberg, Germany), meeting the American Thoracic Society criteria [29] and recommendations of the European Respiratory Society [30, 31].

For the purpose of the study the following lung function variables were assessed: airway resistance (R_{tot}), inspiratory vital capacity, functional residual capacity derived by body plethysmography (FRC_{pleth}), residual volume (RV) and total lung capacity (TLC). Forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1) and maximal expiratory flow at 25% of FVC ($MEF_{25\%}$) were determined by spirometry. FEV_1/FVC (%) and RV/TLC (%) were calculated. All subjects were advised not to smoke tobacco and not to use any inhaler within 1 h prior to the test.

After a break of $\geqslant$3 min, alveolar volume (V_A) using helium dilution [31] and T_{LCO} corrected for current haemoglobin and V_A (T_{LCOc}–V_A) were measured by a single breath manoeuvre [32].

Pre-exercise diagnostics

Sociodemographic and medical variables were assessed by computer-assisted personal interviews. Information on socioeconomic status and behavioural characteristics were retrieved from the computer-guided interview. School education level was categorised based on the East German three-level school system (<10, 10 or >10 years). High physical activity was classified as $\geqslant$2–3 h per week. To precisely assess the participant's tobacco smoking, information was combined: smoking status (never/former/current), daily *versus* less than daily smoking, number of cigarettes smoked per day and, for former smokers, time since quitting smoking. Accordingly, participants were categorised into never-smokers, current less than daily smokers, former smokers who quit $\leqslant$10, >10 and $\leqslant$20 or >20 years ago, and current daily smokers. The number of pack-years was calculated as packs·day^{-1} × years of smoking. Never-smokers were those who answered "No" to the question whether they smoke or had ever smoked every day.

Body height and weight were determined using calibrated scales, and body mass index (BMI) was measured in kg·m^{-2}. Waist circumference was measured to the nearest 0.1 cm of the narrowest part of the waist midway between the lower rib margin and the iliac crest in the horizontal plane in a standing position and with light clothing.

Previous history of diseases was based on self-reported physician's diagnosis. Use of medication influencing lung function was recorded according to the Anatomical Therapeutic Chemical (ATC) code [33]. The following drugs were considered: steroids (ATC A11ED, A14A, D07, G01B, H02, J01XC, M01BA, N02CB, R01AD, S01BA, S01BB, S01BC, S01BX, S01CA, S01CB, S02B, S02C, S03B and S03C) and nonsteroidal antirheumatics (ATC M01). Diabetes mellitus was defined as self-reported physician's diagnosis or intake of antidiabetic medication (ATC A10) in SHIP-0 or as self-reported physician's diagnosis or intake of antidiabetic medication (ATC A10) between baseline and follow-up (SHIP-1). Asthma and COPD were defined using self-reported physician's diagnosis.

Blood sampling

For laboratory examinations, nonfasting blood samples were obtained from the cubital vein in supine position. hs-CRP (Dade Behring, Eschborn, Germany), plasma fibrinogen according to the Clauss method (Electra 1600 analyser; Instrumentation Laboratory, Barcelona, Spain) and leukocyte counts (Coulter MaxM; Coulter Electronics, Miami, FL, USA) were determined.

To adjust diffusing capacity for the potential influence of blood haemoglobin, haemoglobin concentrations were determined on the same day, immediately before lung function measurements. Hence, a sample of capillary blood was taken from the earlobe and immediately transferred to the blood gas and haemoglobin analyser (Radiometer ABL 510; Radiometer, Copenhagen, Denmark).

Statistical analyses

Continuous data were expressed as median (interquartile range). Categorical data were presented as n (%). Subjects were classified as having a low ($\leqslant$) or a high (>) mean CAL value compared to the age- and sex-specific median for mean CAL. Differences between subjects with low and high mean CAL were tested using Mann–Whitney U-tests (continuous data) or Chi-squared tests (categorical data).

Linear regression models were used to assess the association between periodontal and pulmonary variables. First-degree fractional polynomials were applied to explore and graph nonlinear associations [34]. To evaluate goodness of fit, deviances were compared using Chi-squared distributions with corresponding

degrees of freedom [34]. If none of the fractional polynomial models fitted the data significantly better than the linear model, linear regression was applied.

Starting with the exposure effect estimate for mean CAL from the model including age, sex and time between core and pulmonary examination, confounders making the most difference in the estimate were added one by one (forward selection) [35]. A change in estimate of >5% was considered important. Final models were adjusted for age, sex, time between core and pulmonary examination, diabetic status, waist circumference, presence of asthma, physical activity, smoking status, school education and height (as age- and sex-specific quintiles). Presence of COPD did not change estimates for mean CAL by >5%.

Next, to assess the possibility that systemic inflammation might link periodontal disease with lung function, fibrinogen and hs-CRP (M6) were additionally included in the full model. Relative change in estimate for mean CAL (exposure) was estimated to assess a putative intermediate position of systemic inflammation.

In sensitivity analyses, models were adjusted for either height and weight or BMI. Furthermore, subjects were restricted to never-smokers and periodontal variables were substituted by the percentage of surfaces with CAL or probing depth ⩾4 mm.

As recommended for epidemiological studies with missing data, multiple imputations of missing lung function data *via* chained equations were performed to reduce potential bias due to missing values in complete case analyses [36]. Using the STATA procedure interactive collaboration and evaluation with 20 runs [37], parameters of lung function were predicted by age, height, waist circumference, congestive heart failure (self-reported physician's diagnosis, echocardiographic evidence of left ventricular or valvular dysfunction or in accordance with the Rotterdam Study definition of heart failure [38]), systolic blood pressure, diabetes, evidence of coronary artery disease (myocardial infarction, signs of ischaemia in ECG), related medications (chronic use of nonsteroidal antirheumatics and steroid intake) and smoking pack-years in strata of sex and smoking status [39]. Afterwards regression analyses were repeated using the imputed data.

Statistical significance was considered at a two-sided $p<0.05$. Statistical analyses were performed using STATA/SE 12.0 (StataCorp, College Station, TX, USA).

Results

Subjects with high mean CAL were less often well educated, were more often current smokers, and had higher levels of systemic inflammation compared with subjects with low mean CAL (table 1). In addition, they had a deteriorated lung function ($p<0.05$).

Association between mean CAL and pulmonary variables

In the overall sample (table 2), significant associations of mean CAL with dynamic lung volumes (FVC (fig. 2a) and FEV_1 (fig. 2b)), static lung volumes (FRC_{pleth}) and airflow limitation (FEV_1/FVC ratio, $MEF_{25\%}$, R_{tot} and RV/TLC ratio (fig. 2c)) were seen after full adjustment for potential confounders. Restricted to never-smokers, mean CAL was significantly ($p<0.05$) associated with dynamic lung volumes (FVC and FEV_1) and with RV/TLC ratio (fig. 2). Data imputation confirmed associations with dynamic lung volumes (FVC and FEV_1), static lung volumes (FRC_{pleth}) and airflow limitation (FEV_1/FVC ratio, $MEF_{25\%}$ and RV/TLC ratio).

To assess the strength of confounding by smoking, height and education more closely, stepwise adjusted models were evaluated (table 3). After adjustment for age, sex, time between core and pulmonary examination, diabetes, waist circumference, physical activity and asthma (M1), mean CAL was significantly related to all pulmonary variables ($p<0.05$), except TLC. Adjustment for smoking (M2) reduced coefficients for mean CAL by >5% for all variables except R_{tot}. Further adjustment for body height (M3) led to a more pronounced change in coefficients of mean CAL in relation to FVC, FEV_1, $MEF_{25\%}$, FRC_{pleth} and TLC compared with an adjustment for education (M4). In the full model (M5), mean CAL was significantly associated with FVC, FEV_1, FEV_1/FVC ratio, $MEF_{25\%}$, R_{tot}, FRC_{pleth} and RV/TLC ratio ($p<0.05$). Higher levels of mean CAL were related to lower levels of FVC (fig. 2a) and FEV_1 (fig. 2b) and higher levels of RV/TLC ratio (fig. 2c). In addition, fibrinogen and hs-CRP were considered as intermediates linking periodontal disease with lung function. For those pulmonary variables showing significant associations with mean CAL in the full model (M5), inclusion of fibrinogen and hs-CRP (M6) did not change coefficients of mean CAL.

Sensitivity analyses

Considering mean probing depth as periodontal exposure (online supplementary table S2), relevant associations with FEV_1, FEV_1/FVC ratio, FRC_{pleth} and RV/TLC ratio were seen in the overall sample

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TABLE 1 Characteristics of the study population stratified by mean clinical attachment loss (CAL)

	Mean CAL[#]		p-value[¶]
	Low	High	
Subjects n	640	628	
Lung function variables			
Time between core and pulmonary examination days	18 (0–71)	19 (0–82)	0.11
Dynamic lung volumes			
FVC mL	4001 (3367–4744)	3882 (3269–4668)	0.06
FEV_1 mL	3417 (2882–4123)	3298 (2748–3960)	0.01
Obstruction/airflow limitation			
FEV_1/FVC %	85.8 (82.2–88.9)	85.2 (81.5–88.8)	0.056
$MEF_{25\%}$ $L \cdot s^{-1}$	1.60 (1.18–2.08)	1.50 (1.09–1.97)	0.008
R_{tot} $kPa \cdot s^{-1} \cdot L^{-1}$	0.21 (0.17–0.27)	0.22 (0.17–0.28)	0.17
Static lung volumes			
FRC_{pleth} mL	3.54 (3.02–4.15)	3.55 (2.99–4.17)	0.75
TLC mL	6300 (5475–7207)	6317 (5398–7225)	0.82
RV/TLC %	34.4 (28.5–40.2)	35.6 (29.7–41.9)	0.005
Diffusion			
T_{LCOc}-V_A $mmol \cdot kPa^{-1} \cdot min^{-1} \cdot L^{-1}$	1.452 (1.316–1.605)	1.406 (1.267–1.596)	0.009
Periodontal variables			
Mean CAL mm	0.94 (0.37–1.75)	3.03 (1.96–4.25)	<0.001
Percentage of sites with CAL ⩾4 mm %	2.0 (0–10.0)	35.6 (7.7–67.3)	<0.001
Mean PD mm	1.89 (1.71–2.09)	2.46 (2.05–2.97)	<0.001
Percentage of sites with PD ⩾4 mm %	2.3 (0–6.8)	16.0 (4.2–32.7)	<0.001
Tooth count	24 (22–27)	22 (15–26)	<0.001
Laboratory variables			
High-sensitivity CRP $mg \cdot L^{-1}$	1.0 (0.6–2.2)	1.3 (0.6–2.7)	0.003
Fibrinogen (Clauss) $g \cdot L^{-1}$	2.9 (2.5–3.4)	3.0 (2.6–3.6)	<0.001
Leukocyte count $Gpt \cdot L^{-1}$	6.3 (5.2–7.2)	6.5 (5.5–7.8)	<0.001
Subject characteristics			
Male	50.9	51.1	0.95
Age at core examination years	50.1 (39.9–60.3)	50.1 (39.8–60.2)	0.99
School education			
<10 years	18.8	26.8	
10 years	54.8	55.4	
>10 years	26.4	17.8	<0.001
Smoking status			
Never-smoker	49.7	39.3	
Current less-than-daily smoker	4.1	2.2	
Former smoker quit ⩽10 years ago	10.0	12.1	
Former smoker quit >10–⩽20 years ago	8.7	5.6	
Former smoker quit >20 years ago	12.8	12.0	
Current daily smoker	14.7	28.8	<0.001
Pack-years	0 (0–6.9)	3.0 (0–15.1)	<0.001
Diabetes mellitus	4.5	6.7	0.10
High physical activity[+]	22.8	20.1	0.23
Body mass index $kg \cdot m^{-2}$	26.8 (24.1–29.8)	27.2 (24.5–30.8)	0.03
Height cm	171 (164–178)	170 (164–177)	0.11
Weight kg	79.4 (69.1–89.8)	79.4 (69.1–91.8)	0.44
Waist circumference cm	91 (82–100)	92 (82–102)	0.27
Medical diseases			
COPD	1.3	1.8	0.46
Asthma	3.8	7.8	0.002
Coronary artery disease[§]	4.4	5.3	0.46

Data are given as median (interquartile range) or %, unless otherwise stated. n=1268. FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; $MEF_{25\%}$: maximal expiratory flow at 25% of FVC; R_{tot}: total airway resistance; FRC_{pleth}: functional residual capacity derived by body plethysmography; TLC: total lung capacity; RV: residual volume; T_{LCOc}-V_A: diffusing capacity of the lung for carbon monoxide (single breath), corrected for haemoglobin level and alveolar volume (assessed by helium dilution); PD: probing depth; CRP: C-reactive protein; COPD: chronic obstructive pulmonary disease (subject-reported physician's diagnosis). [#]: classified as equal to or less than (low) or greater than (high) the age- and sex-specific median for mean CAL; [¶]: p-values calculated by Mann–Whitney U-test for continuous data and Chi-squared test for categorical data; [+]: defined as sporting activity of ⩾2–3 h per week; [§]: defined as myocardial infarction or signs of ischaemia in ECG.

TABLE 2 Linear regression evaluating the associations between mean clinical attachment loss (CAL) (exposure) and pulmonary variables (outcomes) using fractional polynomials (FPs) in the overall sample, in never-smokers and using imputed data

	Overall sample#		Never-smokers¶		Imputed data+	
	FP	B (95% CI)	FP	B (95% CI)	FP	B (95% CI)
FVC mL	X^2	-360 (-636–-85)*	X^3	-992 (-1668–-316)**	X^2	-385 (-614– -156)**
FEV1 mL	X^2	-480 (-722–-238)***	X^3	-738 (-1306–-170)*	X^2	-367 (-575– -159)**
FEV1/FVC %	X	-4.93 (-7.97–-1.89)**	X	0.63 (-2.96–4.23)	X	-1.61 (-3.42–0.21)
MEF25% L·s^{-1}	X	-0.23 (-0.46–-0.01)*	X	-0.03 (-0.37–0.31)	X	-0.16 (-0.34–0.02)
***R*tot§ kPa·s^{-1}·L^{-1}**	X^3	0.071 (0.024–0.118)**	X	-0.001 (-0.053–0.051)	X^3	0.050 (0.003–0.096)*
FRCpleth§ mL	X^3	0.94 (0.54–1.34)***	X	0.22 (-0.20–0.64)	X^3	0.36 (-0.02–0.73)
TLC§ mL	X	211 (-104–526)	X	126 (-394–646)	X	12 (-286–309)
RV/TLCƒ %	X	5.62 (2.93–8.32)***	X^3	16.94 (8.63–25.26)***	X	3.40 (0.99–5.81)**
***T*LCOc-*V*A## mmol·kPa^{-1}·min^{-1}·L^{-1}**	X	-0.0003 (-0.128–0.127)	X	0.094 (-0.123–0.311)	X	-0.019 (-0.116–0.078)

Linear regression using FPs for mean CAL adjusted for age, sex, time between core and pulmonary examination, diabetes, waist circumference, physical activity (⩾2–3 h per week), asthma, chronic obstructive pulmonary disease, smoking status (six categories), height (age- and sex-specific quintiles) and school education. B: regression coefficient; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 s; MEF25%: maximal expiratory flow at 25% of FVC; *R*tot: total airway resistance; FRCpleth: functional residual capacity derived by body plethysmography; TLC: total lung capacity; RV: residual volume; *T*LCOc-*V*A: diffusing capacity of the lung for carbon dioxide (single breath), corrected for haemoglobin level and alveolar volume (assessed by helium dilution); X: mean CAL/10. #: n=1268; ¶: n=565; +: n=2577; §: one additional missing value; ƒ: three additional missing values; ##: 12 additional missing values in the overall sample model and seven additional missing values in never-smokers. *: p<0.05; **: p<0.01; ***: p<0.001.

(p<0.05). Restricting subjects to never-smokers, the association with FVC missed statistical significance (p=0.063). Data imputation confirmed these results. Associations were highly confounded by smoking and body height (online supplementary table S3).

Considering the number of missing teeth as the exposure (online supplementary table S1), significant associations with FVC, FEV1, FEV1/FVC ratio, *R*tot, FRCpleth and RV/TLC ratio were found (p<0.05). Restricting analyses to never-smokers, number of missing teeth was significantly associated with FVC and *T*LCOc-*V*A (p<0.05). Evaluation of imputed data confirmed the associations with FVC, FEV1, FEV1/FVC, *R*tot, and RV/TLC ratio (p<0.05).

Results were confirmed by exchanging the exposure variable with the percentage of sites with CAL/probing depth ⩾4 mm. Substituting height and waist circumference by either body height and weight or BMI did not change the results substantially.

Discussion

In this study, periodontal disease was independently associated with reduced dynamic and static lung volumes and with airflow limitation, but not with diffusing capacity. These associations, however, were

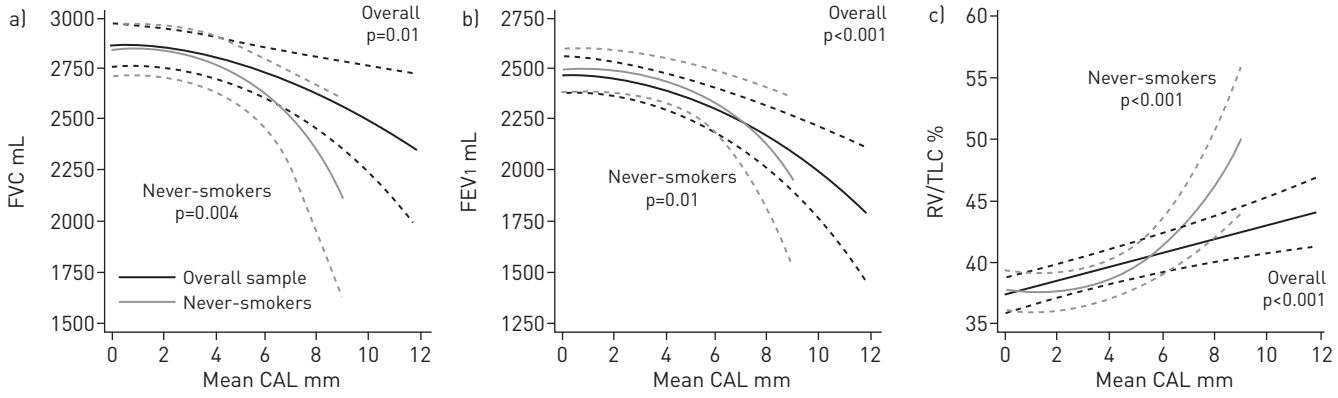

FIGURE 2 Associations between mean clinical attachment loss (CAL) and a) forced vital capacity (FVC), b) forced expiratory volume in 1 s (FEV1) and c) residual volume (RV) to total lung capacity (TLC) ratio in the overall sample (n=1268) and in never-smokers (n=565) according to M5 in table 3. Confidence limits (dashed lines) and p-values from fully adjusted regression analyses are given.

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TABLE 3 Linear regression evaluating the associations between mean clinical attachment loss (CAL) (exposure) and pulmonary variables (outcomes) using fractional polynomials (FP) for the overall sample

	FP	M1	M2	M3	M4	M5	M6
FVC mL	X^2	-557 (-864– -249)***	-457 (-773– -141)**	-377 (-648– -106)**	-391 (-711– -70)*	-360 (-636– -85)*	-360 (-636– -84)*
FEV_1 mL	X^2	-715 (-981– -449)***	-567 (-839– -295)***	-500 (-738– -262)	-508 (-784– -232)***	-480 (-722– -238)***	-481 (-723– -238)***
FEV_1/FVC %	X	-4.82 (-7.03– -2.60)***	-3.26 (-5.55– -0.97)**	-3.28 (-5.58– -0.99)**	-3.36 (-5.69– -1.03)**	-4.93 (-7.97– -1.89)**	-3.39 (-5.73– -1.05)**
$MEF_{25\%}$ $L \cdot s^{-1}$	X	-0.42 (-0.64– -0.21)***	-0.26 (-0.48– -0.04)*	-0.23 (-0.45– -0.01)*	-0.25 (-0.48– -0.03)*	-0.23 (-0.46– -0.01)*	-0.23 (-0.46– -0.01)*
R_{tot}# $kPa \cdot s^{-1} \cdot L^{-1}$	X^3	0.083 (0.036–0.130)**	0.079 (0.031–0.126)**	0.074 (0.028–0.121)**	0.073 (0.024–0.121)**	0.071 (0.024–0.118)**	0.071 (0.024–0.118)**
FRC_{pleth}# mL	X^3	1.08 (0.63–1.53)***	0.90 (0.45–1.35)***	0.97 (0.57–1.36)***	0.93 (0.47–1.38)***	0.94 (0.54–1.34)***	0.94 (0.54–1.35)***
TLC# mL	X	165 (-183–513)	77 (-285–438)	194 (-116–504)	156 (-211–523)	211 (-104–526)	223 (-92–538)
RV/TLC¶ %	X	7.53 (4.97–10.10)***	5.76 (3.11–8.41)***	5.63 (2.98–8.28)***	5.72 (3.03–8.42)***	5.62 (2.93–8.32)***	5.77 (3.08–8.46)***
T_{LCOc}-V_A+ $mol \cdot kPa^{-1} \cdot min^{-1} \cdot L^{-1}$	X	-0.134 (-0.258– -0.009)*	0.019 (-0.106–0.145)	0.010 (-0.115–0.135)	0.005 (-0.123–0.133)	-0.0003 (-0.128–0.127)	0.011 (-0.116–0.139)

Data are presented as regression coefficients (95% CI). n=1268. M1: adjusted for age, sex, time between core and pulmonary examination, diabetes, waist circumference, physical activity (⩾2–3 h per week), asthma and chronic obstructive pulmonary disease; M2: M1 additionally adjusted for smoking status (six categories); M3: M2 additionally adjusted for height (age- and sex-specific quintiles); M4: M2 additionally adjusted for school education; M5: M2 additionally adjusted for height (age- and sex-specific quintiles) and school education (full model); M6: M5 additionally including fibrinogen (continuous) and high-sensitivity C-reactive protein (continuous); FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; $MEF_{25\%}$: maximal expiratory flow at 25% of FVC; R_{tot}: total airway resistance; FRC_{pleth}: functional residual capacity derived by body plethysmography; TLC: total lung capacity; RV: residual volume; T_{LCOc}-V_A: diffusing capacity of the lung for carbon dioxide (single breath), corrected for haemoglobin level and alveolar volume (assessed by helium dilution); X: mean CAL/10. #: one additional missing value; ¶: three additional missing values; +: 12 additional missing values; *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$.

heavily confounded by smoking and body height. Systemic inflammation, as assessed by serum fibrinogen levels and hs-CRP, seemed to mediate associations between periodontal disease and lung function only to a minor degree. In never-smokers, a deteriorated periodontal status was associated with lower lung volumes (FVC and FEV1) and higher RV/TLC ratios. Our findings are consistent with previous evidence about associations between periodontal disease and airflow limitation in predefined populations with COPD [4–10]. Importantly, our study offers more accurate definitions of airflow limitation, providing a comprehensive evaluation of lung function.

Dental plaque induces gingivitis and is the primary aetiological factor for the progression of periodontal diseases [40]. Thus, the effective removal of dental plaque is essential for the prevention of periodontal disease. In SHIP, the percentage of positive plaque sites was associated with lower lung volumes (FVC and FEV1; $p=0.02$) and higher RV/TLC ratios ($p=0.004$; data not shown). Results are in agreement with other studies having reported relationships between plaque and/or oral hygiene with pneumonia [15], ventilator-associated pneumonia [41, 42] and COPD [12]. Oral hygiene may be efficient in reducing home-associated pneumonia [15, 43]. Further, several meta-analyses [41, 42, 44] support the use of oral antiseptics to reduce risk of ventilator-associated pneumonia. Because oral colonisation by oral or respiratory pathogens was not assessed in this study, associations between pathogen burden and lung function were not feasible. However, these studies considerably complement the scientific evidence for an association between periodontitis and lung diseases.

Besides hygiene issues in pneumonia and COPD, associations of oral microorganisms and pulmonary infections due to aspiration have been investigated [45]. Usually, aspiration pneumonia is related to less-virulent bacteria, streptococci and anaerobes that reside in the upper airways or the gastrointestinal tract [45].

Smoking mainly confounds the association between periodontitis and lung function [5]. Smoking is involved in the pathogenesis and progression of periodontal diseases [46]. The peripheral vasoconstrictive effect of tobacco smoke and nicotine reduces the delivery of oxygen and nutrients to gingival tissue [47] and alters gingival inflammatory response [46]. Smoking also affects respiratory defences, promotes chronic lung diseases in respiratory infections, damages the airway epithelium and has effects on lung clearance by suppressing cough and the protective waving action of cilia in the airways [48].

In this study, inclusion of smoking status strongly attenuated coefficients in our models that evaluated lung volumes, airway limitation and diffusion capacity. Because we considered smoking status and number of pack-years for adjustment, residual confounding by smoking was reduced considerably. However, residual confounding by the number of cigarettes smoked appears to be an aspect consistently observed in the current literature, where associations between periodontitis and lung function were only reported among current smokers [5, 10]. To avoid residual confounding by active smoking experience, analyses were also restricted to never-smokers. Restricting analyses to never-smokers halved the number of pulmonary variables associated with mean CAL. This aspect underlines the importance of major confounding by smoking and number of cigarettes smoked on the relationship between periodontal diseases and lung function.

It has been previously described that the socioeconomic status is associated with lung function independently of smoking [49]. In line with this, in our study adjustment for education attenuated associations between periodontal disease and airflow limitation, quantified by FEV1/FVC ratio, R_{tot}, RV/TLC ratio, and diffusion, quantified by T_{LCOc}-V_A, more strongly compared with body height in our study. However, having only adjusted for education, residual confounding by other socioeconomic factors cannot be ruled out.

In this study, adjustment for body height changed coefficients of mean CAL for static and dynamic lung volumes and $MEF_{25\%}$ by >10%. This leads to the question of how body height might be related to both lung volume and periodontitis. Body height reflects intrauterine influences and birthweight, as well as weight and environmental factors in early childhood (*e.g.* nutrition, illness and psychosocial stress), which in consequence constrain the growth of the airways and may be reflected in reduced lung volumes. These constraints occurring in the fetus and early childhood may also hamper inflammatory responses to infections [50–52]. Meisel *et al.* [53] showed that body height was associated with periodontitis and concluded that individuals born with a high susceptibility to infectious and inflammatory diseases in childhood may present impaired growth in length. Upon reaching adulthood, growth comes to a halt, but the individual remains susceptible to inflammatory sequelae. Thus, smaller persons tend to develop more severe periodontitis.

A number of potential mechanisms have been proposed to explain the biological plausibility for an association between periodontal disease and lung function [54, 55]. The oral cavity provides an optimal environment for bacterial growth because of its humidity and temperature. 1 mm^3 of plaque contains $>10^6$ bacteria with 300 different anaerobic and facultative anaerobic species [56]. The most common route by

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which the oral cavity may influence pulmonary function is the aspiration of saliva harbouring oral bacteria into the lung [24]. Aspiration of small amounts of saliva during sleep is quite common, even in healthy subjects [57]. Subjects with severe periodontal disease harbour elevated levels of periodontal pathogens in saliva compared with healthy subjects [58]. The amount of pathogens reflects pathogen burden in periodontal pockets [58]. When aspirated, oral pathogens cause local damage to the small airways [57].

Furthermore, oral bacteria stimulate the inflamed periodontal tissues to release cytokines *via* the sulcus fluid into the saliva. In subjects with periodontal disease salivary biomarker load is higher than in healthy subjects [58]. Aspirated cytokines may promote the adhesion and growth of respiratory pathogens in the lower airways [54]. Subsequently, the respiratory epithelium may release cytokines and attract neutrophils, which in turn infiltrate airway parenchyma and release proteolytic enzymes and toxic oxygen radicals which damage the epithelium [59, 60]. As a consequence, the resultant inflamed mucosal epithelium may be particularly prone to infection.

Low-grade systemic inflammation, specifically addressed in this study, might provide a further plausible link. Elevated levels of cytokines and higher levels of circulating inflammatory markers, such as CRP and fibrinogen, have not only been associated with periodontal diseases [16], but also with reduced lung function [17–20]. However, restricting models to those showing significant associations with mean CAL after full adjustment, inclusion of fibrinogen and hs-CRP did not reduce coefficients for mean CAL by >5%. Thus, systemic inflammation might only be of minor importance when considering the link between periodontal diseases and lung volume. Nevertheless, results are in agreement with others showing that hs-CRP and fibrinogen were associated with TLC [17–20].

There are several strengths of our analysis, the major one being the population-based approach including a general German adult population sample with a broad age range (25–85 years). Second, various clinical periodontal definitions were used, covering both current (probing depth) and cumulative disease extent (attachment loss and tooth count); all definitions presented a consistent impression of the effect of periodontitis on lung function. Dental examiners had been calibrated twice a year. Third, a highly standardised method in obtaining comprehensive lung function parameters using standard spirometry, body plethysmography, helium dilution for measurement of alveolar volume and diffusing capacity measurement for carbon monoxide was used.

Three limitations of our study merit comment. One of these is its cross-sectional design, known to preclude the establishment of a definite cause and effect relationship. Second, selection bias due to nonparticipation in pulmonary function tests may have occurred; younger and healthier subjects volunteered and no subjects with advanced COPD were identified among the study participants. To counter this, multiple imputations of missing lung function data *via* chained equations were performed to reduce potential bias due to missing values in complete case analyses [36]. After imputation, associations between periodontal disease and lung function were confirmed. Third, since periodontal measurements were taken half-mouth, extent of periodontal disease might be underestimated, and observed associations with lung function might be biased towards the null [61]. However, use of mean values of probing depth and CAL limits underestimation and bias of risk estimates.

Conclusion

In conclusion, periodontal disease was significantly associated with reduced lung volumes, hyperinflation and airflow limitation in this general population sample independently of potential confounders. Smoking and height highly confounded the association between periodontitis and lung function. Systemic inflammation did not provide a mechanism linking both diseases. In future, large cohort studies with long observation periods evaluating comprehensive lung function parameters are needed to validate the observed associations and to assess causality more closely. In this context, a comprehensive consideration of confounding bias is strongly suggested and analyses restricted to never-smokers are encouraged. Further investigations on the association between oral pathogen burden and lung function would complement results from clinical trials. Furthermore randomised clinical trials are needed to investigate whether prevention or treatment of periodontitis might have a beneficial impact on lung function.

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