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Complete List of Authors:	Heinrich, Joachim; 1 Ludwig Maximilians University Munich, University Hospital Munich, Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, Munich, Germany ; 2 Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Epidemiology, Neuherberg, Germany ; 3 Comprehensive Pneumology Center Munich (CPC-M), Member of the German Center for Lung Research Thiering, Elisabeth; Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Epidemiology ; 3 Comprehensive Pneumology Center Munich (CPC-M), Member of the German Center for Lung Research ; 4 Ludwig Maximilians University of Munich, Dr. von Hauner Children's Hospital, Munich, Germany Jörres, Rudolf A.; 1 Ludwig Maximilians University Munich, University Hospital Munich, Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, Munich, Germany Schulz, Holger; 2 Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Epidemiology, Neuherberg, Germany ; 3 Comprehensive Pneumology Center Munich (CPC-M), Member of the German Center for Lung Research Kuehnisch, Jan; 5 Ludwig-Maximilians-Universität München, Munich, Germany, Department of Operative Dentistry and Periodontology, University Hospital, Standl, Marie; 2 Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Epidemiology, Neuherberg, Germany
Key Words:	lung function, gingivitis, adolescents, low-grade inflammation, hs-CRP, FeNO

Lung function and oral health in adolescents

Joachim Heinrich[1,2,3], Elisabeth Thiering[2,3,4], Rudolf A. Jörres[1], Holger Schulz[2, 3], Jan Kühnisch[5] , Marie Standl[2,3]

1 Ludwig Maximilians University Munich, University Hospital Munich, Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, Munich, Germany
2 Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Epidemiology, Neuherberg, Germany
3 Comprehensive Pneumology Center Munich (CPC-M), Member of the German Center for Lung Research
4 Ludwig Maximilians University of Munich, Dr. von Hauner Children's Hospital, Munich, Germany
5 Department of Operative Dentistry and Periodontology, University Hospital, Ludwig-Maximilians-Universität München, Munich, Germany

Corresponding author:

Dr. Joachim Heinrich

Ludwig Maximilians University Munich, University Hospital Munich

Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, Munich, Germany Ziemssenstraße 1

80336 München Tel.: +49 89 440023251

Email: joachim.heinrich@med.uni-muenchen.de

"Take home message": The association between oral inflammation and reduced lung function exists in adolescents and is not mediated by systemic nor by lung-specific, low-grade inflammation.

Running title: Lung function and oral health

Keywords: gingivitis, sulcus bleeding, oral health, hs-CRP, FeNO, systemic inflammation, lung function, spirometry, adolescence

Abstract

Background: Oral health and lung function are known to be associated in adults. This study aimed to examine whether such links are present already in adolescents, and whether markers of mediation, via low-grade systemic or local inflammation, can be identified.

Methods: Data from 1198 adolescents, aged 15, with valid lung function measurements and oral examinations were evaluated. All participants were part of the 15-year follow-up of two German birth cohorts, based at the Munich study centre. Spirometric lung function data were evaluated using absolute values and z-scores derived via the Global Lung Initiative (GLI). The associations between spirometric parameters and periodontal health (simplified sulcus bleeding index (s-SBI); community periodontal index (CPI)) were analysed using linear regression models adjusted for confounding factors. In additional analyses, the potential intermediate roles of hs-CRP and FeNO were explored.

Results: Spirometric lung volumes and flow rates were significantly reduced by 71 to 185 ml for participants with the highest s-SBI and CPI indices, regardless of the adjustments for potential confounders. Inclusion of hs-CRP and FeNO, smoking status and asthma did not substantially affect the estimates.

Conclusion: We observed an association between the occurrence of gingivitis and reduced lung function in adolescents. This association was unrelated to inflammatory markers or to smoking.

Introduction

The literature on determinants of lung function only contains a few studies that examined the association between periodontal diseases (PD), such as gingivitis or periodontitis, and lung health. The latest systematic review [1] identified 14 observational studies and reported a pooled odds ratio of 2.08 (95% confidence interval: 1.48 to 2.91) for Chronic Obstructive Pulmonary Disease (COPD) in the presence of PD. Others [2-7], with some notable exceptions [8-10], have also confirmed an association between oral inflammation and lung disease. While these studies were mostly restricted to PD and COPD, a systematic review on PD and asthma also reported a significant association [11]. Smoking is an important co-determinant for both PD and lung diseases, and studies on PD and COPD that adjusted for smoking reported a substantial attenuation of the association [3, 7, 9]. The extent to which smoking explains the association between PD and COPD therefore remains uncertain.

Three interventional trials reported positive effects of periodontal therapy in patients with COPD. Two non-randomized [12, 13] and one randomized trial [14] reported improved lung function and reduced exacerbation rates in COPD patients after oral hygiene instruction and periodontal treatment. All these studies on oral inflammation and lung health were restricted to adults, and smoking was suggested as the underlying mechanism and common risk factor for local inflammation and for indirect effects due to systemic inflammation [15, 16]. Linden et al. [16] concluded that the inflammatory status of airways might be affected by aspiration of dental plaque and/or haematogenous dissemination of inflammatory mediators and periodontal bacteria. In addition, a shared pathogenesis between PD and COPD, via shared pathogens, has been suggested [17]. PD are associated with low-grade systemic inflammation [18-20]. Since systemic low-grade inflammation is associated with both PD and lung function impairment [3, 21-24], it may be that PD affects lung function via systemic inflammation.

To the best of our knowledge, the role of oral health in lung function at a young age has never been investigated. We therefore analysed the association between spirometric lung function and oral health indicators in adolescents. We also studied the potential mediating role of low-grade systemic and local inflammation, using the high sensitivity serum C-reactive protein (hs-CRP) and the fraction of exhaled nitric oxide (FeNO) as indicators.

Materials and methods

Study population

The source study populations consist of two German birth cohorts: GINIplus and LISA. The GINIplus study (German Infant Nutritional Intervention Program PLUS Air pollution and Genetics on Allergy development) is an ongoing population-based birth cohort study for which a total of 5991 neonates were recruited between September 1995 and July 1998 in the German cities of Munich and Wesel, in the intervention (n=2252) and observation (n=3739) arms. Only children that had at least one atopic parent or sibling were allocated to the intervention group in which the effect of different types of hydrolysed formula on allergy development was prospectively investigated. In the prospective population-based birth cohort, LISA (Influence of Life-style related factors on the development of the Immune System and Allergies in East and West Germany), 3097 healthy term-born neonates were recruited in the German cities of Munich, Wesel, Leipzig, and Bad Honnef between December 1997 and January 1999. Three of the recruited subjects subsequently withdrew their consent to participate. Details of the study design and subject recruitment have been previously described [25-27].

Figure 1 shows the flow chart of the 15-year study population and the populations used for the different analyses. The current analyses are restricted to participants from the Munich study centre, who participated in the 15-year follow-up (N=2515). Of these, 1198 participants underwent the physical examinations with valid lung function testing and dental examination (analysis population I). The analysis population II is comprised of 988 participants with valid data on hs-CRP and FeNO. Lung function tests, blood collection, and dental examinations were performed on the same day. Both studies were approved by the respective local ethics committees, and written informed consent was obtained from all participating families.

Lung function testing by spirometry

Spirometry prior to bronchodilation was performed in line with ATS/ERS recommendations [28]. Subjects sat while wearing nose clips, and the EasyOne Worldspirometer (ndd, Zurich, Switzerland) was used to obtain optimal flow-volume curves by instructing the participants to perform at least three, but no more than eight, manoeuvres under the guidance of specifically trained and experienced examiners. All tests were visually inspected by experienced physicians according to the ATS/ERS acceptability criteria [28]. Spirometric indices, taken from the manoeuvre, included the largest forced expiratory

volume in 1 second (FEV_1) and the forced vital capacity (FVC). We then determined the ratio of FEV_1 to FVC (FEV_1/FVC), and the mean flow rate between 25 and 75% of FVC (FEF_{25-75}). Standardised z-scores of the lung function parameters FEV_1, FVC, FEV_1/FVC, and FEF_{25-75} were calculated based on the reference equations for spirometry from the Global Lung Initiative (GLI – http://www.ers-education.org/guidelines/global-lung-function-initiative.aspx) [30].

After completing baseline spirometry, subjects inhaled bronchodilator medication according to ATS/ERS recommendations [28]. Two puffs (of 100 µg each) of salbutamol were delivered into a spacer (Volumatic) by a metered-dose inhaler, and the participant was asked to take five slow and deep breaths over 5-10 seconds for optimal deposition. Spirometry was repeated 15 min after salbutamol inhalation. This analysis used only post bronchodilator lung function data. A positive response was defined as an increase by >12% and >200 ml in FEV_1 and/or an increase in FVC post-bronchodilation compared to pre-bronchodilation, according to ATS/ERS standards [28].

Dental examination

The dental examination methods are described in detail elsewhere [20, 31-34]. Briefly, participants brushed their teeth prior to the dental examination. The oral cavity was illuminated by a halogen lamp (Ri-Magic, Rudolf Riester GmbH, Jungingen, Germany) and cotton rolls were used to dry the surfaces of the teeth for improved visibility. Sulcus bleeding was measured using a blunt CPI-probe (CP-11.5B6, Hu-Friedy, Chicago, IL, USA) [20, 35]. Decisions on whether sulcus bleeding was present were made for each sextant. The total number of bleeding sextants (s-SBI) thus ranged from 0 (no sextant bleeding) to 6 (all sextants affected) and was categorized as “no bleeding of any sextant” (category 0), “bleeding in 1-3 sextants” (category 1), and “bleeding in >3 sextants” (category 2). Due to the young age of the participants, pocket depths and attachment loss were not recorded. To assess the community periodontal index (CPI), the number of sextants with calculus and the number of sextants with bleeding, were tallied and categorized as “none” (no bleeding and no calculus), “one” (either bleeding or calculus in one segment), or “more than one” (bleeding AND calculus in one segment, or bleeding OR calculus in more than one segment). Caries status was determined based on the decayed, missing, filled teeth (DMFT) index for permanent dentition, using WHO standard methodology [36].

Blood sampling and serum hs-CRP concentrations

Blood samples were collected during the physical examination. After disinfecting the skin, venous blood was collected using a Multifly-Needle with Multiadapter (21G, Sarstedt, Nümbrecht, Germany) and Serum-Monovette (7.5ml, Sarstedt, Nümbrecht, Germany). Blood samples were centrifuged and stored at -80°C until assayed for hs-CRP. Serum hs-CRP was measured using the Roche (Mannheim, Germany) Tina-quant CRP (latex) high-sensitivity assay. The limit of detection (LOD) was 0.015 mg/dL. Values below the LOD (n=57) were substituted by random values from the uniform distribution between 0.001 and the LOD.

FeNO measurements

FeNO was measured by NIOX MINO (Aerocrine, Sweden) from controlled expiration during 10 s at a flow rate of 50 ml/s in accordance with ATS/ERS recommendations [28]. The quality control was performed according to the manufacturer's instructions and complemented with a QC-tester procedure. At least two acceptable and reproducible manoeuvres were required, the values of which were averaged.

Statistical analyses

All analyses were performed using the statistical software R (version 3.3.3) **Error! Reference source not found.**[37]. Linear regression models were used to analyse the association between oral health and spirometric lung function parameters post bronchodilation. Two models with different adjustments of potential confounders were fitted to all spirometric outcome variables. Model 1 was adjusted for study ("GINIplus Intervention", "GINIplus Observational arm", or "LISA"), gender, age, height, weight, and education level ("less than 10 years", "10 years", or "more than 10 years", which in the three-tiered German school system corresponds to attendance at either: Hauptschule (lowest academic level), Realschule (intermediate), or Gymnasium (highest level), respectively). Model 2 was adjusted for all variables in Model 1 and additionally for smoking ("no", "yes: less than once per week", "yes: several times a week or daily"), medication within the last 7 days ("antibiotics or NSAID", "inhaled steroids or beta-adrenergic agonists, leukotriene antagonists, or antihistamines", or "antitussives, mucolytic, or nasal spray", "medication of more than one category"), and current asthma or positive bronchodilation ("yes", "no"). Current asthma was defined, based on questions related to physician-diagnosed asthma, wheezing, and asthma medication during the past 12 months. A participant was classified as asthmatic if at least two of the three questions were answered with "yes".

To evaluate the impact of systemic and lung-specific low-grade inflammation, all models were additionally adjusted for hs-CRP or FeNO, which were log transformed due to the skewness of their distribution. Sensitivity analyses were conducted among non-smokers, non-asthmatics, and subjects not taking any relevant medication during the past 7 days. Additionally, the association between DMFT, as a negative control, and lung function parameters was analysed to rule out confounding by other potential factors.

Results

Table 1 presents the characteristics of the analysis populations, which were used to model the association between oral health indicators and spirometric lung function after bronchodilation (analysis population I) and to explore a potential mediation effect of hs-CRP or FeNO (analysis population II). Mean and standard deviations of the spirometric lung function parameters measured after bronchodilation, as well as, the corresponding GLI z-scores are presented in Table 2.

Oral health and lung function

High sulcus bleeding (s-SBI) and CPI indices were associated with spirometric lung volumes (FEV_1) and flow rates (FEF_{25-75}) that were significantly reduced by 71mL s^{-1} and 185 mL s^{-1}, respectively, regardless of which adjustment was used for lung function or potential confounders (Table 3). The associations were statistically significant for FEV_1, FVC, and FEF_{25-75}, expressed as z-scores according to GLI (Model 1 in Table 3), but not for the FEV_1/FVC ratio or the unadjusted values. A more extensive adjustment for smoking, medication within the last 7 days, current asthma, or positive bronchodilator test altered the effect estimates only marginally (Table 3). Neither adjusting for hs-CRP nor FeNO altered the effect estimates for either of the two inflammatory parameters, s-SBI and CPI (Table 4). The analysis of DMFT (as a negative control) and all lung function parameters did not reveal any substantial associations (Table S1 supplement).

Sensitivity analyses

We performed several sensitivity analyses excluding smokers (Table S2 supplement), excluding subjects with asthma assessed by questionnaire or positive bronchodilation (Table S3 supplement), and excluding subjects with anti-inflammatory medication intake during the last 7 days prior to medical examination (Table S4 supplement). None of these potential influencing factors significantly changed the effect estimates reported in Tables 3 and 4.

Discussion

Summary of results

This study investigated the association between spirometric lung function measured after bronchodilation and gingival/periodontal health in 15 year old adolescents. All oral inflammatory markers studied, particularly s-SBI and CPI, were linked to a reduction in lung volume and flow rates. Most associations were statistically significant. The magnitude of the effects extended to a 4% lower lung function, depending on the oral inflammatory category and lung function parameter considered. Additional adjustments for hs-CRP and FeNO did not change the effect estimates. Moreover, effect sizes were almost unchanged after exclusion of smokers, asthmatics, and participants with anti-inflammatory treatment in the sensitivity analyses.

Novelty and interpretation of the study results

This study had two major novel aspects: (i) to the best of our knowledge, no previous study had explored the association between markers of oral cavity inflammation and lung function in adolescents; (ii) this study comprised a large sample of participants who had never been smokers, were not exposed to any occupational toxins, nor presenting any common chronic diseases. As there are no similar studies among adolescents in the literature, a comparative analysis of our findings is not possible. Nevertheless, our results are in good agreement with the conclusions of the systematic review by Zheng XT et al. [1] and also with other studies on adults, published after 2011 [2-7], which reported an association between periodontal inflammation or periodontal disease and decreased lung function.

Our findings indicate that this association is already present in adolescence. This result is important, because a high proportion of participants in our study had never been smokers, while studies on adults typically included both current and former smokers [3, 7]. Since smoking is a strong determinant of periodontal disease in adults [3, 9, 38], and both active and passive smoking are related to poor lung function in adults [39, 40] and children [39, 41], it is difficult to disentangle the effect of smoking from other confounders in adults. Those studies, which provided results for both smokers and non-smokers, showed that the association of oral inflammation with impaired lung function was largely due to smoking [3, 7, 42]. Others concluded that induced inflammation, rather than smoking exposure, were the principal cause of the association between oral inflammation and lung function [9].

Thus, the evidence for smoking being the major cause of the association between periodontal inflammation and lung function impairment is still ambiguous and inconclusive. Possible reasons for these mixed findings include (one or a combination of): methodological limitations due to the lack of prospective study designs, inappropriate inflammatory markers, incomplete adjustment for smoking, inconsistencies in the definitions of oral inflammation, PD, and lung health including COPD. There is only one randomized trial [14] and few intervention studies [12, 13] that support the assumption that induced inflammation is the major cause underlying the association between oral inflammation and lung function. Our results on adolescents who had never been smokers support this interpretation. A recent study revealed differences in the salivary microbiome [43], indicating a potential role of the oral microbiome in oral inflammation and possibly also in lung function. Moreover, the results of the sensitivity analyses, particularly when excluding participants with asthma or participants on current anti-inflammatory medication, suggest that the association between oral inflammation and lung function is affected neither by asthma nor by medication intake.

Strengths and limitations

Our study has several strengths. First, the directionality of the association is plausible, because it is unlikely that lung function affects oral inflammation. Moreover, the results of a randomized trial [14] and a two intervention studies [10, 12] support the assumption that oral inflammation affects lung function and that periodontal treatment lowers the CRP level [44]. Secondly, the reported effect estimates are consistent across several oral inflammatory parameters. Thirdly, the magnitude of the effect on FEV_1 and FVC reached reductions of up to 4%, depending on oral characteristics and lung function parameters, and was thus larger than reductions associated with other determinants of reduced lung function in adolescents, such as exposure to traffic-related pollutants [45, 46] and passive-smoke exposure [41]. Fourthly, no increased risk for reduced lung function was found for DMFT, an indicator for caries rather than oral inflammation. DMFT served as a negative control in this study, because carious or restored teeth are unlikely to have an impact on oral inflammation. Fifth, we considered a population that largely consisted of individual who had never smoked, which further strengthens our results, as smoking affects both oral inflammation and lung function. Sixth, the size of our study population was larger compared to most studies performed among adults, with the exception of the U.S. [47] and Korean [6] National Health and Nutritional Surveys, and the study by Holtfreter et al. [3], which had a comparable study size. Finally, the additional availability of hs-CRP and FeNO data adds further strength to our study.

Nonetheless, several limitations of our study need to be considered before drawing any far-reaching conclusions. Firstly, this was a cross-sectional study, which did not allow us to establish a temporal sequence between the occurrence of oral inflammation and lung function deficits. Secondly, while a decrease in lung function is highly relevant from a public health perspective, its clinical meaning is uncertain. In addition, tracking poor lung function from a young to an advanced age is already well established [39]. Thirdly, this study did not explore any common ground hypotheses for oral inflammation and lung function, such as a genetically defined susceptibility to inflammatory processes or, more speculatively, to epigenetic factors. Fourthly, hs-CRP is a general marker of systemic inflammation which depends on many other influencing factors. Moreover, hs-CRP was measured just once at the time of lung function testing and does not necessarily reflect low-grade inflammation over a longer time period. Fifthly, FeNO is not an ideal local inflammatory marker, because its main use is in asthmatics. Based in these caveats, we cannot rule out that the observed association between markers of gingivitis and lung function is not mediated by inflammatory processes. Finally, the role of smoking cannot be investigated properly due to insufficient power.

Conclusion

An association between indicators of gingivitis and a reduction in spirometric lung function indices was observed in adolescents, who predominantly had never been smokers. Neither the diagnosis of asthma nor the presence of anti-inflammatory medication affected this association. Moreover, the association was not related to serum hs-CRP and FeNO as markers of systemic or local inflammation. It remains to be assessed whether lung function can be improved by improving oral hygiene in adolescents.

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Study Groups

The GINIplus 15 Study Group:

Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Epidemiology I, Neuherberg (Heinrich J, Brüske I, Schulz H, Standl M, Schnappinger M, Sußmann M, Thiering E, Tiesler C, Flexeder C, Zeller C);

Marien Hospital Wesel, Department of Pediatrics, Research Institute, Wesel (Berdel D, von Berg A, Filipiak-Pittroff B);

Ludwig-Maximilians-University, Dr. von Hauner Children's Hospital, Munich (Koletzko S, Werkstetter K);

Technical University Munich, Department of Pediatrics, and Deutsche Rentenversicherung Bayern Süd, (Bauer CP, Hoffmann U);

IUF – Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany (Hoffmann B, Link E, Klümper C, Krämer U, Sugiri D).

The LISA 15 Study Group:

Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Epidemiology I, Neuherberg (Heinrich J, Brüske I, Schulz H, Standl M, Schnappinger M, Sußmann M, Thiering E, Tiesler C, Flexeder C, Zeller C);

Marien Hospital Wesel, Department of Pediatrics, Research Institute, Wesel (von Berg A);

Pediatric Practice, Bad Honnef (Schaaf B);

Technical University Munich, Department of Pediatrics, Munich (Hoffmann U);

Helmholtz Centre for Environmental Research – UFZ, Department of Environmental Immunology/Core Facility Studies, Leipzig (Lehmann I, Bauer M, Herberth G, Müller J, Röder S, Schilde M);

Municipal Hospital 'St. Georg', Department of Pediatrics, Leipzig (Borte M, Diez U, Dorn C, Braun E);

Technical University Munich, ZAUM – Center for Allergy and Environment, Munich (Ollert M, Grosch J).

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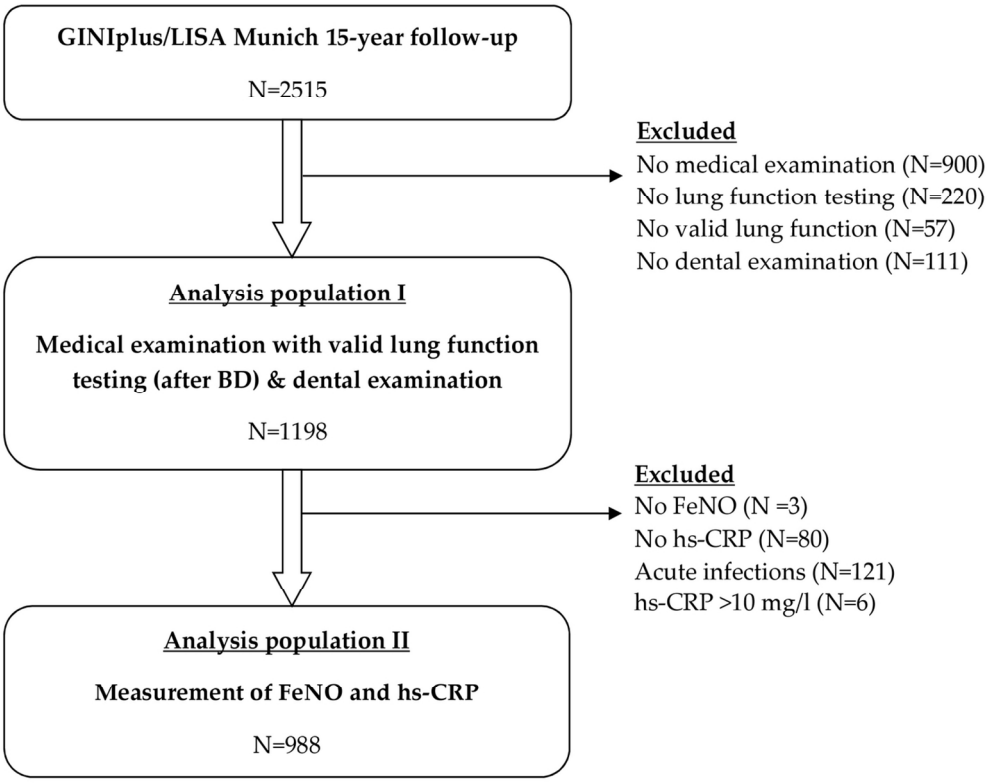

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Table 1: Study population characteristics

	Analysis Population 1 (n=1198)	Analysis Population 2 (N=988)
Study		
GINIplus observation	363(30.3)	300(30.4)
GINIplus intervention	432(36.1)	357(36.1)
LISA	403(33.6)	331(33.5)
Gender		
male	591(49.3)	481(48.7)
female	607(50.7)	507(51.3)
Age [years], mean(sd)	15.3(0.3)	15.3(0.3)
Weight females [kg], mean(sd)	57.7(9.5)	57.2(9.1)
Weight males [kg], mean(sd)	63.4(11)	63.2(11)
Height females[m], mean(sd)	166(6)	166(6.2)
Height males[m], mean(sd)	175.7(7.4)	175.8(7.2)
Education level		
low (< 10 years education)	59(4.9)	48(4.9)
medium (10 years education)	267(22.3)	210(21.3)
high (> 10 years education)	807(67.4)	681(68.9)
other	44(3.7)	37(3.7)
missing	21(1.8)	12(1.2)
Smoking		
no	1022(85.3)	848(85.8)
yes (daily, more than once per week)	44(3.7)	36(3.6)
yes (once per week or less))	54(4.5)	44(4.5)
missing	78(6.5)	60(6.1)
Current asthma or positive bronchodilation		
no	1074(90.4)	885(90.4)
yes	114(9.6)	94(9.6)
Medication last 7 days		
no	984(82.1)	829(83.9)
antibiotics, NSAID	100(8.3)	83(8.4)
betamimetics, steroids, leukotriene antagonists, antihistamines	62(5.2)	47(4.8)
antitussives,mucolytics,nasal spray	28(2.3)	14(1.4)
more than one	24(2)	15(1.5)
hs-CRP [mg/L], geometric mean (sd)	0.5(2.5)	0.4(2.4)
FeNO [ppb], geometric mean (sd)	20.4(1.8)	20(1.8)

Table 2: Descriptive characteristics of the lung function parameters in 1198 adolescents (Analysis population 1)

	mean(sd)
FEV1 L	3.63(0.65)
z-score FEV_1 z-score GLI	-0.23(0.92)
FVC L	4.05(0.77)
FVC z-score GLI, mean(sd)	-0.48(0.92)
FEV_1/FVC	0.9(0.05)
z-score FEV_1/FVC GLI	0.0(0.99)
FEF_{25-75} L/s	4.41(0.94)
z-score FEF_{25-75} L/s GLI	0.16(0.91)

Table 3: Results of linear regression of gingivitis/periodontitis with lung function in two different sets of adjustment (Analysis population I)

	Number sextants with sulcus bleeding						Number sextants with CPI degree 1, 2, or 3					
	SBI		**Model 1***		**Model 2+**		**CPI**		**Model 1***		**Model 2+**	
		n	**beta**	**p**				**n**	**beta**	**p**	**beta**	**p**
FEV_1 L	none	924	Ref		Ref		none	691	Ref		Ref	
	1-3	171	-0.036	0.278	-0.034	0.310	1	316	-0.024	0.392	-0.029	0.299
	3-6	103	**-0.09**	**0.036**	-0.078	0.070	2-6	**191**	**-0.071**	**0.032**	-0.064	0.056
FVC L	none	924	Ref		Ref		none	691	Ref		Ref	
	1-3	171	-0.012	0.753	-0.011	0.771	1	316	-0.024	0.437	-0.029	0.352
	3-6	103	**-0.108**	**0.023**	**-0.097**	**0.044**	2-6	191	-0.049	0.182	-0.043	0.240
FEV_1/FVC	none	924	Ref		Ref		none	691	Ref		Ref	
	1-3	171	-0.008	0.078	-0.007	0.091	1	316	-0.001	0.678	-0.002	0.635
	3-6	103	-0.000	0.960	0	0.996	2-6	191	-0.008	0.074	-0.007	0.096
FEF_{25-75} L/s	none	924	Ref		Ref		none	691	Ref		Ref	
	1-3	171	**-0.152**	**0.033**	**-0.140**	**0.048**	1	316	-0.032	0.594	-0.041	0.486
	3-6	103	-0.119	0.189	-0.104	0.255	2-6	**191**	**-0.185**	**0.009**	**-0.165**	**0.019**
z-score FEV_1 GLI	none	924	Ref		Ref		none	691	Ref		Ref	
	1-3	171	-0.083	0.265	-0.078	0.302	1	316	-0.064	0.306	-0.077	0.221
	3-6	103	**-0.189**	**0.049**	-0.162	0.094	2-6	**191**	**-0.16**	**0.030**	-0.143	0.055
z-score FVC GLI	None	924	Ref		Ref		none	691	Ref		Ref	
	1-3	171	-0.031	0.672	-0.028	0.700	1	316	-0.063	0.306	-0.073	0.234
	3-6	103	**-0.195**	**0.036**	-0.171	0.070	2-6	191	-0.097	0.176	-0.086	0.240
z-score FVC/FEV_1 GLI	None	906	Ref		Ref		none	677	Ref		Ref	
	1-3	170	-0.114	0.166	-0.111	0.176	1	311	-0.036	0.601	-0.040	0.564
	3-6	102	-0.008	0.939	-0.015	0.884	2-6	190	-0.112	0.169	-0.105	0.196
z-score FEF_{25-75} GLI	None	924	Ref		Ref		none	691	Ref		Ref	
	1-3	171	**-0.16**	**0.034**	-0.147	0.053	1	316	-0.032	0.608	-0.043	0.494
	3-6	103	-0.12	0.215	-0.102	0.294	2-6	191	**-0.193**	**0.010**	**-0.172**	**0.022**

* Model 1: adjusted for study, gender, age, height, weight, and education level

+ Model 2: additionally adjusted for smoking, medication within the last 7 days, and current asthma or positive bronchodilation

Table 4: Results of linear regression of gingivitis/periodontitis with lung function with additional adjustment for hs-CRP and FeNO (Analysis population II)

	Number sextants with sulcus bleeding								**Number sextants with CPI degree 1, 2, or 3**							
	SBI		**Model 2+**		**Adjustment hs-CRP**		**Adjustment FeNO**		**CPI**		**Model 2+**		**Adjustment hs-CRP**		**Adjustment FeNO**	
		n	**beta**	**p**	**beta**	**p**	**beta**	**p**		**n**	**beta**	**p**	**beta**	**p**	**beta**	**p**
FEV_1 L	none	753	Ref		Ref		Ref		none	563	Ref		Ref		Ref	
	1-3	145	-0.019	0.584	-0.015	0.668	-0.020	0.569	1	261	-0.028	0.344	-0.025	0.412	-0.029	0.340
	3-6	81	**-0.093**	**0.049**	-0.091	0.053	**-0.093**	**0.049**	2-6	155	-0.056	0.116	-0.055	0.123	-0.056	0.116
FVC L	none	753	Ref		Ref		Ref		none	563	Ref		Ref		Ref	
	1-3	145	0.007	0.868	0.012	0.761	0.005	0.9	1	261	-0.026	0.436	-0.021	0.525	-0.027	0.427
	3-6	81	**-0.115**	**0.028**	**-0.113**	**0.031**	**-0.116**	**0.028**	2-6	155	-0.033	0.407	-0.032	0.426	-0.033	0.408
FEV_1/FVC	none	753	Ref		Ref		Ref		none	563	Ref		Ref		Ref	
	1-3	145	-0.007	0.119	-0.007	0.111	-0.007	0.123	1	261	-0.003	0.489	-0.003	0.468	-0.003	0.494
	3-6	81	0.001	0.810	0.001	0.819	0.001	0.809	2-6	155	-0.007	0.138	-0.007	0.136	-0.007	0.138
FEF_{25-75} L/s	none	753	Ref		Ref		Ref		none	563	Ref		Ref		Ref	
	1-3	145	-0.119	0.114	-0.114	0.132	-0.12	0.114	1	261	-0.032	0.614	-0.027	0.673	-0.032	0.616
	3-6	81	-0.092	0.358	-0.09	0.369	-0.092	0.358	2-6	155	**-0.151**	**0.046**	**-0.150**	**0.048**	**-0.151**	**0.046**
z-score FEV_1 GLI	none	753	Ref		Ref		Ref		none	563	Ref		Ref		Ref	
	1-3	145	-0.045	0.571	-0.037	0.644	-0.045	0.570	1	261	-0.073	0.274	-0.066	0.326	-0.073	0.275
	3-6	81	-0.204	0.052	-0.201	0.056	-0.204	0.052	2-6	155	-0.13	0.102	-0.128	0.108	-0.13	0.102
z-score FVC GLI	None	753	Ref		Ref		Ref		none	563	Ref		Ref		Ref	
	1-3	145	0.006	0.936	0.016	0.834	0.005	0.949	1	261	-0.064	0.331	-0.055	0.401	-0.064	0.328
	3-6	81	**-0.221**	**0.032**	**-0.217**	**0.034**	**-0.221**	**0.031**	2-6	155	-0.073	0.350	-0.07	0.366	-0.073	0.351
z-score FVC/FEV_1 GLI	None	737	Ref		Ref		Ref		none	551	Ref		Ref		Ref	
	1-3	145	-0.081	0.357	-0.087	0.326	-0.084	0.340	1	257	-0.024	0.745	-0.029	0.695	-0.025	0.738
	3-6	80	-0.009	0.938	-0.011	0.925	-0.01	0.933	2-6	154	-0.088	0.323	-0.089	0.316	-0.087	0.325
z-score FEF_{25-75} GLI	None	753	Ref		Ref		Ref		none	563	Ref		Ref		Ref	
	1-3	145	-0.126	0.121	-0.120	0.140	-0.127	0.120	1	261	-0.037	0.587	-0.032	0.646	-0.037	0.588
	3-6	81	-0.095	0.376	-0.093	0.388	-0.095	0.376	2-6	155	**-0.163**	**0.046**	**-0.161**	**0.048**	**-0.163**	**0.046**

+Model 2: additionally adjusted for smoking, medication within the last 7 days, and current asthma or positive bronchodilation

Online Supplement on

Lung function and oral health in adolescents

Joachim Heinrich[1,2,3], Elisabeth Thiering[2,3,4], Rudolf Jorres[1], Marie Standl[2,3], Holger Schulz[2, 3,] , Jan Kühnisch[5]

1 Ludwig Maximilians University Munich, University Hospital Munich, Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, Munich, Germany

2 Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Epidemiology I, Neuherberg, Germany

3 Comprehensive Pneumology Center Munich (CPC-M), Member of the German Center for Lung Research

4 Ludwig Maximilians University of Munich, Dr. von Hauner Children's Hospital, Munich, Germany

5 Department of Operative Dentistry and Periodontology, University Hospital, Ludwig-Maximilians-Universität München, Munich, Germany

Corresponding author:

Dr. Joachim Heinrich

Ludwig Maximilians University Munich, University Hospital Munich,

Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, Munich, Germany Ziemssenstraße 1

80336 München Tel.: +49 89 440023251

Email: joachim.heinrich@med.uni-muenchen.de

Table S1: Results of linear regression caries (DMFT) with lung function in two different sets of adjustment (Analysis population I)

	Caries DMFT		Model 1*		Model 2+	
		n	beta	p	beta	p
FEV_1 L	0	768	Ref		Ref	
	1-2	279	-0.007	0.800	-0.004	0.899
	>2	151	0.067	0.059	**0.072**	**0.045**
FVC L	0	768	Ref		Ref	
	1-2	279	-0.008	0.792	-0.009	0.783
	>2	151	0.065	0.098	0.069	0.082
FEV_1/FVC	0	768	Ref		Ref	
	1-2	279	0.001	0.818	0.002	0.629
	>2	151	0.002	0.720	0.002	0.669
FEF_{25-75} L/s	0	768	Ref		Ref	
	1-2	279	-0.05	0.399	-0.038	0.527
	>2	151	0.061	0.418	0.066	0.388
z-score FEV_1 GLI	0	768	Ref		Ref	
	1-2	279	-0.018	0.773	-0.012	0.849
	>2	151	0.143	0.074	0.153	0.057
z-score FVC GLI	0	768	Ref		Ref	
	1-2	279	-0.025	0.681	-0.027	0.658
	>2	151	0.125	0.109	0.132	0.092
z-score FVC/FEV_1 GLI	0	753	Ref		Ref	
	1-2	275	0.024	0.725	0.049	0.472
	>2	150	0.037	0.674	0.043	0.620
z-score FEF_{25-75} GLI	0	768	Ref		Ref	
	1-2	279	-0.047	0.454	-0.034	0.591
	>2	151	0.055	0.493	0.061	0.454

* Model 1: adjusted for study, gender, age, height, weight, and education level

+ Model 2: additionally adjusted for smoking, medication within the last 7 days, and current asthma or positive bronchodilation

Table S2: Sensitivity analysis: results of linear regression of gingivitis/periodontitis with lung function in non-smokers (Analysis population II)

	Number sextants with sulcus bleeding						Number sextants with CPI degree 1, 2, or 3					
	SBI		**Model 1***		**Model 2+**		**CPI**		**Model 1***		**Model 2+**	
		n	**beta**	**p**	**beta**	**p**		**n**	**beta**	**p**	**beta**	**p**
FEV$_1$ L	none	795	Ref		Ref		none	603	Ref		Ref	
	1-3	141	-0.061	0.101	-0.056	0.132	1	263	-0.053	0.086	-0.058	0.059
	3-6	86	-0.088	0.063	-0.081	0.086	2-6	156	**-0.088**	**0.017**	**-0.082**	**0.027**
FVC L	none	795	Ref		Ref		none	603	Ref		Ref	
	1-3	141	-0.031	0.442	-0.028	0.490	1	263	-0.062	0.069	**-0.068**	**0.049**
	3-6	**86**	**-0.107**	**0.040**	-0.100	0.056	2-6	156	-0.061	0.131	-0.057	0.164
FEV$_1$/FVC	none	795	Ref		Ref		none	603	Ref		Ref	
	1-3	**141**	**-0.009**	**0.045**	-0.009	0.058	1	263	-0.001	0.874	-0.001	0.854
	3-6	86	-0.001	0.906	-0.001	0.907	2-6	156	-0.009	0.051	-0.009	0.063
FEF$_{25-75}$ L/s	none	795	Ref		Ref		none	603	Ref		Ref	
	1-3	**141**	**-0.192**	**0.014**	**-0.180**	**0.021**	1	263	-0.050	0.442	-0.058	0.377
	3-6	86	-0.096	0.334	-0.091	0.361	2-6	156	**-0.200**	**0.010**	**-0.186**	**0.017**
z-score FEV$_1$ GLI	none	795	Ref		Ref		none	603	Ref		Ref	
	1-3	141	-0.13	0.115	-0.121	0.143	1	263	-0.131	0.057	**-0.145**	**0.035**
	3-6	86	-0.169	0.107	-0.156	0.140	2-6	156	**-0.182**	**0.027**	**-0.170**	**0.038**
z-score FVC GLI	None	795	Ref		Ref		none	603	Ref		Ref	
	1-3	141	-0.062	0.438	-0.058	0.475	1	263	**-0.139**	**0.039**	**-0.151**	**0.025**
	3-6	86	-0.175	0.088	-0.162	0.117	2-6	156	-0.107	0.181	-0.099	0.218
z-score FVC/FEV$_1$ GLI	None	778	Ref		Ref		none	589	Ref		Ref	
	1-3	**140**	**-0.185**	**0.041**	-0.168	0.062	1	259	0.011	0.886	0.009	0.901
	3-6	85	-0.034	0.768	-0.039	0.738	2-6	155	-0.158	0.079	-0.146	0.103
z-score FEF$_{25-75}$ GLI	None	795	Ref		Ref		none	603	Ref		Ref	
	1-3	**141**	**-0.202**	**0.015**	**-0.190**	**0.022**	1	263	-0.059	0.391	-0.068	0.324
	3-6	86	-0.091	0.390	-0.086	0.419	2-6	156	**-0.205**	**0.013**	**-0.192**	**0.021**

* Model 1: adjusted for study, gender, age, height, weight, and education level

+ Model 2: additionally adjusted for medication within the last 7 days, and current asthma or positive bronchodilation

Table S3: Sensitivity analysis: results of linear regression of gingivitis/periodontitis with lung function in non-asthmatics/ no positive bronchodilation (Analysis population II)

	Number sextants with sulcus bleeding						Number sextants with CPI degree 1, 2, or 3					
	SBI	**n**	**Model 1*** **beta**	**p**	**Model 2+** **beta**	**p**	**CPI**	**n**	**Model 1*** **beta**	**p**	**Model 2+** **beta**	**p**
FEV_1 L	none	833	Ref		Ref		none	624	Ref		Ref	
	1-3	150	-0.016	0.652	-0.018	0.612	1	287	-0.027	0.365	-0.027	0.354
	3-6	91	**-0.101**	**0.026**	**-0.102**	**0.025**	2-6	163	**-0.075**	**0.034**	**-0.077**	**0.030**
FVC L	none	833	Ref		Ref		none	624	Ref		Ref	
	1-3	150	0.002	0.962	-0.001	0.977	1	287	-0.026	0.435	-0.026	0.419
	3-6	91	**-0.117**	**0.021**	**-0.119**	**0.019**	2-6	163	-0.062	0.118	-0.064	0.106
FEV_1/FVC	none	833	Ref		Ref		none	624	Ref		Ref	
	1-3	150	-0.005	0.216	-0.005	0.233	1	287	-0.002	0.611	-0.002	0.618
	3-6	91	-0.001	0.912	-0	0.937	2-6	163	-0.006	0.179	-0.006	0.189
FEF_{25-75} L/s	none	833	Ref		Ref		none	624	Ref		Ref	
	1-3	150	-0.118	0.117	-0.117	0.123	1	287	-0.033	0.597	-0.033	0.599
	3-6	91	-0.148	0.123	-0.147	0.128	2-6	163	**-0.179**	**0.017**	**-0.180**	**0.017**
z-score FEV_1 GLI	none	833	Ref		Ref		none	624	Ref		Ref	
	1-3	150	-0.035	0.656	-0.038	0.632	1	287	-0.067	0.306	-0.068	0.298
	3-6	91	**-0.204**	**0.043**	**-0.208**	**0.041**	2-6	163	**-0.161**	**0.042**	**-0.165**	**0.039**
z-score FVC GLI	None	833	Ref		Ref		none	624	Ref		Ref	
	1-3	150	-0.001	0.985	-0.006	0.937	1	287	-0.062	0.332	-0.064	0.320
	3-6	91	**-0.210**	**0.033**	**-0.215**	**0.031**	2-6	163	-0.116	0.135	-0.12	0.122
z-score FVC/FEV_1 GLI	None	816	Ref		Ref		none	611	Ref		Ref	
	1-3	149	-0.091	0.28	-0.091	0.282	1	282	-0.055	0.431	-0.054	0.443
	3-6	90	-0.029	0.787	-0.029	0.789	2-6	162	-0.096	0.258	-0.097	0.253
z-score FEF_{25-75} GLI	None	833	Ref		Ref		none	624	Ref		Ref	
	1-3	150	-0.123	0.124	-0.12	0.136	1	287	-0.036	0.589	-0.036	0.59
	3-6	91	-0.144	0.157	-0.143	0.164	2-6	163	**-0.185**	**0.021**	**-0.184**	**0.022**

* Model 1: adjusted for study, gender, age, height, weight, and education level

+ Model 2: additionally adjusted for smoking and medication within the last 7 days

Table S4: Sensitivity analysis: results of linear regression of gingivitis/periodontitis with lung function in participants without medication in the last 7 days prior lung function testing (Analysis population II)

	Number sextants with sulcus bleeding					Number sextants with CPI degree 1, 2, or 3				
	SBI		**Model 1***		**Model 2+**	**CPI**		**Model 1***		**Model 2+**	
		n	**beta**	**p**	**beta**	**p**		**n**	**beta**	**p**	**beta**	**p**
FEV_1 L	none	760	Ref		Ref		none	565	Ref		Ref	
	1-3	139	-0.026	0.487	-0.026	0.482	1	265	-0.025	0.412	-0.028	0.363
	3-6	85	-0.107	0.023	**-0.101**	**0.033**	2-6	154	**-0.078**	**0.033**	**-0.076**	**0.039**
FVC L	none	760	Ref		Ref		none	565	Ref		Ref	
	1-3	139	-0.015	0.720	-0.015	0.717	1	265	-0.022	0.519	-0.026	0.450
	3-6	85	**-0.132**	**0.011**	**-0.125**	**0.017**	2-6	154	-0.065	0.110	-0.065	0.115
FEV_1/FVC	none	760	Ref		Ref		none	565	Ref		Ref	
	1-3	139	-0.005	0.293	-0.005	0.282	1	265	-0.003	0.452	-0.003	0.455
	3-6	85	0.001	0.889	0.001	0.873	2-6	154	-0.006	0.193	-0.006	0.221
FEF_{25-75} L/s	none	760	Ref		Ref		none	565	Ref		Ref	
	1-3	139	-0.094	0.236	-0.089	0.265	1	265	-0.025	0.699	-0.028	0.671
	3-6	85	-0.149	0.140	-0.141	0.164	2-6	154	**-0.182**	**0.020**	**-0.169**	**0.032**
z-score FEV_1 GLI	none	760	Ref		Ref		none	565	Ref		Ref	
	1-3	139	-0.058	0.480	-0.057	0.496	1	265	-0.073	0.284	-0.082	0.235
	3-6	85	**-0.219**	**0.037**	-0.204	0.053	2-6	154	**-0.171**	**0.037**	**-0.165**	**0.046**
z-score FVC GLI	None	760	Ref		Ref		none	565	Ref		Ref	
	1-3	139	-0.035	0.665	-0.033	0.685	1	265	-0.062	0.355	-0.07	0.294
	3-6	85	**-0.240**	**0.019**	**-0.226**	**0.028**	2-6	154	-0.126	0.113	-0.124	0.122
z-score FVC/FEV_1 GLI	None	743	Ref		Ref		none	552	Ref		Ref	
	1-3	139	-0.08	0.371	-0.086	0.338	1	261	-0.068	0.366	-0.06	0.421
	3-6	85	0.03	0.793	0.025	0.824	2-6	154	-0.083	0.349	-0.075	0.399
z-score FEF_{25-75} GLI	None	760	Ref		Ref		none	565	Ref		Ref	
	1-3	139	-0.101	0.229	-0.094	0.267	1	265	-0.032	0.647	-0.037	0.600
	3-6	85	-0.142	0.184	-0.133	0.215	2-6	154	**-0.189**	**0.024**	**-0.174**	**0.038**

* Model 1: adjusted for study, gender, age, height, weight, and education level

+ Model 2: additionally adjusted for smoking and current asthma or positive bronchodilation