Lung function and oral health in adolescents

To the Editor:

Only a few studies have investigated the association between periodontal diseases (PD), such as gingivitis or periodontitis, and lung health. The latest systematic review identified 14 observational studies and reported a pooled OR of 2.08 (95% CI 1.48–2.91) for chronic obstructive pulmonary disease (COPD) [1]. More recent studies have confirmed the adverse effects of oral inflammation on lung disease [2], but not all [3]. Three interventional trials in adults showed the positive effects of periodontal therapy on lung function in patients with COPD. Two nonrandomised trials [3, 4] and a randomised trial [5] found improved lung function and reduced exacerbation rates in COPD patients after oral hygiene instructions and periodontal treatment. All of these studies on oral inflammation and lung health were restricted to adults, in whom smoking as a common risk factor for local inflammation and indirect effects due to systemic inflammation was suggested as an underlying mechanism [6, 7]. However, Linden *et al.* [6] summarised that the inflammatory status of the airways might be affected by aspiration of dental plaque and/or haematogenous dissemination of inflammatory mediators and periodontal bacteria.

We therefore analysed the association between lung function assessed using spirometry and oral health indicators in adolescents, as well as the potential mediating role of low-grade systemic and local inflammation indicated by high sensitivity serum C-reactive protein (hs-CRP) and exhaled nitric oxide fraction (F_{ENO}).

The source study populations were two German birth cohorts, GINIplus (German Infant Nutritional Intervention Program PLUS Air pollution and Genetics on Allergy development) and LISA (Influence of Life-style related factors on the development of the Immune System and Allergies in East and West Germany). Both population-based cohorts recruited term-born, normal weight neonates of Caucasian origin in the years 1995–1999. The details of the study design and its recruitment have been described previously [8, 9]. The current analyses were restricted to 988 participants from the Munich (Germany) study centre, who participated in the 15-year follow-up with valid lung function testing and dental examination, as well as data on hs-CRP and F_{ENO}. Both studies were approved by the local ethics committees and written informed consent was obtained.

Spirometry and inhalation of bronchodilator medication was performed in line with American Thoracic Society (ATS)/European Respiratory Society (ERS) recommendations [10]. The EasyOne Worldspirometer (ndd, Zurich, Switzerland) was used to obtain flow–volume curves; details of spirometry testing are described elsewhere [11]. Standardised z-scores of the lung function parameters, the largest sum of forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), FEV_1/FVC, and the mean forced expiratory flow at 25–75% of FVC ($FEF_{25–75}$) were calculated based on the reference equations for spirometry from the Global Lung Initiative (GLI) [12, 13]. The analysis used only post-bronchodilator lung function data.

The methods for dental examination are described in detail elsewhere [14, 15]. Sulcus bleeding index (SBI) was measured using a blunt probe. Decisions were made for each sextant if sulcus bleeding was present or not. Due to the young age of the participants, no periodontal pockets were measured (scores 3 and 4). We labelled the SBI as "gingival bleeding". To assess the community periodontal index (CPI), the number of sextants with calculus and the number of sextants with bleeding was summed. As severe periodontal status was not recorded in young subjects, we labelled the CPI-derived data as "oral hygiene". The caries status was determined as the decayed, missing, filled teeth (DMFT) index for permanent dentition, using World Health Organization (WHO) standard methodology [16].

@ERSpublications
Poor oral health is associated with poor lung function in adolescents
http://ow.ly/h2Yw30n4B9A

Cite this article as: Heinrich J, Thiering E, Jörres RA, *et al.* Lung function and oral health in adolescents. *Eur Respir J* 2019; 53: 1801951 [https://doi.org/10.1183/13993003.01951-2018].

TABLE 1 Results of linear regression of oral health inflammation with lung function post-bronchodilation and additional adjustment for high sensitivity serum C-reactive protein (hs-CRP) and exhaled nitric oxide fraction (F_{eNO})

	Subjects n	Gingival bleeding[#]									Subjects n	Oral hygiene[¶]								
		Adjusted model[+]			Additional adjustment hs-CRP			Additional adjustment F_{eNO}				Adjusted model[+]			Additional adjustment hs-CRP			Additional adjustment F_{eNO}		
		Beta	95% CI	p-value	Beta	95% CI	p-value	Beta	95% CI	p-value		Beta	95% CI	p-value	Beta	95% CI	p-value	Beta	95% CI	p-value
FEV_1 L																				
None	753	Ref.			Ref.			Ref.												
1–3	145	−0.019	−0.10–0.06	0.584	−0.015	−0.09–0.06	0.668	−0.020	−0.10–0.06	0.569										
3–6	81	**−0.093**	−0.19–0.01	**0.049**	−0.091	−0.19–0.01	0.053	**−0.093**	−0.19–0.01	**0.049**										
FVC L																				
None	753	Ref.			Ref.			Ref.												
1–3	145	0.007	−0.07–0.09	0.868	0.012	−0.07–0.09	0.761	0.005	−0.07–0.08	0.900										
3–6	81	**−0.115**	−0.21– −0.02	**0.028**	**−0.113**	−0.21– −0.01	**0.031**	**−0.116**	−0.21– −0.02	**0.028**										
FEV_1/FVC																				
None	753	Ref.			Ref.			Ref.												
1–3	145	−0.007	−0.01– −0.01	0.119	−0.007	−0.01– −0.01	0.111	−0.007	−0.01– −0.01	0.123										
3–6	81	0.001	−0.02–0.02	0.810	0.001	−0.02–0.02	0.819	0.001	−0.02–0.02	0.809										
$FEF_{25–75}$ L·s^{-1}																				
None	753	Ref.			Ref.			Ref.												
1–3	145	−0.119	−0.28–0.04	0.114	−0.114	−0.27–0.04	0.132	−0.12	−0.28–0.04	0.114										
3–6	81	−0.092	−0.29–0.10	0.358	−0.09	−0.29–0.11	0.369	−0.092	−0.29–0.10	0.358										
FEV_1 GLI z-score																				
None	753	Ref.			Ref.			Ref.												
1–3	145	−0.045	−0.20–0.11	0.571	−0.037	−0.19–0.12	0.644	−0.045	−0.20–0.11	0.570										
3–6	81	−0.204	−0.42–0.01	0.052	−0.201	−0.42–0.01	0.056	−0.204	−0.42–0.01	0.052										
FVC GLI z-score																				
None	753	Ref.			Ref.			Ref.												
1–3	145	0.006	−0.15–0.16	0.936	0.016	−0.14–0.17	0.834	0.005	−0.15–0.16	0.949										
3–6	81	**−0.221**	−0.42– −0.02	**0.032**	**−0.217**	−0.41– −0.02	**0.034**	**−0.221**	−0.42– −0.02	**0.031**										
FVC/FEV_1 GLI z-score																				
None	737	Ref.			Ref.			Ref.												
1–3	145	−0.081	−0.26–0.10	0.357	−0.087	−0.26–0.09	0.326	−0.084	−0.26–0.09	0.340										
3–6	80	−0.009	−0.24–0.23	0.938	−0.011	−0.25–0.22	0.925	−0.010	−0.25–0.23	0.933										
$FEF_{25–75}$ GLI z-score																				
None	753	Ref.			Ref.			Ref.												
1–3	145	−0.126	−0.28–0.03	0.121	−0.120	−0.28–0.04	0.140	−0.127	−0.28–0.03	0.120										
3–6	81	−0.095	−0.31–0.12	0.376	−0.093	−0.31–0.12	0.388	−0.095	−0.31–0.12	0.376										
FEV_1 L																				
None											563	Ref.			Ref.			Ref.		
1											261	−0.028	−0.09–0.03	0.344	−0.025	−0.08–0.03	0.412	−0.029	−0.09–0.03	0.340
2–6											155	−0.056	−0.13–0.02	0.116	−0.055	−0.13–0.02	0.123	−0.056	−0.13–0.02	0.116
FVC L																				
None											563	Ref.			Ref.			Ref.		
1											261	−0.026	−0.08–0.03	0.436	−0.021	−0.08–0.04	0.525	−0.027	−0.09–0.03	0.427
2–6											155	−0.033	−0.11–0.05	0.407	−0.032	−0.11–0.05	0.426	−0.033	−0.11–0.05	0.408
FEV_1/FVC																				
None											563	Ref.			Ref.			Ref.		
1											261	−0.003	−0.00– −0.00	0.489	−0.003	−0.00– −0.00	0.468	−0.003	−0.00– −0.00)	0.494
2–6											155	−0.007	−0.01– −0.01	0.138	−0.007	−0.01– −0.01	0.136	−0.007	−0.01– −0.01	0.138
$FEF_{25–75}$ L·s^{-1}																				
None											563	Ref.			Ref.			Ref.		
1											261	−0.032	−0.15–0.09	0.614	−0.027	−0.14–0.09	0.673	−0.032	−0.15–0.09	0.616
2–6											155	**−0.151**	−0.31–0.01	**0.046**	**−0.150**	−0.31–0.01	**0.048**	**−0.151**	−0.31–0.01	**0.046**
FEV_1 GLI z-score																				
None											563	Ref.			Ref.			Ref.		
1											261	−0.073	−0.21–0.06	0.274	−0.066	−0.20–0.07	0.326	−0.073	−0.21–0.06	0.275
2–6											155	−0.13	−0.29–0.03	0.102	−0.128	−0.28–0.03	0.108	−0.130	−0.29–0.03	0.102
FVC GLI z-score																				
None											563	Ref.			Ref.			Ref.		
1											261	−0.064	−0.20–0.07	0.331	−0.055	−0.19–0.08	0.401	−0.064	−0.20–0.07	0.328
2–6											155	−0.073	−0.23–0.08	0.350	−0.070	−0.23–0.09	0.366	−0.073	−0.23–0.08	0.351
FVC/FEV_1 GLI z-score																				
None											551	Ref.			Ref.			Ref.		
1											257	−0.024	−0.16–0.11	0.745	−0.029	−0.19–0.13	0.695	−0.025	−0.16–0.11	0.738
2–6											154	−0.088	−0.26–0.09	0.323	−0.089	−0.27–0.09	0.316	−0.087	−0.26–0.09	0.325
$FEF_{25–75}$ GLI z-score																				
None											563	Ref.			Ref.			Ref.		
1											261	−0.037	−0.17–0.10	0.587	−0.032	−0.17–0.11	0.646	−0.037	−0.17–0.10	0.588
2–6											155	**−0.163**	−0.32– −0.01	**0.046**	**−0.161**	−0.32–−0.00	**0.048**	**−0.163**	−0.32– −0.01	**0.046**

Bold indicates statistically significant relationships. FEV_1: forced expiratory volume in 1 s; Ref.: reference; FVC: forced vital capacity; $FEF_{25–75}$: forced expiratory flow at 25–75% of FVC; GLI: Global Lung Initiative. [#]: number of sextants with sulcus bleeding; [¶]: number of sextants with a community periodontal index degree >0; [+]: adjusted for study, sex, age, height, weight, education level, smoking, medication within the last 7 days, and current asthma or positive bronchodilation.

Serum hs-CRP was measured using the Tina-quant CRP (latex) high-sensitivity assay (Roche, Mannheim, Germany). *F*eNO was measured using the NIOX MINO (Aerocrine, Sweden) from controlled expiration for 10 s at a flow rate of 50 $mL \cdot s^{-1}$ in accordance with the ATS/ERS recommendation [10]. Height and weight were measured during physical examination without shoes and with light clothing [11]. Education level was considered to be a proxy for socioeconomic status. Moreover, information was collected on smoking and medication within the last 7 days [11].

All analyses were performed using the statistical software R, version 3.3.3 (https://www.r-project.org/). Linear regression models were used to analyse the association between oral health (independent variable) and spirometric lung function parameters post-bronchodilation (dependent variable) adjusted for study, sex, age, height, weight, education level, smoking, medication within the last 7 days, and current asthma or positive bronchodilation.

Sensitivity analyses of oral health and spirometric lung function parameters post-bronchodilation were conducted in nonsmokers, non-asthmatics and subjects who had not taken any relevant medication during the past 7 days. The association of DMFT as a negative control with lung function parameters post-bronchodilation was also analysed to rule out confounding by other potential factors.

The highest categories of gingival bleeding (3–6 sextants with sulcus bleeding) and poor oral hygiene (2–6 sextants with CPI degree >0) were associated with significantly reduced spirometric lung volumes and flow rates post-bronchodilation, compared with those with no gingival bleeding or good oral hygiene, respectively (table 1). Table 1 also shows also that these associations were not affected by additional adjustment for hs-CRP or *F*eNO. The association analysis of DMFT (as a negative control) with all lung function parameters post-bronchodilation did not reveal any substantial adverse association (data not shown). We performed several sensitivity analyses with lung function parameters post-bronchodilation, excluding smokers and second-hand smokers, subjects with asthma, and subjects with anti-inflammatory medication drug intake during the last 7 days prior to medical examination. The exclusion of these potential influencing factors did not substantially change the effect estimates (data not shown).

There are several reasons why oral health may be related to lung function [6, 7]: by aspiration of dental plaque and/or haematogenous dissemination of inflammatory mediators and periodontal bacteria, a shared pathogenesis between impaired lung function and oral inflammatory indicators. PD may also be associated with low-grade systemic inflammation, which might affect lung function. This study is novel in two major aspects. To the best of our knowledge, no previous study has explored the association between markers of inflammation in oral cavity and lung function in adolescents. Secondly, this study comprised a large sample of participants who were certainly never-smokers, were not exposed to any occupational toxicants and did not demonstrate common chronic diseases.

Our findings indicate that the adverse effects of oral inflammation on lung function may start during adolescence. This result is important, because a high proportion of participants were never-smokers, while the studies in adults mostly included smokers or exsmokers. As smoking is a strong determinant for PD in adults, and active and passive smoking is related to poor lung function in adults and children, it is difficult to disentangle the effect of smoking from other factors in adults.

Our study has several strengths: consistent findings across several oral inflammatory parameters; a large sample size; an almost never-smoking population; robust associations across several sensitivity analyses; plausible direction of the effects; and hs-CRP and *F*eNO data. However, it also has a few limitations: a cross-sectional study design; selective drop-out; uncertain clinical meaning of the lung function decrease; limitations of included inflammatory blood markers; and *F*eNO.

As no effect modification was observed for markers of systemic or local inflammation, we conclude that aspiration of bacteria or bacterial components from the oral cavity might be considered an underlying pathomechanism for oral inflammatory and lung function.

Joachim Heinrich[1,2,3], Elisabeth Thiering[2,4], Rudolf A. Jörres[1], Holger Schulz[2], Jan Kühnisch[5] and Marie Standl[2]
[1]Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, Ludwig Maximilians University of Munich, University Hospital Munich, Munich, Germany. [2]Helmholtz Zentrum München – German Research Center for Environmental Health, Institute of Epidemiology, Neuherberg, Germany. [3]Allergy and Lung Health Unit, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Australia. [4]Ludwig Maximilians University of Munich, Dr. von Hauner Children's Hospital, Munich, Germany. [5]Dept of Operative Dentistry and Periodontology, Ludwig Maximilians University of Munich, University Hospital Munich, Munich, Germany.

Correspondence: Joachim Heinrich, Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, Ludwig Maximilians University Munich, University Hospital Munich, Ziemssenstraße 1, Munich 80336, Germany. E-mail: joachim.heinrich@med.uni-muenchen.de

Received: Jan 16 2018 | Accepted after revision: Nov 15 2018

Acknowledgements: We thank all participants and their families for taking part in the study, the obstetric units for allowing recruitment and the GINIplus and LISA study team for its excellent work. The GINIplus 15 Study Group was made up of the following: Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Epidemiology I, Neuherberg, Germany (J. Heinrich, I. Brüske, H. Schulz, M. Standl, M. Schnappinger, M. Ferland, E. Thiering, C. Tiesler, C. Flexeder and C. Zeller); Dept of Pediatrics, Marien Hospital Wesel, Research Institute, Wesel, Germany (D. Berdel, A. von Berg and B. Filipiak-Pittroff); Dr. von Hauner Children's Hospital, Ludwig Maximilians University Munich, Munich, Germany (S. Koletzko and K. Werkstetter); Dept of Pediatrics, Technical University of Munich, Munich, Germany, and Deutsche Rentenversicherung Bayern Süd (C.P. Bauer and U. Hoffmann); and IUF – Leibniz Research Institute for Environmental Medicine, Dusseldorf, Germany (T. Schikowski, E. Link, C. Klümper, U. Krämer and D. Sugiri). The LISA 15 Study Group was made up of the following: Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Epidemiology I, Neuherberg, Germany (J. Heinrich, I. Brüske, H. Schulz, M. Standl, M. Schnappinger, M. Ferland, E. Thiering, C. Tiesler, C. Flexeder and C. Zeller); Dept of Pediatrics, Research Institute, Marien Hospital Wesel, Wesel, Germany (A. von Berg); Pediatric Practice, Bad Honnef, Germany (G. Schaaf); Dept of Pediatrics, Technical University Munich, Munich, Germany (U. Hoffmann); Dept of Environmental Immunology/Core Facility Studies, Helmholtz Centre for Environmental Research – UFZ, Leipzig, Germany (I. Lehmann, M. Bauer, G. Herberth, J. Müller, S. Röder and M. Schilde); Dept of Pediatrics, Municipal Hospital "St. Georg", Leipzig, Germany (M. Borte, U. Diez, C. Dorn and E. Braun); and ZAUM – Center for Allergy and Environment, Technical University of Munich, Munich, Germany (M. Ollert and J. Grosch).

Conflict of interest: None declared.

Support statement: The 15-year follow-up examination of the GINIplus and LISA studies was partially supported by the Commission of the European Communities, the 7th Framework Programme, the MeDALL project as well as by the companies Mead Johnson and Nestlé. The dental examination was funded by grants obtained from the German Research Foundation (KU-2518/1-1, KU-2518/1-2, HE-3294/7-1, and HE-3294/7-2). GABA GmbH, Lörrach, Germany, supported this study by providing oral healthcare packages for all the participating adolescents as incentives. This work was supported by the Comprehensive Pneumology Center Munich (CPC-M) as member of the German Center for Lung Research. Funding information for this article has been deposited with the Crossref Funder Registry.

References

1 Zeng XT, Tu ML, Liu DY, *et al.* Periodontal disease and risk of chronic obstructive pulmonary disease: a meta-analysis of observational studies. *PloS one* 2012; 7: e46508.
2 Perez Barrionuevo AM, Gomez Real F, Igland J, *et al.* Periodontal health status and lung function in two Norwegian cohorts. *PloS one* 2018; 13: e0191410.
3 Shen TC, Chang PY, Lin CL, *et al.* Periodontal treatment reduces risk of adverse respiratory events in patients with chronic obstructive pulmonary disease: a propensity-matched cohort study. *Medicine (Baltimore)* 2016; 95: e3735.
4 Kucukcoskun M, Baser U, Oztekin G, *et al.* Initial periodontal treatment for prevention of chronic obstructive pulmonary disease exacerbations. *J Periodontol* 2013; 84: 863–870.
5 Zhou X, Han J, Liu Z, *et al.* Effects of periodontal treatment on lung function and exacerbation frequency in patients with chronic obstructive pulmonary disease and chronic periodontitis: a 2-year pilot randomized controlled trial. *J Clin Periodontol* 2014; 41: 564–572.
6 Linden GJ, Lyons A, Scannapieco FA. Periodontal systemic associations: review of the evidence. *J Periodontol* 2013; 84: Suppl. 4, S8–s19.
7 Scannapieco FA, Stewart EM, Mylotte JM. Colonization of dental plaque by respiratory pathogens in medical intensive care patients. *Crit Care Med* 1992; 20: 740–745.
8 Berg A, Kramer U, Link E, *et al.* Impact of early feeding on childhood eczema: development after nutritional intervention compared with the natural course – the GINIplus study up to the age of 6 years. *Clin Exp Allergy* 2010; 40: 627–636.
9 Zutavern A, Brockow I, Schaaf B, *et al.* Timing of solid food introduction in relation to atopic dermatitis and atopic sensitization: results from a prospective birth cohort study. *Pediatrics* 2006; 117: 401–411.
10 Miller MR, Hankinson J, Brusasco V, *et al.* Standardisation of spirometry. *Eur Respir J* 2005; 26: 319–338.
11 Luzak A, Fuertes E, Flexeder C, *et al.* Which early life events or current environmental and lifestyle factors influence lung function in adolescents? Results from the GINIplus & LISAplus studies. *Respir Res* 2017; 18: 138.
12 Global Lung Function Initiative. www.ers-education.org/guidelines/global-lung-function-initiative.aspx Date last accessed: September 30, 2018.
13 Quanjer PH, Stanojevic S, Cole TJ, *et al.* Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012; 40: 1324–1343.
14 Kuhnisch J, Thiering E, Heinrich-Weltzien R, *et al.* Fluoride/vitamin D tablet supplementation in infants-effects on dental health after 10 years. *Clin Oral Investig* 2017; 21: 2283–2290.
15 Pitchika V, Thiering E, Metz I, *et al.* Gingivitis and lifestyle influences on high-sensitivity C-reactive protein and interleukin 6 in adolescents. *J Clin Periodontol* 2017; 44: 372–381.
16 World Health Organization. Guidelines for ATC Classification and DDD Assignment. Geneva, World Health Organization, 1996.