**Heterogeneous pattern of differences in respiratory parameters between elderly with either good or poor FEV1**

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**Abstract**

Spirometric indices as well as other respiratory and functional parameters decline with age, but the link between the changes is not well studied. We assessed their relationship in elderly subjects with either good or poor spirometric parameters to reveal whether different domains of lung function show comparable differences between the two groups.

Among subjects of the population-based KORA-Age cohort (n=935, 65-90y; 51% male) two groups were selected from either the lower (LED; n=51) or the upper (UED; n=72) end of the FEV1 distribution. All subjects did not have a history of lung disease and were non-smokers at the time of the study. Measurements included spirometry, body plethysmography, diffusing capacity for NO and CO, respiratory pump function and exhaled NO (FeNO). In addition, 6-minute walking distance as a functional overall measure, as well as telomere length of blood leukocytes and serum 8-hydroxydeoxyguanosine (8-OHdG) as potential markers of overall biological ageing and stress were determined.

In the majority of parameters, LED subjects showed significantly impaired values compared to UED subjects. Differences in spirometric parameters, airway resistance and respiratory pump function ranged between 10% and more than 90% in terms of predicted values. In contrast, volume-related CO and NO diffusing capacity showed differences between groups of lower than 5%, while telomere length, 8-OHdG and FeNO were similar. This was reflected in the differences in functional age as derived from prediction equations.

In elderly subjects without a history of lung disease the differences in lung-mechanical parameters of spirometry and body plethysmography were higher than those of gas exchange. Thus, the concept of a general functional “lung age” might be inadequate and specific terms such as “spirometric age” should be preferred.

**Keywords:** Spirometry, lung age, aging, diffusing capacity, body plethysmography

**Introduction**

The decline of spirometric indices with age reflects changes in structure and function of the respiratory system associated with the ageing process [[1](#_ENREF_1" \o "Lalley, 2013 #24)]. After accounting for age and determinants like sex, height and ethnicity there still remains a large inter-individual variability of spirometric results within the general population, and for several parameters the coefficient of variation even increases with age [[2](#_ENREF_2" \o "Quanjer, 2012 #15)]. This heterogeneity from better than normal to borderline normality could indicate the transition to early pathologic alterations and particularly confer information on biological ageing. The relationship between the variations of functional indices as measured in the same lung-healthy subjects has not been extensively studied. It is not only of pathophysiological interest but also since the deterioration of spirometric values is often used to support smoking cessation by presentation of a “lung age” [[3](#_ENREF_3), [4](#_ENREF_4)]. The question whether this term is adequate beyond spirometry is unclear and requires a more comprehensive analysis.

We therefore investigated in subjects of advanced age who were free of lung disease according to their clinical history, whether various functional indices show similar changes indicative of a general “lung age”. For this purpose we analyzed the relationship between alterations in FEV1 and alterations in static lung volumes, airway conductance, respiratory pump function, pulmonary gas exchange, exhaled biomarkers, systemic oxidative stress and cell-biological age, as well as general physical capacity. The study population comprised two subgroups of the KORA-Age cohort who had been selected based on their percent predicted values either being at the upper or the lower end of the FEV1 distribution.

**Material and Methods**

Spirometry was performed in the KORA study center (Augsburg, Germany) within the frame of the KORA-Age study conducted in 2009-10 [[5](#_ENREF_5" \o "Peters, 2011 #2)]. The study was approved by the Ethics Committee of the Bavarian Medical Association, and its details have been described previously [[6](#_ENREF_6" \o "Karrasch, 2013 #1)]. Briefly, in 935 individuals aged 65-90 years from the Augsburg region spirometric measurements were performed in line with ATS/ERS recommendations [[7](#_ENREF_7" \o "Miller, 2005 #3)], and 840 subjects gave their written consent to be contacted to participate in the current sub-study, for which 200 individuals were selected from the upper and lower tails of the FEV1%pred distribution based on reference equations of the lung-healthy population of the Augsburg region [[6](#_ENREF_6)]. Subjects were further examined at the University Hospital of the Ludwig-Maximilians-Universität in Munich: 104 with high (upper end of distribution, UED) and 96 with low (lower end of distribution, LED) FEV1%pred. The examination focused on the respiratory system but also covered biomarkers and physical capacity. For the present analysis, current smokers and subjects with symptoms of chronic bronchitis or a respiratory infection within 3 weeks prior to examination were excluded. Non-smoking status was defined via self-report; additionally an exhaled carbon monoxide value of < 7 ppm was required [[8](#_ENREF_8)]. These criteria led to an analysis sample of n = 72 (69% of total) in the upper and n = 51 (53%) in the lower group.

A detailed description of the methods is given in Additional file 1. According to current guidelines, the following assessments were performed and parameters obtained: spirometry (FEV1, FVC, expiratory flow rates) [[7](#_ENREF_7)], body plethysmography (airway conductance (Gaw), specific airway conductance (sGaw), total lung capacity (TLCpleth), intrathoracic gas volume (ITGV), residual volume (RV)) [[9](#_ENREF_9), [10](#_ENREF_10)], determination of CO and NO uptake of the lung (transfer factors TLCO, TLNO, transfer coefficients KCO, KNO; alveolar volume (VA), TLC by helium dilution (TLCHe)) [[11](#_ENREF_11)], measurements of mouth occlusion pressure (0.1 s after the onset of tidal inspiration (P01), peak maximal static inspiratory mouth occlusion pressure (PImax)) [[12](#_ENREF_12)], exhaled carbon monoxide (eCO) and exhaled nitric oxide at 50 ml/s (FeNO) [[13](#_ENREF_13)]. Furthermore, a 6-minute walk test was performed [[14](#_ENREF_14)]. The telomere length of circulating leukocytes [[15](#_ENREF_15)] and the serum level of 8-hydroxydeoxyguanosine (8-OHdG) were assessed from samples collected in the KORA study centre in Augsburg.

*Data analysis*

Group comparisons were performed as Student's t-test if not stated otherwise. The robustness of results was tested with analysis of covariance (ANCOVA) and different confounders. Similarly, the associations of the functional indices with telomere length or 8-OHdG were examined using multiple linear regression analysis, with chronological age and sex as confounders. Statistical analyses were done using the software packages Statgraphics (Statpoint Technologies, Inc., Warrenton, VA) and SPSS Statistics 23 (IBM Corp., Armonk, NY, USA). Statistical significance was assumed at a level of 0.05.

For the different lung function indices and 6MWD the following reference values were used: Quanjer et al. for spirometric parameters [[2](#_ENREF_2)], Koch et al. for plethysmographic parameters [[16](#_ENREF_16)], van der Lee et al. for pulmonary gas exchange [[17](#_ENREF_17)], Enright et al. for PImax [[18](#_ENREF_18)], and Enright & Sherrill for 6MWD [[19](#_ENREF_19)].

**Results**

*Baseline characteristics*

The anthropometric characteristics of the two study groups are given in Table 1. There were no significant differences between UED and LED subjects regarding age, height and sex. Weight and body mass index (BMI) were slightly higher in the LED group (p<0.01 each). The prevalences of cardiovascular diseases, diabetes and arthritis were similar; neurological diseases were only present in 4 subjects of the LED group.

*Spirometry*

Data on spirometry are given in Table 2. Corresponding to the selection criterion for the groups, LED subjects showed lower mean FEV1 and FVC (difference of predicted values between groups Δ=39.4%pred and Δ=25.4%pred, respectively; p<0.001 each) as well as a lower FEV1/FVC ratio (Δ=10.7%). If the LLN criterion for FEV1/FVC [[20](#_ENREF_20)] was applied, 37.3% of subjects from the LED group showed airflow limitation, in the absence of respiratory symptoms or a history of respiratory disease.

*Body plethysmography*

sGaw and Gaw in terms of %predicted were different between both groups (p<0.001 each; Table 3). In 13.8% of subjects (31.4% LED, 1.4% UED) sGaw was below the 5th percentile [[16](#_ENREF_16)]. TLCpleth was lower (Δ=10.9%pred) in LED subjects (p<0.001), whereas no significant differences occurred for RV and ITGV. RV/TLCpleth and ITGV/TLCpleth were higher (Δ=14.0%pred and Δ=10.3%pred, respectively; p<0.001 each)in the LED group (Table 3).

*CO and NO uptake of the lung*

The transfer factors TLCO (p<0.001), TLNO (p<0.001) and the ratio TLNO/TLCO (p<0.001) were lower in the LED group, whereas no significant differences occurred for the transfer coefficients TLCO/VA (KCO) and TLNO/VA (KNO) (Table 4). There were also significant differences regarding the ratio TLCHe/TLCpleth with higher values in the UED subjects (p<0.05). Haemoglobin levels for which CO transfer factors were corrected did not significantly differ between LED and UED subjects.

*Respiratory pump function, 6-minute-walk distance and biomarkers*

PImax was lower in LED subjects (Δ=11.0%pred), while P01 and P01/PImax were higher (p<0.001 each; Table 5). LED subjects had a lower 6MWD (Δ=14.1%pred)than UED subjects (p<0.001). Moreover, baseline values of perceived fatigue and dyspnoea during the walk test were higher in LED subjects (p=0.001 and p=0.025, respectively; Table 5).

No significant differences between both groups were found for FeNO (Table 5). eCO was slightly higher (Δ=0.8 ppm) in LED versus UED subjects (p<0.001). For 8-OHdG no significant difference between groups was observed. The same was true for telomere length but there was a tendency towards shorter telomeres in LED subjects (p=0.058).

*Correlation of functional indices with biomarkers*

In multiple regression analyses including all subjects, no significant relationships between lung function indices and telomere length or 8-OHdG levels were found, except for a positive association between RV/TLC and telomere length (p=0.048).

**Discussion**

In the present study we compared two subgroups from a larger population-based cohort which were selected to show FEV1 either at the lower end (LED) or the upper end (UED) of the distribution in the whole cohort. These subgroups were selected to be lung-healthy according to clinical history, symptoms and risk factors. The broad set of parameters allowed to compare the two groups regarding a number of functional domains. Deteriorations in spirometric values are sometimes interpreted as indicators of premature aging of the lung [[3](#_ENREF_3)] but it is not clear whether these reflect a general “lung age”. The adequacy of this term can only be evaluated by analysis of a broad panel of lung function parameters. Our study was particularly suited for the functional comparison, as it comprised spirometry, body plethysmography, transfer factors for CO and NO, and respiratory pump function. Additionally, telomere length of peripheral blood leukocytes and 8-OHdG were included as markers of biological age and stress.

We found a difference of about 40 percent predicted FEV1 between the LED and UED group. This was the result of the definition of both groups but nonetheless reflected the huge difference in FEV1 even among lung-healthy elderly subjects. The differences in FVC and in FEV1/FVC were smaller. On the other hand, those of the FEFs as well as airway conductance and specific airway conductance were even larger. The scales of these parameters were comparable with each other, since airway conductance was chosen instead of resistance and impairment was always associated with a reduction towards zero. The comparison with the differences in plethysmographic volume parameters was less straightforward, since in principle, although not in practice, there is no upper bound of these parameters and no commonly accepted transformation analogous to conductance. Based on the differences in scale and physiologically possible range, it is understandable that the volume parameters showed smaller differences between the two groups.

In contrast, NO and CO transfer factors also decrease upon impairment, having zero as lower bound, and are in this respect comparable to the spirometric and airway conductance parameters. Despite this similarity the differences between LED and UED groups were only about 10% in case of TLCO and about 15% in case of TLNO. Both of these parameters involve lung volume, therefore the transfer coefficients which in first order correct for volume are of additional interest. Remarkably, the differences in KCO and KNO between the two groups were even smaller and not significantly different from zero. The 95%-confidence intervals for the differences in transfer factors and coefficients did not overlap with those of FEV1%pred and FVC%pred as well as airway conductance. This indicated a marked difference between the mechanical and gas uptake domains. There were no significant differences in Hb values which might have influenced the values of CO transfer factor which nevertheless had been corrected for Hb.

The differences in PImax they were lower than those of FEV1 and sGAW, which showed values in a range of 30%pred or more, but still beyond 10%pred and larger than those of transfer coefficients KCO and KNO. The fact that elderly, lung-healthy subjects markedly differed regarding lung mechanics but not regarding gas transfer is particularly interesting, since KCO and KNO were nearly equal, whereas the observed differences in TLCO and TLNO can be attributed to the differences in lung volumes, i.e. ultimately lung mechanics, where the major difference between groups occurred. Regarding the term “lung age” our observations suggest that more specific terms such as “spirometric age” are more adequate and substantiated. This specification should not lower the usefulness as a motivational tool in smoking cessation.

The difference in 6MWD between the LED and UED group was between those of mechanical and gas exchange parameters. Dyspnoea and fatigue scores could not be scaled as percent predicted, therefore their differences were not directly comparable to the other parameters. Still, the fact that they differed between the two groups, in terms of pre and post values, indicated a greater 6MWD and at the same time lower dyspnoea and fatigue in subjects of the UED group.

FeNO was included as it might indicate eosinophilic airway inflammation if elevated, or oxidative stress if decreased, but no significant differences were found. There was a small difference regarding eCO despite the fact that we had excluded current smokers and subjects with values >6 ppm. The source of this small difference might be unreported active or passive smoking, or endogenous production related to oxidative stress [[21](#_ENREF_21)]. However, serum 8-OHdG, as an indicator of systemic oxidative stress, was similar in the two groups. The same was true for telomere length in peripheral blood leukocytes which is often considered as a marker of biological age and/or stress but there was a tendency (p=0.058) towards decreased telomere length in the LED group.

One might argue that the results in terms of percent predicted values simply reflected different coefficients of age-dependence in the reference equations despite the fact that the mean age was similar in the two groups. To evaluate this we inserted the measured values into the respective reference equations and solved for the age that resulted in the observed values; for non-linear equations (e.g. GLI) linear approximations within the adequate range were used. This analysis was not meaningful for all parameters as it made sense only with an obvious and monotonous relationship to age to avoid absurd individual age estimates. Figure 1 shows median values and quartiles for FEV1, FVC, FEF25-75, FEF75, ITGV/TLC, KCO and KNO. It illustrates the large differences for mechanical versus much smaller differences for gas uptake parameters, taking into account the coefficients of age-dependence via the prediction equations.

As one of the limitations of our study, we did not measure individual rates of ageing. The cross-sectional analysis did not hamper the comparison of functional domains but the question remains whether the subjects of the LED group were at the lower end of the distribution from an early age or showed a higher rate of deterioration over time [[22](#_ENREF_22)]. Even telomere length might also have been shorter from the beginning. The sample size of n=123 did not allow to adjust for a broad variety of potential confounders; we therefore present only pairwise comparisons. Adjustment for weight or sex did not markedly change the results. Furthermore, it was not possible to directly compare all parameters, either because no reference values were available, or because, e.g. for ITGV, pathological changes can occur in both directions and scales were different. Our study has the strength of a broad panel of high-quality assessments that allowed direct comparisons in the same subjects. This aspect seems particularly important in view of the marked differences between the functional domains.

**Conclusion**

Two groups of elderly, lung-healthy subjects were chosen from the lower and upper end of the distribution of FEV1%predicted from a population-based sample. The differences of lung function parameters between groups depended on the functional domain. While those of FEV1, FVC and (specific) airway conductance were large, those of KCO and KNO transfer coefficients were small and not significantly different from zero. Therefore, the differences in the mechanical domain that were partially generated by the definition of the two groups were not in parallel with those in gas uptake. The results translated into corresponding differences of functional age, using the respective prediction equations. Based on this it does not seem justified to follow the concept of an overall functional “lung age” in aging subjects without apparent lung disease. For scientific purposes, specific terms such as “spirometric age” appear more adequate.

**Abbreviations**

6MWD, six minute walking distance; 8-OHdG, 8-hydroxydeoxyguanosine; ANCOVA, analysis of covariance; BMI, body mass index; CO, carbon monoxide; eCO, exhaled carbon monoxide; FEF25-75, forced expiratory flow at 25-75% of forced vital capacity; FEF75, forced expiratory flow when 75% of FVC has been exhaled; FeNO, fraction of exhaled nitric oxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; Gaw, airway conductance; ITGV, intrathoracic gas volume; KCO, transfer coefficient for carbon monoxide; KNO, transfer coefficient for nitric oxide; LED, lower end of the FEV1 distribution; LLN, lower limit of normal; NO, nitric oxide; P01, mouth occlusion pressure 0.1 s after the onset of tidal inspiration; PImax, peak maximal static inspiratory mouth occlusion pressure; RV, residual volume; sGaw, specific airway conductance; TLCHe, total lung capacity determined by helium dilution; TLCO, transfer factor of the lung for carbon monoxide; TLCpleth, total lung capacity determined by body plethysmography; TLNO, transfer factor of the lung for nitric oxide; UED, upper end of the FEV1 distribution; VA, alveolar volume

**Declarations**

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**Ethics approval and consent to participate**

The KORA-Age study was approved by the Ethics Committee of the Bavarian Medical Association, written informed consent has been obtained from all participants and the investigations have been conducted according to the principles expressed in the Declaration of Helsinki.

**Availability of data and materials**

The informed consent given by KORA study participants does not cover data posting in public databases. However, data are available upon request from KORA (https://epi.helmholtz-muenchen.de/) by means of a project agreement. Requests should be sent to kora.passt@helmholtz-muenchen.de and are subject to approval by the KORA Board.

**Competing interests**

The authors declare that they have no competing interests.

**Authors’ contributions**

SK, RAJ, and HS conceptualized the paper. SK performed the statistical analysis and SK, RAJ, HS, JB, RMH, DN, AP and RH interpreted the data. RAJ, HS, JB, RMH, DN, AP, and RH were involved in the conception of the study, SK, RAJ, HS, SP, RH, and AP were involved in the coordination and the data acquisition of the study. SK, RAJ and HS drafted the manuscript. All authors critically reviewed the manuscript drafts and approved the final manuscript.

**Consent for publication**

Not applicable.

**References**

1. Lalley PM: The aging respiratory system--pulmonary structure, function and neural control. *Respir Physiol Neurobiol* 2013, 187:199-210.

2. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, Enright PL, Hankinson JL, Ip MS, Zheng J, 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.

3. Morris JF, Temple W: Spirometric "lung age" estimation for motivating smoking cessation. *Prev Med* 1985, 14:655-662.

4. Spiegelhalter D: How old are you, really? Communicating chronic risk through 'effective age' of your body and organs. *BMC Med Inform Decis Mak* 2016, 16:104.

5. Peters A, Doring A, Ladwig KH, Meisinger C, Linkohr B, Autenrieth C, Baumeister SE, Behr J, Bergner A, Bickel H, et al: [Multimorbidity and successful aging: the population-based KORA-Age study]. *Z Gerontol Geriatr* 2011, 44 Suppl 2:41-54.

6. Karrasch S, Flexeder C, Behr J, Holle R, Huber RM, Jorres RA, Nowak D, Peters A, Wichmann HE, Heinrich J, et al: Spirometric reference values for advanced age from a South german population. *Respiration* 2013, 85:210-219.

7. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, et al: Standardisation of spirometry. *Eur Respir J* 2005, 26:319-338.

8. Middleton ET, Morice AH: Breath Carbon Monoxide as an Indication of Smoking Habit. *Chest* 2000, 117:758-763.

9. Criée CP, Berdel D, Heise D, Jörres RA, Kardos P, Köhler D, Leupold W, Magnussen H, Marek W, Merget R, et al: Recommendations on whole body plethysmography: Part 1. *Atemwegs- und Lungenkrankheiten* 2009, 35:256-272.

10. Criée CP, Berdel D, Heise D, Jörres RA, Kardos P, Köhler D, Leupold W, Magnussen H, Marek W, Merget R, et al: Recommendations for whole body plethysmography: Part 2. *Atemwegs- und Lungenkrankheiten* 2009, 35:349-370.

11. Macintyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CP, Brusasco V, Burgos F, Casaburi R, Coates A, Enright P, et al: Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J* 2005, 26:720-735.

12. Criee CP: [Recommendations of the German Airway League (Deutsche Atemwegsliga) for the determination of inspiratory muscle function]. *Pneumologie* 2003, 57:98-100.

13. American Thoracic S, European Respiratory S: ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med* 2005, 171:912-930.

14. A. T. S. Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories: ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002, 166:111-117.

15. Albrecht E, Sillanpaa E, Karrasch S, Alves AC, Codd V, Hovatta I, Buxton JL, Nelson CP, Broer L, Hagg S, et al: Telomere length in circulating leukocytes is associated with lung function and disease. *Eur Respir J* 2014, 43:983-992.

16. Koch B, Friedrich N, Volzke H, Jorres RA, Felix SB, Ewert R, Schaper C, Glaser S: Static lung volumes and airway resistance reference values in healthy adults. *Respirology* 2013, 18:170-178.

17. van der Lee I, Zanen P, Stigter N, van den Bosch JM, Lammers JW: Diffusing capacity for nitric oxide: reference values and dependence on alveolar volume. *Respir Med* 2007, 101:1579-1584.

18. Enright PL, Adams AB, Boyle PJ, Sherrill DL: Spirometry and maximal respiratory pressure references from healthy Minnesota 65- to 85-year-old women and men. *Chest* 1995, 108:663-669.

19. Enright PL, Sherrill DL: Reference equations for the six-minute walk in healthy adults. *Am J Respir Crit Care Med* 1998, 158:1384-1387.

20. Quanjer PH, Pretto JJ, Brazzale DJ, Boros PW: Grading the severity of airways obstruction: new wine in new bottles. *Eur Respir J* 2014, 43:505-512.

21. Gajdocsy R, Horvath I: Exhaled carbon monoxide in airway diseases: from research findings to clinical relevance. *J Breath Res* 2010, 4:047102.

22. Fletcher C, Peto R: The natural history of chronic airflow obstruction. *Br Med J* 1977, 1:1645-1648.

23. Cawthon RM: Telomere length measurement by a novel monochrome multiplex quantitative PCR method. *Nucleic Acids Res* 2009, 37:e21.

24. Borg GA: Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 1982, 14:377-381.

**Tables**

**Table 1:** Characteristics of the study population.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Parameter**  | **UED group** | **LED group** | **mean difference(UED-LED)** | **95% CI of difference** | **p-value for difference** |
| **Mean ± SD** | **Median (25%; 75%)** | **Mean ± SD** | **Median (25%; 75%)** | **lower** | **upper** |
| **n** | 72 | 51 | na | na | na | na |
| **Sex, m/f** | 28 / 44 | 27 / 24 | na | na | na | 0.1231 |
| **Age, years** | 76.8 ± 6.4 | 76.5 (71.3; 81.9) | 77.8 ± 7.2 | 77.6 (70.6; 83.9) | -1.0 | -3.5 | 1,5 | 0.425 |
| **Height, m** | 1.63 ± 0.09 | 1.63 (1.56; 1.70) | 1.64 ± 0.09 | 1.64 (1.57; 1.71) | -0.00 | -0.04 | 0.03 | 0.793 |
| **Weight, kg** | 73.1 ± 10.2 | 72.9 (65.3; 81.0) | 79.6 ± 13.3 | 78.9 (69.3; 88.6) | -6.4 | -10.8 | -2.0 | **0.005** |
| **BMI, kg/m2** | 27.5 ± 3.9 | 27.2 (25.1; 29.5) | 29.7 ± 4.4 | 28.6 (26.9; 32.2) | -2.2 | -3.7 | -0.6 | **0.006** |
| **Diseases, n (percentage)** |  |  |  |  |  |  |
|  | **cardiovascular diseases** | 54 (75.0%) | 44 (86.3%) | na | na | na | 0.1261 |
|  | **diabetes** | 8 (11.3%) | 8 (15.7%) | na | na | na | 0.4761 |
|  | **neurological diseases** | 0 (0.0%) |  4 (7.8%) | na | na | na | na |
|  | **arthritis** | 5 (6.9%) | 8 (15.7%) | na | na | na | 0.1201 |

1Chi-Square test.

**Table 2:** Spirometric parameters.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Parameter**  | **UED group** | **LED group** | **mean difference(UED-LED)** | **95% CI of difference** | **p-value for difference** |
| **n** | **Mean ± SD** | **Median (25%; 75%)** | **n** | **Mean ± SD** | **Median (25%; 75%)** | **lower** | **upper** |
| **FEV1 %pred** | 72 | 124.9 ± 10.3 | 124.6 (116.9; 131.4) | 51 | 85.5 ± 10.9 | 85.1 (77.1; 91.4) | **39.4** | 35.5 | 43.3 | **<0.001** |
| **FVC %pred** | 72 | 127.2 ± 10.9 | 129.8 (119.3; 134.4) | 51 | 101.8 ± 13.0 | 102.0 (95.6; 108.8) | **25.4** | 21.0 | 29.8 | **<0.001** |
| **FEV1/FVC %pred** | 72 | 97.5 ± 6.2 | 97.7 (92.7; 102.3) | 51 | 83.9 ± 10.4 | 84.4 (78.3; 91.0) | **13.6** | 10.4 | 16.9 | **<0.001** |
| **FEF25-75 %pred** | 72 | 124.7 ± 34.8 | 120.4 (99.3; 148.8) | 49 | 56.1 ± 23.6 | 49.2 (39.5; 65.0) | **69.8** | 59.3 | 80.2 | **<0.001** |
| **FEF75 %pred** | 72 | 168.0 ± 66.3 | 159.7 (118.3; 204.9) | 49 | 74.1 ± 39.5 | 65.5 (49.2; 86.8) | **93.9** | 74.8 | 113.0 | **<0.001** |
|  |  |  |  |  |  |  |  |  |  |  |
| **FEV1/FVC** | 72 | 0.749 ± 0.048 | 0.752 (0.713; 0.785) | 51 | 0.642 ± 0.079 | 0.652 (0.595; 0.697) | **0.107** | 0.082 | 0.132 | **<0.001** |

Reference values were calculated according to Quanjer et al. [[2](#_ENREF_2)].

**Table 3:** Body plethysmographic parameters.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Parameter**  | **UED group** | **LED group** | **mean difference(UED-LED)** | **95% CI of difference** | **p-value for difference** |
| **n** | **Mean ± SD** | **Median (25%; 75%)** | **n** | **Mean ± SD** | **Median (25%; 75%)** | **lower** | **upper** |
| **TLCpleth %pred** | 72 | 113.2 ± 11.9 | 115.9 (104.8; 122.2) | 51 | 102.3 ± 12.4 | 102.6 (94.4; 112.2) | **10.9** | 6.5 | 15.4 | **<0.001** |
| **RV %pred** | 72 | 94.4 ± 16.7 | 96.6 (82.9; 103.5) | 51 | 99.7 ± 18.5 | 102.5 (92.1; 110.5) | **-5.3** | -11.8 | 1.1 | 0.104 |
| **RV/TLCpleth %pred** | 72 | 84.9 ± 9.4 | 85.2 (78.1; 91.7) | 51 | 98.9 ± 11.9 | 98.0 (91.2; 108.0) | **-14.0** | -18.0 | -10.0 | **<0.001** |
| **ITGV %pred** | 72 | 99.7 ± 18.8 | 100.4 (85.8; 110.2) | 51 | 101.3 ± 19.5 | 101.1 (86.2; 118.0) | **-1.6** | -8.5 | 5.4 | 0.656 |
| **ITGV/TLCpleth %pred** | 72 | 83.8 ± 9.0 | 83.1 (76.8; 89.9) | 51 | 94.1 ± 10.4 | 93.8 (86.9; 102.1) | **-10.3** | -13.9 | -6.7 | **<0.001** |
| **GAW %pred** | 72 | 125.7 ± 40.1 | 121.0 (97.8; 145.3) | 51 | 77.2 ± 36.1 | 70.2 (52.0; 97.6) | **48.6** | 34.8 | 62.3 | **<0.001** |
| **sGAW %pred** | 72 | 138.4 ± 42.1 | 134.6 (112.8; 153.2) | 51 | 88.3 ± 47.7 | 84.2 (62.3; 107.7) | **50.0** | 33.5 | 66.5 | **<0.001** |

Reference values were calculated according to Koch et al. [[16](#_ENREF_16)].

**Table 4:** Parameters of the diffusing capacity for CO and NO.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Parameter**  | **UED group** | **LED group** | **mean difference(UED-LED)** | **95% CI of difference** | **p-value for difference** |
| **n** | **Mean ± SD** | **Median (25%; 75%)** | **n** | **Mean ± SD** | **Median (25%; 75%)** | **lower** | **upper** |
| **TLCO %pred** | 70 | 92.1 ± 16.7 | 89.8 (81.3; 102.2) | 51 | 82.2 ± 14.2 | 83.2 (68.4; 92.9) | **9.8** | 4.3 | 15.4 | **0.001** |
| **KCO %pred** | 70 | 98.6 ± 16.7 | 98.7 (89.0; 110.3) | 51 | 101.8 ± 17.7 | 100.1 (89.3; 112.1) | **-3.2** | -9.5 | 3.1 | 0.316 |
| **TLNO %pred** | 70 | 95.0 ± 17.4 | 94.1 (83.8; 106.2) | 51 | 80.0 ± 14.8 | 79.6 (70.1; 92.1) | **15.0** | 9.2 | 20.8 | **<0.001** |
| **KNO %pred** | 70 | 102.7 ± 17.8 | 102.5 (93.3; 113.9) | 51 | 100.0 ± 16.5 | 101.1 (87.4; 108.5) | **2.7** | -3.6 | 8.9 | 0.400 |
|  |  |  |  |  |  |  |  |  |  |  |
| **TLNO/TLCO** | 70 | 4.74 ± 0.34 | 4.67 (4.54; 4.92) | 51 | 4.53 ± 0.29 | 4.52 (4.36; 4.65) | **0.21** | 0.10 | 0.33 | **<0.001** |
| **TLCHe/TLCpleth** | 70 | 0.834 ± 0.052 | 0.832 (0.798; 0.867) | 51 | 0.806 ± 0.071 | 0.810 (0.755; 0.851) | **0.028** | 0.005 | 0.052 | **0.018** |

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Hb, mg/dl** | 53 | 13.9 ± 1.1 | 13.9 (13.2; 14.8) | 48 | 13.7 ± 1.3 | 13.7 (12.8; 14.5) | **0.2** | -0.3 | 0.7 | 0.469 |

Reference values were calculated according to van der Lee et al. [[17](#_ENREF_17)].

**Table 5:** Parameters of respiratory pump function, exercise capacity and biomarkers.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Parameter**  | **UED group** | **LED group** | **mean difference(UED-LED)** | **95% CI of difference** | **p-value for difference** |
| **n** | **Mean ± SD** | **Median (25%; 75%)** | **n** | **Mean ± SD** | **Median (25%; 75%)** | **lower** | **upper** |
| **PImax %pred** | 66 | 102.9 ± 34.0 | 100.7 (81.5; 123.2) | 50 | 91.9 ± 31.9 | 90.9 (70.4; 111.0) | **11.0** | -1.3 | 23.3 | 0.079 |
|  |  |  |  |  |  |  |  |  |  |  |
| **log10(P01, kPa)** | 66 | -0.72 ± 0.22 | -0.69 (-0.89; -0.55) | 50 | -0,53 ± 0,20 | -0.53 (-0.64; -0.41) | **-0.19** | -0.27 | -0.11 | **<0.001** |
| **log10(P01/PImax)** | 66 | -1.57 ± 0.27 | -1.52 (-1.74; -1.41) | 50 | -1.34 ± 0.30 | -1.34 (-1.54; -1.12) | **-0.22** | -0.33 | -0.12 | **<0.001** |
|  |  |  |  |  |  |  |  |  |  |  |
| **6MWD %pred** | 71 | 113.0 ± 17.9 | 114.2 (98.8; 126.1) | 51 | 98.9 ± 21.1 | 101.4 (91.1; 112.4) | **14.1** | 6.9 | 21.4 | **<0.001** |
|  |  |  |  |  |  |  |  |  |  |  |
| **PRE Dyspnoea** | 60 | 0.06 ± 0.21 | 0.00 (0.00; 0.00) | 49 | 0.51 ± 0.92 | 0.00 (0.00; 1.00) | **-0.45** | -0.72 | -0.18 | **0.001** |
| **POST Dyspnoea** | 60 | 1.63 ± 1.51 | 1.00 (0.50; 3.00) | 49 | 2.62 ± 1.78 | 3.00 (1.00; 4.00) | **-1.00** | -1.63 | -0.36 | **0.002** |
| **PRE Fatigue** | 60 | 0.26 ± 0.61 | 0.00 (0.00; 0.00) | 49 | 0.62 ± 0.97 | 0.00 (0.00; 1.00) | **-0.36** | -0.68 | -0.05 | **0.025** |
| **POST Fatigue** | 60 | 0.61 ± 1.20 | 0.00 (0.00; 0.88) | 49 | 1.09 ± 1.30 | 0.50 (0.00; 2.00) | **-0.48** | -0.96 | -0.01 | **0.048** |
|  |  |  |  |  |  |  |  |  |  |  |
| **eCO, ppm** | 72 | 3.5 ± 1.3 | 3.0 (3.0; 4.0) | 51 | 4.4 ± 1.2 | 4.0 (3.0; 5.0) | **-0.8** | -1.3 | -0.4 | **<0.001** |
| **log10(FeNO, ppb)** | 72 | 1.305 ± 0.164 | 1.306 (1.206; 1.422) | 51 | 1.334 ± 0.222 | 1.317 (1.179; 1.508) | **-0.029** | -0.102 | 0.044 | 0.433 |
| **serum 8-OHdG, ng/mL** | 72 | 0.181 ± 0.065 | 0.186 (0.129; 0.228) | 50 | 0.178 ± 0.065 | 0.180 (0.144; 0.212) | **0.002** | -0.022 | 0.026 | 0.845 |
| **Telomere length, T/S ratio** | 72 | 1.562 ± 0.244 | 1.564 (1.412; 1.699) | 50 | 1.489 ± 0.179 | 1.472 (1.344; 1.609) | **0.073** | -0.003 | 0.149 | 0.058 |

Reference values were calculated according to Enright et al. [[18](#_ENREF_18)] for PImax and according to Enright and Sherrill [[19](#_ENREF_19)] for 6MWD.

**Figures**

**Figure 1:** Median functional age of UED (white) and LED (grey) subjects for selected parameters; whiskers indicate lower and upper quartiles, the dashed black line indicates the mean chronological age of all subjects.



**Additional file 1**

**Supplementary Methods**

*Lung volumes and airway conductance*

Body plethysmography was performed in a 830 L whole body box (Masterscreen Body, Jaeger, Höchberg, Germany) in line with the recommendations of the German Airway League and the German Society for Pneumology and Ventilatory Support [[9](#_ENREF_9" \o "Criée, 2009 #10), [10](#_ENREF_10" \o "Criée, 2009 #11)]. Subjects used a flanged rubber mouthpiece in an upright sitting position while wearing nose clips. The measurement started with quiet tidal breathing until a stable FRC level was reached and at least three acceptable breathing loops were recorded. Subsequently, up to 5 occlusion maneuvers were performed until two acceptable assessments were achieved. Occlusion maneuvres were followed by spirometric maneuvers involving slow expiration and inspiration and forced expiration. If necessary, additional spirometric maneuvers were carried out until three acceptable and reproducible flow-volume curves were gained in line with ATS/ERS recommendations [[7](#_ENREF_7" \o "Miller, 2005 #3)].

*Pulmonary gas exchange*

Pulmonary gas exchange was assessed via the single-breath technique using a device for the combined measurement of CO and NO transfer factors of the lung (TLCO and TLNO; MasterScreen® PFT Pro, Jaeger, Höchberg, Germany). Tests were performed in line with ATS/ERS recommendations for CO [[11](#_ENREF_11)] in an upright sitting position while subjects were wearing nose clips and the breath-hold time was set to 8 s. Up to 5 single-breath maneuvers were carried out to obtain two acceptable and reproducible measurements. Results for TLCO were corrected for haemoglobin (Hb) measured on the day of the examination. If Hb was not available (32 cases), a value of 14.6 mg/dL for men and 13.5 mg/dL for women was used.

*Respiratory pump function*

Mouth occlusion pressure 0.1 s after the onset of tidal inspiration (P01) and peak maximal static inspiratory mouth occlusion pressure (PImax) were measured in an upright sitting position using a flanged rubber mouthpiece based on the recommendations of the German Airway League [[12](#_ENREF_12" \o "Criee, 2003 #7)] (Masterscreen Body, Jaeger, Höchberg, Germany). Again, subjects were wearing nose clips. P01 was calculated as the median of three tests. For each test, at least 5 occlusions occurred irregularly 100 ms after start of an inspiration during stable quiet tidal breathing. The test result was calculated as the mean of the measured values disregarding the two highest and two lowest (MasterScreen Body, Jaeger). For the PImax measurement, a complete expiration to residual volume (RV) was followed by a maximal inspiratory effort against occlusion under the guidance and vigorous motivation of an experienced operator. PImax was defined as the maximal peak static inspiratory pressure achieved during at least 7 inspiratory maneuvers.

*Markers of oxidative stress and biological age*

The telomere length of circulating leukocytes and the serum level of 8-hydroxydeoxyguanosine (8-OHdG) were measured from blood samples collected during the main study phase in the KORA study center in Augsburg. Telomere length measurements were performed according to the method proposed by Cawthon [[23](#_ENREF_23)], for details see Albrecht et al. [[15](#_ENREF_15)]. 8-OHdG was measured using an enzyme-linked immunosorbent assay (Highly Sensitive 8­OHdG Check; Japan Institute for the Control of Aging, Fukuroi, Japan) after ultrafiltration according to manufacturer’s instructions, except for the fact that duplicate measurements instead of triplicates were performed. Each plate contained a calibrator sample (biological control) and its results were used to correct the results for plate effects.

*Exhaled biomarkers*

For nitric oxide (FeNO) measurements, subjects were instructed to exhale after maximal inspiration at a constant flow rate of 50 mL/s and a mouthpiece pressure of 12 mbar in line with ATS/ERS recommendations [[13](#_ENREF_13" \o "American Thoracic, 2005 #4)]. The NO concentration was measured using an ozone-chemiluminescence analyzer (NOA 280, Sievers, Boulder, Colorado, USA) and the result was calculated as the mean of three reproducible maneuvers. Exhaled carbon monoxide (CO) was measured during slow expiration after maximal inspiration and a 10 s breath-hold using an electrochemical device (BreathCO Carbon Monoxide Monitor, Vitalograph, Hamburg, Germany).

*Physical capacity*

A 6-minute walk test (6MWT) was performed in a straight and flat corridor over a 30 m course marked by traffic cones, in line with ATS guidelines [[14](#_ENREF_14)]. Immediately before and after the walk, the subject’s perceived dyspnoea and overall fatigue levels were assessed using the Borg scale [[24](#_ENREF_24)].