Physical activity is not associated with spirometric indices in lung-healthy German youth

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Summary: In lung-healthy adolescents, spirometric indices were not associated with accelerometric measures of physical activity or active lifestyle.

 **Abstract**

***Introduction:*** In lung disease, physical activity (PA) improves lung function and reduces morbidity. However, healthy populations are not well studied. We estimate the relationship between spirometric indices and accelerometric PA in lung-healthy adolescents.

***Methods*:** 895 non-smoking German adolescents without chronic lung disease (45% male, age 15.2 ± 0.26 years) from the GINIplus and LISAplus cohorts completed questionnaires, spirometry, 7-day accelerometry, and activity diary. PA was measured as minutes, quintiles, and regularity of daily moderate, vigorous, and moderate-to-vigorous PA (MVPA), participation in sport, and active commuting to school. Primary outcomes were FEV1, FVC, FEV1/FVC and FEF2575; they were separately correlated with PA and adjusted for confounders of respiratory function including early-life exposures.

***Results*:** Adolescents averaged 40 min MVPA per day, typical for European youth. 79% did sports and 51% commuted actively. Association was suggested between 3% higher FVC (approximately 100 mL) and either extreme MVPA quintile or percent days with over 30 minutes MVPA (p<0.05). However, after Bonferroni correction all associations between spirometry, active lifestyle and PA were non-significant.

***Conclusion*:** Spirometric indices were not significantly associated with active lifestyle or measures of activity in lung-healthy adolescents after adjustment for confounding and multiple-comparisons artefact. **Introduction**:

 Beneficial health effects of physical activity (PA) apply across the lifespan, both in the general population [1] and in populations with chronic diseases including diabetes, neurodegenerative and cardiovascular diseases, and cancer. Benefits of PA for lung function are known for smokers [2] [3] and patients with cystic fibrosis, [4] asthma [5, 6] and chronic obstructive pulmonary disease (COPD) [7]. Accordingly, PA has become a standard part of pulmonary rehabilitation [8, 9].

 Benefits of activity for healthy lungs are less studied. Better lung function [10] and slower age- related decline [11] [12] have been reported in active adults, improved spirometric indices after exercise interventions have been observed in young adults [13, 14] and athletes have better lung function than sedentary peers in some, but not all, sports. [14] Active schoolgirls experienced faster lung growth, but boys did not [15], active children had better lung function [16] and physically fit children were less likely to develop asthma. [5] These all suggest that PA benefits healthy lungs, but are equally consistent with lung-healthy subjects being preferentially active. However, effects are heterogeneous both between and within studies: benefits sometimes appear to be limited to one sex [15] or, in populations of athletes, to particular sports. [14]

 Furthermore, neither PA nor lung function is measured in the same way across studies. Many studies do not consider lung diseases, particularly asthma, which can interact with activity in complex ways [5, 17-20]. Reported spirometric indices focus on volumes such as FEV1 and FVC, while flow rates (PEF, FEFs) are less addressed. Lastly, PA is often assessed by self-report or parental report, which poorly reflect activity as measured by accelerometry.[18] For all these reasons, evidence for the positive association between PA and lung function appears to be suggestive, but not conclusive.

 The aim of this study was to investigate this association in non-smoking adolescents without chronic lung disease (asthma or cystic fibrosis). Spirometric indices (FEV1, FVC, FEV1/FVC, and FEF2575) were the primary outcomes of our analyses, and we controlled for different early-life factors known to affect lung function. Activity was objectively measured by accelerometry, and activity habits were inferred from participation in sport or active commuting to school.

**Methods**

***Study population***

We combined spirometry, accelerometric PA, physical examinations, and interviews from GINIplus and LISAplus, two cohorts of German Caucasians born between 1995 and 1999 and followed up at age 15. Further details on study designs of GINIplus [21]and LISAplus [22] are published elsewhere; abbreviations are defined in Appendix 1. Both studies were approved by the respective local Ethics Committees (Bavarian General Medical Council, Medical Council of North Rhine-Westphalia) and by written consent from participating families.

 GINIplus (German Infant Nutritional Intervention PLUS environmental and genetic influences on allergy development) was initiated to investigate allergy development after intervention with hydrolysed formulas. Of 5991 healthy, full-term newborns recruited in the regions of Munich and Wesel, 2252 (38%) with family history of atopy who consented to participate in a randomized trial (nutritional intervention) were randomized in almost equal numbers to either partially or extensively hydrolysed whey, extensively hydrolysed casein, or cow’s milk formula. The observation arm, made up of 3739 unselected children (62%) was given no formula. At age 15, 3199 adolescents from both study arms were recontacted and approached for accelerometry. Of these, 925 (29%) completed both accelerometry and spirometry; of these 665 had complete data on confounders and were non-smokers without known lung disease. Only these complete cases are included in the analyses. Further details on study design, formulas and followup are in in Appendices 1 and 2, [21] and [23].

 LISAplus is a population-based cohort of 3097 unselected infants from the cities of Munich, Wesel, Bad Honnef and Leipzig. No intervention, nutritional or otherwise, was used in LISAplus. 1534 subjects were followed up at age 15, of which 1107 were from Munich or Wesel and thus approached for accelerometry. Of these 271 (24%) completed both accelerometry and spirometry, and 230 were non-smokers, free of lung disease and provided all data for the model analysis. Details on study design are in [24].

 We thus sampled 895 subjects, 665 from GINIplus and 230 from LISAplus; followup is in Figure 1 and Appendix 1. Both cohorts are population-based, but the fifteen-year followup is not representative of the underlying study cohorts because of non-random loss to followup.

  Information on sociodemographic confounders (e.g. parental education), birthweight, breastfeeding, and pre- and postnatal tobacco exposure up to age 6 were obtained from standardized questionnaires from the initial survey (age 4 -6 months) and followups to 6 years. Height and weight were measured during the physical examination at 15 years. With respect to the considered confounders, questions and protocols were comparable between GINIplus and LISAplus.

***Spirometric protocol***

Spirometry was performed seated, wearing nose clips and after 15 minutes’ acclimation to the indoor environment, in line with ATS/ERS recommendations [25]. Subjects performed at least three but not more than eight trials per test to obtain optimal flow-volume curves. Quality guidelines [25] and visual inspection by physicians were applied to exclude manoeuvres incorrectly performed or with artefact (for more details see [26] and Appendix 1.) Spirometric indices were taken from the valid manoeuvre with the largest sum of FEV1 and FVC. Indices measured were FEV1, FVC, FEV1/FVC ratio and flow rates (PEF, FEFs). Z-scores were based on Global Lung Initiative (GLI) reference values[27].

***Accelerometric protocol***

For detailed description of accelerometer protocol, quality control, and data cleaning, see [28]and Appendix 1. Accelerometers (ActiGraph GT3X, Pensacola, Florida) were worn at the hip. Sampling rate was 30 Hz; accelerations were stored at 1 Hz and converted into activity levels in one-minute epochs using the algorithm from Freedson et al. [29]

 In a standardized diary subjects documented times of getting up and going to bed, sport, and active commuting to school. Valid days had at least 7-10 hours of valid recording. Valid subjects provided at least 3 valid weekdays, and one valid weekend day. Of the 1689 subjects who returned the accelerometer, 1411 (8832 days) ultimately provided valid data.

***Physical activity***

We considered the following PA measures:

* Average daily minutes of moderate, vigorous, and moderate-to-vigorous PA (MPA, VPA, MVPA);
* MVPA quintiles, to check for nonlinearity;
* Regularity of MVPA throughout the week: health effects of short periods of PA may differ from those for long periods. [30] For each subject we averaged the fraction of days with over 30, 45, and 60 minutes MVPA, to create 3 variables ranging from 0 (never) to 1 (every day.)
* Active commuting was defined as walking or bicycling to school at any point during accelerometry. Participation in sport at least once during accelerometry was also considered.

***Exclusion criteria***

*Asthma:* Asthma is a lung condition associated with lower PA so to avoid biasing our results, we excluded asthmatics (n=80, Figure 1). Asthma was defined as at least 2 of the 3 following characteristics[31]:

* Asthma diagnosed by a doctor at any year since age 3. Evaluations took place at ages 4, 6, 10 and 15, with the question asked separately for each year of life since the last examination.
* Took asthma medication in the past 12 months
* Asthma symptoms (wheezing, shortness of breath) in the past 12 months.

*Other lung diseases:* No children in our study population had cystic fibrosis or other known chronic lung disease.

*Smoking*: Only subjects who self-reported current abstinence from tobacco smoking were included in the study. 50 smokers were identified and excluded (Figure 1).

*Missing data:* We also excluded 67 children with missing data on asthma and/or smoking.

***Inclusion criteria***

Of 1011 non-asthmatic, non-smoking 15-year-olds without cystic fibrosis who completed accelerometry and spirometry, 895 (88.5%) had data on all confounders. To maximize comparability between models we restricted our analysis to these complete cases (Figure 1).

***Statistical Methods***

All analyses were done using SAS 9.2. Population characteristics (Table 1) are given as mean (SD) for centrally-distributed variables, and as mean (median); 5th, 95th percentile for skewed variables such as weight, BMI and VPA. P-values for group comparisons were calculated with

Wilcoxon’s two-tailed rank-sum test for binary and skewed variables, Kruskal-Wallis test for

categorical variables, and t-test for centrally-distributed variables.

 Statistical models were fit using generalized linear modelling. Spirometric indices and GLI Z-scores (FEV1, FVC, FEV1/FVC, and FEF2575) were modelled as normally-distributed functions of known confounders and one PA measure at a time. Inspection of Q-Q plots confirmed normality. No model contained either more than one PA measure or more than one spirometric index. Confounders were chosen a priori and left in the models regardless of statistical significance. For more statistical details see Appendix 2.

 Confounders considered were sex, age, height, weight, BMI, study centre, accelerometer weartime, nutritional intervention, parental education, birthweight, breastfeeding, and pre- and postnatal tobacco-smoke exposure. Alternate models adjusted for subsets of these confounders (the crude and basic models); adjusted further for air pollution (annual average exposure to NOx and PM2.5); modelled only the subset of the population without extreme values for spirometry or PA; or modelled flows (PEF, FEF25, FEF50, and FEF75) as outcome. Selected models are given in the main text, and the remainder in Appendix 3.

 At p≤0.05 we have 80% power to detect a difference of about 100 mL FEV1 or FVC (3%) between the top and bottom PA quintiles. This is comparable to the effect size estimated in the literature, so we choose the traditional p≤0.05 to avoid missing an effect. Bonferroni correction is p≤0.0003 (the basic, crude and main models; four spirometric indices; and 12 PA measures, counting each MVPA quintile).

**Results**

***Study population***

Height, weight and BMI of study participants (Table 1) fit the German reference population well.[32] Sociodemographic data confirmed a predominance of highly-educated and urban families. Over half were from urban Munich rather than rural Wesel, 10% were born to mothers who smoked during pregnancy, and one-third were exposed to tobacco smoke at home in the first 6 years. 55% of participants were female compared to 51% of the 15-year followup, but otherwise representative of it (Appendix 1, Table 1b). However, the 15-year followup differed significantly from the original study population (Appendix 1, Table 1c) suggesting differential loss to followup.

***Lung function***

FEV1 and FVC in this sample averaged 3.83 (SD 0.65) and 4.50 (0.73) L for boys, 3.23(0.42) and 3.66 (0.51) for girls. This is about half a standard deviation below GLI predicted values [27]; however, Z-score differences between sexes were small. Offset was smaller ( Table 1d) for the German reference values established in the LUNOKID study [33]. However, the two sets of Z-scores correlated extremely closely with each other (all R2 >0.99.)

***Activity habits***

Each day averaged about 900 minutes of accelerometry, of which time 2/3 was spent sedentary, 1/3 in light activity, and about 5% in MVPA. See Table 1. Boys were more active than girls, but had similar participation levels in sport (77 and 80% of boys and girls) and active commuting (55 and 49%). These values are typical for European youth [34] and well below WHO recommendations. [35]

***PA and spirometric indices:***

At p≤0.05 there was no association between PA and any flow index (FEF2575 in Tables 2-4, others in Appendix 3) or between any index and either participation in sport or active commuting to school. There was no evidence for nonlinear effect of MVPA or for confounding by air pollution. Effect estimates were consistent between models of varying complexity.

FVC was associated with both MVPA quintile and percent of days with over 30 min MVPA. Though Type 3 tests often found no significant difference among all quintiles (global null hypothesis), at p<0.05 pairwise comparisons often showed significantly higher FVC in the most-active quintile than the least-active, and there was generally a monotone trend across the others (Figure 2a). In the main model (Table 2) children in the top quintile of MVPA averaged 113 mL greater FVC (pairwise p<0.02; global null p >0.10) than those in the bottom quintile, and getting over 30 min MVPA every day, versus never, was associated with 113 mL increase in FVC (p<0.05.) Effects were similar when outliers were excluded (Table 3); when z-scores were modelled as outcome, instead of raw values (Table 4) and in simpler models or when air pollution was considered (Appendix 3, Tables 1.1-1.3 and 2.1–2.3.)

 Relationships with indices other than FVC were often not monotone: for example, the MVPA quintiles that had the most different FEV1/FVC from the least-active (reference) were the second and fourth, not the fifth (highest); see Figure 2b. While PEF was associated at p≤0.05 with VPA and MVPA in the full population, this effect disappeared after exclusion of outliers. Relationships with spirometric flows (PEF, FEFs) are given in Appendix 3, Tables 3.1 and 3.2.

 After Bonferroni correction, there was no statistically significant relationship between PA and any spirometric index.

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| **Table 1: Population Characteristics**Mean (SD) unless stated otherwise. |
|  | Boys | Girls | P for sex difference |
| Male (N, %) | 401, 45 | -- |
| Age at exam (years) | 15.2 (0.25) | 15.2 (0.27) | -- |
| Height at spirometry (cm) | 176 (7.6) | 167 (6.1) | <0.0001 |
| Weight (kg); Mean (Median); 5th, 95th percentiles | 64.4 (63.8)47, 85 | 58.7 (57.2)46, 76 | <0.0001 |
| BMI (kg/m2); Mean (Median); 5th, 95th percentiles | 20.6 (20.0)17, 26 | 20.9 (20.4)17, 26 | -- |
| Parents highly educated1 (%) | 68 | 70 | -- |
| Study centre Munich (%) | 61 | 54 | 0.038 |
| Nutritional intervention (%)2 | 36 | 37 | -- |
| BMI category (%)3 |  |  | 0.28 |
| Underweight | 7.73 | 6.47 | \*\* |
| Normal weight | 81.3 | 84.4 | \*\* |
| Overweight | 8.23 | 5.47 | \*\* |
| Obese | 2.74 | 3.64 | \*\* |
| FEV1 (L) | 3.83 (0.65) | 3.23 (0.42) | <0.0001 |
| FVC(L) | 4.50 (0.73) | 3.66 (0.51) | <0.0001 |
| FEV1 / FVC (%) | 85 (5.8) | 88 (5.8) | <0.0001 |
| FEV1 z-score4 | -0.55 (0.99) | -0.48 (0.91) | -- |
| FVC z-score4 | -0.56 (0.95) | -0.43 (0.91) | 0.035 |
| FEV1 / FVC z-score4 | -0.06 (0.94) | -0.075 (0.96) | -- |
| FEF2575 z-score4 | -0.43 (0.98) | -0.32 (0.88) | -- |
| PEF (L/sec) | 7.65 (1.3) | 6.56 (0.95) | <0.0001 |
| FEF25(L/sec) | 6.56 (1.3) | 5.93 (0.91) | <0.0001 |
| FEF50 (L/sec) | 4.71 (1.2) | 4.26 (0.86) | <0.0001 |
| FEF75 (L/sec) | 2.31 (0.78) | 2.15 (0.64) | <0.0001 |
| FEF2575 (L/sec) | 4.13 (1.03) | 3.76 (0.76) | <0.0001 |
| Birthweight (g) | 3526 (443) | 3422 (451) | 0.0006 |
| Exclusively breastfed: (%) |  |  | -- |
| Never | 35 | 35 | \*\* |
| Months 1-4 only | 10 | 9.11 | \*\* |
| Past month 4 | 55 | 56 | \*\* |
| Mother smoked tobacco when pregnant (%) | 9.47 | 10.3 | -- |
| Tobacco smoke at home up to age 6 (%) | 31 | 30 | -- |
| Activity levels (min/day)5; Mean (Median); 5th, 95th percentiles |  |  |  |
| Moderate | 30.8 (29)14, 54 | 25.3 (24)9.2, 45 | <0.0001 |
| Vigorous  | 14.1 (11)2.0, 35 | 10.3 (8.1)0.86, 29 | <0.0001 |
| MVPA | 44.9 (42.0)17, 83 | 35.6 (32.1)13, 67 | <0.0001 |
|  MVPA > (% of days); Mean (Median); 5th, 95th percentiles |  |  |  |
| 30 min | 56 (57)14, 100 | 48 (42)0, 100 | <0.0001 |
| 45 min | 39 (33)0, 86 | 28 (29)0, 71 | <0.0001 |
| 60 min | 26 (20)0, 71 | 16 (14)0, 57 | <0.0001 |
| Any sport (%) | 77 | 80 | -- |
| Any active commuting to school (%) | 54 | 49 | -- |
| Lung-healthy population with complete data: excludes smokers, asthmatics, and those missing data.Centrally distributed variables given as mean (SD) and P-value from unequal-variance T-test. Categorical variables given as % for each category, and p-values from Kruskal-Wallis test; binary variables given as % and p-value from Wilcoxon’s two-tailed rank-sum test; skewed variables given as mean (median); 5th, 95th percentiles and p-value from Wilcoxon’s two-tailed rank-sum test.1)Better-educated parent college admission or higher2) See [21] and [23] for details.3) According to 10th, 90th, and 97th BMI percentiles from a German reference [32]4) Z-scores from [27]5) Accelerometric cutpoints from [29, 36]. Moderate, vigorous and moderate-to-vigorous PA (MVPA) imputed for diaried nonwear due to sport.-- if p>0.05, \*\* if p-value given as type 3 for global null hypothesis (top line.)  |

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| **Table 2: Activity as Correlate of Lung Function**Adjusted for age, sex, height, study centre, nutritional intervention, device weartime, BMI, parental education, birthweight, exclusive breastfeeding, prenatal tobacco, and tobacco smoke at home up to age 6 |
|  | FEV1 (mL) | FVC (mL) | FEV1/FVC (%) | FEF2575 (mL/sec) |
|  | Parameter estimate | 95% CI | P | Parameter estimate | 95% CI | P | Parameter estimate | 95% CI | P | Parameter estimate | 95% CI | P |
| Daily mean minutes |  |  |  |  |  |  |  |  |  |  |  |  |
| Moderate | 1.009 | -1.1; 3.1 | 0.34 | 1.343 | -0.91; 3.6 | 0.24 | -0.0048 | -0.034; 0.024 | 0.75 | 1.58 | -2.6; 5.8 | 0.46 |
| Vigorous | 0.979 | -1.6; 3.6 | 0.46 | 2.636 | -0.17; 5.4 | 0.066 | -0.0344 | -0.070; 0.002 | 0.060 | -0.439 | -5.7; 4.8 | 0.87 |
| MVPA | 0.700 | -0.66; 2.1 | 0.31 | 1.296 | -0.18; 2.7 | 0.084 | -0.0114 | -0.030; 0.007 | 0.23 | 0.554 | -2.2; 3.3 | 0.69 |
| MVPA quintile1 | -- | -- | 0.22 | -- | -- | 0.21 | **--** | **--** | **0.022** | **--** | **--** | **0.050** |
| 12 | 0 | -- | -- | 0 | -- | -- | 0 | -- | -- | 0 | -- | -- |
| 22 | -5.52 | -89; 78 | 0.90 | 58.1 | -33; 149 | 0.21 | **-1.45** | **-2.6; 0.29** | **0.014** | **-172** | **-342; -1.8** | **0.048** |
| 32 | 43.4 | -40; 127 | 0.31 | 63.0 | -28; 154 | 0.18 | -0.46 | -1.6; 0.70 | 0.44 | 10.1 | -160; 181 | 0.91 |
| 42 | -19.0 | -103; 65 | 0.66 | 51.1 | -40; 142 | 0.27 | **-1.73** | **-2.9; -0.58** | **0.0033** | -155 | -326; 14.7 | 0.073 |
| 52 | 67.0 | -18; 151 | 0.12 | **113** | **21; 205** | **0.016** | -0.86 | -2.0; 0.31 | 0.15 | 16.1 | -156; 188 | 0.85 |
| Percent days with MVPA > |  |  |  |  |  |  |  |  |  |  |  |  |
| 30 min | 96.1 | -2.5; 195 | 0.056 | **113** | **6.4; 221** | **0.038** | -0.331 | -1.7; 1.0 | 0.64 | 117 | -84; 318 | 0.26 |
| 45 min | 72.3 | -33; 177 | 0.18 | 95.5 | -18; 209 | 0.10 | -0.428 | -1.9; 1.0 | 0.56 | 106 | 109; -107 | 0.33 |
| 60 min | 48.0 | -77; 172 | 0.45 | 98.7 | -36; 234 | 0.15 | -1.200 | -2.9; 0.53 | 0.17 | 23.6 | -230; 277 | 0.86 |
| Any sport | 34.3 | -31; 100 | 0.30 | 46.6 | -25; 118 | 0.20 | -0.189 | -1.1; 0.72 | 0.68 | 22.5 | -111; 156 | 0.74 |
| Any active transportation | 23.9 | -32; 76 | 0.39 | 40.0 | -21; 95 | 0.18 | -0.189 | -0.95; 0.54 | 0.68 | 11.9 | -99; 120 | 0.83 |
| 95% confidence interval (CI) calculated using Wald’s chi-square.1) Top row is p-value for global null hypothesis (i.e. all quintiles equal.) Quintiles stratified by sex.2) P-value and parameter estimate for each quintile compared with the lowest (reference.)3) Active transportation defined as commuting to school by walking or cycling at least once during accelerometry.Moderate, vigorous and moderate-to-vigorous PA (MVPA) imputed for diaried nonwear time due to sport. Accelerometric cutpoints using Freedson’s algorithm from [29, 36]**Bold** text if p<0.05  |

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| **Table 3: Activity as Correlate of Lung Function, Outliers Excluded**Associations for subjects with moderate, vigorous, MVPA, FEV1, FVC and FEV1/FVC all within 2 standard deviations of sex-specific meanAdjusted for age, sex, height, study centre, nutritional intervention, device weartime, BMI, parental education, birthweight, exclusive breastfeeding, prenatal tobacco, and tobacco smoke at home up to age 6 (same as Table 2.) |
|  | FEV1 (mL) | FVC (mL) | FEV1/FVC (%) | FEF2575 (mL/sec) |
|  | Parameter estimate | 95% CI | P | Parameter estimate | 95% CI | P | Parameter estimate | 95% CI | P | Parameter estimate | 95% CI | P |
| Daily mean minutes |  |  |  |  |  |  |  |  |  |  |  |  |
| Moderate | 1.93 | -0.72, 4.6 | 0.15 | 2.05 | -0.80, 4.9 | 0.16 | 0.0040 | -0.033, 0.041 | 0.83 | 3.01 | -2.6, 8.6 | 0.29 |
| Vigorous | 1.97 | -1.7, 5.7 | 0.30 | **4.11** | **-0.18, 8.1** | **0.041** | -0.043 | -0.094, 0.0090 | 0.11 | -2.15 | -9.9, 5.6 | 0.59 |
| MVPA | -1.37 | -0.44, 3.2 | 0.14 | **1.94** | **0.0041, 3.9** | **0.050** | -0.0083 | -0.034, 0.017 | 0.52 | 0.879 | -2.9, 4.7 | 0.65 |
| MVPA quintile1 | -- | -- | 0.27 | -- | -- | 0.16 | -- | -- | **0.024** | -- | -- | 0.078 |
| 12 | 0 | -- | -- | 0 | -- | -- | 0 | -- | -- | 0 | -- | -- |
| 22 | 28.8 | -67, 58 | 0.89 | **91.4** | **7.4, 175** | **0.033** | **-1.27** | **-2.4, -0.18** | **0.022** | -127 | -291, 36 | 0.13 |
| 32 | 42.6 | -50, 107 | 0.47 | 62.9 | -20, 146 | 0.14 | -0.46 | -1.55, 0.62 | 0.40 | 9.34 | -153, 172 | 0.91 |
| 42 | -2.26 | -35, 120 | 0.28 | 62.4 | -22, 147 | 0.15 | **-1.53** | **-2.63, -0.43** | **0.0064** | -135 | -301, 30 | 0.11 |
| 52 | 88.4 | -1.7, 179 | 0.055 | **109** | **13, 206** | **0.026** | -0.14 | -1.40, 1.12 | 0.83 | 77.0 | -111, 265 | 0.42 |
| Percent days with MVPA > |  |  |  |  |  |  |  |  |  |  |  |  |
| 30 min | **109** | **7.4, 210** | **0.035** | **115** | **6.4, 224** | **0.038** | 0.142 | -1.3, 1.6 | 0.84 | 139 | -74, 352 | 0.20 |
| 45 min | 104 | -11, 219 | 0.076 | 96.2 | -27, 219 | 0.13 | 0.483 | -1.1, 2.1 | 0.56 | 160 | -81, 400 | 0.19 |
| 60 min | 75.9 | -74, 225 | 0.32 | 132 | -28, 292 | 0.11 | -1.026 | -3.1, 1.1 | 0.34 | -12.0 | -325, 301 | 0.94 |
| Any sport | -15.4 | -79, 48 | 0.64 | 10.1 | -58, 78 | 0.77 | -0.600 | -1.5, 0.30 | 0.19 | -50.0 | -183, 83 | 0.46 |
| Any active transportation3 | -3.10 | -55, 49 | 0.91 | 10.8 | -45, 67 | 0.71 | -0.333 | -1.1, 0.40 | 0.37 | -44.3 | -154, 65 | 0.43 |
| 95% confidence interval (CI) calculated using Wald’s chi-square.1) Top row is p-value for global null hypothesis (i.e. all quintiles equal.) Quintiles stratified by sex.2) P-value and parameter estimate for each quintile compared with the lowest (reference.)3) Active transportation defined as commuting to school by walking or cycling at least once during accelerometry.Moderate, vigorous and moderate-to-vigorous PA (MVPA) imputed for diaried nonwear time due to sport. Accelerometric cutpoints using Freedson’s algorithm from [29, 36]**Bold** text if p<0.05  |

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| **Table 4: Activity as Correlate of GLI Z-Score [27]**Adjusted for age, sex, height, study centre, nutritional intervention, device weartime, BMI, parental education, birthweight, exclusive breastfeeding, prenatal tobacco, tobacco at home up to age 6 (same as Tables 2 and 3.) |
|  | FEV1 ( Z-score \* 1,000) | FVC ( Z-score \* 1,000) | FEV1/FVC ( Z-score\* 1,000) | FEF2575 ( Z-score \* 1,000) |
|  | Parameter estimate | 95% CI | P | Parameter estimate | 95% CI | P | Parameter estimate | 95% CI | P | Parameter estimate | 95% CI | P |
| Daily mean minutes |  |  |  |  |  |  |  |  |  |  |  |  |
| Moderate | 1.93 | -2.6, 6.5 | 0.41 | 2.56 | -1.9, 7.0 | 0.26 | -0.892 | -5.6, 3.8 | 0.71 | 1.56 | -3.1, 6.2 | 0.51 |
| Vigorous | 2.22 | -3.5, 7.9 | 0.45 | **5.77** | **0.26, 11.3** | **0.040** | -5.88 | -12, 0.0041 | 0.050 | -1.24 | -7.1, 4.6 | 0.68 |
| MVPA | 1.43 | -1.6, 4.4 | 0.35 | 2.67 | -0.21, 5.6 | 0.070 | -1.99 | -5.1, 1.1 | 0.21 | 0.330 | -2.7, 3.4 | 0.83 |
| MVPA quintile1 | -- | -- | 0.20 | -- | -- | 0.14 | -- | -- | **0.016** | -- | -- | 0.057 |
| 12 | 0 | -- | -- | 0 | -- | -- | 0 | -- | -- | 0 | -- | -- |
| 22 | -7.20 | -192, 177 | 0.94 | **121** | **-57, 300** | **0.18** | **-252** | **-441, -62** | **0.0093** | -188 | -376, 0.23 | 0.050 |
| 32 | 113 | -71, 298 | 0.22 | 147 | -31, 327 | 0.11 | -102 | -292, 89 | 0.30 | 21.5 | -167, 210 | 0.82 |
| 42 | -29.5 | -214, 155 | 0.75 | 123 | -55, 302 | 0.18 | **-302** | **-492, 112** | **0.0018** | -166 | -354, 22 | 0.083 |
| 52 | 155 | -32, 341 | 0.10 | **241** | **60, 421** | **0.0089** | -154 | -346, 38 | 0.12 | 9.01 | -181, 199 | 0.93 |
| Percent days with MVPA > |  |  |  |  |  |  |  |  |  |  |  |  |
| 30 min | **218** | **0.72, 435** | **0.049** | **252** | **42, 462** | **0.019** | -64.7 | -289, 160 | 0.57 | 115 | -108, 337 | 0.31 |
| 45 min | 155 | -76, 386 | 0.19 | 204 | -20, 427 | 0.074 | -76.3 | -315, 162 | 0.53 | 91.7 | -144, 328 | 0.45 |
| 60 min | 88.6 | -186, 363 | 0.53 | 203 | -62, 469 | 0.13 | -217 | -500, 66 | 0.13 | -15.8 | -296, 264 | 0.91 |
| Any sport | 62.1 | -82, 206 | 0.40 | 82.5 | -57, 222 | 0.25 | -57.2 | -206, 92 | 0.45 | 21.9 | -126, 169 | 0.77 |
| Any active transportation3 | 56.1 | -62, 175 | 0.35 | 72.9 | -42, 188 | 0.21 | -31.8 | -154, 90 | 0.61 | 16.0 | -105, 137 | 0.80 |
| All parameter estimates multiplied by 1,000 for interpretability; e.g. subjects who got at least 30 minutes MVPA per day averaged an FVC Z-score that was 0.252 units higher.95% confidence interval (CI) calculated using Wald’s chi-square.1) Top row is p-value for global null hypothesis (i.e. all quintiles equal.) Quintiles stratified by sex.2) P-value and parameter estimate for each quintile compared with the lowest (reference.)3) Active transportation defined as commuting to school by walking or cycling at least once during accelerometry.Moderate, vigorous and moderate-to-vigorous PA (MVPA) imputed for diaried nonwear time due to sport. Accelerometric cutpoints using Freedson’s algorithm from [29, 36] GLI Z-scores for spirometric indices from [27]**Bold** text if p<0.05  |

**Discussion:**

After correction for multiple comparisons, we found no significant associations in lung-healthy adolescents between PA, active lifestyle and spirometric indices. While existing literature suggests that physically active healthy people average 1-10% higher spirometric volumes, particularly FVC, than inactive peers [10, 13, 16] [15] [37] these effects in athletes were found only in some sports [14], and in one study [13] FVC declined by 4% after 8 weeks of aerobic exercise. We found that at p≤0.05 only the association between FVC and either percent of days with at least 30 min MVPA, or extreme MVPA quintile, was both robust across models and consistent with a monotone trend between spirometry and PA. The observed difference of 113 ml FVC (3%) between top and bottom MVPA quintile was consistent with the literature [10, 13, 15, 16] [37]: however, results for other indices often were not plausible, such as larger spirometric differences between intermediate MVPA quintiles than between extreme quintiles. To reduce multiple-comparisons we suggest that further research focus on some spirometric index chosen a priori, such as FVC.

 Possible reasons for the discrepancies between studies may include statistical models used, study population, confounding, correction for multiple comparisons, or PA measurement methods; measurement methods for lung function were comparable. We accelerometrically measured PA in adolescents and considered levels, thresholds and lifestyle, while other studies [15] [10, 13, 16] [37] mostly studied younger children, relied on PA questionnaires, and/or dichotomized PA into active vs. non-active.

 While we considered nonlinear effects by modelling MVPA quintiles and thresholds in addition to continuous minutes, we may have missed a more complex relationship. The association between FVC and percent of days with over 30 minutes of MVPA, but no higher threshold, hints at nonlinearity. Although almost the whole population (87% of subjects) had sport and/or commuted actively, PA was highly variable: 5th and 95th percentiles were 15 and 75 minutes per day MVPA, and 1.2 and 31 minutes VPA. Nevertheless, the full range of PA may not have been sampled. In light of findings in athletes, who experienced approximately 5% higher spirometric volumes, [14] our observed PA may have been insufficient to measurably affect lung function.

 Furthermore, activity type may be important in determining size or direction of the association between PA and lung function: some sports were associated with increased volumes, others were associated with no difference and others with decreases. [14] Though we found no change in spirometry with sport participation, we did not consider the type of sport; and with regards to total PA, one sport associated with increased FVC (about 6%) was cycling, which accelerometry is known to undermonitor. [38]

***Strengths and limitations***

The strength of our study is that we applied several different quantifications of PA and measured PA objectively with accelerometry rather than questionnaires: only 1-10% of the variance of accelerometric PA is captured by self-report [18] and this error is not likely to be uniform across subjects. However, accelerometry also has well-known limitations, including the “snapshot” nature of data recorded over the course of a single week and the known undermonitoring of low-acceleration sports [38]. Although participants may be more active when they know measurement is taking place[39], our subjects were no more active on the first weekday of accelerometry than on the others which suggests this effect is negligible. Likewise,, although spirometry is the standard measurement of lung function it does not measure mechanical properties of the lung, respiratory pump functions or gas-exchange capacity although in the healthy lung close correlations have been reported with FVC.

 Well-known limitations arise from our cross-sectional design. Selection bias began with recruitment of German Caucasians born full term and continued with selective loss to followup by age 15; successful completion of accelerometry, examinations and questionnaires at age 15 may have introduced further bias. Relative to GINIplus and LISAplus at birth, we oversample girls from urban Munich and well-educated families who breastfed more and smoked less, all of which may indicate greater health-consciousness. The intervention arm of GINIplus (selected for atopy risk) was likelier to be followed up successfully than the unselected observation arm, further suggesting health-consciousness bias. However, representation of the 4 different nutritional interventions did not change and FEV1 and FVC did not vary between study formulas [40] suggesting that the intervention itself did not drive results. Thus while we adjusted for conditions that may affect lung function, and carefully excluded smokers, asthmatics or those with suspected asthma, residual effects cannot be ruled out and our findings may not generalize to all populations.

**Conclusion**

In a cohort of healthy and active adolescents, we found no clear evidence for an association between spirometric indices and physical activity or activity habits.

**Acknowledgements:**

 This study was part of the 15-year followup of two German birth cohorts, GINIplus (German Infant Study on the influence of Nutrition Intervention PLUS environmental and genetic influences on allergy development) and LISAplus (Influence of lifestyle factors on the development of the immune system and allergies Plus the influence of traffic emissions and genetics). We thank the GINIplus and LISAplus Study Groups for all their excellent work.

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**Figures:**

**Figure 1 Title: GINIplus and LISAplus Recruitment and Followup**

**Figure 1 Legend:**

GINIplus is “German Infant Study on the influence of Nutrition Intervention Plus environmental and genetic influences on allergy development.” GINIplus is an ongoing birth cohort recruited between 1995 and 1999 with the 15-year follow up addressed in this study. For details see Appendix 1 or ginistudie.de.

LISAplus is “Lifestyle-Immune System-Allergy: Influence of life-style factors on the development of the immune system and allergies in East and West Germany Plus the influence of traffic emissions and genetics.” LISAplus is an ongoing birth cohort recruited between 1995 and July 1998. This study is based on the 15-year followup. For details see Appendix 1 or lisastudie.de. Details on accelerometry response rate and quality control are provided in Appendix 1.

**Figure 2 Title: Spirometric Indices by Physical-Activity Quintile**

**Figure 2 Legend:**

Boxes span from 25th-75th percentiles of spirometric z-score by sex; circular markers show mean; horizontal lines show median. Whiskers represent 1.5 interquartile ranges. Spirometric Z-scores are from Global Lung Initiative (Quanjer, 2012). Daily mean minutes of moderate-to-vigorous physical activity (MVPA) are provided at the bottom for each quintile. Daily minutes in MVPA were calculated using Freedson‘s accelerometric algorithm (Freedson, 2005). Quintiles calculated separately for each sex.

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