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LuftiBus in the school (LUIS): a population-based study on respiratory health in schoolchildren

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Summary

Respiratory disease is common in children and strongly associated with lifestyle and environmental exposures. Thus, it is important to study the epidemiology locally. The LuftiBus in the School (LUIS) study was set up to assess the respiratory health of schoolchildren in the canton of Zurich, Switzerland.

LUIS is a cross-sectional population-based study that was carried out 2013 to 2016. Children aged 6–17 years living in the canton of Zurich were eligible to participate. All schools in the canton were approached and the school head decided whether the school would participate and with which classes. Consenting parents answered a standardised questionnaire at home and assenting children completed a shorter questionnaire by interview at school. Trained technicians measured children's lung function, including spirometry, double tracer gas single-breath washout (DTG-SBW) and fractional exhaled nitric oxide (FeNO). Address histories of participants were geocoded to be linked with area-based socioeconomic measures and environmental exposures such as spatiotemporal air pollution estimates for specific time periods and locations. A subgroup was seen again 12 months later using the same procedures to collect longitudinal data.

The study included 3870 children at baseline and 655 at the 1-year follow-up. Median age was 12.7 years; 281 (8%) had wheezed in the past year. At baseline we collected 3457 (89%) parental and 3546 (92%) child questionnaires, and 3393 (88%) FeNO, 3446 (89%) spirometry, and 1795 (46%) DTG-SBW measurements.

LUIS is a rich resource of health-related data, with information on lung function, environmental exposures and respiratory health on Swiss schoolchildren.

Introduction

Respiratory disease is common and can affect quality of life and school performance in children [1]. Symptoms and diseases result from complex interactions between genetic factors and modifiable behavioural and environmental influences, such as physical activity, passive and active smoking, and air pollution [2]. The prevalence of respiratory symptoms such as wheeze and cough varies widely between countries, so local studies are important [3, 4]. Geographic differences in the prevalence of respiratory diseases may result from differences in lifestyle, health care, socioeconomic factors and environmental exposures, which have been the focus of many studies [2, 3, 5–7].

Previous research on the respiratory health of Swiss children focused on self-reported lower respiratory symptoms and a farming environment [8–14]. None of the recent population-based studies included a detailed assessment of lung function and airway inflammation. Different examinations measure diverse aspects of lung physiology, such as airway inflammation, lung volumes, flows representing function of larger airways, and ventilation inhomogeneity representing the ventilation in peripheral airways. The same symptom might be caused by different underlying mechanisms, and similar underlying mechanisms may cause diverse symptoms in children. Thus, joint evaluation of results from different examinations and of reported symptoms would improve understanding of this complexity. This article explains the methodology of LuftiBus in the School (LUIS) and presents first results.

Study objectives

LUIS is a multipurpose school-based study on respiratory health in children. Its objectives are: (1) to describe the frequency of common upper and lower respiratory symptoms such as chronic cough, rhinitis, habitual snoring and wheeze reported by schoolchildren and their parents; (2)

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Alexander Moeller, Claudia E. Kuehni and Philipp Latzin conceptualised and designed the study. Rebeca Mozun analysed the data and drafted the manuscript. Eva S.L. Pedersen supported the statistical analysis. All authors gave input for interpretation of the data. All authors critically revised and approved the manuscript.

to assess risk factors for respiratory symptoms, with a special interest in lifestyle and environmental exposures such as smoking and air pollution; (3) to study lung function phenotypes, determinants of lung function and associations with lifestyle and environmental exposures; (4) to assess the distribution of lung function (spirometry and double tracer gas single breath washout, [DTG-SBW]) and airway inflammation (fractional exhaled nitric oxide [FeNO]) measurements in healthy schoolchildren and to provide normative data; (5) to gain methodological insights into questionnaire design and performance of novel lung function tests such as DTG-SBW in school-based settings to help guide future research.

Materials and methods

Study design and setting

Throughout the manuscript we use the past tense for procedures or analyses that were done in the past and the present or future tense for those that are underway or planned. LUIS is a cross-sectional study that was conducted from November 2013 to December 2016 among schoolchildren aged 6 to 17 years living in the canton of Zurich (ClinicalTrials.gov: NCT03659838). A subsample of children was seen again 1 year later for collection of longitudinal data. The canton of Zurich is located in the north-eastern part of Switzerland and is the most populated canton in the country with over 1.5 million inhabitants, 18% of the Swiss population [15].

Study procedures

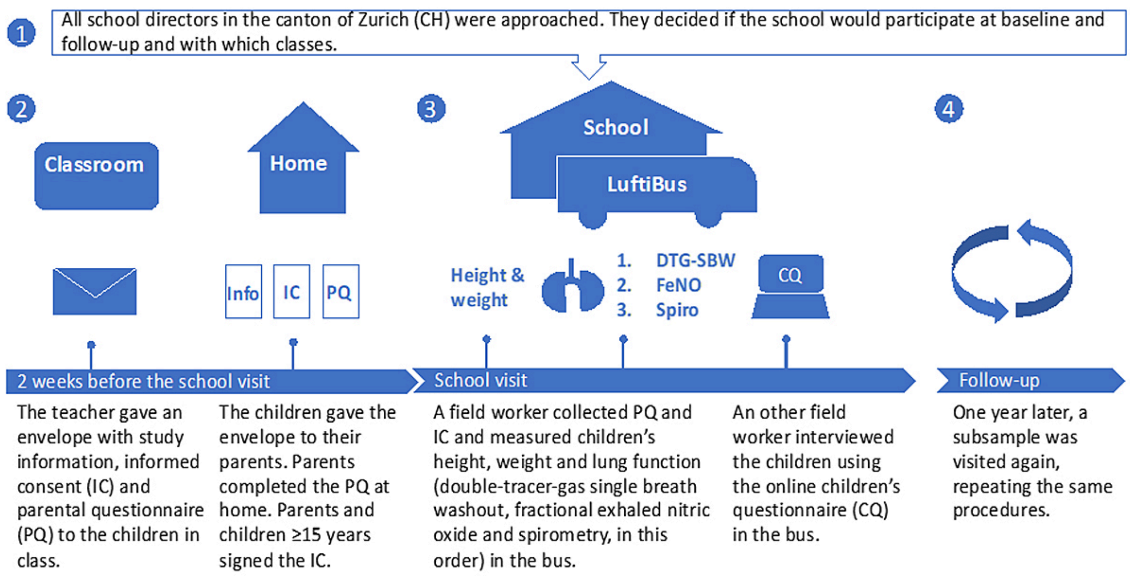
LUIS was embedded in a respiratory health promotion activity offered by Lunge Zürich [16-18]. Lunge Zürich is a non-profit organisation that promotes respiratory health prevention and research [16]. LUIS used a special bus from Lunge Zürich, the LuftiBus, to visit schools within the canton of Zurich, further details on the LuftiBus are described in the appendix [16]. All school heads in the canton of Zurich were invited to participate (fig. 1). They decided whether to take part in the project and with which classes, independently of the health status on the students. Participating schools contributed CHF 500 for a 2-day visit and CHF 800 for a visit lasting 1 week, from their reserved budget for health prevention activities in schools. Main reasons for non-participation of schools were lack of time and commitment to other health prevention activities. The study coordinator provided the participating schools with closed envelopes containing study information for parents and for children, and an informed consent form and a questionnaire for parents. Teachers gave these envelopes to the students 2 weeks before the visit. Parents were asked to complete the questionnaire. Two study field workers, who were trained lung function technicians, visited each school with the study bus, the LuftiBus [16]. They collected the parental questionnaires and consent forms from the teachers and asked all students for oral and, where appropriate, written consent. The study bus contained computers and equipment for lung function testing. One field worker measured the children’s height and weight and performed the lung function tests, and the other interviewed the children using a short electronic questionnaire.

Where the heads of the participating schools agreed, the school was visited again 1 year later (2015–2016), with the same procedures and the same tests as in the baseline visit.

Study participants

Eligible were children aged 6 to 17 years, living in the canton of Zurich with consent to participate. Participants were recruited from whole school classes selected for participation by the heads of participating schools. There were no predefined exclusion criteria. However, basic German language knowledge from the children and their parents was required to understand the study information and to complete the questionnaires.

Figure 1: Design of the LuftiBus in the school (LUIS) study.



Data collection

The questionnaires

The study used two questionnaires: one for parents and one for children. Both included questions on respiratory symptoms and diagnoses including the key questions from the International Study on Asthma and Allergies in Childhood study and additional questions from the Leicester Respiratory Cohort questionnaires [3, 7]. The questionnaire to parents included questions about frequency, duration, severity and triggers of upper and lower respiratory symptoms, doctors' diagnosis of asthma, medication, environmental factors, household characteristics, family history of asthma, and current and past addresses (table 1). We geocoded participant's addresses using a reference file from the Swiss Federal Statistical Office (Neuchâtel) [15]. The data from the parental questionnaire were entered into an Epidata database (version 4.2.0.0, EpiData Association, Denmark) at the Institute for Social and Preventive Medicine (ISPM) in Bern.

Children replied to the questionnaire via interview by the field workers in the bus. It included questions about current respiratory health such as rhinitis, cough and wheeze, the presence of cough or a cold on the day of the school visit, inhaled or oral asthma medication on the day of the visit, active smoking and parental smoking. To help the children correctly report asthma medications, the field workers used a poster with pictures and commercial names of all commonly used inhaled and oral medications in Switzerland (supplementary fig. S1). Children's answers were directly entered by field workers into the web-based Research Electronic Data Capture (REDCap) database [19].

Area-based index of socioeconomic position in Switzerland (Swiss-SEP)

The Swiss-SEP was developed by the Swiss National Cohort (SNC) as an area-based measure of socioeconomic status that incorporates information on rent per square meter, education and occupation of household heads, and number of persons per household room [20, 21]. The Swiss-SEP ranges from 0 (lowest) to 100 (highest). We estimated the Swiss-SEP for our participants by matching the geocodes of our participants addresses to the nearest geocode in the Swiss-SEP dataset. If the address of a participant was missing, we assigned the median Swiss-SEP among participants of the same school. In this manuscript we used a dataset from the SNC to assess the distribution of Swiss-SEP among households from the canton of Zurich with at least one child in school-age (6–17 years) and compared it with the distribution of Swiss-SEP of our study participants.

Lung function measurements

Children's standing height and weight were measured without shoes and recorded in the spirometry database. Lung function tests were performed inside the bus in the

Table 1: Details of data collected in the LuftiBus in the school (LUIS) study.

Data sources		Collected data
1. Questionnaires	For parents	Upper and lower respiratory symptoms in the past 12 months: colds, rhinitis, snoring, cough, wheeze, frequency of wheeze/asthma attacks, triggers of cough and wheeze [3, 7]
		Asthma diagnosis and hay fever [3, 7]
		Management of wheeze/asthma in the past 12 months: number of doctor visits; medication use including short- and long-acting beta-2 agonists, inhaled corticosteroids, leukotriene receptor antagonists, and antihistamines
		Household: Current and past address, living on which floor, type of cooking stove, presence of oven or chimney, living on a farm
		Environment and lifestyle: paternal and maternal smoking indoors or outdoors and number of cigarettes smoked, physical activity of the child, type of commuting to school, sports outside school, pets at home
		Family: country of birth of the child, country of origin of the parents, siblings, parental education, parental history of asthma and chronic cough
	For children	Currently having a cold; currently coughing
		Upper and lower respiratory symptoms in the past 12 months: colds, rhinitis, waking up with a dry mouth as a proxy for mouth breathing, cough, wheeze, triggers of cough and wheeze [3, 7]
		Asthma diagnosis and hay fever [3, 7]
		Medication during the day of the visit: inhaled short- and long-acting beta-2 agonists, inhaled corticosteroids, leukotriene receptor antagonists
		Environment and lifestyle: frequency of active smoking of cigarettes, shishas and e-cigarettes; paternal and maternal smoking
2. Anthropometrics		Height and weight measured in the bus without wearing shoes Body mass index z-scores calculated using World Health Organization reference tables [37]
3. Lung function measurements	Spirometry	Masterlab, Jaeger, Würzburg, Germany. Mouthpiece, filter, nasal clamp Main outcomes: forced expiratory flows and volumes [28]
	FeNO	Fast response chemiluminescence analyzer CLD 88, Eco Medics AG, Duernten, Switzerland. Mouthpiece, filter, no nasal clamp Main outcome: mean FeNO (ppb) of at least two reproducible exhalations in the same child [27, 43]
	DTG-SBW (He, SF_6)	Exhalyzer D, Eco Medics AG, Duernten, Switzerland. Mouthpiece, filter, nasal clamp [23] Main outcome: phase III slope
4. Air pollution		We will use data from air pollution models developed by de Hoogh et al. [30, 31] to estimate participants' average exposure to NO_2 and $PM_{2.5}$ for specific time windows and locations, based on participants' exact address history.
5. Swiss-SEP		An area-based measure of socioeconomic status based on data about rent per square meter, education and occupation of households' heads, and household crowding, which ranges from 0 (lowest) to 100 (highest), developed as part of the Swiss National Cohort study [20, 21]

FeNO = Fractional exhaled nitric oxide; ppb = parts per billion; DTG-SBW = double tracer gas single breath washout; He = helium; SF_6 = sulphur hexafluoride; NO_2 = nitrogen dioxide; $PM_{2.5}$: particulate matter of aerodynamic diameter of 2.5 μm or less; Swiss-SEP = socioeconomic position in Switzerland following order: (1) double tracer gas single-breath washout (DTG-SBW), (2) fractional exhaled nitric oxide (FeNO), and (3) spirometry.

DTG-SBW

DTG-SBW was measured using a validated and commercially available setup (Exhalyzer D®, Eco Medics AG, Duernten, Switzerland) [22]. The patient interface consisted of a bacterial filter and a snorkel mouthpiece to prevent air leaks near the mouth. According to current paediatric equipment recommendations, a dead space reducer and a disposable hygienic insert provided by the manufacturer were used [23]. The DTG mixture contained 26.3% helium (He), 5% sulphur hexafluoride (SF_6), 21% oxygen (O_2), and balance dinitrogen (N_2) from pressurised cylinders (Carbagas, Bern, Switzerland). Children watched a video for distraction while breathing through an open bypass system. Directly before tracer gas wash-in, the apparatus dead space and the bias flow was flushed with double-tracer gas or 100% O_2 during expiration to prevent re-inspiration of expired or ambient gas [24]. DTG-SBW was performed in accordance with the European Respiratory Society (ERS) consensus on inert gas washout testing [23]: after establishing natural tidal breathing for at least 5 breaths monitored by online flow-volume loops and tidal volumes varying less than 10%, the system was flushed with the DTG mixture. Within only one breath, the children inhaled the double-tracer gas and exhaled it back. SBW tests were done in triplicate. Each test was followed by at least 10 breaths of room air, until the online monitoring of the gas signals returned to baseline [23]. Primary outcome of the DTG-SBW was the mean slope from the tidal (alveolar) phase III from three technically acceptable DTG-SBW curves, normalised for tidal volume (SnIII) [25]. The magnitude of phase III slopes from He and SF_6 relates to acinar branching asymmetry and small airways obstruction [26]. DTG-SBW is a fast and easy to perform test with low variability and high repeatability [22].

FeNO

FeNO was measured with a single breath on-line method according to recommendations [27]. We used a fast response chemiluminescence analyser CLD 88, Eco Medics AG, Duernten, Switzerland. The field workers calibrated the FeNO device every morning and the gas was calibrated once per month. Children breathed air free of nitric oxide via the Denox system (EcoMedics, Dürnten). This setup also included a bacterial filter and disposable hygienic mouthpiece. After 10 breaths, children exhaled against an adjusted expiratory resistance with a constant target flow of 50 ml/sec for at least 4 seconds for children younger than 12 years and 6 seconds for children aged 12 years or older. We aimed for at least two reproducible exhalations with the nitric oxide plateau values within 10% of each other. Results were stored digitally, including information on FeNO (parts per billion, ppb), expiratory time (seconds), duration of the plateau (seconds), and average flow in the plateau (ml/s). The primary outcome was FeNO.

Spirometry

Spirometry was performed using Masterlab, Jaeger, Würzburg, Germany according to American Thoracic Society (ATS) / ERS recommendations [28]. The children performed three to five forced expiratory manoeuvres. Spirometry parameters were recorded and stored digitally using the Sentry Suite software, Carefusion, Hoechberg, Germany. Spirometry parameters included forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), peak expiratory flow (PEF), FEV_1/FVC ratio, maximum expiratory flow at 75%, 50% and 25% FVC (FEF_{75}, FEF_{50}, FEF_{25}) and between the 25% and 75% of FVC ($FEF_{25–75}$). The spirometry flow-volume curve of the best effort was printed on paper. Primary outcomes were forced expiratory flows and volumes. Absolute values of spirometry parameters were expressed as z-scores according to Global Lung Initiative reference values [29].

Air pollution assessment

Spatiotemporal data on nitrogen dioxide (NO_2) and particulate matter with an aerodynamic diameter of 2.5 µm or less ($PM_{2.5}$) will be obtained from models developed by de Hoogh et al. [30, 31]. Daily average NO_2 concentrations were modelled across Switzerland using a multistage framework with mixed-effect and random forest models at a fine spatial resolution of 100 × 100 m [30] combining the Ozone Monitoring Instrument (OMI) NO_2 product with Copernicus Atmosphere Monitoring Service (CAMS), land use and meteorological variables. Daily $PM_{2.5}$ concentrations across Switzerland were estimated first by a combination of a mixed effect model and a generalised additive mixed model at a 1 × 1 km resolution using Multiangle Implementation of Atmospheric Correction (MAIAC), spectral aerosol optical depth (AOD) data, and second by support vector machine algorithms used to predict precise exposure estimates at a 100 × 100 m resolution with spatiotemporal predictor data [31]. These air pollution models allow estimation of participants' average exposure to NO_2 and $PM_{2.5}$ for specific time windows and locations. We will link the geocoded residential and school addresses of study participants to NO_2 and $PM_{2.5}$ data by GIS (geographic information system) overlay.

Ethics and data safety

The ethics committee of the canton of Zurich approved the study (KEK-ZH-Nr: 2014-0491). Parents signed the informed consent form and completed a detailed questionnaire. Children assented orally and those aged 15 years or older also signed. Participant identifiable information was stored in a separate database and only pseudoanonymised datasets are used for analysis. Paper-based data were securely locked at ISPM and only accessible to the study team. Raw data of DTG-SBW, FeNO and spirometry measurements were stored in a safe study server during recruitment and were thereafter encrypted and securely stored in the ISPM protected server. Access to the server and the study databases is restricted to members of the study team. Study datasets are securely stored and routinely backed up in protected servers of ISPM Bern. Study collaborators and other researchers can obtain datasets for analysis if a detailed concept sheet is presented for the planned analyses and approved by the principal investigators (AM, PL and CK).

Sample size considerations

We aimed to recruit over 3000 children to address the main objectives of the LUIS study. In this section we describe examples of sample size estimations for our main aims [32]. LUIS aimed to describe the frequency of respiratory symptoms in schoolchildren. To estimate the prevalence of current wheeze we need a sample size of 2501 participants, if we assume a level of acceptable error of 1% [3], and we expect a proportion of wheeze in the population of around 7% [14], at the 5% type I error rate (i.e., $\alpha = 0.05$). Another study aim was to assess risk factors for respiratory symptoms. If we expect the proportion of wheeze to be 7% higher among students who smoke compared with never smokers [33], and a proportion of smokers of 15% [34], to be 80% certain of detecting a prevalence difference at the 5% Type I error rate, we need a sample with 160 smokers and 890 never smokers. LUIS also aimed to examine associations between lung function measurements and environmental exposures. If we want to compare the difference in FEV_1 (ml) between a group of participants with high exposure to air pollution (e.g., $PM_{2.5}$) with a group with lower exposure levels, using a two-sided 5% significance test (i.e., $\alpha = 0.05$), to be 80% sure of detecting a difference of −50ml between the high and the low exposure groups, with an estimated standard deviation of FEV_1 of 326 ml [35], we need at least 668 participants per group. LUIS data will be used to assess the fit of global lung function initiative (GLI) reference equations, for which we need at least 150 healthy boys and girls of white ethnicity [29, 36]. If we want to assess the fit of GLI for several age groups, at least 300 children per age group are needed. At follow-up, we aimed to re-visit a sub-sample of 1000 children for longitudinal analyses.

Data preparation and analysis

We calculated body mass index (BMI) z-scores according to World Health Organization references and categorised BMI z-scores ≥2 as obesity, ≥1 to <2 as overweight and ≤−2 as underweight [37]. In this manuscript, we compared participants' characteristics between age groups using p-values for a trend. We used the software STATA (Version 16.1, StataCorp., College Station, TX) for statistical analysis. In our planned analyses, we will select confounders *a priori* based on Directed Acyclic Graphs (DAGs). Results from DTG-SBW, FeNO or spirometry tests that did not meet the quality standards described in the appendix will not be included in analyses. Details on data quality assessments can be found in the appendix. We will adhere to STROBE reporting guidelines in manuscripts using LUIS datasets [38].

Results

Participating schools

All 490 schools in the canton of Zurich were invited to participate (supplementary table S1 in the appendix). At baseline, 37 schools took part and 3870 participants consented. One year later, 19 schools were visited a second time and 655 children were followed up. The canton of Zurich (fig. 2) had mostly schools in small (47%) and large urban areas (41%) and fewer in rural areas (12%) (fig. 3, online Table S1) [39, 40]. At baseline, LUIS visited 18 schools in small (49%) and 15 in large (40%) urban areas and 4 in rural areas (11%). At follow up, 13 schools in small (68%) and 4 in large (21%) urban areas and 2 in rural areas (11%) were visited. Median Swiss-SEP was 66.2 (interquartile range [IQR] 58.2–73.0) for households with at least one school-aged child in the canton of Zurich, 69.2 (IQR 61.2–76.3) for LUIS participants at baseline and 69.4 (IQR 64.7–74.8) at follow-up (fig. 4, supplementary fig. S2).

Completeness of datasets

At baseline, 3457 participants (89%) provided parental questionnaires, 3546 (92%) answered the children's questionnaire, 3446 (89%) did spirometry, 3393 (88%) FeNO and 1795 (46%) DTG-SBW tests (supplementary table S2

Figure 2: Areas from the canton of Zurich that were visited by the LuftiBus in the School (LUIS) study. The area of the circle is proportional to the number of participants per location. The colour of the circle indicates the degree of urbanisation of the region (from darker to lighter grey: large urban, small urban, rural areas) according to the Swiss Federal Office of Statistics classification. Definition of urbanisation degree: cities or large urban area: at least 50% lives in high-density clusters. Towns and suburbs or small urban area: less than 50% of the population living in rural grid cells and less than 50% living in a high-density cluster. Rural area: more than 50% of the population living in rural grid cells.

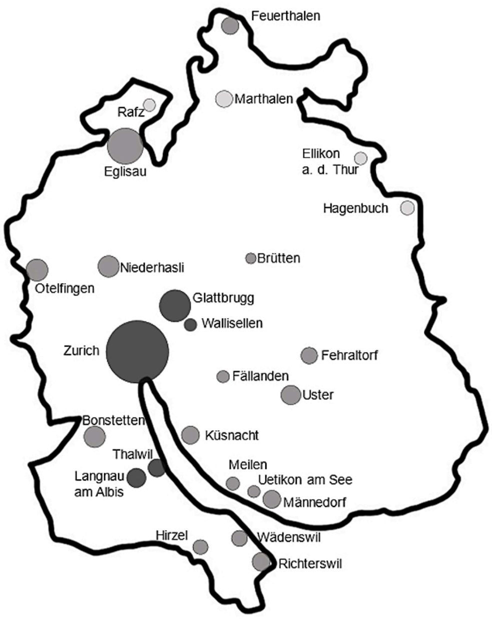
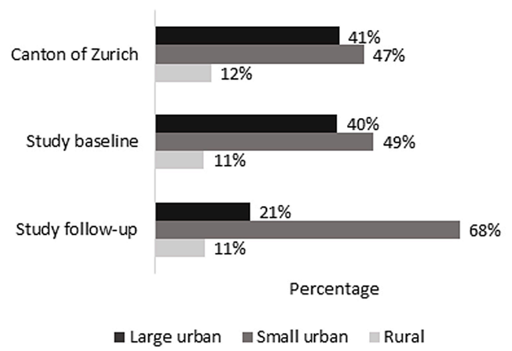
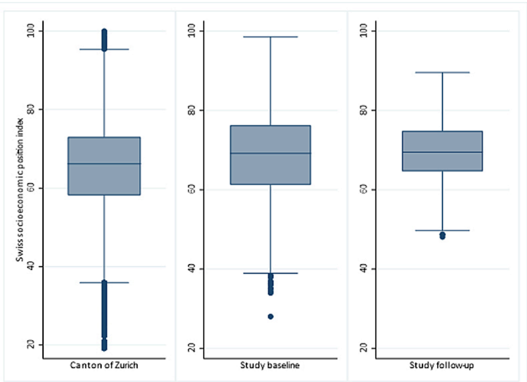


Figure 3: Proportion of schools by degree of urbanisation in the canton of Zurich and in the LuftiBus in the School (LUIS) study at baseline and follow-up. Definition of urbanisation degree: cities or large urban area: at least 50% lives in high-density clusters. Towns and suburbs or small urban area: less than 50% of the population living in rural grid cells and less than 50% living in a high-density cluster. Rural area: more than 50% of the population living in rural grid cells.



in the appendix). At the 1-year follow-up, data from parental questionnaires was available for 629 children (96%), data from children's questionnaires for 640 (98%), results from spirometry for 614 (94%), results from FeNO testing for 588 (90%) and results from DTG-SBW for 496 children (76%).

Figure 4: Box plots showing the distribution of Swiss socioeconomic position index (Swiss-SEP) for families with at least one child aged 6–17 years and living in the canton of Zurich and in the LuftiBus in the School (LUIS) study at baseline and follow-up. The median is represented by a horizontal line inside the box, 25 and 75 percentiles by the upper and lower box horizontal lines of the box, minimum and maximum values are shown as whiskers, and points outside the whiskers are outliers.



Characteristics of study participants and first results

LUIS included 987 children aged 6–9 years (2%), 1723 aged 10–13 years (45%) and 1160 aged 14–17 years (30%) at baseline (table 2). Current wheeze was reported by parents of 281 (8%) children. Exercise-induced wheeze was more common among older children, and night cough among younger children. Use of inhaled short-acting beta-2 agonists (SABA) and inhaled corticosteroid (ICS) in the past year was reported by parents of 257 (8%) and 179 (5%) children, respectively. Parents of 1108 (32%) reported that their child had a high physical activity level. This was more common for younger children. Mothers of 574 (17%) and fathers of 758 (22%) children reported smoking. A total of 580 children (15%) were overweight and 194 (5%) obese, with obesity being more common in older children. Most children were born in Switzerland (n = 3042; 88%), but only over half of children's mothers (n = 1934; 56%) and fathers (n = 2045; 59%).

The volume of air that was exhaled in the first second (FEV_1) was higher in boys (median 2556 ml, IQR 1963–3358) than in girls (2485 ml, IQR 1910–2953) and increased with age, particularly during the pubertal growth spurt (fig. 5).

FeNO had a right skewed distribution. Median (IQR) values of FeNO were 12.9 ppb (7.3–24) in boys and 12.0 ppb (7.0–19.2) in girls (fig. 6). FeNO levels were lower in younger than in older in children with reported hay fever (age 6–9 years: median 11.9 ppb, IQR 6.5–24.3; age 10–13 years: 20.9 ppb, 10.6–43.9; age 14–17 years: 20.1 ppb, 11.6–39.3) and also in children without hay fever (age 6–9

Table 2: LuftiBus in the School (LUIS) study: characteristics of the study participants.

		Total	Age groups (years)			P trend
			6 to 9	10 to 13	14 to 17	
		n = 3870	n = 987	n = 1723	n = 1160	
Male sex		1937 (50%)	509 (52%)	842 (49%)	586 (51%)	-
Age in years, mean (SD)		12.1 (2.7)	8.2 (1.0)	12.4 (1.2)	15.0 (0.7)	-
Height for age z-scores, mean (SD)		0.55 (1.0)	0.76 (1.0)	0.51 (1.1)	0.45 (1.0)	<0.001
Body mass index z-scores, mean (SD)		0.06 (1.2)	–0.06 (1.1)	0.04 (1.2)	0.19 (1.1)	<0.001
Body mass index	Underweight (z-score ≤−2)	139 (4%)	34 (4%)	76 (4%)	29 (3%)	0.002
	Normal weight (z-score >−2, <1)	2850 (76%)	752 (80%)	1251 (74%)	847 (75%)	
	Overweight (z-score ≥1, <2)	580 (15%)	126 (13%)	276 (16%)	178 (16%)	
	Obese (z-score ≥2)	194 (5%)	33 (3%)	93 (5%)	68 (6%)	
Level of physical activity	Low	332 (10%)	26 (3%)	140 (9%)	166 (18%)	<0.001
	Moderate	1976 (58%)	484 (51%)	928 (60%)	564 (61%)	
	High	1108 (32%)	443 (46%)	475 (31%)	190 (21%)	
Practice of sports outside school		2612 (76%)	767 (81%)	1216 (79%)	629 (68%)	<0.001
Symptoms in the past 12 months	Wheeze	281 (8%)	75 (8%)	137 (9%)	69 (8%)	0.864
	Exercise-induced wheeze	274 (8%)	43 (5%)	134 (9%)	97 (11%)	<0.001
	Night cough apart from colds	394 (12%)	142 (15%)	154 (10%)	98 (11%)	0.003
	Rhinitis apart from colds	1049 (31%)	217 (23%)	501 (33%)	331 (36%)	<0.001
	Habitual snoring (almost every night)	163 (5%)	55 (6%)	60 (4%)	48 (5%)	0.584
Use of inhaled medication in the past 12 months	Short acting beta-2 agonists	257 (8%)	63 (7%)	123 (8%)	71 (8%)	0.344
	Inhaled corticosteroids	179 (5%)	36 (4%)	90 (6%)	53 (6%)	0.050
Hay fever		767 (23%)	134 (14%)	373 (25%)	260 (28%)	<0.001
Maternal smoking		574 (17%)	121 (13%)	266 (17%)	187 (20%)	<0.001
Paternal smoking		758 (22%)	171 (18%)	335 (22%)	252 (27%)	<0.001
Pets in the household		1469 (43%)	313 (33%)	720 (47%)	436 (47%)	<0.001
Living on a farm		85 (2%)	12 (1%)	46 (3%)	27 (3%)	0.021

Information obtained from the parental questionnaires at baseline. P trend: p value for a trend across ordered categories of age groups. Height for age and body mass index z-scores were based on WHO references.

years: median 7.9 ppb, IQR 5.0–13.6; age 10–13 years: 11.6 ppb, 6.9–18.2; age 14–17 years: 14.3 ppb, 9.2–21.8).

Discussion

LUIS is a large school-based study performed in 2013–2016 in the canton of Zurich, Switzerland, which comprised a thorough assessment of respiratory symptoms, lung function, lifestyle and environmental exposures. LUIS data will help to increase knowledge on respiratory health in schoolchildren by assessing risk factors, studying phenotypes, contributing to normative lung function and airway inflammation data, and providing recommendations for future research.

Strengths and weaknesses

The main strength of LUIS is the wealth of health data that were collected, which includes three different lung function tests: spirometry, FeNO measured using high resolution equipment and the novel DTG-SBW. This permits the investigation of different physiological aspects of lung health. A subsample of participants had repeat lung function measurements a year later, which allows assessment of lung growth. We collected detailed questionnaire data on respiratory symptoms, diagnoses and lifestyle from both parents and children, which allows comparisons between their answers. Information was collected on lower respiratory symptoms such as wheeze and chronic cough, and on upper respiratory symptoms such as rhinitis, hay fever and snoring. Respiratory symptoms are influenced by seasonality, but the LuftiBus visited the schools throughout different seasons, which makes it possible to take seasonality into account in our analyses. Participants' address histories enable us to use state-of-the-art methods [30, 31] to estimate air pollution exposure during specific time windows.

Figure 5: Distribution of forced expiratory volume in one second (FEV_1) by age and sex in children from the LuftiBus in the School (LUIS) study at baseline. FEV_1 measured in litres (L)

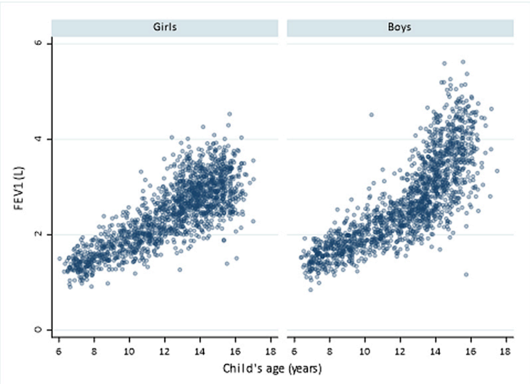
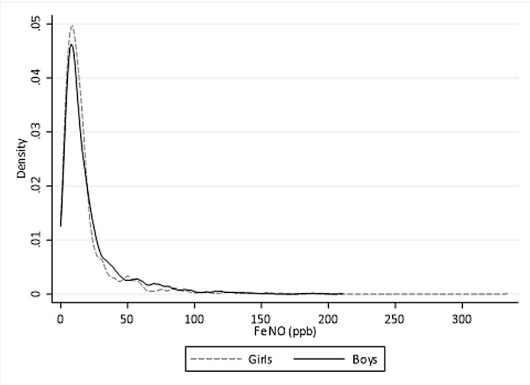


Figure 6: Distribution of fractional exhaled nitric oxide (FeNO) by sex in children from the LuftiBus in the School (LUIS) study at baseline. FeNO measured in parts per billion (ppb).



The main weakness is that it was not a perfectly random sample of schoolchildren. Participation was decided by the heads of the schools, and classes were recruited as a whole. We do not have individual data on non-participating students, which limits the possibilities to assess representativeness of the sampled population. However, the distribution of participating schools in rural and urban areas at baseline was similar to the average distribution of schools in the canton of Zurich. At follow-up, schools from small urban areas were slightly overrepresented in our study. The cost associated with the health promotion activity in which the LUIS study was embedded was covered by the public budget for health prevention activities available to school heads. This cost and time availability might have contributed to a school head's decision to participate to the study. The area-based socioeconomic index of participating families was roughly comparable to that of all households with school-aged children from the canton of Zurich. Thus, we think LUIS gives a fair picture of the school-aged population from the canton of Zurich. We recruited over 3000 participants at baseline, but the sub-sample followed-up was smaller than originally planned because of budget restraints, which limits the possibility of longitudinal analyses. Another limitation is the lack of objective measurements of atopy such as skin prick tests or serum IgE levels. This limits the interpretation of FeNO data. We had, however, proxy measures of atopy, namely reported hay fever and atopic dermatitis.

Outlook

LUIS will cover knowledge gaps on children's respiratory health. This dataset allows determination of the prevalence of upper and lower respiratory symptoms, description of lifestyle characteristics such physical activity and smoking [41], and a study of associations with lung function. We are able to use information from both parents and children and several lung function tests, including markers of ventilatory function (spirometry), ventilation inhomogeneity (DTG-SBW) and Th2 airway inflammation (FeNO), to answer research questions in a comprehensive way [42, 43]. For example, DTG-SBW data allows detection of even subtle changes in peripheral airways, which may not be identified by spirometry alone [42]. The broad set of data collected allows us to describe lung function in healthy children, and to report normal values. The LUIS study makes it also possible to study effects of air pollution on respiratory symptoms and lung function.

In conclusion, LuftiBus in the School (LUIS) provides a unique opportunity to assess the respiratory health of Swiss schoolchildren, and its association with health behaviours and air pollution. Better understanding of factors that influence Swiss schoolchildren's respiratory health may help to establish new recommendations and influence policy makers' decisions.

The LuftiBus in the school (LUIS) study group

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The study principal investigators Prof. Alexander Moeller, Prof. Claudia Kuehni and Prof. Philipp Latzin conceptualised and designed the study. Alexander Moeller supervised data collection and was responsible for the overall conduct of the study. Philipp Latzin was responsible for the lung function measurements. Claudia Kuehni was responsible for the questionnaire design and data analysis. Rebeca Mozun was responsible for data management and coordination. Florian Singer and Johanna Kurz are responsible for management and analysis of DTG-SBW data. Myrofora Goutaki, Eva S.L. Pedersen, Maria Christina Mallet and Cristina Ardura-Garcia (Institute of Social and Preventive Medicine, University of Bern, Switzerland) support statistical analysis. Jakob Usemann and Kees de Hoogh are responsible for the air pollution data.

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Conflicts of interest

Dr Moeller reports grants from Lunge Zuerich, personal fees from Vertex Inc., during the conduct of the study. Dr Singer reports personal fees from Novartis, personal fees from Vertex, outside the submitted work. Dr Usemann reports personal fees from Vertex, during the conduct of the study. Dr Latzin reports personal fees from Vertex, personal fees from Novartis, personal fees from Roche, personal fees from Polyphor, personal fees from Vifor, personal fees from Gilead, personal fees from Schwabe, personal fees from Zambon, personal fees from Santhera, grants from Vertex, outside the submitted work.

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Appendix

Table of contents

Additional methods

LuftiBus in the school (LUIS) is a study funded by Lunge Zürich, a non-profit organization that promotes respiratory health prevention and research. LUIS used a special bus ("LuftiBus") to visit schools within the canton of Zurich. Inclusion criteria were consent to participate and age 6 to 17 years. There were no predefined exclusion criteria.

LuftiBus

LuftiBus is a broader project of Lunge Zürich for the prevention and early detection of lung diseases and has been ongoing for 30 years [1, 2]. LuftiBus offers lung function tests to adults of the general public living in the metropolitan region of Zurich at a non-profit cost of 10 CHF [3]. Previous research has used data from the LuftiBus lung function campaign to calculate reference equations for lung function [3, 4]. LuftiBus data was linked with data form the Swiss National Cohort [5] to assess time trends in the prevalence of airway obstruction among adults from the general population [6], occupational risk factors for airway obstruction [7], and spatial risk pattern of respiratory morbidity [8].

Data collection: double tracer gas single breath washout (DTG-SBW)

The gas mixture had the same molar mass (MM, g.mol-1) as medical-grade air, such that any detectable changes compared with normally expired molar mass can be attributed to relative changes in helium (He) and sulphur hexafluoride (SF_6) concentrations [9]. MM was measured by a side-stream ultrasonic flowmeter, tidal flows by a main-stream ultrasonic flowmeter. On each test day, signal calibration and verification were performed prior to testing. The main-stream ultrasonic flowmeter was calibrated using a 1 L precision syringe. The side-stream ultrasonic flowmeter and the oxygen (O_2) and carbon dioxide (CO_2) sensors were calibrated using medical-grade calibration gas and pure O_2 (Carbagas, Bern, Switzerland).

Air pollution assessments

Individual air pollution exposure will be estimated for nitrogen dioxide (NO_2) and for particulate matter with an aerodynamic diameter of 2.5 µm or less (PM 2.5) using air pollution models developed by de Hoogh et. al [10, 11]. Daily average NO_2 concentrations from 2005 to 2016 were modelled in a multistage framework with mixed-effect and random forest models at a fine spatial resolution (100x100 m) [10]. The model incorporates spatial and temporal predictors including satellite-derived data from the Ozone Monitoring Instrument and Copernicus Atmosphere Monitoring Service, and road, land use, topography and meteorological information. Daily NO_2 monitoring data were obtained from the Immisionsdatabank Luft (IDB Luft, FOEN, Bern, Switzerland) measured at 67 sites in 2005 and increased to 110 sites in 2016. The model was able to explain approximately 73% of the overall spatiotemporal variation in NO_2 measurements [10].

Spatiotemporal resolved models were developed to predict daily PM 2.5 exposure [11]. First, daily PM 2.5 concentrations were estimated by a combination of a mixed effect model and a generalized additive mixed model at a 1×1km resolution across Switzerland using Multiangle Implementation of Atmospheric Correction (MAIAC) spectral aerosol optical depth (AOD) data. Second, support vector machine algorithms were used to predict precise exposure estimates at a 100 x 100m resolution in using spatiotemporal predictor data. The global (1 km) and local (100 m) models explain on average 73% of the total, 71% of the spatial and 75% of the temporal variation globally, and on average 89% of the total, 95% of the spatial and 88% of the temporal variation locally in measured PM 2.5 concentrations [11]. From these data we will calculate the mean exposure of each subject to specified air pollution during specific exposure windows.

Other available data on air pollution include ozone in parts per billion, fine particles (number of particles per cm^3, average particle diameter in nm, lung-deposited particle surface in um^2/cm^3), and temperature and humidity measurements obtained at schools on the day of the study visit using a wireless collection system installed on the roof of the bus in collaboration with the OpenSense team of the ETH (Swiss Federal Institute of Technology in Zurich). The system sent data continuously to a central database at the ETH and sensors were calibrated when the bus passed a reference station.

Data quality

Parental questionnaires

The data entry form of the parental questionnaire contained automatic plausibility checks to reduce data entry errors. We did double data entry for a random 10% of the parental questionnaires using the software Epidata. Variables had one to five entry fields. We found a low field error percentage (1%) and thus did not double enter the remaining 90% of questionnaires.

DTG-SBW

Quality control of DTG-SBW measurements was performed by the field workers on site. A double check of DTG-SBW test results is on-going, to see if the phase III was linear and constituted at least 50% of expired volume [9, 12]. Quality control criteria for DTG-SBW were defined as: 1) no evidence of air leaks as monitored by volume and MM signals, 2) similar flow-volume-loops in pre-test and test breaths, 3) breath volumes of the five tidal pre-test and the test breaths were within 10%, 4) inspiratory peak flow within the by-pass flow.

For signal processing and analyses we used software developed by our group (LungSim, Numerical Modeling, Thalwil, Switzerland) running in (Matlab® R2014a, The Mathworks Inc., Natick, MA, USA) [9]. MM, CO_2 and volume signals were aligned in time accounting for different signal rise times [9]. To extract the double-tracer gas signal from MM we subtracted the naturally exhaled CO_2 fraction from the MM signal [9]. The corrected MM and CO_2 expirograms were plotted against expired volume (Figure S3). The SDTG was computed automatically by linear regression between 65 to 95% of expired volume and under visual control. If required, we manually adjusted volume limits to exclude adjacent tidal phases. Quality criteria were presence of both MM and CO_2 phase III over at least 50% of expired volume.

Fractional exhaled nitric oxide (FeNO)

Required average flow in the plateau was 40-60 ml/s and required duration of exhalation was at least 4 seconds for children younger than 12 years and 6 seconds for children aged 12 years or older. Mean FeNO was calculated using at least two reproducible exhalations with the nitric oxide plateau values within 10% of each other. Field workers checked the quality of the FeNO measurements on site according to ATS/ERS criteria for online FeNO measurement in children [13].

Spirometry flow-volume curves

In a dedicated workshop, a paediatric pulmonologist and lung function expert (FS) explained the fundamental concepts of paediatric spirometry quality control to all participants. Five pairs of team members assessed and scored by consensus the quality of spirometry curves into “good”, “moderate” or “bad” quality” depending on the presence of hesitation at start of expiration, submaximal effort, forced flow deviations (e.g. cough or glottis closure) within or after the first second, and premature ending of the exhalation within or after the first second. Three paediatric respiratory physicians (FS, CK, JU) assessed all spirometry curves marked as “moderate” or “bad” quality during the first screening and set their own score. If the paediatric respiratory physicians had doubts on the scoring of a spirometry curve, they discussed the curve among them and reached an agreement.

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Table S1: Characteristics of schools in the canton of Zurich and visited by the *LuftiBus in the school study* (LUIS) at baseline and at one-year follow-up, by degree of urbanisation.

	Urbanisation degree						**Total**
	Large urban		**Small urban**		**Rural**		
Schools in canton of Zurich							
Number of schools: n (%)	201	(41)	228	(47)	61	(12)	490
Number of classes: n (%)	2450	(45)	2602	(48)	381	(7)	5433
Number of students: n (%)	48718	(45)	51588	(48)	7333	(7)	107639
Average number of students per class	19.9		19.8		19.2		19.8
Schools visited by LUIS, baseline							
Number of schools: n (%)	15	(40)	18	(49)	4	(11)	37
Number of classes: n (%)	149	(39)	204	(54)	26	(7)	379
Number of students: n (%)	2959	(40)	3842	(53)	536	(7)	7337
Average number of students per class	19.9		18.8		20.6		19.4
Schools visited by LUIS, follow-up							
Number of schools: n (%)	4	(21)	13	(68)	2	(11)	19
Number of classes: n (%)	45	(23)	143	(73)	7	(4)	195
Number of students: n (%)	917	(24)	2679	(72)	143	(4)	3739
Average number of students per class	20.4		18.7		20.4		19.2

Calculations are based on aggregated data provided by the Swiss federal statistical office. The number of schools in the canton of Zurich corresponds to the year 2013. Definition of urbanization degree [14]: Large urban area: At least 50% lives in high-density clusters. Small urban area: Less than 50% of the population lives in rural grid cells and less than 50% lives in a high-density cluster. Rural area: More than 50% of the population lives in rural grid cells.

Table S2: Number of participants in the LuftiBus in the school (LUIS) study with available information on parental questionnaires (PQ), children's questionnaires (CQ), spirometry (Spiro), and fractional exhaled nitric oxide (FeNO) at baseline and at the one-year follow-up.

Available data					**Baseline** N=3870		**Follow-up** N=655	
					n	(%)	n	(%)
PQ					3457	(89)	629	(96)
CQ					3546	(92)	640	(98)
Spiro					3446	(89)	614	(94)
FeNO					3393	(88)	588	(90)
DTG-SBW					1795	(46)	496	(76)
PQ	& CQ				3171	(82)	614	(94)
PQ	& Spiro				3071	(79)	589	(90)
PQ	& FeNO				3030	(78)	565	(86)
PQ	& DTG-SBW				1627	(42)	472	(72)
CQ	& Spiro				3230	(83)	610	(93)
CQ	& FeNO				3183	(82)	584	(89)
CQ	& DTG-SBW				1784	(46)	492	(75)
Spiro	& FeNO				3165	(82)	561	(86)
Spiro	& DTG-SBW				1585	(41)	472	(72)
FeNO	& DTG-SBW				1595	(41)	451	(69)
CQ	& Spiro	& FeNO			2964	(77)	557	(85)
CQ	& Spiro	& DTG-SBW			1579	(41)	469	(72)
CQ	& FeNO	& DTG-SBW			1585	(41)	448	(68)
PQ	& Spiro	& FeNO			2824	(73)	539	(82)
PQ	& Spiro	& DTG-SBW			1429	(37)	449	(69)
PQ	& CQ	& Spiro			2882	(74)	585	(89)
PQ	& CQ	& FeNO			2845	(74)	561	(86)
PQ	& FeNO	& DTG-SBW			1429	(37)	429	(65)
Spiro	& FeNO	& DTG-SBW			1460	(38)	430	(66)
PQ	& CQ	& Spiro	& FeNO		2646	(68)	535	(82)
PQ	& CQ	& FeNO	& DTG-SBW		1421	(37)	426	(65)
PQ	& Spiro	& FeNO	& DTG-SBW		1305	(34)	409	(62)
PQ	& CQ	& FeNO	& DTG-SBW		1421	(37)	426	(65)
CQ	& Spiro	& FeNO	& DTG-SBW		1454	(38)	427	(65)
PQ	& CQ	& Spiro	& FeNO	& DTG-SBW	1300	(34)	406	(62)

Number of measurements before quality control.

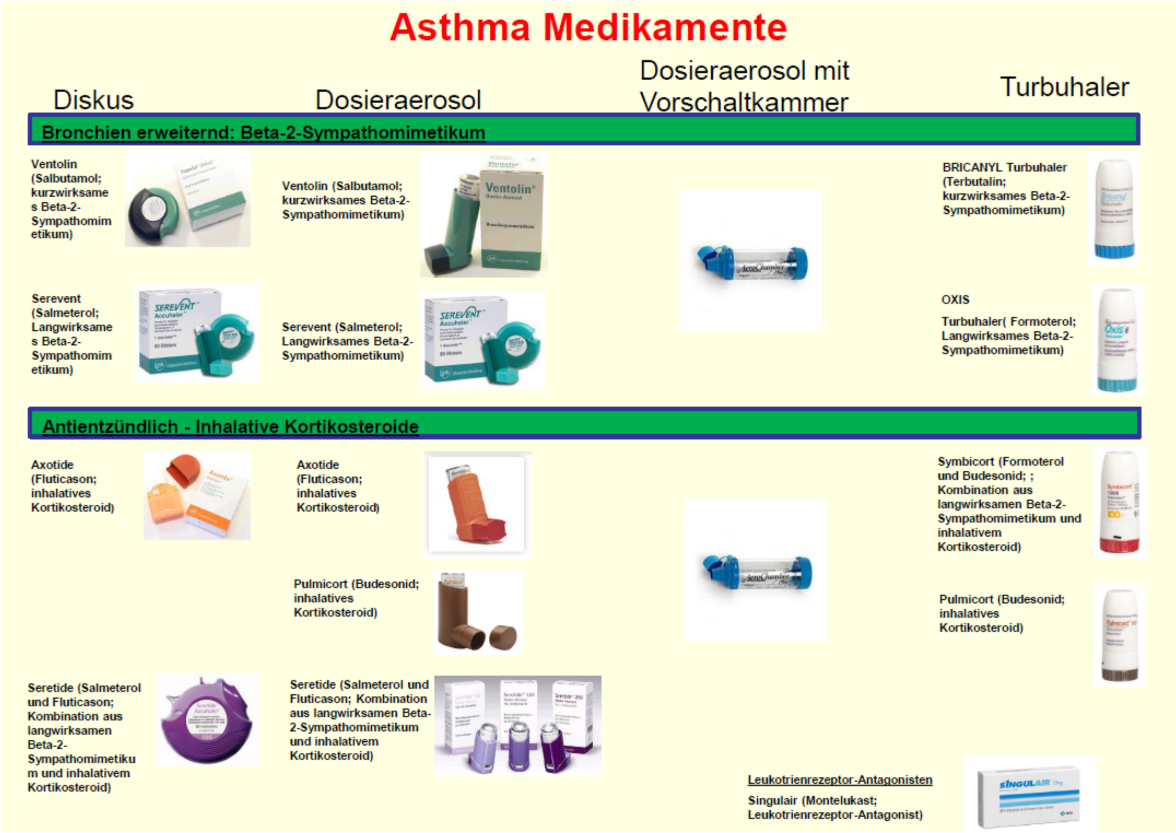

Figure S1: Poster of asthma medications used in the *LuftiBus in the school* (LUIS) study to help children answer which medication they had taken the day of the visit (in German).

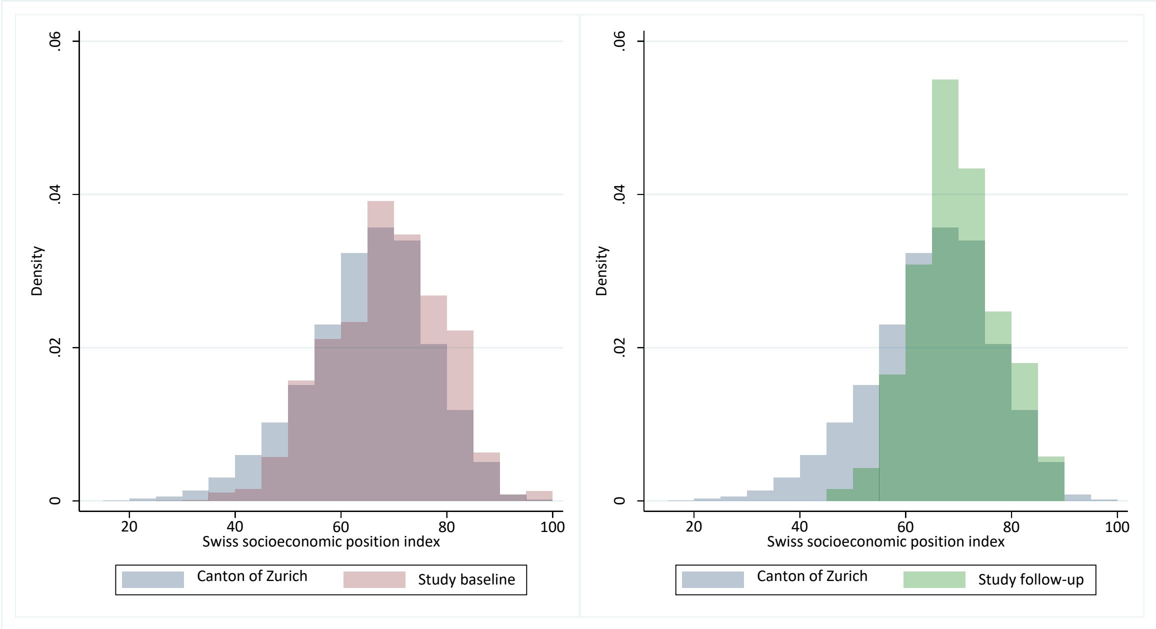

Figure S2: Histograms showing the distribution of the Swiss socioeconomic position index for families from the canton of Zurich with at least one child aged 6-17 years living in the household and in the *LuftiBus in the school* (LUIS) study at baseline and one-year follow-up.

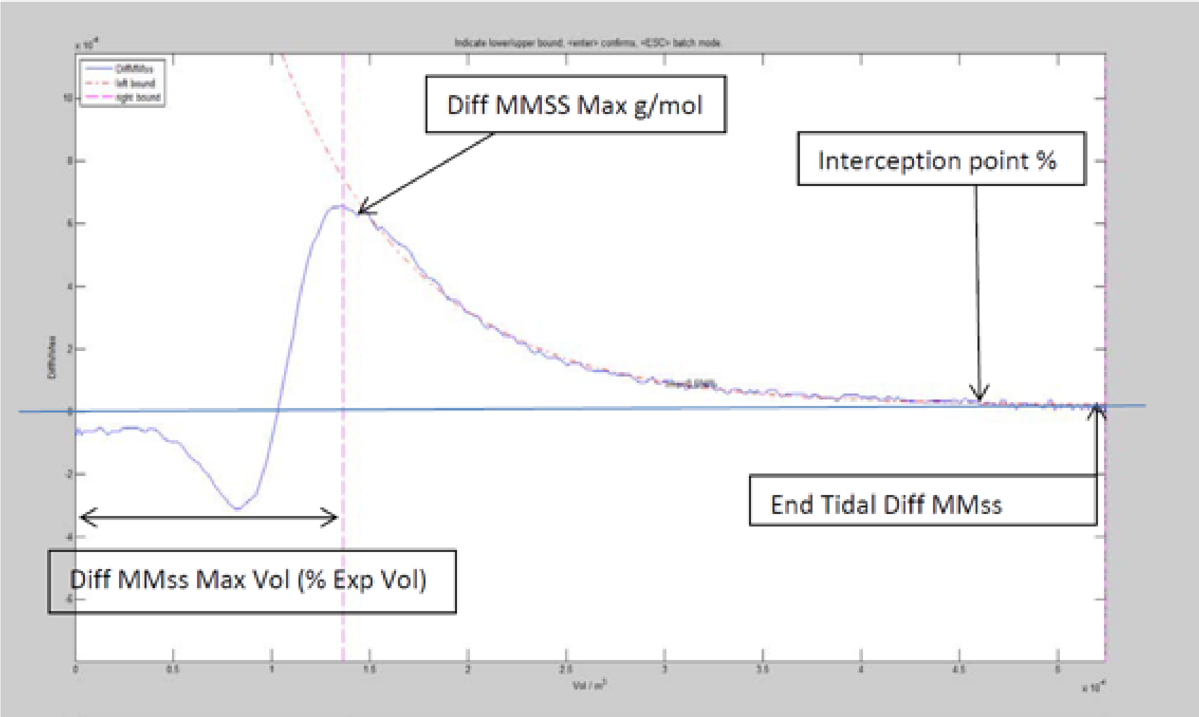

Figure S3: Fit lines of double tracer gas single breath washout (DTG-SBW), differences in molar mass (MM) plotted against expired volume.

Abbreviations: MMss = Molar mass signal of the side stream; MMss calc = Calculated molar mass signal of the side stream using measured gas proportion of a normal breath; Diff MMss = MMss – MMss calc; End Tidal Diff MMss: Difference of MMss – MMss calc (in %) at the end of expiration; Interception point (%): % of expired volume where Diff MMss = 0; Diff MMss Max Vol (% Exp Vol): Difference of MMss-MMss calc at the maximum expired volume; Left and right bound= 65-95% of expired volume.