Exercise-induced bronchoconstriction is associated with air humidity and particulate matter concentration in preschool children

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Abbreviations: AH = absolute humidity of air; CI = confidence interval; EIB = exercise-induced bronchoconstriction; grains/m^3 = grains per cubic meter; IgE = immunoglobulin E; IOS = impulse oscillometry; IQR = interquartile range; ISO-BMI = child body mass index corresponding to adult values; NO_2 = nitrogen dioxide; O_3 = ozone; $PM_{2.5}$ = particulate matter diameter under 2.5 µm; RH =

relative humidity; R5 = impulse oscillometry resistance at 5 Hz; TRAP = traffic-related air pollution; WHO = World Health Organization; μg/m^3 = μg per cubic meter

Abbreviated title: Exercise-induced bronchoconstriction and particulate matter concentration

Abstract

Background: Long-term exposure to air pollution is connected to asthma morbidity in children. Exercise-induced bronchoconstriction is common in asthma, and the free running test outdoors is an important method for diagnosing asthma in children. It is not known whether momentary air pollution exposure affects the results of outdoor exercise tests in children.

Methods: We analyzed all reliable exercise challenge tests with impulse oscillometry in children (n=868) performed between January 2012 and April 2015 at Tampere University Hospital. Pollutant concentrations ($PM_{2.5}$, NO_2 and O_3) at the time of the exercise test were collected from public registers. We compared the pollutant concentrations with the proportion and severity of exercise-induced bronchoconstriction and adjusted the analyses for air humidity and pollen counts.

Results: Pollution levels were rarely high (median $PM_{2.5}$ 6.0 μg/m^3, NO_2 12.0 μg/m^3 and O_3 47.0 μg/m^3). The relative change in resistance at 5 Hz after exercise did not correlate with O_3, NO_2 or $PM_{2.5}$ concentrations (p values 0.065-0.884). In multivariate logistic regression, we compared the effects of $PM_{2.5}$ over 10 μg/m^3, absolute humidity over 10 g/m^3 and alder or birch pollen concentration over 10 grains/m^3. High (over 10 g/m^3) absolute humidity was associated with decreased incidence (OR 0.31, p value 0.004), and $PM_{2.5}$ over 10 μg/m^3 was associated with increased incidence (OR 1.69, p value 0.036) of exercise-induced bronchoconstriction.

Conclusions: Even low $PM_{2.5}$ levels may have an effect on exercise-induced bronchoconstriction in children. Of the other properties of air, only absolute humidity was associated with the incidence of exercise-induced bronchoconstriction.

Introduction

Asthma is a heterogeneous disease characterized by chronic airway inflammation and bronchial hyperreactivity. It is one of the most common long-term diseases among children, and its burden is increasing globally [1]. In addition to genetic factors [2], environmental exposure also increases the risk for asthma [3]. The Global Burden of Disease report lists outdoor air pollution as a marked cause of death and disability globally, contributing an estimated more than 3 million premature deaths per year [4]. Children are more vulnerable than adults to the adverse effects of air pollution because their lungs and immune systems are still developing, their breathing rate is higher, they spend more time outdoors and they are also physically more active [5]. It has been estimated that 13% of asthma incidence in children globally and 33% in Europe may be due to traffic-related air pollution (TRAP) or other outdoor pollution [1,6,7].

The most important air pollutants, nitrogen dioxide (NO_2) and particulate matter with aerodynamic diameter < 2.5 µm ($PM_{2.5}$), are emitted, e.g., in motor vehicle exhaust, and $PM_{2.5}$ is also emitted during wood combustion. Ozone (O_3) is formed when nitrogen oxides and volatile organic compounds react with ultraviolet radiation. Several previous studies have addressed the long-term and short-term adverse effects of air pollution in children. Long-term exposure to air pollution during the prenatal period or during childhood is associated with lower lung function as measured by spirometry [8–10], impulse oscillometry [11] or forced oscillation techniques [12] and with persistent wheezing and asthma morbidity [13–15]. In asthmatic children, acute exposure to air pollution may induce oxidative stress in the airways and is connected to lower lung function and to exacerbation of asthma [16,17].

In 2005, the World Health Organization (WHO) updated threshold limits [18] for various air pollutants based on information about the adverse effects of different pollutant levels, and these air quality guidelines were further updated in September 2021 [19]. Nevertheless, safe long-term threshold values are difficult to define, and proper threshold values for momentary exposure are not described for all pollutants. However, recent studies have shown that adverse health effects occur at pollutant levels below the former long-term threshold values and that these adverse effects are dose-dependent [20,21]. The long-term threshold value defined by the WHO in 2005 for NO_2 was 40 µg/m^3 mean annual concentration, whereas the 1-hour threshold for acute exposure was 200 µg/m^3. The updated long-term thresholds defined in 2021 for NO_2 are markedly lower, 10 µg/m^3 for mean annual concentration and 25 μg/m^3 for mean daily (24-hour) concentration. Correspondingly, threshold values for $PM_{2.5}$ were previously 10 μg/m^3 mean annual concentration and 25 μg/m^3 mean daily concentration, and in the recent guideline they are markedly lower, 5 μg/m^3 and 15 μg/m^3, respectively. The threshold for shorter acute exposure is not described. The 8-hour threshold value of 100 μg/m^3 for O_3 remained the same in the recent guidelines as in 2005, but a mean threshold value of 60 μg/m^3 for the peak season was also defined [18,19].

Exercise is thought to increase the effects of air pollution on airways in various ways. Elevated minute ventilation increases the total amount of inspired particles. Shifting from nose-breathing to mouth-breathing at exercise decreases the absorption of pollutants in the upper airway. However, increased ventilation causes turbulence of the inhaled air, increasing the absorption of particles in the upper airway. Exercise-induced bronchoconstriction (EIB) is a frequent finding in asthma and can be triggered by exercise challenge testing [1]. In preschool children, impulse oscillometry (IOS) is generally used as a lung function test to detect hyperresponsiveness during exercise or reversibility with inhaled beta-2-agonists. It is the most important diagnostic test when asthma is suspected in this age group [22,23]. IOS is a rapid, noninvasive and reliable lung function test that requires minimal cooperation from the patient and is thus commonly used [24]. To our knowledge, there are no previous studies of the connection between short-term exposure to ambient outdoor air pollution and EIB measured with IOS in children.

Our aim in this study was to assess whether the concentrations of various air pollutants at the time of the free-running exercise test conducted outdoors affect the probability or severity of EIB and whether pollen concentrations and absolute humidity modify the results.

Materials and Methods

Study design and subjects

We analyzed the IOS results obtained during all outdoor free-running exercise challenge tests conducted in children between January 2012 and April 2015 at Tampere University Hospital, Finland. Exercise tests were performed due to suspicion of asthma or a need to evaluate the efficacy of treatment in children with persistent asthma. If several exercise tests were conducted in a single child, we included only the results of the first test. We collected information from patient records on possible asthma diagnoses before or after exercise testing and known risk factors for asthma, including the results of allergy testing (skin prick test or allergen-specific immunoglobulin E (IgE) levels), atopy and atopic dermatitis, gestational age, birth weight and height, tobacco exposure during pregnancy and childhood, atopy and asthma in parents and siblings, pets at home, respiratory symptoms, number of episodes of and hospitalizations for wheezing, and other diseases and medications [25]. We also calculated the children's heights adjusted for age as z scores and child body mass index corresponding to adult values (ISO-BMI) [26]. The study was a retrospective chart review of subjects studied under normal clinical routine due to suspicion of asthma. The Ethics Committee of Tampere University Hospital approved the study (R15022).

Air properties and pollution concentration

In this study, we observed the momentary outdoor air concentrations of NO_2, O_3 and $PM_{2.5}$ at the time of each exercise test. Information on these concentrations was collected from the database maintained by the city of Tampere environmental protection unit; those data are based on measurements performed at a location approximately 1 km from the exercise test site. We used 1-hour measures covering the hour in which the exercise test was conducted. We also collected data on the most important pollen particles in Finland, birch (*Betula*) and alder (*Alnus*). Pollen counts at the time of each exercise test were collected from the register of the Biodiversity Unit of the University of Turku, Finland, and were expressed as pollen grains per cubic meter (grains/m^3) of air. The Hirst-Burkard pollen trap from which our data were originated was located on the roof of a building located next to Tampere University Hospital and the exercise test site [27]. Pollen data from Tampere were available only for the period between January 2012 and December 2014.

Relative humidity (RH), temperature and air pressure at the time of each exercise test were collected from the register of the Meteorological Institute of Finland (license: CC BY 4.0, https://creativecommons.org/licenses/by/4.0/). The absolute humidity (AH) of air was calculated based on RH, temperature and pressure.

The city of Tampere has a borderline humid continental climate/subarctic climate and is located at 61°30′ northern latitude. It experiences daily mean temperatures of -6.9 °C in February and +16.9 °C in July. The AH of the air is usually under 5 g/m^3 in winter and close to 10 g/m^3 in summer [28]. Approximately 240 000 inhabitants live in Tampere, and the level of air pollution is relatively low. However, during winter, occasional temperature inversions and peaks in emissions due to residential heating may cause a significant increase in air pollution close to the ground.

IOS measurements and exercise challenge

IOS (Jaeger Gmbh, Würzburg, Germany) was measured according to international recommendations [29]. Technical problems during the measurements, such as opening of the lips, postural problems, physical movement or holding of breath, were noted. To confirm that the measurements met the international quality criteria, the technical properties were reviewed retrospectively by trained physicians who were blinded to the pollution concentrations and properties of the outdoor air [30]. If the measurements were repeatable and the coherence values were within acceptable limits, the results were considered technically acceptable. The majority of the exercise tests involved running between two points outdoors. In younger subjects with cooperation difficulties, some tests also included other high-intensity activities such as kicking and fetching a soccer ball. Experienced nurses monitored the heart rate and the intensity of the exercise. The intensity of the exercise was considered sufficient if maximal heart rate (measured with FT4, Polar Ltd, Kempele, Finland) was > 85% of the calculated maximal value (205-age/2) or if clear symptoms of obstruction appeared [31]. The nurses controlled that the heart rate was greater than 85% of the maximal value for at least 6 minutes and that the exercise was continuous. Possible symptoms during exercise (such as wheezing, cough and dyspnea) were documented. IOS was measured before exercise and 1-2, 5, 10 and 15 min after exercise. As specified in the provocation protocol, all the children were given 300 µg of salbutamol (Ventoline evohaler via Babyhaler®), and IOS was measured 15-20 min after salbutamol inhalation. Height-dependent reference values were used for IOS [23]. R5 values were retrieved for each subject at each time point. An increase in R5 of ≥

40% after exercise compared to baseline was the criterion for EIB [22,29,30]. The criterion for a significant bronchodilation effect was a decrease in R5 of ≥40% compared to baseline [23,29].

Statistics

Statistical analysis was performed using R-program version 4.0.2 (R Foundation, Vienna, Austria). The distributions of NO_2 and $PM_{2.5}$ concentrations were markedly skewed; therefore, pollutant concentrations were categorized as under or over specific threshold levels. Commonly defined thresholds for momentary exposure were not suitable for our data because measured concentrations did not exceed the thresholds. Instead, we used the following thresholds: 25 and 40 $\mu g/m^3$ for NO_2, 60 and 100 $\mu g/m^3$ for O_3 and 10 and 25 $\mu g/m^3$ for $PM_{2.5}$. The distributions of pollen concentrations were also markedly skewed; therefore, they were categorized using threshold values for a moderate pollen level of 10 grains/m^3 [27]. The allergens produced by alder and birch resemble each other structurally and immunochemically, and cross-reactivity is common. Alder and birch pollen counts were ≥ 10 grains/m^3 in only a small number of cases; thus, these counts were combined in the analysis (if either the alder or the birch pollen count was ≥ 10 grains/m^3, the combined count was defined as true). Subjects with missing values were excluded from the analysis. Logarithmic transformation was used for skewed variables (NO_2 and $PM_{2.5}$). The chi-squared test, the t test, Pearson´s correlation or Fisher´s exact test was used in single-parameter comparisons between different groups and correlations. Linear multivariate regression was used to analyze the effects of O_3, pollen concentration, AH and age on the change in R5. Logistic multivariate regression was used to analyze the effects of $PM_{2.5}$, pollen concentration, AH and age on the incidence of EIB. P values under 0.05 were considered to indicate statistical significance.

Results

Demographic characteristics of the study subjects and mean pollutant levels

Overall, 926 subjects completed the IOS exercise test during the study period. Following a review of the IOS results, tests that were considered unreliable (n=58) were excluded, and only technically reliable IOS results, n=868 (94%), were used in the analyses. Pollutant and pollen data had variable numbers of missing values (n=14-69), and these were excluded from the analyses case-by-case. Table 1 presents the clinical and demographic characteristics of the study population. Ninety-seven percent of the study subjects were 3-7 years old (range 3.0-14.1). Gestational age at birth was under 37 weeks in 73 subjects (8.4%), of whom four (0.5%) were born before the 28th gestational week. In 53 subjects (6.1%), birth weight was low (<2500 g). After exercise challenge, EIB occurred in 13.9% of the study subjects. Median (interquartile range) pollutant concentrations during the exercise tests were 6.0 µg/m^3 (4.4–8.3 µg/m^3) for $PM_{2.5}$, 12.0 µg/m^3 (8.0–18.0 µg/m^3) for NO_2 and 47.0 µg/m^3 (33.0–61.0 µg/m^3) for O_3.

Table 2 presents subject characteristics and IOS results for subjects with or without EIB. Children with EIB more often had IgE-mediated sensitization, and they were on average older and taller. There were no statistically significant differences between groups in ISO-BMI, gender, parental smoking, asthma or allergy in parents or siblings, birth weight, gestational age or use of asthma or allergy medications. Abnormal auscultation findings and symptoms during or after exercise were more frequent in children with EIB. Children with EIB had lower R5 at baseline. There was no difference between groups in the prevalence of bronchial obstruction before exercise.

Relation between pollutant levels and degree of airway obstruction after exercise

There was no correlation between the O_3 concentration and the change in R5 (Pearson´s correlation coefficient r=0.064, confidence interval (CI) [-0.00 – 0.13], p value 0.065). The logarithmically transformed $PM_{2.5}$ or NO_2 concentrations also had no correlation with the change in R5 (r=0.018, CI [-0.05 – 0.09], p value 0.603 and r=0.005, CI [-0.06 – 0.07], p value 0.884, respectively). We chose the O^3 concentration for further multivariate analysis because it showed the highest correlation with the change in R5. Thus, a multivariate linear regression analysis of the change in R5 was performed using O_3, AH, alder or birch pollen ≥ 10 grains/m^3 and age as independent variables. Only AH (coefficient -0.84, CI [-1.43 – -0.25], p value 0.005) but not O_3 (coefficient 0.08, CI [-0.02–0.18], p value 0.115) was significantly related to the change in R5.

Relation between pollutant levels and probability of EIB

EIB occurred in 13.1% of cases when the $PM_{2.5}$ concentration was < 10 µg/m^3 and in 18.9% of cases when the $PM_{2.5}$ concentration was ≥ 10 µg/m^3, but the difference was not statistically significant (p value 0.096, Figure 1). The concentration of $PM_{2.5}$ exceeded 10 µg/m^3 in 22.9% and 16.2% of cases with and without EIB, respectively, but the difference was not statistically significant (p value 0.096). There were no statistically significant differences between the EIB-positive and EIB-negative groups in the percentage of cases in which other pollutant concentrations exceeded the predefined thresholds (Table 3).

As $PM_{2.5}$ ≥ 10 µg/m^3 showed the largest difference between the EIB-positive and EIB-negative groups, we performed a logistic multivariate regression analysis (n=799) of the incidence of EIB using $PM_{2.5}$ ≥ 10 µg/m^3, AH ≥ 10 g/m^3, alder or birch pollen ≥ 10 grains/m^3 and age as independent variables. We found that AH ≥ 10 g/m^3 (OR 0.31, CI [0.13–0.65], p value 0.004) and $PM_{2.5}$ ≥ 10 µg/m^3 (OR 1.69, CI [1.02–2.75], p value 0.036) were significantly related to the incidence of EIB (Table 4). In the subgroup of allergic subjects (n=425), the results were similar; in that subgroup, both AH ≥ 10 g/m^3 (OR 0.41, CI [0.16–0.89], p value 0.036) and $PM_{2.5}$ ≥ 10 µg/m^3 (OR 1.83, CI [1.00–3.28], p value 0.045) were statistically significant predictors of EIB.

Discussion

In our large set of real-life data, we found that higher momentary $PM_{2.5}$ concentration was associated with a higher incidence of EIB in the outdoor free-running test in preschool children. In our study, the average pollutant levels were relatively low, and we did not find NO_2 or O_3 levels to be associated with the presence or severity of EIB. In our previous publications, we reported the effects of other physical and biological characteristics of the outdoor air on EIB incidence in preschool children. We found that lower air humidity was associated with a higher probability of EIB and more severe EIB but that pollen concentrations were not related to EIB [27,28]. As higher AH was associated with a lower probability of EIB, negative test results obtained under conditions of high AH should be interpreted with caution. Additionally, in this study conducted under the climatic conditions of a small city in Finland, when pollutant levels were considered, the strongest predictor of EIB among the properties of air was AH. Since all inhaled air is warmed to body temperature in the airways and saturated with water vaporizing from the epithelial lining fluid, the rate of water loss from airways is determined by the minute ventilation and the AH of the inhaled air. The results of this study showed that AH was independently associated with the occurrence of EIB, a finding that is very consistent with the theories that explain water loss from airways and the osmotic theory of EIB. In addition to low AH, $PM_{2.5}$, even at relatively low concentrations, may be an independent predictor of EIB.

To our knowledge, this is the first study to use real-life clinical data to evaluate the relationship between outdoor pollution levels at the time of exercise testing and the incidence of EIB measured using IOS. In one small previous study, exposure to a number of different pollutants did not affect the exercise test results measured with spirometry in schoolchildren with chronic respiratory symptoms, but air pollution was connected to poorer spirometry results at baseline [32]. The exercise tests performed in that study used a bicycle ergometer, possibly decreasing the sensitivity of the test. In addition, relative humidity rather than absolute humidity was reported in that study; this may be another confounding factor, since low absolute humidity is the most important factor that triggers EIB. Another recent study showed that greater exposure to NO_2 was associated with greater lung-function reduction postexercise measured by spirometry in children in New York City [33]. The association was attenuated when adjustment was made for exhaled nitric oxide, suggesting that inflammation may mediate the association between NO_2 and EIB.

In our study, $PM_{2.5}$ was the only pollutant that was found to be associated with the probability of EIB. One previous study has shown that exposure to elevated indoor $PM_{2.5}$ levels on the previous day is related to higher airway resistance and airway inflammation at rest [34]. Higher levels of $PM_{2.5}$ have also been reported to reduce lung function in schoolchildren [35] and to be associated with emergency department visits due to respiratory causes in children [16]. The mechanisms underlying the effects of $PM_{2.5}$ on the respiratory system are not completely understood. $PM_{2.5}$ may increase airway oxidative stress and inflammation and decrease small airway function [17,36]. Animal and human studies suggest that inflammation due to PM exposure is due to phenotypic differentiation of Th2 and Th17 cells [37,38]. These mechanisms may increase bronchial hyperresponsiveness during exercise.

In a previous study [16], $PM_{2.5}$, but not other pollutants such as NO_2, O_3 and PM_{10}, was associated with emergency visits due to respiratory causes in children. The concentrations noted in that study were lower than the upper limits recommended by the European Union. Additionally, in our study, only $PM_{2.5}$ concentrations, not NO_2 or O_3 concentrations, were associated with EIB. However, decreased lung function in adults has been reported previously in connection with much higher concentrations of NO_2 and O_3 than measured in our study [39,40]. Thus, the NO_2 and O_3 levels that were present when the tests reported in our data were performed may have been so low that an association with EIB would be unlikely.

Recent evidence from epidemiological studies shows that long-term exposure to air pollution, even at relatively low concentrations, may cause morbidity. It has been estimated that approximately 92% of pediatric asthma cases that may be attributable to NO_2 exposure occurred in areas in which the annual average NO_2 concentration did not exceed the WHO 2005 threshold [6]. Furthermore, long-term exposure to air pollution, even at exposure levels near the current limits, has been reported to be associated with adult-onset asthma [20]. Exposure to air pollution in childhood may have long-term effects on lung function, since exposure to TRAP during early life has been shown to correlate with lung function measured using IOS in adolescence [9].

Further studies are needed to determine safe threshold values for pollutants so that regulations regarding air pollution concentrations can be made based on scientific evidence. In our study, $PM_{2.5}$

concentrations of 10 μg/m^3 or more had a small effect on the incidence of EIB after short-term exposure during the exercise test. Our measured values were recorded hourly, but there are no known limits for hourly concentrations of $PM_{2.5}$. The European Union directive-based annual threshold value for $PM_{2.5}$ is higher than the health-based limit recently recommended by WHO (25 μg/m^3 versus 5 μg/m^3). The hourly $PM_{2.5}$ concentration reported in our data exceeded the European Union´s guideline value only twice during the study period. In California, a positive effect of improved air quality on children´s lung function has already been detected [41]. Additionally, the United States Environmental Protection Agency's current annual guideline of 12 μg/m^3 for $PM_{2.5}$ is higher than the recent WHO guideline.

Our study has some limitations. Better assumptions about causality between outdoor air properties and EIB could have been made with longitudinal study design. However, a longitudinal study of this scale would be difficult and costly to perform. Although spirometry is the gold standard test of lung function in older children and adults, IOS has been shown to be a reliable instrument for detecting asthma in preschool children who are not able to undergo spirometry [22,24]. Removing all confounding factors and collinearity between pollution concentrations and other physiological properties of the outdoor air, for example, air humidity, would be difficult in practice. Additionally, we were not able to study the effects of high concentrations of pollutants other than $PM_{2.5}$. We did not find significant associations between pollutant levels and EIB in simple group comparisons or univariate regression analyses, only in multivariate analyses. Replication studies are needed to verify the results. The strengths of the study are a large sample of real-world data, technical validation of the measurements, and reliable data on pollutants and other characteristics of the outdoor air at the time of each exercise test.

In conclusion, momentary exposure to $PM_{2.5}$ may increase the incidence of EIB in preschool children, even when the concentration is below recent EU, US and WHO short-term thresholds. However, the observed effect was so small that it is probably not necessary to take the $PM_{2.5}$ concentration into account when interpreting the results of free-running outdoor exercise tests at low pollution levels. O_3 and NO_2 levels were not associated with the incidence of EIB in our analysis. The most significant physical characteristic of the outdoor air that affected the incidence of EIB in our study is absolute humidity, and this factor should be taken into account when planning exercise test timetables and interpreting exercise test results. Further studies are needed to verify the results presented here and to study the effects of higher pollution concentrations.

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Table 1. Subject characteristics and frequency of exercise-induced bronchoconstriction in the study population with technically reliable IOS (n = 868).

	Mean (SD) or %
Age (years)	5.4 (1.4)
Height (cm)	113.0 (9.6)
Males (%)	64.2
R5 change after exercise (% from baseline)	17.4 (25.9)
Exercise induced bronchoconstriction (%)	13.9
Any IgE test positive (%)	52.2
Significant bronchodilator effect (%)	3.8
Physician diagnosed asthma (%)	73.6

Note: R5 change is reported as percentage change compared to baseline (mean and SD). Criterion for exercise-induced bronchoconstriction was ≥ 40% increase in R5 after exercise compared to baseline. Criterion for significant bronchodilation effect was ≥40% decrease in R5 compared to baseline. Asthma diagnosed by physician was collected from patient records and is a combination of diagnoses before or after exercise test (missing values not included). Abbreviations: IOS = impulse oscillometry. IgE = immunoglobulin E. R5 = impulse oscillometry resistance at 5 Hz.

Table 2. Subject characteristics and exercise test results in subjects with technically reliable IOS (n=868) divided into those with and without EIB.

	EIB (-)	EIB (+)	
	n=747	n=121	p-value
	Mean (SD) or %		
Age (years)	5.4 (1.4)	5.7 (1.4)	0.013
Height (cm)	112.6 (9.6)	115.2 (9.5)	0.005
Iso-BMI ($kg*m^{-2}$)	22.8 (4.8)	22.5 (4.4)	0.419
Gender Male (%)	64.0	65.3	0.861
Parental smoking (%)	28.4	33.9	0.259
Asthma in either parent (%)	33.9	38.8	0.335
Controller medications pause over 14days (%)	96.8	97.3	0.979
Any IgE test positive (%)	49.8	66.9	0.001
R5 percent of reference value	95.4 (17.1)	89.8 (15.5)	0.001
Obstruction before exercise (%)	22.2	24.8	0.610
R5 change after exercise (% from baseline)	9.4 (12.8)	66.8 (31.3)	<0.001
Wheezing in auscultation (%)	6.3	52.9	<0.001
Physician diagnosed asthma (%)	69.6	95.4	<0.001

Note: Any IgE test positive = any positive allergy test in either prick or RAST. Controller medication pause = period without either inhaled corticosteroids, leukotriene receptor antagonists or long-acting beta-2-agonists before exercise test. Asthma diagnosed by physician was collected from patient records and is a combination of diagnoses before or after exercise test (missing values not included). Abbreviations: EIB = Exercise-induced bronchoconstriction, IOS = impulse oscillometry, ISO-BMI = Body mass index corresponding to adult values, R5 = resistance at 5 Hz measured using impulse oscillometry. The Chi-squared test or t-test was used where appropriate in single parameter comparison between groups.

Table 3. Proportions of subjects with pollutant levels above established thresholds at the time of the exercise test in subjects with technically reliable IOS (n=868) divided into those with and without EIB.

	EIB (-)	EIB (+)	
	n=747	n=121	p-value
$NO_2 \geq 25$ µg/ m^3 (%)	11.9	16.5	0.198
$NO_2 \geq 40$ µg/ m^3 (%)	3.3	3.3	1.000
$O_3 \geq 60$ µg/m^3 (%)	28.3	30.5	0.701
$O_3 \geq 100$ µg/m^3 (%)	0.4	0	1.000
$PM_{2.5} \geq 10$ µg/m^3 (%)	16.2	22.9	0.096
$PM_{2.5} \geq 25$ µg/m^3 (%)	0.3	0	1.000

Note: Abbreviations: EIB = Exercise-induced bronchoconstriction, IOS = impulse oscillometry, NO_2 = Nitrogen dioxide, O_3 = Ozone, $PM_{2.5}$ = Particulate matter < 2.5 µm. The Chi-squared test or Fisher´s exact test was used.

Table 4. Results of a multivariate regression analysis on the incidence of EIB explained with $PM_{2.5} \geq 10$ µg/ m^3, absolute humidity ≥ 10 g/m^3, alder or birch pollen count ≥ 10 grains/m^3 and age (n = 799).

	OR	95% CI			p-value
AH ≥ 10 g/m^3	0.31	0.13	–	0.65	0.004
$PM_{2.5} \geq 10$ µg/ m^3	1.69	1.02	–	2.75	0.036
Alder or birch pollen ≥10 grains/m^3	1.09	0.60	–	1.89	0.755
Age	1.18	1.02	–	1.35	0.017

Abbreviations: EIB = Exercise-induced bronchoconstriction, $PM_{2.5}$ = Particulate matter < 2.5µm, AH = Absolute humidity, OR = Odds ratio, CI = Confidence interval. Age is included as a covariate and its results are reported only for reference.