

ORIGINAL ARTICLE: DIAGNOSTIC TESTING

Association of air humidity with incidence of exercise-induced bronchoconstriction in children

Anna P. Tikkakoski MD¹  | Antti Tikkakoski MD² | Juho E. Kivistö MD, PhD³  |
Heini Huhtala MSc⁴ | Kalle Sipilä MD, PhD² | Jussi Karjalainen MD, PhD³ |
Mika Kähönen MD, PhD² | Lauri Lehtimäki MD, PhD^{1,3}

¹Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland

²Department of Clinical Physiology, Tampere University Hospital, Tampere, Finland

³Allergy Centre, Tampere University Hospital, Tampere, Finland

⁴Faculty of Social Sciences, Tampere University, Tampere, Finland

Correspondence

Anna P. Tikkakoski, Faculty of Medicine and Health Technology, Tampere University, Arvo Ylpön katu 34, 33520 Tampere, Finland.
Email: pauliina.tikkakoski@tuni.fi

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Abstract

Background: The effects of humidity and temperature on results of free running test in children are not known.

Objective: Assess the relation of outdoor air temperature, relative humidity (RH), and absolute humidity (AH) to airway obstruction in children after free running exercise test.

Methods: We analyzed all exercise challenge tests with impulse oscillometry in children between January 2012 and April 2015 in the Tampere University Hospital. The associations of AH, RH, and temperature of outdoor air with change in airway resistance were studied using regression analysis and by comparing the frequency of exercise-induced bronchoconstriction (increase $\geq 40\%$ in resistance at 5 Hz) at different levels of temperature and humidity.

Results: Overall, 868 children with reliable results were included (mean age: 5.4 years; range: 3.0–14.1). In regression analysis, the relative change in resistance at 5 Hz after exercise was related to temperature (regression coefficient = -0.223 , $P = .020$) and AH (regression coefficient = -0.893 , $P = .002$), but not to RH. If absolute air humidity was $< 5 \text{ g/m}^3$, exercise-induced bronchoconstriction (EIB) occurred in 17.6% of study subjects and at AH levels $\geq 10 \text{ g/m}^3$, it occurred in 5.9% of study subjects ($P = .008$). In multiple regression analysis comparing the effects of temperature and humidity and adjusting for covariates, only AH was independently associated with change in airway resistance ($P = .009$).

Conclusion: High AH of air is associated with lower incidence of EIB after outdoor exercise test in children. A negative test result at AH $\geq 10 \text{ g/m}^3$ should be interpreted with caution.

KEYWORDS

asthma, exercise test, exercise-induced asthma, pulmonary function tests

Abbreviations: AH, absolute humidity of air; CI, confidence interval; EIB, exercise-induced bronchoconstriction; IgE, immunoglobulin E; IOS, impulse oscillometry; RH, relative humidity; R5, impulse oscillometry resistance at 5 Hz.

Anna P. Tikkakoski and Antti Tikkakoski contributed equally to this study.

1 | INTRODUCTION

Asthma is one of the most prevalent chronic diseases in children worldwide.¹ Exercise-induced bronchoconstriction (EIB) is a common

feature in asthma, but its mechanisms are not fully understood.² There are two major hypotheses explaining the link between exercise and bronchial smooth muscle contraction, the thermal and the osmotic hypotheses. Exercise can cause cooling of the airways due to elevated ventilation, which is followed by rewarming at rest. Thermal hypothesis suggests that these effects initiate reactive hyperemia and vasoconstriction of lung microvasculature, which cause bronchial obstruction.^{3,4} The osmotic hypothesis is based on the assumption that during exercise, more water is vaporized from the liquid layer above airway epithelium of the bronchial tree because of elevated ventilation.^{5,6} This would cause the airway surface fluid to become hypertonic which, in turn, would activate leukocytes to release inflammatory mediators like leukotrienes, histamine, and tryptase.⁷ These would finally cause smooth muscle cell contraction and elevate mucus secretion, leading to obstruction.⁶

Impulse oscillometry (IOS) is a noninvasive and rapid technique to measure lung function requiring only passive cooperation from the patient.⁸ IOS is therefore widely used and is a reliable method in diagnosing asthma in children from age 3 to 7 years.^{9–12} IOS can be used to detect responsiveness to inhaled beta-2-agonists or bronchial hyperresponsiveness in connection with exercise.^{11,13} IOS can be used to measure the airway resistance at different frequencies; most commonly, the numeric evaluation is done at 5 and 20 Hz. A peripheral bronchial obstruction presents as rise in resistance at 5 Hz (R5) and a smaller rise in resistance at 20 Hz.^{8,14,15} Change in reactance at 5 Hz (X5) can also be used to evaluate obstruction, but it is not as repeatable in children and is hypothesized to be more in connection with the elastic properties of the lung.^{8,16} In addition, other values, such as the reactance and impedance, can be used.^{13,17} Previous studies have shown that R5 is the most reliable and reproducible parameter in diagnosing obstruction.^{11,13,18–21}

In adults, there are data showing that the probability of EIB is affected by temperature, humidity, and season.^{22–26} However, there are only two studies assessing the relation between probability of EIB and outdoor conditions during free running test. One study in children from Ghana using peak expiratory flow rate measurements showed more EIB reactions during dry season than wet season,²⁷ and another study from Finland showed partial correlation between the change in R5 measured with IOS and outdoor temperature.¹¹

Absolute humidity (AH) is the mass of water vapor divided by the mass of dry air in a volume of air at a given temperature. Relative humidity (RH) is the ratio of the current AH and the maximal AH at current temperature. The previous studies assessing the relation between physical properties of inhaled air and probability of EIB have not consistently taken into account temperature and both AH and RH.^{11,22–25,27–29} These three factors are closely related (Figure SE1), and their relative importance in provoking EIB is not known. Theoretically, low AH should be the most important factor driving water vaporization from airway epithelial fluid. The aim of this study was to assess if physical factors of outdoor air affect the probability of EIB during outdoor free running exercise testing in children and which factor is the most important.

2 | MATERIALS AND METHODS

2.1 | Study design and subjects

The study was a retrospective chart review. We analyzed all IOSs with exercise challenge test in children between January 2012 and April 2015 in Tampere University Hospital, Finland, who had been tested because of suspicion of asthma or need to assess efficacy of treatment in subjects with persistent asthma. If several exercise tests had been conducted in one child, we included only the first. We collected the known risk factors of asthma from patient records. Those were 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 and hospitalizations of wheezing, other diseases, medications, and whether asthma was diagnosed or not.³⁰ Major respiratory infection within 4 weeks was considered contraindication for exercise challenge. We additionally calculated the height adjusted to age as z-scores.³¹

The city of Tampere lies on 61°30' northern latitude and has a borderline humid continental climate/subarctic climate (daily mean temperature of -6.9°C in February and +16.9°C in July). The AH of air is mostly under 5 g/m³ in winter and near 10 g/m³ in summer (Figure SE2). The physical properties of air (RH, temperature, and pressure) at the time of each exercise test were collected from the register of Meteorological Institute of Finland (license: CC BY 4.0, <https://creativecommons.org/licenses/by/4.0/>). The meteorological institute had recorded values at 10-minute intervals, so time periods were well matched. AH was calculated using RH, temperature, and pressure. The study was approved by the Ethics Committee of Tampere University Hospital (R15022).

2.2 | IOS measurements and exercise challenge

IOS (Jaeger GmbH, Würzburg, Germany) was measured according to international recommendations.¹⁹ Trained nurses performed the measurements and commented on the possible technical problems during the measurements, such as opening of the lips, postural problems, physical movement, or holding of breath. To ensure the measurements meet the international quality criteria,^{14,16} their technical properties were reviewed retrospectively by trained physicians blinded to the humidity and temperature. The physicians defined the results technically acceptable if they were repeatable and coherence values were within acceptable limits. The exercise challenge was conducted as free running outdoors. Possible symptoms (wheezing, cough, and dyspnea) were recorded. The exercise level was considered sufficient if heart rate (measured with FT4, Polar Ltd, Kempele, Finland) was >85% from calculated maximal value (205–age/2) and the duration of exercise was over 6 minutes.³² IOS was measured before exercise and 1 to 2, 5, 10, and 15 minutes after exercise. Then children were given 300 µg of salbutamol

(Ventoline evohaler via Babyhaler) and IOS was measured again 15 to 20 minutes after inhalation. IOS reference values were chosen according to the age group of the subject.^{13,33} R5 and X5 values were retrieved for analyses from each time point for each subject. The criterion for EIB was increase in IOS R5 $\geq 40\%$ after exercise compared to baseline.^{11,19,21} The criterion for the significant bronchodilation effect was a decrease in R5 $\geq 40\%$ compared to baseline.^{11,13,18-20,34}

2.3 | Statistics

Statistical analysis was performed by using R-program version 3.5.1 (R foundation, Vienna, Austria). Seasons were defined as follows: from December to February as winter, from March to May as spring, from June to August as summer, and from September to November as autumn. The χ^2 test, Mann-Whitney *U* test, or *t* test were used, where appropriate, in single parameter comparison between EIB-positive and -negative groups. Relations between physical factors of outdoor air and EIB were studied in two ways. First, continuous variables were used in univariable regression analysis (AH, RH, and temperature against relative change in R5). Multiple linear regression analysis was used to adjust for covariates (age, sex, height, any positive IgE test, and season) and to compare the effects of temperature, RH, and AH on the change in R5. The results were reported as coefficients and confidence intervals (CI). Second, to account for possible linearity problems, the key variables were categorized, and the probability of EIB was calculated at different levels of AH (<5, 5-10, and ≥ 10 g/m³), RH (<50, 50-75, and $\geq 75\%$) and temperature (<0, 0-10, and $\geq 10^\circ\text{C}$). Further, logistic regression was used to adjust for same covariates and to compare the effects of temperature, AH and RH. *P* values under .05 were considered statistically significant.

3 | RESULTS

3.1 | Demographic characteristics of study subjects

Altogether, 926 patients had gone through the exercise test at study period and data from these were collected. After a review of the IOS results, technically unreliable IOS results were excluded (*n* = 58). IOS was technically reliable in 94% (*n* = 868), and these subjects were chosen for the main analyses. There were no significant differences in the environmental conditions between accepted and non-accepted IOS tests (AH: 5.3 g/m³ vs 5.9 g/m³, *P* = .142; RH: 76% vs 78%, *P* = .375; temperature 4.0°C vs 5.0°C, *P* = .392). Ninety-seven percent of study subjects were 3 to 7 years old (range: 3.0-14.1 years and six subjects were 10 years old or older). In 78 subjects (8.4%), the gestational age was under 37 weeks, of which four subjects (0.4%) were born before 28 weeks. Birth weight was under 2500 g in 56 subjects (6.0%). In the study population, 13.9% had EIB after exercise challenge. Table 1 represents the clinical and demographic characteristics of the study population.

TABLE 1 Subject characteristics in the whole study population (*n* = 926). Values are mean (SD) or percentages

	Mean, %	SD
Age, y	5.4	1.4
Birth weight, g	3451	631
Gestational age, wk	39.0	2.4
Sex (male; %)	65	
IOS technically reliable (%)	94	

Abbreviation: IOS, impulse oscillometry.

Table 2 presents subject characteristics and IOS values in subjects with and without EIB. Children with EIB were older and taller and had more often IgE-mediated sensitization. There were no significant differences in sex, birth weight, gestational age, use of asthma medication, child body mass index adjusted to adult values, frequencies of parental smoking, and asthma or allergy in parents or siblings. There was no difference in the proportion of subjects who had asthma controller medication paused for at least 14 days before the test. However, the proportion of subjects with pause at least 28 days was significantly lower in children with EIB. Symptoms and wheezing in auscultation during or after exercise were more frequent in children with EIB. There was no difference in the baseline level of X5 between subjects with and without EIB.

3.2 | Association between physical properties of air and EIB

In our study, the mean outdoor temperature during exercise tests was 5.3°C (standard deviation [SD]: 9.2), RH was 78% (SD: 18.2), and AH was 5.8 g/m³ (SD: 3.1). R5 change after outdoor free running test was related to AH (regression coefficient = -0.89, CI = -1.45 to -0.34, *P* = .002; Figure SE3A) and temperature (regression coefficient = -0.22, CI = -0.41 to -0.04, *P* = .020; Figure SE3B). RH was not significantly related to R5 change (Figure SE3C).

When AH, RH, and temperature were put to the same linear regression analysis, only AH was a statistically significant predictor of change in R5 (regression coefficient = -2.14, CI = -3.91 to -0.37, *P* = .018; Table 3). When the model was further adjusted with age, sex, and height, the relation between AH and change in R5 remained statistically significant (regression coefficient = -2.26, CI = -4.02 to -0.50, *P* = .012; Table SE1). This relation was statistically significant (regression coefficient = -2.67, CI = -4.67 to -0.66, *P* = .009; Table 4) even after adding the presence of any positive IgE test result and season as an independent variable to the model. In addition, if gestational age and birth weight, interaction term of age and height, or height compared to reference values were added, the association remained statistically significant (regression coefficient = -2.68 to -2.74, *P* = .009-.013; Table SE3-E5).

EIB was more frequent at lower levels of AH and occurred in 17.6%, 12.1%, and 5.9% of exercise tests at AH levels of <5, 5 to 10, and ≥ 10 g/m³, respectively. There was a statistically significant difference in EIB incidence between AH levels of <5 and ≥ 10 g/m³

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

	EIB (-)		EIB (+)		P
	n = 747	SD	n = 121	SD	
Age, y	5.4	1.4	5.7	1.4	.013
Iso BMI (kg/m ²)	23	5	22	4	.419
Height (cm)	113	10	115	10	.005
Height of reference values in z-score	-0.18	1.09	-0.10	1.00	.424
Sex, male (%)	64		65		.884
Any IgE positive allergy (%)	50		67		.001
Atopic dermatitis (%)	40		48		.131
Any asthma medication (%)	54		55		.890
Controller medication pause over 14 d (%)	91		92		.977
Controller medication pause over 28 d (%)	64		49		.048
Asthma in either parent (%)	34		39		.335
Parental smoking (%)	28		34		.259
Asthma in siblings (%)	15		14		.806
Heart rate from the calculated maximum (%)	97	6	97	4	.314
R5 baseline (kPa/l ⁻¹ /s ⁻¹)	0.84	0.18	0.76	0.16	<.001
R5 of reference values (%)	95	17	90	15	.001
X5 baseline (kPa/l ⁻¹ /s ⁻¹)	-0.31	0.11	-0.30	0.12	.404
R5 change after exercise (%)	9	13	67	31	<.001
Marked symptoms in exercise (%)	4		54		<.001
Wheezing in auscultation (%)	6		53		<.001
Marked bronchodilator response (%)	4		2		.282
Temperature (°C)	5.4	9.2	2.9	8.8	.005
Relative humidity (%)	78	18	79	18	.710
Absolute humidity (g/m ³)	6.0	3.2	5.1	2.7	.002

Note: Data are either percentages or mean (SD). IOS = impulse oscillometry, ISO BMI = Body mass index adjusted to adult values. Any IgE positive allergy = any positive allergy test in either prick or RAST. Controller medication pause = period without either inhaled corticosteroids or long acting beta-2-agonists before exercise test in the whole study population. R5 = resistance at 5 Hz measured using impulse oscillometry. X5 = reactance at 5 Hz measured using impulse oscillometry. The χ^2 test, Mann-Whitney U test, or t test were used where appropriate in single parameter comparison between groups. Bold value indicates $P < 0.05$.

($P = .008$; Figure 1). Similarly, EIB was more frequent at lower temperatures and occurred in 17.8%, 15.1%, and 9.2% of cases at temperature levels of $<0^\circ\text{C}$, 0°C to 10°C , and $\geq 10^\circ\text{C}$. There was a statistically significant difference in EIB incidence between $<0^\circ\text{C}$ and $\geq 10^\circ\text{C}$ temperature levels ($P = .025$; Figure SE4). However, there

TABLE 3 Relative change of resistance at 5 Hz explained with absolute humidity, temperature and relative humidity using linear regression. Subjects with technically reliable lung function studies included (n = 868)

Intercept = 18.70	Coefficients	95% Confidence interval	P
Absolute humidity (g/m ³)	-2.14	-3.91, -0.37	.018
Temperature (°C)	0.46	-0.17, 1.09	.149
Relative humidity (%)	0.11	-0.06, 0.29	.189

Bold value indicates $P < 0.05$.

were no differences in frequencies of EIB at different levels of RH: EIB occurred in 12.0%, 14.0%, and 14.2% of cases at RH levels of $<50\%$, 50% to 75% , and $\geq 75\%$ (Figure SE5). In logistic regression model with covariates and AH, temperature and RH levels, there was statistically significant difference in EIB incidence only between AH groups <5 and $\geq 10\text{ g/m}^3$ (odds ratio = 0.28, CI = 0.09-0.92, $P = .036$; Table SE2).

4 | DISCUSSION

Our results show that AH of the outdoor air is an important physical factor affecting the probability of EIB in children undergoing free running test. Higher AH was associated with lower incidence of EIB, whereas RH, temperature, and season were not significant independent predictors of EIB.

There are not only patient-related factors but also environmental factors that affect the appearance of EIB. International recommendations suggest that exercise testing should be performed with the

TABLE 4 Relative change of resistance at 5 Hz explained with absolute humidity, relative humidity, and temperature using linear regression. Results adjusted with age, sex, season, any IgE test positive, and height (n = 868)

Intercept = -14.6	Coefficient	95% confidence interval	P
Absolute humidity (g/m ³)	-2.67	-4.67, -0.66	.009
Temperature (°C)	0.54	-0.11, 1.18	.103
Relative humidity (%)	0.13	-0.66, 0.33	.179
Age (y)	0.26	-2.20, 2.72	.837
Sex (male)	-0.89	-4.47, 2.69	.626
Height (cm)	0.25	-0.10, 0.60	.164
Any IgE test positive (yes)	7.13	3.66, 10.61	<.001
Season (winter as reference)			
Spring	0.94	-5.50, 7.37	.775
Summer	2.83	-6.20, 11.86	.539
Autumn	2.73	-2.62, 8.09	.316

Abbreviation: IgE, immunoglobulin E.
Bold value indicates $P < 0.05$.

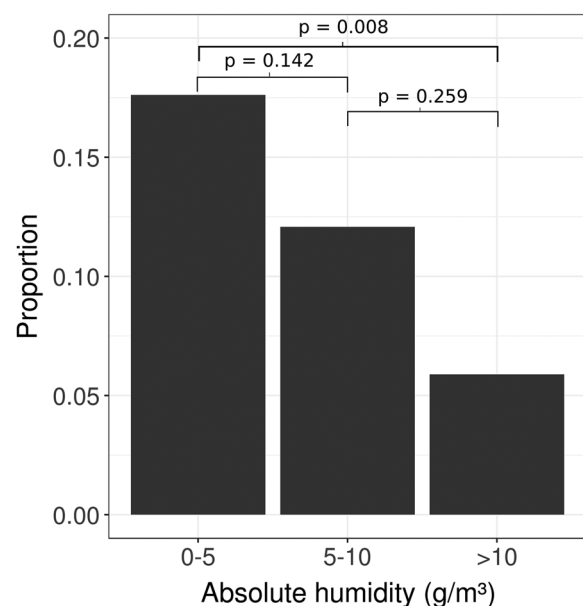


FIGURE 1 Proportion of free running tests with exercise-induced bronchoconstriction reactions at different absolute humidity levels (only reliable impulse oscillometry studies included, $n = 868$)

inhaled air AH of $<10 \text{ g/m}^3$.³² This is based on one relatively small experimental study with 10 asthmatic male subjects published in 1984.³⁵ In the study, four exercise tests were conducted for each subject: two were conducted randomly in AH of 29 g/m^3 or 9 to 10 g/m^3 at a temperature of 35°C , and two at a temperature of 9°C to 10°C and AH 9 to 10 g/m^3 . The result was that temperature was not as significant a factor as AH in affecting the probability of EIB. The authors also noticed that high AH inhibited the development of EIB, suggesting that the osmotic hypothesis is more valid than the thermal hypothesis regarding pathogenesis of EIB. However, although important in advancing our understanding on the basic mechanisms of EIB and relative effects of AH and temperature, this was a quite small study conducted in laboratory conditions using only two fixed levels of AH and temperature.

Although the temperature was not an important factor provoking EIB in the seminal laboratory study, later on, several clinical studies have shown that temperature correlates with the incidence of EIB in free running exercise test outdoors.^{11,24,25} Two of the studies also measured RH^{24,25} and found that it also correlates with the probability of EIB, but none of them measured and reported AH. Some of the studies have also reported that the probability of EIB varies between seasons.^{22,23,26}

To our knowledge, this is the first study in a large clinical sample simultaneously assessing the effects of season, temperature, RH, and AH on the probability of EIB after free running exercise test. Since temperature, RH, and AH are closely interrelated, any of these can be found to correlate with EIB in univariate analysis. However, as RH is defined as the ratio of the partial pressure of water vapor to the equilibrium vapor pressure of water at a given temperature, RH is actually determined by AH and temperature. Since all inhaled air is warmed up to body temperature in airways and saturated with water

vaporizing from epithelial lining fluid, the rate of water loss from airways is determined by minute ventilation and AH of inhaled air, not by RH or temperature. The results of this study showed that only AH was independently associated with occurrence of EIB, which fits well the theoretical background of water loss from airways and the osmotic theory of EIB.

Previous studies focusing on physical factors of outdoor air and EIB have been conducted in older children and adults. Childhood asthma and its pathology and phenotypes are different from adult asthma, and, therefore, the study results in adult patients should be verified in children.³⁶⁻³⁸ Atopic sensitization defined as positive IgE test to any usual pollen or animal allergen was related with a more marked increase in resistance after exercise test.

IOS measurement of resistance is thought to represent the dissipative mechanical properties of the respiratory system.^{8,16} Higher values especially in lower frequencies are related to small airway disease.³⁹ Reactance is thought to represent the elastic properties of the lung. R5 was statistically significantly lower in subject with EIB. However, the difference was probably clinically insignificant, because the mean difference was only 5%. In addition, there was no difference in baseline X5 values between the groups.

Some previous studies have reported higher prevalence of EIB in different patient populations.^{23,25} The lower incidence of EIB in our study probably reflects high suspicion rate for asthma in Finland and that according to the national guideline all cases of asthma in children at least 3-years old should be diagnosed based on objective lung function measures.⁴⁰

Our study has some limitations. Due to the retrospective study design, we could not collect all the clinical data in every patient. The study was also finalized in the year 2015 and most recent results are not included. With longitudinal study design, we could have made better assumptions about causality between AH and EIB. However, a longitudinal study of this magnitude would be laborious and expensive to perform. Though spirometry is gold standard for older children and adults, IOS has been shown to be a reliable tool in asthma diagnostics in small children.^{9,11,12,34} Further, asthma can be inactive during certain seasons, but due to retrospective study design we were not able to measure the activity of asthma and symptom frequencies in individual patients at the time of exercise test. The mechanism of EIB is complicated with environmental and host-relating factors affecting it. Removal of all confounding factors would be difficult in practice.

In summary, we have shown in a large clinical sample that AH of outdoor air rather than temperature or RH is an important physical factor that is markedly and independently associated with the probability of EIB in children undergoing free running test. Our study is the first to show the association between AH and EIB in children. Higher AH was associated with lower incidence of EIB. We conclude that AH of outdoor air should be recorded in connection with free running test to guide clinicians with decision making. RH should be left out of the reports because it often creates only confusion and often is not relevant to the result. Our

results suggest that a negative free running test at AH of $>10 \text{ g/m}^3$ should be interpreted with caution. However, more studies are needed to verify the results.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

ORCID

Anna P. Tikkakoski  <http://orcid.org/0000-0001-6106-0355>

Juho E. Kivistö  <http://orcid.org/0000-0003-1313-9178>

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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