



Exposure to indoor endocrine-disrupting chemicals and childhood asthma and obesity

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Abstract

Background: Indoor air contaminants may act as endocrine-disrupting chemicals (EDCs). However, to what extent these contaminants affect health is poorly known. We aimed to assess the association between EDCs exposure and asthma, respiratory symptoms and obesity in schoolchildren.

Methods: Data from a cross-sectional analysis of 815 participants from 20 schools in Porto, Portugal, were analysed. Symptoms were assessed, asthma was defined on lung function, and airway reversibility and body mass index (BMI) were calculated. The concentrations of 13 volatile organic compounds and 2 aldehydes identified as EDCs were measured in 71 classrooms throughout 1 week. Principal component analysis (PCA) was used to assess the effect of co-exposure. Associations were estimated by regression coefficients using linear and logistic regression models.

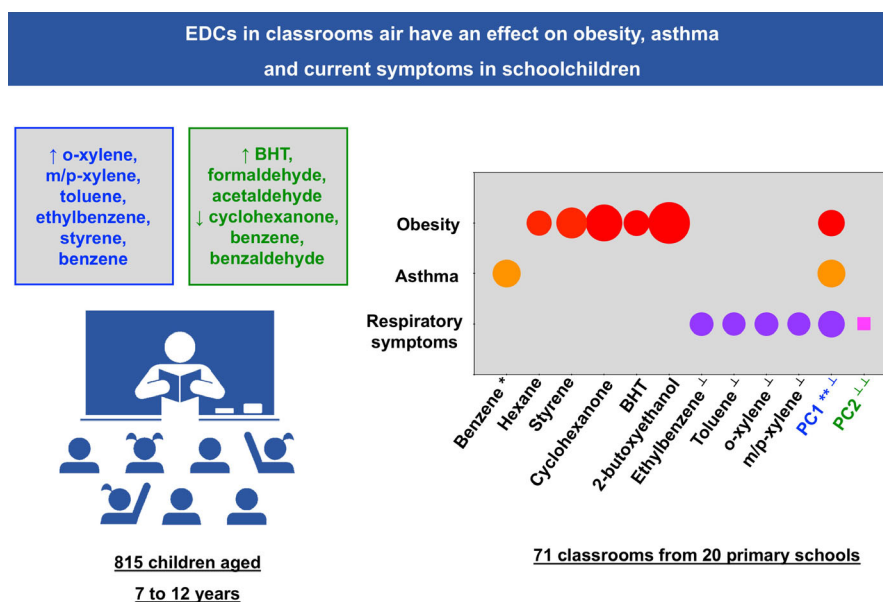
Results: Increased individual and combined EDCs levels were found in classrooms having more children with asthma and obesity. Higher levels of hexane, styrene, cyclohexanone, butylated hydroxytoluene and 2-butoxyethanol were associated with obesity, and higher levels of cyclohexanone were associated with increased child BMI. Toluene, o-xylene, m/p-xylene and ethylbenzene were significantly associated with nasal obstruction. A positive association was found between PC1 and the risk of obese asthma (OR = 1.43, 95% CI 1.01, 1.98) and between PC2 and overweight (OR = 1.51, 95% CI 1.28, 1.79). PC1 and PC2 were also associated with nasal obstruction, and PC2 was associated with breathing difficulties and lean body mass, although EDCs concentrations were low.

Conclusions: Our findings further support the role of EDCs in asthma and obesity development. Moreover, even low levels of indoor exposure may influence the risk of asthma, respiratory symptoms and obesity.

KEYWORDS

asthma, children, endocrine-disrupting chemicals, indoor air, obesity

Abbreviations: ACV, average constriction velocity; ADV, average dilation velocity; ATS, American Thoracic Society; BHT, butylated hydroxytoluene; BMI, body mass index; CDC, Centres for Disease Control and Prevention; CI, confidence interval; EBC, exhaled breath condensate; EDCs, endocrine-disrupting compounds; ERS, European Respiratory Society; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; IOTF, International Obesity Task Force; MCV, maximum constriction velocity; NO, nitric oxide; PCA, principal component analysis; PC, principal component; SPT, skin prick test; T4CE, 4-chloroethylene; T75, total time taken by the pupil to recover 75% of its initial resting diameter after it reached the peak of constriction; TRPA1, transient receptor potential ankyrin; TRP, transient receptor potential; TRPV1, transient receptor potential vanilloid type 1; VOC, volatile organic compounds; WHO, World Health Organization.



GRAPHICAL ABSTRACT

Exposure to low levels of EDCs have an effect on asthma, current symptoms and obesity in school-age children. Individual or combined EDCs also associate with ANS changes, that may possibly mediate the interaction between EDCs and childhood asthma and obesity. Our findings may contribute to action plans to reduce exposures to EDCs and to promote a healthy indoor school environment.

ANS: autonomic nervous system; BHT: butylated hydroxytoluene; EDCs: endocrine-disrupting chemicals;

The circles represent the Odds ratio (OR) values, being the size proportional do the OR.

Circles: OR <1; square: OR >1.

*Positive bronchodilatation; **Obese asthma; ⁺ Nasal obstruction; ⁺⁺ Breathing difficulties

1 | INTRODUCTION

Growing urbanization and the rapid development of new building materials and consumer products have resulted in a changing pattern in the production and use of chemical compounds and consequently in an increase in of these compounds indoors.¹ Some chemicals used in building materials, furnishings and consumer products have been shown to be endocrine-disrupting chemicals (EDCs), making them potentially important indoor contaminants/pollutants and suggesting that indoor exposure may be a greater contributor to overall EDCs exposure.^{1,2} Furthermore, people spend most of their time indoors, where EDCs concentrations can be more relevant than the outdoor concentrations to assessments of human EDCs exposure.^{3,4} This observation led to the recognition that changes in modifiable environmental exposures are likely to play a critical role in the increasing prevalence of noncommunicable diseases such as asthma and obesity among children in developed countries,^{5,6} an increase that cannot be explained only by genetic changes.⁷

Despite the widespread presence of these chemicals indoors, the understanding of the extent as well as the health effects of the exposure is limited by insufficient data on exposure patterns and the action of EDCs over the lifespan.⁸ According to the World Health Organization (WHO), approximately 800 chemicals are known or suspected to be capable of interfering with various mechanisms of

the endocrine system, such as receptor binding and/or hormone synthesis, potentially inducing adverse health effects in exposed individuals or populations and possibly playing a substantial role in many endocrine disorders.^{8,9}

In recent decades, growing evidence has suggested that EDCs exposure is implicated in the development of several human diseases and that multiple mechanisms might be involved.^{9,10} Exposure to EDCs has been associated with an increase in oxidative stress and changes in cytokines production. For instance, EDCs may have a role in T_H2 cells modulation, changing IgE production and eosinophilic responses, and in the hypomethylation of the promoter region of TNF- α .^{11,12} Some EDCs can also disrupt or interfere with lipid homeostasis, promoting adipogenesis and lipid accumulation, thus leading to weight gain and obesity.^{13,14} Furthermore, exposure to EDCs may also interfere with the normal activity of the autonomic nervous system (ANS), which is partly responsible for the development of asthma^{15,16} and weight changes.¹⁷ Furthermore, the dose and timing of EDCs exposure have important implications in adverse health effects.¹⁸

Childhood is a critical window of susceptibility to EDCs exposure, as exposure in childhood can induce long-lasting effects persisting into adulthood and affecting future generations.^{8,18} This highlights the need for a better understanding of the effect of EDCs exposure on the health of children, who may be especially susceptible to low-concentration effects, considering the large amount of

time spent indoors. Therefore, we aimed to assess the association between indoor EDCs exposure in classrooms and asthma, respiratory symptoms and obesity in school-age children.

2 | METHODS

The present study included participants from a cross-sectional study. Twenty of 53 primary schools within the city of Porto, Portugal, were selected, corresponding to a total of 71 assessed classrooms (see the Methods section in the Online Repository). The University Health Ethics Committee approved the study, and informed consent was obtained from children's legal guardians.

2.1 | Participants and assessments

A self-administered ISAAC-based questionnaire¹⁹ covering information on social, demographic and behavioural characteristics and including questions regarding the respiratory/allergic health and current symptoms (previous 3 months) of children was filled out by the children's caregivers and reviewed by a research nurse (see the Methods section in the Online Repository). Children were considered to have current symptoms in the previous 3 months if there was a positive answer to the question "During the past 3 months, has your child had any of the following symptoms?": "Itching on the face or neck," "Eye irritation (redness, dryness, itching)," "Swollen eyes," "Runny nose," "Nasal obstruction," "Dry throat," "Sore throat," "Irritative cough" and "Breathing difficulties."

Anthropometry and clinical assessments were performed in the primary schools by a research nurse. Weight (Kg), body fat percentage, body fat mass (Kg) and total body water (TBW, %) were measured using a digital scale (Tanita™ BC-418 Segmental Body Analyzer), and height in centimetres (cm) was measured with a portable stadiometer. Body fat percentage was classified in accordance with sex-specific centile curves for body fat in children.²⁰ Body mass index (BMI) was calculated using the ratio of weight/height² (Kg/m²) and classified according to the age- and sex-specific percentiles defined by the US Centers for Disease Control and Prevention (CDC),²¹ World Health Organization (WHO)²² and International Obesity Task Force (IOTF).²³

Lung function and airway reversibility were assessed by spirometry according to ATS/ERS guidelines²⁴ using a portable spirometer (MIR Spiro bank, A23-04003237) before and 15 minutes after the inhalation of 400 µg of salbutamol. Different asthma and asthma-like conditions were considered: (a) *Medical diagnosis of asthma*: self-reported medical diagnosis; (b) *Positive bronchodilation (BD+)*: at least a 12% and over 200 mL increase in FEV1 after bronchodilation; (c) *Medical diagnosis of asthma and symptoms or BD+*: at least a 12% and over 200 mL increase in forced expiratory volume in 1 second (FEV1) after bronchodilation or a self-reported medical diagnosis with reported symptoms (wheezing, dyspnoea or dry cough) in the past 12 months; iv) *Medical diagnosis of asthma or BD+*: at least a 12% and over 200 mL increase in FEV1 after bronchodilation or a

self-reported medical diagnosis (see Table S1 in the Online Repository).

Airway inflammation was assessed by measuring the fractional exhaled nitric oxide level using a NObreath analyzer (Bedfont Scientific, Ltd.) in accordance with the ATS guidelines.²⁵ The pH of the exhaled breath condensate (EBC) was measured before and 10 minutes after deaeration with oxygen using a calibrated pH meter (pHEnomenal® pH 1100 H) to an accuracy of ± 0.005 pH units. (see the Methods section in the Online Repository).

Pupillometry was performed with a portable infrared PLR-200 pupillometer (NeuroOptics PLR-200™ Pupillometer, NeuroOptics Inc., CA). The children spent at least 15 minutes in a semi-dark and quiet room to allow pupil adjustment to the low level of light, after which they were instructed to focus on a small object 3 metres away with the eye that was not being tested, keeping their head straight and eyes wide open during targeting and measurement. The eye was briefly illuminated by light-emitting diodes with a single light stimulus having a peak wavelength of 180 nm. A pupillary light response curve for each eye was recorded for each child. Data were recorded for each child for the diameter of the pupil before (initial) and at constriction peak (minimal), in millimetres; for the relative constriction amplitude, as a percentage; for the maximum constriction velocity (MCV) and the average constriction and dilation velocities (ACV and ADV, respectively), all in mm/s; and the total time taken by the pupil to recover to 75% of the initial resting pupil size after reaching peak of constriction (T75), in seconds. Pupillometry is a simple non-invasive technique that can provide valuable data concerning the functioning of both branches of the autonomic nervous system. The pupil diameter, ACV, MCV and constriction amplitude are related to parasympathetic activity, while ADV and T75 are measures of sympathetic activity.²⁶ All pupillary data reported were from one eye, since no side-to-side difference was observed in the pupil responses.

In total, 1602 children (7-12 years old) in the 3rd and/or 4th grades were invited to participate. Of those, 686 did not return the signed informed consent form, and 58 refused to perform clinical tests. These children had a significantly higher BMI z-score than the included children but no differences in gender, age, parental education, or the prevalence of asthma and respiratory symptoms. Among the 858 included children, 13 were excluded due to poor quality data (participation rate of 52.7%). Thus, this study was based on data from 845 children (49.2% girls) (Table 1). The prevalence of atopy, rhinitis and current rhinitis was 35.4%, 13.4% and 31.9%, respectively. The prevalence of asthma ranged between 6.5% (medical diagnosis of asthma criteria) and 12.3% (medical diagnosis of asthma or BD+ criteria). The prevalence of overweight or obesity was nearly 30% (Table 1).

2.2 | Indoor air exposure

The indoor levels of volatile organic compounds (VOC) and aldehydes (formaldehyde and acetaldehyde) were measured in each classroom over 1 week, from early Monday until late Friday, during regular daily activities and under representative conditions of

TABLE 1 Characteristics of the participants

Characteristics	Total n = 845	Girls n = 416	Boys n = 429
Age (y [mean ± SD])	9.0 (8.0-9.0)	9.0 (8.0-9.0)	9.0 (8.0-9.0)
Parental education (n [%])			
0-9 y	219 (32.1)	97 (29.6)	122 (34.5)
10-12 y	201 (29.5)	103 (31.4)	98 (27.7)
≥13 y	262 (38.4)	128 (39.0)	134 (37.9)
Asthma (n [%]) defined by ^a			
Medical diagnosis	53 (6.5)	27 (6.7)	26 (6.3)
Positive bronchodilatation (BD+)	57 (6.7)	35 (8.4)	22 (5.1)
Medical diagnosis and symptoms or BD+	80 (9.5)	49 (11.8)	31 (7.2)
Medical diagnosis or BD+	104 (12.3)	60 (14.4)	44 (10.3)
Symptoms in previous 3 mo (n [%])			
Itching on the face or neck	54 (7.1)	22 (5.9)	32 (8.4)
Eye irritation	97 (12.6)	41 (10.8)	56 (14.4)
Swollen eyes	58 (7.8)	29 (7.9)	29 (7.7)
Runny nose	345 (45.5)	181 (48.0)	164 (42.0)
Nasal obstruction	404 (53.1)	199 (53.1)	205 (53.1)
Dry throat	154 (20.5)	81 (21.7)	73 (19.4)
Sore throat	302 (39.7)	168 (44.6)	134 (31.2)
Irritative cough	232 (30.5)	119 (31.7)	113 (29.4)
Breathing difficulties	82 (10.8)	44 (11.7)	38 (9.9)
Wheezing symptoms (n [%])	78 (9.2%)	38 (9.1)	40 (9.3)
Wheezing previous year (n [%])	64 (31.4)	31 (25.6)	35 (24.8)
More than 4 wheezing episodes previous year (n [%])	16 (7.8)	9 (8.8)	7 (6.9)
Cough symptoms (n [%])	97 (11.5)	50 (12.0)	47 (11.0)
Asthma symptoms (n [%]) ^b	119 (14.1)	59 (14.2)	60 (14.0)
Atopy (n [%]) ^c	296 (35.4)	145 (35.3)	151 (35.6)
Rhinitis (n [%])	101 (13.4)	40 (10.8)	61 (16.0)
Current rhinitis (n [%])	89 (31.9)	36 (26.1)	53 (37.6)
Body fat percentage (%)	21.4 (18.2-26.2)	23.2 (20.2-27.6)	19.5 (16.7-23.8)
Body fat mass (Kg)	6.6 (5.0-9.6)	7.4 (5.6-10.4)	6.0 (4.6-8.4)
Total body water (%)	17.9 (16.0-20.4)	17.5 (15.7-20.1)	18.2 (16.4-20.7)
BMI (n [%])			
CDC			
Underweight	39 (4.6)	21 (5.0)	18 (4.2)
Normal weight	575 (68.0)	281 (67.5)	194 (68.5)
Overweight	128 (15.1)	67 (16.1)	61 (14.2)
Obese	103 (12.2)	47 (11.3)	56 (13.1)
WHO			
Underweight	12 (1.4)	5 (1.2)	7 (1.6)
Normal weight	541 (64.0)	260 (62.5)	281 (65.5)
Overweight	172 (20.4)	98 (23.6)	74 (17.2)
Obese	120 (14.2)	53 (12.7)	67 (15.6)
IOTF			
Underweight	75 (8.9)	42 (10.1)	33 (7.7)
Normal weight	539 (63.8)	253 (60.8)	286 (66.7)

(Continues)

TABLE 1 (Continued)

Characteristics	Total n = 845	Girls n = 416	Boys n = 429
Overweight	168 (19.9)	88 (21.2)	80 (18.6)
Obese	63 (7.5)	33 (7.9)	30 (7.0)
Percentage of body fat			
Underfat	8 (1.0)	3 (0.7)	5 (1.2)
Normal	556 (66.7)	286 (70.1)	270 (63.5)
Overfat	134 (16.1)	63 (15.4)	71 (16.7)
Obese	135 (16.2)	56 (13.7)	79 (18.6)
EBC pH (n [%])			
<7.4	527 (62.4)	268 (64.4)	259 (60.4)
≥7.4	274 (32.3)	122 (29.3)	151 (35.2)
Exhaled NO (ppb)	11.0 (6.0-20.0)	10.0 (6.0-17.5)	12.0 (6.0-21.0)
Pupillometry			
Baseline pupil diameter (mm)	5.3 (4.7-5.9)	5.3 (4.6-5.9)	5.4 (4.8-5.9)
Final pupil diameter (mm)	3.4 (3.0-3.8)	3.4 (2.9-3.8)	3.4 (3.0-3.8)
ACV (mm/s)	4.0 (3.6-4.4)	4.0 (3.5-4.4)	4.0 (3.6-4.4)
MCV (mm/s)	5.3 (4.7-5.9)	5.2 (4.6-5.8)	5.4 (4.8-6.0)
Constriction amplitude (%)	35.0 (32.0-38.0)	35.0 (32.0-38.0)	36.0 (33.0-39.0)
ADV (mm/s)	1.1 (1.0-1.3)	1.1 (1.0-1.3)	1.2 (1.0-1.3)
T75 (s)	1.7 (1.2-2.1)	1.7 (1.1-2.1)	1.7 (1.2-2.2)

ACV, average constriction velocity; ADV, average dilation velocity; BD, bronchodilation; BMI, body mass index; CDC, US Centres for Disease Control; EBC, exhaled breath condensate; FEV₁, forced expiratory volume in the first second of forced vital capacity; IOTF, International Obesity Task Force; MCV, maximum constriction velocity; T75, the total time taken by the pupil to recover 75% of the initial resting pupil size after it reached the peak of constriction; WHO, World Health Organization.

Data reported as median (25th, 75th percentile) unless otherwise stated. Significant differences in bold.

^aThe following asthma definitions were adopted: (a) *Medical diagnosis of asthma*: self-reported medical diagnosis; (b) *Positive bronchodilatation (BD+)*: at least a 12% and over 200 mL increase in FEV₁ after bronchodilation; (c) *Medical diagnosis of asthma and symptoms or BD+*: at least a 12% and over 200 mL increase in forced expiratory volume in 1 second (FEV₁) after bronchodilation or self-reported medical diagnosis with reported symptoms (wheezing, dyspnoea or dry cough) occurring in the past 12 mo; (d) *Medical diagnosis of asthma or BD+*: at least a 12% and over 200 mL increase in FEV₁ after bronchodilation or self-reported medical diagnosis.

^bReported symptoms (wheezing, dyspnoea or dry cough) occurring in the past 12 mo.

^cdefined by a positive skin prick test to at least one of the allergens.

occupancy and use of the classrooms in winter. Previous studies revealed that the indoor VOC concentration is usually higher during winter than during summer²⁷; however, no measurements were performed in spring/summer. VOC were collected passively onto thermally desorbed adsorbents (see the Methods section in the Online Repository). Formaldehyde and acetaldehyde were sampled by Radiello® passive devices (RAD 165, Sigma Aldrich), and concentrations were determined using isocratic reverse phase high-performance liquid chromatography (HPLC) (Agilent Technologies, 1220 Infinity LC) with a UV detector operated at 360 nm, according to the ISO 16000-4 standard²⁸ (see the Methods section in the Online Repository).

The concentrations of 13 VOC and 2 aldehydes identified as EDCs by *The Endocrine Disruption Exchange Research Institute* (TEDX)²⁹ were considered, including toluene, o-xylene, m/p-xylene, hexane, ethylbenzene, styrene, cyclohexanone, butylated hydroxytoluene (BHT), benzene, benzaldehyde, 4-chloroethylene (T4CE), 2-butoxyethanol, 2-ethyl-1-hexanol, formaldehyde and acetaldehyde.

The median indoor air concentrations of these EDCs and their frequency in the classrooms are presented in Table S2 (Online Repository).

2.3 | Data analysis

The Kolmogorov-Smirnov test was used to check continuous variables for normality. The Mann-Whitney test was used to compare variables between the girls and the boys. Significant differences were reported with an α -value of less than 5% ($P < 0.05$). Principal component analysis (PCA) was used to identify major EDCs patterns based on the 15 individual compounds. Varimax rotation was performed to simplify the interpretation of the factor loading structure. The number of components was chosen based on eigenvalues greater than one. The PCA divided the EDCs into two principal components (PC1 and PC2), which were included in each PC if the correlation coefficient was equal to or greater than 0.30. Of the two factors, PC1 had a higher absolute correlation with toluene, o-xylene,

TABLE 2 EDCs and asthma, respiratory symptoms in the previous 3 mo and body mass index (BMI)

	Median (25th-75th percentile)		Spearman's rho	P value
	No	Yes		
Toluene (µg/m³)				
Symptoms in previous 3 mo				
Nasal obstruction	8.8 (5.3; 11.8)	10.1 (5.7; 14.9)	-	0.006
Dry throat	8.9 (5.6; 13.4)	10.3 (6.0; 14.9)	-	0.027
Sore throat	8.9 (5.3; 13.4)	10.1 (5.7; 14.9)	-	0.015
BMI (WHO criteria)				
Underweight	-	6.0 (3.1; 12.4)	-	0.023
Normal weight	-	8.9 (5.5; 14.1)	-	
Overweight	-	9.1 (5.6; 14.1)	-	
Obese	-	10.6 (6.9; 14.7)	-	
o-xylene (µg/m³)				
Medical diagnosis asthma or BD+ ^a	2.2 (1.0; 3.5)	2.7 (1.3; 4.0)	-	0.016
Symptoms in previous 3 mo				
Nasal obstruction	2.0 (1.0; 3.1)	2.5 (1.1; 3.9)	-	0.008
m/p-xylene (µg/m³)				
Medical diagnosis asthma or BD+ ^a	3.8 (2.1; 6.2)	5.0 (2.3; 7.6)	-	0.015
Symptoms in previous 3 mo				
Nasal obstruction	3.7 (2.1; 6.1)	4.3 (2.2; 7.5)	-	0.016
Dry throat	3.8 (2.0; 6.7)	4.9 (2.6; 7.5)	-	0.030
Sore throat	3.8 (2.0; 6.2)	4.2 (2.2; 7.5)	-	0.042
BMI (WHO criteria)				
Underweight	-	2.9 (1.6; 8.2)	-	0.023
Normal weight	-	3.8 (2.1; 6.7)	-	
Overweight	-	4.2 (2.1; 6.1)	-	
Obese	-	5.0 (3.2; 7.4)	-	
z-score CDC	-	-	0.072	0.036
z-score WHO	-	-	0.069	0.045
Ethylbenzene (µg/m³)				
Medical diagnosis asthma ^a	1.0 (0; 2.6)	1.7 (0.6; 4.0)	-	0.031
Medical diagnosis asthma or BD+ ^a	1.0 (0; 2.5)	1.7 (0.6; 3.6)	-	0.002
Medical diagnosis asthma and symptoms or BD+ ^a	1.0 (0.0; 2.5)	1.6 (0.4; 3.6)	-	0.024
Symptoms in previous 3 mo				
Nasal obstruction	1.0 (0; 2.5)	1.2 (0; 2.8)	-	0.021
Styrene (µg/m³)				
BMI (percentage of body fat criteria)				
Underfat	-	0.1 (0; 0.6)	-	0.046
Normal	-	0.3 (0.03; 0.9)	-	
Overfat	-	0.6 (0.2; 1.2)	-	
Obese	-	0.4 (0.03; 0.9)	-	
z-score CDC	-	-	0.091	0.008
z-score WHO	-	-	0.090	0.009
Cyclohexanone (µg/m³)				
Symptoms in previous 3 mo ^b				
Runny nose	0.7 (3.2)	1.3 (4.9)		0.006

(Continues)

TABLE 2 (Continued)

	Median (25th-75th percentile)		Spearman's rho	P value
	No	Yes		
BMI (percentage of body fat criteria) ^b				
Underfat	-	0.0 (0.0)	-	0.017
Normal	-	0.8 (3.6)	-	
Overfat	-	0.9 (4.2)	-	
Obese	-	2.0 (5.6)	-	
z-score CDC	-	-	0.078	0.023
z-score WHO	-	-	0.080	0.020
Butylated hydroxytoluene (μg/m ³)				
Symptoms in previous 3 mo				
Dry throat	2.1 (0; 5.1)	0.8 (0; 4.1)	-	0.005
Benzene (μg/m ³)				
Medical diagnosis asthma or BD+ ^a	0.7 (0.4; 1.3)	1.0 (0.4; 1.5)	..	0.033
Symptoms in previous 3 mo				
Itching on the face or neck	0.7 (0.4; 1.4)	1.2 (0.4; 1.9)		0.027
4-chloroethylene (μg/m ³)				
BMI (CDC criteria)				
Underweight	-	0.3 (0.8)	-	0.020
Normal weight	-	0.4 (1.2)	-	
Overweight	-	0.5 (1.4)	-	
Obese	-	0.1 (0.6)	-	
2-butoxyetanol (μg/m ³)				
Symptoms in previous 3 mo				
Eye irritation	9.0 (5.5; 61.5)	15.2 (6.6; 118.7)	-	0.031
2-ethyl-1-hexanol (μg/m ³)				
Medical diagnosis asthma ^a	3.4 (2.1; 5.6)	4.8 (3.4; 9.6)	-	0.003
Medical diagnosis asthma or BD+ ^a	3.4 (2.1; 5.6)	4.5 (2.8; 6.8)	-	0.017
Symptoms in previous 3 mo				
Swollen eyes	3.4 (2.1; 5.3)	5.3 (2.4; 7.1)	-	0.012
Runny nose	3.3 (2.1; 5.3)	4.5 (2.4; 5.6)	-	0.006
Irritative cough	3.4 (2.0; 5.3)	4.6 (2.8; 5.6)	-	0.007
PCA1				
Medical diagnosis asthma or BD+ ^a	−0.3 (−0.5; −0.03)	−0.2 (−0.4; −0.004)	-	0.023
Symptoms in previous 3 mo				
Nasal obstruction	−0.3 (−0.5; −0.04)	−0.2 (−0.4; −0.004)	-	0.017
PCA2				
Symptoms in previous 3 mo				
Nasal obstruction	−0.01 (−0.5; 0.7)	−0.1 (−0.7; 0.6)	-	0.036

BMI, body mass index; CDC, US Centers for Disease Control; WHO, World Health Organization.

^aThe following asthma definitions were adopted: (a) *Medical diagnosis of asthma*: self-reported medical diagnosis; (b) *Positive bronchodilatation (BD+)*: at least a 12% and over 200 mL increase in FEV1 after bronchodilation; (c) *Medical diagnosis of asthma and symptoms or BD+*: at least a 12% and over 200 mL increase in forced expiratory volume in 1 second (FEV1) after bronchodilation or self-reported medical diagnosis with reported symptoms (wheezing, dyspnoea or dry cough) occurring in the past 12 mo; (d) *Medical diagnosis of asthma or BD+*: at least a 12% and over 200 mL increase in FEV1 after bronchodilation or self-reported medical diagnosis.

^bData reported as mean (standard deviation).

m/p-xylene, ethylbenzene, styrene and benzene, while PC2 had a higher absolute correlation with cyclohexanone, BHT, benzene, benzaldehyde, formaldehyde and acetaldehyde (Table S3).

Generalized linear models and multinomial logistic regression models were used to measure the effect of individual or combined EDCs on asthma, the presence of respiratory symptoms in the

previous 3 months, obesity and body composition in the children. Model 0, crude; model 1, adjusted for age and sex; and model 2, additionally adjusted for the following variables: (a) BMI (according to the CDC criteria), atopy and parental education; (b) asthma (according to the medical diagnosis of asthma and symptoms or BD+ criteria), parental education, physical activity and energy intake; (c) asthma (medical diagnosis of asthma and symptoms or BD+) and parental education; and (d) asthma (medical diagnosis of asthma and symptoms or BD+), BMI (the CDC criteria), parental education, physical activity and energy intake. PCA and mixed effect models were analysed using RStudio software, version 1.0.

3 | RESULTS

Classrooms with higher levels of o-xylene, m/p-xylene, ethylbenzene, benzene, 2-ethyl-1-hexanol and higher PC1 scores had a higher number of children with asthma (Table 2). Higher levels of several EDCs were also found in classrooms with a higher number of children reporting respiratory symptoms in the previous 3 months. Runny nose was reported by children in classrooms with higher concentrations of cyclohexanone and 2-ethyl-1-hexanol (Table 2). Additionally, higher classroom concentrations of toluene, m/xylene, styrene and cyclohexanone showed a tendency to be associated with an increased number of overweight and obese children (Table 2). The results showed that classrooms with higher concentrations of toluene, o-xylene, m/p-xylene, ethylbenzene, 2-ethyl-1-hexanol and higher PC1 scores but lower PC2 scores had significantly higher numbers of children reporting nasal obstruction symptoms (Table 2). Higher concentrations of toluene, o-xylene, m/p-xylene, ethylbenzene, cyclohexanone, benzene and benzaldehyde and higher PC1 scores were found in classrooms with a higher number of children with significantly lower values of parasympathetic activity parameters (see Table S4 in the Online Repository). However, higher levels of BHT, formaldehyde and acetaldehyde and higher PC2 scores were found in classrooms with a higher number of children with higher values of parasympathetic activity parameters. Furthermore, higher EBC pH values were also found in children exposed to significantly higher levels of ethylbenzene, styrene and formaldehyde (see Table S4 in the Online Repository).

After adjustment, the risk of positive bronchodilation by exposure to higher levels of benzene increased by 1.5-fold (OR = 1.49, 95% CI 1.01, 2.53). Toluene, o-xylene, m/p-xylene and ethylbenzene were significantly associated with nasal obstruction (OR = 1.01, 95% CI 1.00, 1.03; OR = 1.04, 95% CI 1.01, 1.08; OR = 1.01, 95% CI 1.00, 1.03; and OR = 1.04, 95% CI 1.01, 1.09, respectively). The levels of hexane, styrene, cyclohexanone, BHT and 2-butoxyethanol were also associated with obesity, and the level of cyclohexanone was associated with increased child BMI. Additionally, positive associations were found between cyclohexanone, BHT and acetaldehyde and body composition (Table 3). Furthermore, a positive association was found between PC1 and the risk of obese asthma (OR = 1.43,

95% CI 1.01, 1.98) and between PC2 and overweight (OR = 1.51, 95% CI 1.28, 1.79). In addition, PC1 and PC2 were associated with nasal obstruction, and PC2 was associated with breathing difficulties and lean body mass (Table 3), although the concentrations of the EDCs were relatively low. Higher concentrations of individual EDCs and higher PC1 and PC2 scores were also positively associated with asthma, and child BMI and respiratory symptoms; however, after adjustment, the effect size estimates were similar but not statistically significant (Table S5).

Children exposed to higher levels of m/p-xylene and benzaldehyde exhibited decreased baseline pupil diameters; additionally, children exposed to higher levels of toluene, ethylbenzene and benzene exhibited decreased ADV (Table 4). Toluene, cyclohexanone and benzene were also negatively associated with constriction amplitude. Moreover, a negative association was found between both formaldehyde and acetaldehyde and ACV and between benzaldehyde and the baseline and final pupil diameters (Table 4). Nevertheless, toluene, o-xylene, m/p-xylene, ethylbenzene and benzene were also positively associated with constriction velocity (MCV and ACV), and 2-butoxyethanol, formaldehyde and acetaldehyde were positively associated with constriction amplitude. Positive associations were found between T4CE and MCV and between cyclohexanone and ACV. In addition, PC1 was positively associated with both MCV and ACV (Table 4), and PC2 was positively associated with baseline pupil diameter and constriction amplitude. However, higher PC2 scores were associated with lower values of MCV and ACV (Table 4).

4 | DISCUSSION

Our findings suggest that exposure to endocrine-disrupting compounds in classrooms is associated with an increased risk of asthma and obesity and an increased body fat percentage, as well as with an increased prevalence of nasal obstruction symptoms in the previous 3 months. Significant associations between compounds grouped by principal component analysis and obese asthma, current respiratory symptoms, obesity and body composition were also observed, even for low levels of EDCs exposure. Furthermore, our results showed that exposure to individual or combined EDCs is associated with changes in the ANS, specifically parasympathetic dysautonomia assessed through pupillometry,^{30,31} thus suggesting that EDCs may increase parasympathetic activity, resulting in a subsequent increase in the risk of asthma and obesity.

Surprisingly, our findings showed that even low-level exposures of EDCs may increase the risk of asthma, the presence of respiratory symptoms in the previous 3 months or obesity in schoolchildren. This result suggests that no safe exposure level exists, especially when children are constantly exposed to these compounds. Indeed, other studies have shown that exposure to lower concentrations of EDCs may cause even stronger effects than higher doses, especially considering that exposure is lifelong.³²⁻³⁴ Similar to natural hormones, even low concentrations of EDCs (in the parts-per-trillion to parts-per-billion

TABLE 3 Association between EDCs and asthma, respiratory symptoms in the previous 3 mo, and body mass index (BMI)

	OR (95% CI)		
	Model 0	Model 1	Model 2
Toluene			
Symptoms in previous 3 mo ^a			
Nasal obstruction	1.01 (1.00; 1.02)	1.01 (1.00; 1.02)	1.01 (1.00-1.03)
o-xylene			
Symptoms in previous 3 mo ^a			
Nasal obstruction	1.03 (1.00; 1.07)	1.03 (1.00; 1.07)	1.04 (1.01; 1.08)
m/p-xylene			
Symptoms in previous 3 mo ^a			
Nasal obstruction	1.01 (1.00; 1.02)	1.01 (1.00; 1.02)	1.01 (1.00; 1.03)
Hexane			
BMI (WHO criteria) ^b			
Underweight	Reference	Reference	Reference
Normal weight	1.00 (0.99; 1.02)	1.55 (1.54; 1.56)	1.18 (1.17; 1.19)
Overweight	1.00 (0.99; 1.02)	1.55 (1.54; 1.56)	1.18 (1.17; 1.19)
Obese	1.00 (0.99; 1.02)	1.55 (1.54; 1.56)	1.18 (1.17; 1.19)
Ethylbenzene			
Symptoms in previous 3 mo ^a			
Nasal obstruction	1.03 (1.00; 1.08)	1.03 (1.01; 1.08)	1.04 (1.01; 1.09)
Styrene			
BMI (WHO criteria) ^b			
Underweight	Reference	Reference	Reference
Normal weight	1.20 (0.69; 2.06)	1.59 (0.39; 6.52)	1.65 (1.45; 1.88)
Overweight	1.20 (0.67; 2.13)	1.53 (0.37; 6.34)	1.54 (1.30; 1.83)
Obese	1.34 (0.76; 2.37)	1.81 (0.44; 7.51)	1.78 (1.52; 2.10)
Cyclohexanone			
BMI (WHO criteria) ^b			
Underweight	Reference	Reference	Reference
Normal weight	1.02 (0.88; 1.20)	1.59 (0.01; 1.59E2)	2.45 (2.36; 2.55)
Overweight	1.04 (0.88; 1.22)	1.61 (0.01; 1.61E2)	2.54 (2.43; 2.65)
Obese	1.06 (0.90; 1.24)	1.61 (0.01; 1.61E2)	2.53 (2.41; 2.65)
z-score CDC ^c	0.02 (0.005; 0.04)	0.02 (0.001; 0.04)	0.03 (0.01; 0.05)
z-score WHO ^c	0.03 (0.007; 0.05)	0.02 (0.002; 0.04)	0.03 (0.01; 0.06)
Body composition^{b,c}			
Body fat (%)	0.18 (0.08; 0.27)	0.17 (0.07; 0.26)	0.21 (0.10; 0.32)
Butylated hydroxytoluene			
BMI (WHO criteria) ^b			
Underweight	Reference	Reference	Reference
Normal weight	1.35 (0.43; 4.18)	1.36 (0.4; 4.26)	1.23 (1.18; 1.29)
Overweight	1.33 (0.43; 4.14)	1.35 (0.43; 4.22)	1.25 (1.18; 1.32)
Obese	1.33 (0.43; 4.13)	1.35 (0.43; 4.22)	1.23 (1.16; 1.31)
Body composition^{b,c}			
Lean body mass	0.10 (0.02; 0.19)	0.09 (0.01; 0.17)	0.10 (0.01; 0.19)
Total body water	0.08 (0.01; 0.14)	0.06 (0.006; 0.12)	0.07 (0.01; 0.14)
Benzene			
Positive bronchodilatation ^{d,a}	1.67 (1.02; 2.66)	1.64 (1.00; 2.65)	1.49 (1.01; 2.53)

(Continues)

TABLE 3 (Continued)

	OR (95% CI)		
	Model 0	Model 1	Model 2
2-butoxyethanol			
BMI (Percentage of body fat criteria) ^b			
Underfat	Reference	Reference	Reference
Normal	1.81 (0.08, 43.1)	4.36 (4.34; 4.38)	3.90 (3.85; 3.95)
Overfat	1.81 (0.07, 43.1)	4.35 (4.33; 4.38)	3.90 (3.85; 3.96)
Obese	1.80 (0.07, 42.9)	4.33 (4.30; 4.36)	3.81 (3.72; 3.91)
Acetaldehyde			
Body composition ^{b,c}			
Lean body mass	0.07 (−0.04; 0.18)	0.10 (−7.66E-4; 0.21)	0.16 (0.02; 0.30)
PC1			
Obese asthma ^a	1.45 (1.04; 1.94)	1.38 (0.98; 1.86)	1.43 (1.01; 1.98)
Symptoms in previous 3 mo ^a			
Nasal obstruction	1.25 (1.09; 1.47)	1.24 (1.08; 1.45)	1.32 (1.13; 1.58)
BMI (WHO criteria) ^b			
Underweight	Reference	Reference	Reference
Normal weight	0.89 (0.57; 1.39)	0.90 (0.57; 1.41)	0.89 (0.80; 1.01)
Overweight	0.79 (0.49; 1.27)	0.79 (0.49; 1.27)	0.80 (0.69; 0.92)
Obese	0.92 (0.58; 1.47)	0.94 (0.59; 1.51)	0.85 (0.73; 0.98)
BMI (Percentage of body fat criteria) ^b			
Underfat	Reference	Reference	Reference
Normal	1.40 (0.46; 4.32)	1.39 (0.47; 4.14)	1.39 (1.23; 1.57)
Overfat	1.29 (0.42; 4.03)	1.27 (0.42; 3.84)	1.17 (0.97; 1.40)
Obese	1.34 (0.43; 4.15)	1.33 (0.44; 4.01)	1.29 (1.10; 1.51)
PC2			
Symptoms in previous 3 mo ^a			
Nasal obstruction	0.86 (0.74, 0.99)	0.85 (0.73; 0.99)	0.83 (0.71; 0.98)
Breathing difficulties	0.80 (0.63, 1.01)	0.78 (0.61; 1.00)	0.74 (0.55; 0.97)
BMI (WHO criteria) ^b			
Underweight	Reference	Reference	Reference
Normal weight	1.19 (0.66; 2.15)	1.18 (0.65; 2.13)	1.18 (1.04; 1.33)
Overweight	1.12 (0.61; 2.05)	1.15 (0.63; 2.11)	1.24 (1.06; 1.45)
Obese	1.08 (0.58; 1.98)	1.12 (0.60; 2.07)	1.10 (0.93; 1.30)
BMI (Percentage of body fat criteria) ^b			
Underfat	Reference	Reference	Reference
Normal	1.35 (0.65, 2.82)	1.33 (0.63; 2.78)	1.31 (1.15; 1.48)
Overfat	1.41 (0.67, 2.97)	1.37 (0.65; 2.92)	1.51 (1.28; 1.79)
Obese	1.16 (0.55, 2.45)	1.17 (0.55; 2.48)	1.10 (0.93; 1.30)
Body composition ^{b,c}			
Lean body mass	0.33 (0.03; 0.63)	0.33 (0.03; 0.63)	0.40 (0.04; 0.76)

BMI, body mass index; CDC, US Centres for Disease Control; CI, confidence interval; IOTF, International Obesity Task Force; WHO, World Health Organization.

Model 0 is null model; model 1 is adjusted for age and sex; model 2 is additionally adjusted for:

^aBMI (according to CDC criteria), atopy and parental education.

^bAsthma (according to medical diagnosis asthma and symptoms or BD+ criteria), parental education, physical activity, energy intake.

^cData reported as β (95% CI).

^dThe following asthma definitions were adopted: (a) *Medical diagnosis of asthma*: self-reported medical diagnosis; (b) *Positive bronchodilatation (BD+)*: at least a 12% and over 200 mL increase in FEV1 after bronchodilation; (c) *Medical diagnosis of asthma and symptoms or BD+*: at least a 12% and over 200 mL increase in forced expiratory volume in 1 second (FEV1) after bronchodilation or self-reported medical diagnosis with reported symptoms (wheezing, dyspnoea or dry cough) occurring in the past 12 mo; (d) *Medical diagnosis of asthma or BD+*: at least a 12% and over 200 mL increase in FEV1 after bronchodilation or self-reported medical diagnosis.

TABLE 4 Association between EDCs and autonomic nervous system activity

	OR (95% CI) ^a		
	Model 0	Model 1	Model 2 ^b
Toluene			
MCV	−0.004 (−0.01; −7.79E-4)	−0.004 (−0.01; −4.17E-4)	0.005 (8.00E-4; 0.009)
ACV	−0.003 (−0.006; −7.14E-4)	−0.003 (−0.006; −4.70E-4)	0.004 (0.001; 0.007)
Constriction amplitude	−0.02 (−0.004; 6.51E-4)	0.009 (−0.04; 9.76E-4)	−0.02 (−0.04; −0.004)
ADV	−0.001 (−0.003; −2.18E-4)	−0.001 (−0.003; −1.51E-4)	−0.002 (−0.003; −2.00E-4)
o-xylene			
MCV	−0.01 (−0.02; −0.002)	−0.01 (−0.02; −0.003)	0.01 (0.002; 0.02)
ACV	−0.01 (−0.02; −0.003)	−0.01 (−0.02; −0.003)	0.01 (0.003; 0.02)
m/p-xylene			
Baseline pupil diameter	−0.004 (−0.007; −0.001)	−0.004 (−0.007; −0.001)	−0.003 (−0.006; −4.14E-5)
MCV	−0.005 (−0.008; −0.001)	−0.005 (−0.008; −0.002)	0.005 (0.001; 0.008)
ACV	−0.004 (−0.006; −0.001)	−0.004 (−0.006; −0.001)	0.004 (0.001; 0.006)
Ethylbenzene			
MCV	−0.01 (−0.02; −0.002)	−0.01 (−0.02; −0.002)	0.01 (0.002; 0.03)
ACV	−0.01 (−0.02; −0.003)	−0.01 (−0.02; −0.003)	0.01 (0.003; 0.02)
ADV	−0.004 (−0.008; −1.55E-4)	−0.004 (−0.009; −1.93E-4)	−0.005 (−0.01; −1.00E-4)
Cyclohexanone			
ACV	−0.01 (−0.02; 7.69E-4)	−0.01 (−0.002; 0.001)	0.01 (0.002; 0.03)
Constriction amplitude	−0.09 (−0.17; −0.002)	−0.08 (−0.17; 0.004)	−0.10 (−0.20; −0.01)
Benzene			
MCV	−0.15 (−0.24; −0.05)	−0.12 (−0.22; −0.02)	0.15 (0.04; 0.26)
ACV	−0.13 (−0.20; −0.06)	−0.12 (−0.19; −0.04)	0.14 (0.06; 0.22)
Constriction amplitude	−0.59 (−1.10; −0.09)	−0.50 (−1.10; 0.005)	−0.74 (−1.30; −0.18)
ADV	−0.001 (−0.003; 0.001)	−0.004 (−0.009; −1.93E-4)	−0.05 (−0.09; −0.007)
Benzaldehyde			
Baseline pupil diameter	−0.01 (−0.02; −0.005)	−0.01 (−0.02; −0.003)	−0.01 (−0.02; −0.004)
Final pupil diameter	−0.007 (−0.01; −0.002)	−0.006 (−0.01; −0.001)	−0.008 (−0.01; −0.03)
4-chloroethylene			
MCV	−0.06 (−0.12; 0.001)	−0.07 (−0.14; −0.01)	0.07 (0.005; 0.14)
2-butoxyethanol			
Constriction amplitude	0.01 (0.002; 0.02)	0.01 (0.003; 0.02)	0.02 (0.005; 0.03)
Formaldehyde			
ACV	0.01 (0.003; 0.02)	0.01 (0.003; 0.02)	−0.010 (−0.02; −0.003)
Constriction amplitude	0.08 (0.03; 0.13)	0.08 (0.03; 0.13)	0.10 (0.05; 0.16)
Acetaldehyde			
ACV	0.03 (0.01; 0.05)	0.04 (0.02; 0.05)	−0.03 (−0.05; −0.010)
Constriction amplitude	0.14 (0.003; 0.28)	0.17 (0.03; 0.31)	0.16 (0.004; 0.31)
PC1			
MCV	−0.09 (−0.16; −0.02)	−0.09 (−0.16; −0.02)	0.10 (0.02; 0.18)
ACV	−0.07 (−0.12; −0.02)	−0.07 (−0.12; −0.02)	0.08 (0.03; 0.14)
PC2			
Baseline pupil diameter	0.11 (0.04; 0.17)	0.09 (0.02; 0.16)	0.09 (0.01; 0.16)
MCV	0.09 (0.02; 0.17)	0.09 (0.01; 0.17)	−0.10 (−0.19; −0.02)
ACV	0.11 (0.06; 0.17)	0.11 (0.06; 0.17)	−0.12 (−0.18; −0.06)
Constriction amplitude	0.70 (0.32; 1.09)	0.72 (0.33; 1.12)	0.86 (0.44; 1.29)

ACV, average constriction velocity; ADV, average dilation velocity; CI, confidence interval; MCV, maximum constriction velocity.

Model 0 is null model; model 1 is adjusted for age and sex; model 2 is additionally adjusted for:

^aData reported as β (95% CI).

^basthma (according to medical diagnosis asthma and symptoms or BD+ criteria) and parental education.

range) may have effects that influence human metabolism. These studies showed that very low levels of individual or combined EDCs were associated with reduced intelligence, disrupting reproductive system and cause other health problems.³²⁻³⁴ Thus, the statement by Paracelsus that "the dose makes the poison" may not apply to EDCs exposure because of potential low-dose effects, which cannot be predicted by the effects of exposure to higher concentrations.³⁴

Our findings may contribute to action plans aimed at improving indoor air quality and decreasing EDCs exposure, thereby improving children's health. This study assessed the effect of individual exposure and co-exposure to VOC identified as EDCs; however, most previous studies have focused primarily on the effects of exposure to individual semi-volatile organic compounds such as phthalates and bisphenol on respiratory health³⁵⁻³⁷ and obesity in children^{38,39} and on compounds that interact with the oestrogen, androgen and thyroid hormone systems.^{8,40} Our results suggested that exposure to individual or combined EDCs may interfere with other systems, increasing the risk of asthma, the presence of respiratory symptoms in the previous 3 months and obesity in schoolchildren, and these results contribute to the understanding of the potential health risk of co-exposure. Additionally, exposure to combined EDCs (PC1) may also increase the risk of obese asthma, suggesting that children with obese asthma may be more sensitive than healthy children to EDCs.

Individual EDCs, such as toluene, hexane, styrene, o-,m/p-xylene, ethylbenzene, cyclohexanone, BHT, benzene and 2-butoxyethanol, and combined EDCs obtained in our study by principal component analysis were significantly associated with different health effects, suggesting that different EDCs may target different organs and systems. Exposure to EDCs may change cytokine production, T_H1 and T_H2 balance and activate the immune system.^{41,42} Kuo et al⁴³ showed that human bronchial epithelial cells treated with different EDCs increased bronchial smooth-muscle cell proliferation and migration by increasing the secretion of IL-8 and regulated on activation and normal T-cell expression and secreted (RANTES), suggesting a possible role for EDCs in asthma airway remodelling. In addition, EDCs may mediate changes through alterations in DNA methylation, which are proposed to play a role in the development of asthma.⁴⁴ Higher exposure to EDCs is related to lower methylation of TNF- α 5' CGI, which is associated with airway inflammation, hyperresponsiveness, the regulation of immune cells and a higher risk of asthma in children.⁴⁴ Similar to other air pollutants, EDCs may also stimulate airway C-fibre sensory nerves, which express transient receptor potential (TRP) cation channels; when exposed to irritants, TRP channels release neuropeptides locally, resulting in cough, airway irritation, mucous secretion and bronchoconstriction mediated by the efferent pathways of the autonomic nervous system.^{45,46} Nassi et al⁴⁷ and Cantero-Recasens et al⁴⁸ reported the role of activation and/or increased expression of transient receptor potential vanilloid 1 (TRPV1) and ankyrin 1 (TRPA1) channels in the pathogenesis of asthma, providing evidence for the role of ANS in the regulation of airway function.

In obesity, EDCs inappropriately regulate lipid metabolism and adipogenesis by targeting peroxisome proliferator-activated receptors (PPAR α , δ and γ) and the retinoic X receptor (RXR), which are

essential for the control of intracellular lipid homeostasis as well as the proliferation and differentiation of adipocytes, and the aryl hydrocarbon receptor in adipocytes, thus increasing adipogenesis.^{38,49} Obesogenic effects of EDCs may also be mediated by the methylation of PPAR γ and RXR α , changing the regulation of adipogenesis and increasing triglycerides accumulation, glucose metabolism, and insulin sensitivity in mature adipocytes.^{50,51} Additionally, Baillie-Hamilton⁵² reported that exposure to different chemicals, such as EDCs, is also associated with weight gain, possibly by interfering with the normal activity of the ANS. These changes in the ANS may suppress appetite, enable the body to mobilize fat stores for use and stimulate physical activity levels.⁵² The ANS plays an important role in the communication between the gastrointestinal system and the central nervous system, as a mediator of the sense of satiety after gastric distension, in the release of gut hormones, in the modulation of satiety and in the release of leptin and insulin, which regulate body weight and adiposity.⁵³

Different mechanisms, such as mechanical, immunological, genetic, epigenetic, hormonal and environmental pathways, may mediate the association between obesity and asthma.⁵⁴ Recently, the microbiome has gained interest as an important factor in the development of both obesity and asthma.⁵⁵ In addition, our results described a possible noninflammatory mechanism underlying obese asthma from the disruption of the ANS by leptin due to exposure to indoor EDCs. These EDCs can mimic, block or interfere with the production of leptin,⁵⁶ a consequence that may also be involved in increasing the risk of asthma and obesity.⁵⁷ The lack of leptin signalling may affect airway smooth muscles by disrupting the activity of the parasympathetic nervous system. Additionally, leptin resistance in obesity also leads to increased parasympathetic signalling, with subsequent bronchoconstriction.^{58,59}

This study has a few limitations. The cross-sectional design does not allow the establishment of causal relationships or the analysis of cumulative exposure to different indoor and outdoor environments. Furthermore, no on-site monitoring data regarding the levels of other indoor air pollutants, such as other chemical compounds, particulate matter, moulds or allergens, were considered in the analysis. The effect of sore throat as a potential co-exposure was not considered, since no significant associations were found between this symptom and asthma, the presence of other respiratory symptoms or EDCs exposure. Additionally, all questions regarding asthma symptoms and clinical assessment were performed under the assumption that the children did not have colds or flu, thus reducing the effect of co-exposure factors and the probability of chance findings. Additionally, our study considers classroom exposure only. However, after home, children spend most of their day at school, especially indoors, and usually stay in the same classroom through primary school years, being expected that indoor air quality in schools has an important role in the assessment of the effects of EDCs exposure. In addition, schools are important settings for the implementation of programmes that promote efforts to improve indoor air quality and behaviours that contribute to minimizing the effects of EDCs and promoting health and healthy lifestyles. Rudel et al¹ and Oziol et al⁶⁰ reported that EDCs concentrations are often highest

indoors because many sources are indoors and can influence outdoor EDCs concentrations and because of limited degradation indoors than outdoors. Most EDCs considered in this study were synthetic organic chemicals used in a wide range of materials and goods and can be found in many products in schools, including materials used in building construction and furnishing, along with cleaning products.⁶¹ Moreover, indoor VOC concentrations were measured only in winter because during this period, VOC concentrations are usually high indoors, probably due to the lower mobility of air in winter and the prolonged persistence of the compounds due to reduced photochemical degradation and gradual accumulation.²⁷ Although several studies identified a significant seasonal cycle in VOC concentrations,²⁷ our findings showed that even low-level exposure to EDCs, which may be expected in summer or spring, may increase the risk of asthma, respiratory symptoms or obesity in schoolchildren. Nevertheless, it will be important to assess the effect of seasonality on EDCs concentrations to understand the extent of exposure as well as the health effects.

Our study also has important strengths. To our knowledge, this study is the first community-based study evaluating the effect of EDCs on asthma, current respiratory symptoms, obesity, body composition and ANS activity in school-age children. Additionally, we performed a comprehensive clinical assessment on a large number of participants, and we measured the concentrations of several EDCs in a substantial number of classrooms. In addition, the anthropometry and clinical assessments were performed in each primary school, in the children's normal environment, which would help reduce the co-effect of stress in the schoolchildren. Furthermore, the assessment week was arranged with the school principal and teachers to avoid examinations and special days. Even assuming an increase in stress levels, the effect of stress is expected to be independent of EDCs exposure. The children not included in the study were similar to those included, except for in the BMI z-scores, which may result in an underestimated association between exposure to EDCs and obesity. Despite the sampling of VOC at a single time point (limiting the temporal analysis) and the short period of exposure assessment, the 1-week sampling period and the use of passive samplers allowed the assessment of average indoor air concentrations and the detection of relatively low concentrations of EDCs, as suggested by recent reports,^{62,63} and the levels are representative of the prevailing conditions/activities in each classroom and of the exposure to EDCs. We evaluated the effects of EDCs either alone or in combination, since EDCs can be released as mixtures and interact within or between classes, and combinations of low doses of EDCs that are individually inactive may cause a biological effect.^{32,33} According to Kortenkamp⁶⁴ and Oziol et al,⁶⁰ it is important to understand the effects of co-exposure to EDCs, which may interact additively, synergistically or antagonistically, with potentially unknown intrinsic effects. The EDCs represented by PC1 (positive loadings on toluene, o-xylene, m/p-xylene, ethylbenzene, styrene and benzene) and PC2 (positive loadings on BHT, formaldehyde and acetaldehyde and negative loadings on cyclohexanone, benzene and benzaldehyde) showed that compounds may have different and even opposite effects, suggesting that diverse mechanisms may be involved. In addition, EDCs were

measured in indoor air, which has been identified as an important source of chemical exposure.⁸ Over the past decade, it has become clear that humans, particularly children, are exposed to EDCs via particles in indoor environments.⁶⁵⁻⁶⁷ Urinary levels of EDCs were not measured; however, several studies have observed correlations between urinary levels of EDCs metabolites and indoor air concentrations, indicating that indoor air is a significant route of exposure.^{68,69} Furthermore, different criteria were used to define BMI and to determine the effect of EDCs exposure on obesity. However, the establishment of different cut-offs is generally statistical rather than based on risk or the degree of body fatness. As a result, different definitions often do not give the same results. In this study, we assessed the effect of EDCs on BMI considering that the reference values resulted in similar but not identical estimates. Exposure to EDCs may also be associated with other important confounders related to asthma, respiratory symptoms and obesity, and those confounders may increase the risk of exposure compared to that of healthy children. Although several confounders were considered, there may be other unknown or unmeasured confounders.

Exploring the effects of individual or co-exposure to EDCs is crucial for planning and making recommendations to decision-makers to prevent the use of materials that could be indoor sources of these compounds, create monitoring programmes to characterize spatiotemporal trends and create healthier indoor environments, with the potential to decrease the risk of asthma and obesity in childhood. Thus, our results meet the goals of the WHO and the United Nations Environment Programme (UNEP), demonstrating the importance of understanding EDCs, their effects on human health, and policies and scientific evidence for health development and reduce exposures to EDCs.³²

In conclusion, the present study suggests that both individual exposure and co-exposure to low concentrations of EDCs in classrooms may affect child health, specifically on asthma, obesity and the presence of respiratory symptoms in the previous 3 months. These results also highlight the negative health effects of EDCs, contributing to the implementation of recommendations to minimize exposure and promote a healthy indoor environment.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors were involved in investigation and gave constructive criticism of the study manuscript. IP and AM were involved on study conceptualization and interpretation. IP, MS and AM contributed to the statistical analysis. IP and AM wrote the manuscript with input from all authors. EOF and AM obtained funding.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Supporting Information

Exposure to indoor endocrine disrupting chemicals and childhood asthma and obesity

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Supplementary Materials

Supplementary methodology

TABLE S1 Definitions of asthma

TABLE S2 Indoor air concentration of EDCs in school classrooms (n=71).

TABLE S3 Rotated Component Matrix

TABLE S4 EDCs and asthma, symptoms in previous 3 months and obesity.

TABLE S5 Association between individual and combined EDCs and asthma, symptoms in previous 3 months, obesity, body composition, autonomic nervous system activity and EBC pH.

Methods

From the 53 public primary schools of Porto Municipality, 20 schools with the highest number of students were selected. In each school, four classrooms of 3rd and/or 4th grades were selected among those with similar conditions and representative of the school building. Most of school (84.2%) were built before 1980 and all of them were refurbished after 2000. All schools are masonry (concrete brick), and the same building materials are used, such as floor type (PVC/vinyl, linoleum=77.8 % and wooden=22.2 %). All schools were naturally ventilated through windows and doors, and were mainly open during breaks (1). Classrooms were selected based on ISAAC Phase II criteria, where children of this age group were more likely to understand the procedures than 6-7-year-old children and to be more compliant than 13-14 year old adolescents (2), highest density of occupation, full-week occupation time by the same class, and, if possible, on the location of classrooms on different floors (3).

Participants and assessments

Parental education level was recorded as the number of successfully completed years of formal schooling, and we classified the children according to the parent with the higher education level. Physical activity was defined based on a positive answer to the question “Does your child partake in any sport activity outside of normal school-period, at least once per week?”. Total energy intake was recorded using the interviewer-administered 24-hour recall method (4). Participants were questioned accurately about their food and drinks consumption, even reporting brands and consuming time and place. The software Food Processor[®], (ESHA Research, USA) was used to convert food into total energy intake.

Wheezing and cough symptoms were defined as a positive answer to the questions “In the past 12 months, has your child had wheezing or whistling in the chest?” or to any of the two following questions “In the last 12 months, has your child suffered coughing at night?” or “In last year, has your child suffered coughing more than three months?”, respectively. Asthma symptoms were defined considering the presence of wheezing and cough symptoms, shortness of breath and chest tightness. Children were

considered to have current symptoms in previous 3 months if there was a positive answer to the question “During the past 3 months, has your child had any of the following symptoms?”: “Itching on the face or neck”, “Eye irritation (redness, dryness, itch)”, “Swollen eyes”, “Runny nose”, “Nasal obstruction”, “Dry throat”, “Sore throat”, “Irritative cough” and “Breathing difficulties”. Children were considered to have allergic rhinitis if there was a positive answer to the question “Has your child ever had a problem with sneezing, or a runny nose or blocked nose when he/she did not have a cold or the flu?” and a positive skin prick test. Current allergic rhinitis was defined as a positive answer to the question “In the past 12 months, has your child had a problem with sneezing, or a runny nose or blocked nose when he/she did not have a cold or the flu?” and a positive skin prick test. The obese asthma criterion included overweight or obese children (defined according to CDC) with medical diagnosis asthma and symptoms or positive bronchodilatation (BD+).

Exhaled breath condensate (EBC) was collected by breathing at regular tidal volumes and respiratory rates, 10 to 15 minutes, to an exhaled air condensing system (portable Turbo DECCS) (5). EBC samples were transferred to sterile tubes and stored at -80°C until analysis. Deaeration was performed by bubbling oxygen through the sample for 10 minutes at 0.3 L/min (6, 7).

The pH meter was calibrated before each measurement using solutions with pH values of 4, 7 and 10. EBC pH was categorized into two classes: <7.4 and ≥ 7.4 . Categorization was performed using a density estimation based on finite normal mixture modelling.

Skin-prick-tests (SPT) were performed on children’s forearm using a QuickTest™ applicator containing house dust mite, mix of weeds, mix of grasses, cat dander, dog dander and *Alternaria alternata*, negative control, and a positive control consisting of histamine at 10mg/ml (Hall Allergy, Netherlands). Results were read 15 minutes afterwards and atopy was defined by a positive SPT to at least one of the allergens (8).

Indoor air exposure

After sampling, the Tenax tubes were thermally desorbed (Dani STD 33.50) and the samples were quantified by gas chromatography (Agilent Technologies 6890N) coupled to a mass spectrometry detector (GC-MS) (Agilent Technologies 5973), according to the standard ISO 16000-6 (9). Compound concentrations were calculated based on their own response factor or, in case of inexistence of the specific standards, toluene's response factor was used. Cyclodecane was injected simultaneously as an internal standard, to assess the sample loss during desorption. The uncertainty of the analytical method calculated for toluene is $\pm 5.1\%$. All samples were collected in duplicate to verify the reproducibility of measurements. Aldehydes were identified and quantified by comparing their retention times and peak areas with those of standard solutions. As an internal quality control, duplicate samplings were collected in one school per each three.

TABLE S1 Definitions of asthma

Variable	Definition
Medical diagnosis of asthma	self-reported medical diagnosis
Positive bronchodilatation (BD+)	at least a 12% and over 200mL increase in FEV1 after bronchodilation
Medical diagnosis of asthma and symptoms or BD+	at least a 12% and over 200mL increase in forced expiratory volume in 1 second (FEV1) after bronchodilation or self-reported medical diagnosis with reported symptoms (wheezing, dyspnea or dry cough) occurring in the past 12 months
Medical diagnosis of asthma or BD+	at least a 12% and over 200mL increase in FEV1 after bronchodilation or self-reported medical diagnosis

TABLE S2 Indoor air concentration of EDCs in school classrooms (n=71)

Parameter ($\mu\text{g}/\text{m}^3$)	Classrooms (n) with concentration $>0 \mu\text{g}/\text{m}^3$	Median (25 th -75 th percentile)	Minimum-Maximum
Toluene	71	9.11 (5.61-14.1)	1.44-109.0
o-xylene	64	2.35 (0.98-3.49)	0-35.1
m/p-xylene	65	4.07 (2.16-6.88)	0-114.0
Hexane	5	22.9 (0-94.6)	0-568.5
Ethylbenzene	53	1.13 (0-2.63)	0-37.3
Styrene	58	0.36 (0.03-0.88)	0-6.97
Cyclohexanone	5	9.89 (0-14.0)	0-28.3
Butylated hydroxytoluene	10	0.89 (0-5.12)	0-5.12
Benzene	68	0.74 (0.37-1.37)	0-3.08
Benzaldehyde	60	10.1 (6.88-17.6)	0-48.7
4-chloroethylene	8	0 (0-0)	0-5.58
2-butoxietanol	14	8.99 (5.47-61.5)	0-188.4
2-ethyl-1-hexanol	43	3.66 (2.15-5.57)	0-45.3
Formaldehyde	71	16.4 (12.4-21.1)	0.31-37.9
Acetaldehyde	71	7.57 (5.68-9.54)	0.39-12.8

TABLE S3 Rotated Component Matrix

Compounds	Components and factor loadings	
	PC1	PC2
Toluene	0.85*	-0.01
o-xylene	0.97*	-0.03
m/p-xylene	0.97*	0.00
Hexane	-0.10	-0.04
Ethylbenzene	0.97*	0.00
Styrene	0.45*	0.14
Cyclohexanone	-0.05	-0.37*
Butylated hydroxytoluene	-0.09	0.40*
Benzene	0.54*	-0.34*
Benzaldehyde	-0.07	-0.33*
4-chloroethylene	0.16	0.00
2-butoxietanol	-0.02	0.26
2-ethyl-1-hexanol	-0.03	-0.10
Formaldehyde	0.01	0.86*
Acetaldehyde	-0.05	0.78*

*Compounds which were included in each principal component (PC)

TABLE S4 EDCs and asthma, respiratory symptoms in the previous 3 months and obesity

	Median (25 th -75 th percentile)		Spearman's rho	p value
	No	Yes		
Toluene (µg/m³)				
Symptoms in previous 3 months				
Nasal obstruction	8.8 (5.3; 11.8)	10.1 (5.7; 14.9)	--	0.006
Dry throat	8.9 (5.6; 13.4)	10.3 (6.0; 14.9)	--	0.027
Sore throat	8.9 (5.3; 13.4)	10.1 (5.7; 14.9)	--	0.015
BMI (WHO criteria)				0.023
Underweight	--	6.0 (3.1; 12.4)	--	
Normal weight	--	8.9 (5.5; 14.1)	--	
Overweight	--	9.1 (5.6; 14.1)	--	
Obese	--	10.6 (6.9; 14.7)	--	
Pupillometry				
MCV	--	--	-0.096	0.013
Constriction amplitude	--	--	-0.093	0.016
o-xylene (µg/m³)				
Asthma defined by ^T				
Medical diagnosis asthma or BD+	2.2 (1.0; 3.5)	2.7 (1.3; 4.0)	--	0.016
Symptoms in previous 3 months				
Nasal obstruction	2.0 (1.0; 3.1)	2.5 (1.1; 3.9)	--	0.008
Basal metabolic rate	--	--	-0.068	0.049
Total body water	--	--	-0.080	0.015
Pupillometry				
Baseline pupil diameter	--	--	-0.088	0.023
MCV	--	--	-0.079	0.042
m/p-xylene (µg/m³)				
Asthma defined by ^T				
Medical diagnosis asthma or BD+	3.8 (2.1; 6.2)	5.0 (2.3; 7.6)	--	0.015
Symptoms in previous 3 months				
Nasal obstruction	3.7 (2.1; 6.1)	4.3 (2.2; 7.5)	--	0.016
Dry throat	3.8 (2.0; 6.7)	4.9 (2.6; 7.5)	--	0.030
Sore throat	3.8 (2.0; 6.2)	4.2 (2.2; 7.5)	--	0.042
BMI (WHO criteria)				0.023
Underweight	--	2.9 (1.6; 8.2)	--	
Normal weight	--	3.8 (2.1; 6.7)	--	
Overweight	--	4.2 (2.1; 6.1)	--	
Obese	--	5.0 (3.2; 7.4)	--	
z-score CDC	--	--	0.072	0.036
z-score WHO	--	--	0.069	0.045
Pupillometry				

MCV	--	--	-0.086	0.028
Ethylbenzene ($\mu\text{g}/\text{m}^3$)				
Asthma defined by [†]				
Medical diagnosis asthma	1.0 (0; 2.6)	1.7 (0.6; 4.0)	--	0.031
Medical diagnosis asthma and symptoms or BD+	1.0 (0.0; 2.5)	1.6 (0.4; 3.6)	--	0.024
Medical diagnosis asthma or BD+	1.0 (0; 2.5)	1.7 (0.6; 3.6)	--	0.002
Symptoms in previous 3 months				
Nasal obstruction	1.0 (0; 2.5)	1.2 (0; 2.8)	--	0.021
Basal metabolic rate	--	--	-0.095	0.006
Total body water	--	--	-0.124	<0.05
EBC pH				0.013
<7.4	--	0.9 (0; 2.6)		
≥ 7.4	--	1.3 (0.4; 2.7)		
Pupillometry				
Baseline pupil diameter	--	--	-0.085	0.028
ACV	--	--	-0.098	0.012
MCV	--	--	-0.092	0.018
Styrene ($\mu\text{g}/\text{m}^3$)				
BMI (percentage of body mass criteria)				0.046
Underfat	--	0.1 (0; 0.6)	--	
Normal	--	0.3 (0.03; 0.9)	--	
Overfat	--	0.6 (0.2; 1.2)	--	
Obese	--	0.4 (0.03; 0.9)	--	
z-score CDC	--	--	0.091	0.008
z-score WHO	--	--	0.090	0.009
EBC pH				0.002
<7.4	--	0.3 (0; 0.9)	--	
≥ 7.4	--	0.6 (0.2; 1.0)	--	
Cyclohexanone ($\mu\text{g}/\text{m}^3$)				
Symptoms in previous 3 months*				
Runny nose	0.7 (3.2)	1.3 (4.9)		0.006
Body fat percentage	--	--	0.114	0.001
Body fat mass	--	--	0.080	0.021
BMI (percentage of body mass criteria)*				0.017
Underfat	--	0.0 (0.0)	--	
Normal	--	0.8 (3.6)	--	
Overfat	--	0.9 (4.2)	--	
Obese	--	2.0 (5.6)	--	
z-score CDC	--	--	0.078	0.023
z-score WHO	--	--	0.080	0.020

Pupillometry				
Baseline pupil diameter	--	--	-0.118	0.002
Final pupil diameter	--	--	-0.078	0.045
ACV	--	--	-0.123	0.002
MCV	--	--	-0.082	0.035
Constriction amplitude	--	--	-0.121	0.002
T75	--	--	-0.086	0.041
Butylated hydroxytoluene ($\mu\text{g}/\text{m}^3$)				
Symptoms in previous 3 months				
Dry throat	2.1 (0; 5.1)	0.8 (0; 4.1)	--	0.005
Pupillometry				
Baseline pupil diameter	--	--	0.121	0.002
Final pupil diameter	--	--	0.145	<0.05
Benzene ($\mu\text{g}/\text{m}^3$)				
Asthma defined by [†]				
Medical diagnosis asthma or BD+	0.7 (0.4; 1.3)	1.0 (0.4; 1.5)	..	0.033
Symptoms in previous 3 months				
Itching on the face or neck	0.7 (0.4; 1.4)	1.2 (0.4; 1.9)		0.027
Pupillometry				
Baseline pupil diameter	--	--	-0.078	0.046
ACV	--	--	-0.145	<0.05
MCV	--	--	-0.117	0.003
Constriction amplitude	--	--	-0.085	0.030
Benzaldehyde ($\mu\text{g}/\text{m}^3$)				
Pupillometry				
Baseline pupil diameter	--	--	-0.091	0.019
Final pupil diameter	--	--	-0.085	0.029
4-chloroethylene ($\mu\text{g}/\text{m}^3$)				
BMI (CDC criteria)				
Underweight	--	0.3 (0.8)	--	
Normal weight	--	0.4 (1.2)	--	
Overweight	--	0.5 (1.4)	--	
Obese	--	0.1 (0.6)	--	
2-butoxietanol ($\mu\text{g}/\text{m}^3$)				
Symptoms in previous 3 months				
Eye irritation	9.0 (5.5; 61.5)	15.2 (6.6; 118.7)	--	0.031
2-ethyl-1-hexanol ($\mu\text{g}/\text{m}^3$)				
Asthma defined by [†]				
Medical diagnosis asthma	3.4 (2.1; 5.6)	4.8 (3.4; 9.6)	--	0.003
Medical diagnosis asthma or BD+	3.4 (2.1; 5.6)	4.5 (2.8; 6.8)	--	0.017
Symptoms in previous 3 months				

Swollen eyes	3.4 (2.1; 5.3)	5.3 (2.4; 7.1)	--	0.012
Runny nose	3.3 (2.1; 5.3)	4.5 (2.4; 5.6)	--	0.006
Irritative cough	3.4 (2.0; 5.3)	4.6 (2.8; 5.6)	--	0.007
Formaldehyde ($\mu\text{g}/\text{m}^3$)				
EBC pH				0.008
<7.4	--	16.2 (12.3; 20.1)	--	
≥ 7.4	--	16.8 (12.7; 23.1)	--	
Pupillometry				
ACV	--	--	0.098	0.012
Constriction amplitude	--	--	0.080	0.041
Acetaldehyde ($\mu\text{g}/\text{m}^3$)				
Pupillometry				
Baseline pupil diameter	--	--	0.099	0.011
ACV	--	--	0.142	<0.05
MCV	--	--	0.090	0.020
Constriction amplitude	--	--	0.093	0.016
PCA1				
Asthma defined by [†]				
Medical diagnosis asthma or BD+	-0.3 (-0.5; -0.03)	-0.2 (-0.4; -0.004)	--	0.023
Symptoms in previous 3 months				
Nasal obstruction	-0.3 (-0.5; -0.04)	-0.2 (-0.4; -0.004)	--	0.017
Total body water	--	--	-0.097	0.005
Pupillometry				
Baseline pupil diameter				
ACV	--	--	-0.106	0.006
MCV	--	--	-0.120	0.002
PCA2				
Symptoms in previous 3 months				
Nasal obstruction	-0.01 (-0.5; 0.7)	-0.1 (-0.7; 0.6)	--	0.036
Pupillometry				
Baseline pupil diameter	--	--	0.112	0.004
MCV	--	--	0.088	0.024
Constriction amplitude	--	--	0.104	0.007

*Data reported as mean (standard deviation); [†]The following asthma definitions were adopted: i) *Medical diagnosis of asthma*: self-reported medical diagnosis; ii) *Positive bronchodilation (BD+)*: at least a 12% and over 200mL increase in FEV1 after bronchodilation; iii) *Medical diagnosis of asthma and symptoms or BD+*: at least a 12% and over 200mL increase in forced expiratory volume in 1 second (FEV1) after bronchodilation or self-reported medical diagnosis with reported symptoms (wheezing, dyspnea or dry cough) occurring in the past 12 months; iv) *Medical diagnosis of asthma or BD+*: at least a 12% and over 200mL increase in FEV1 after bronchodilation or self-reported medical diagnosis; BMI: body mass index; CDC: US Centers for Disease Control; WHO: World Health Organization; EBC: Exhaled breath condensate; ACV: Average constriction velocity; MCV: Maximum constriction velocity; T75: the total time taken by the pupil to recover 75% of the initial resting pupil size after it reached the peak of constriction.

TABLE S5 Association between individual and combined EDCs and asthma, respiratory symptoms in the previous 3 months, obesity, body composition, autonomic nervous system activity and EBC pH

	OR (95% CI)		
	Model 0	Model 1	Model 2
Toluene			
Asthma ^{Ta}			
Medical diagnosis asthma	1.00 (0.97, 1.02)	1.00 (0.97; 1.02)	0.99 (0.97; 1.02)
BD+	1.00 (0.97, 1.01)	0.99 (0.96; 1.01)	0.99 (0.96; 1.01)
Medical diagnosis asthma and symptoms or BD+	1.00 (0.97, 1.01)	0.99 (0.97; 1.01)	0.99 (0.97; 1.01)
Medical diagnosis asthma or BD+	1.00 (0.98, 1.01)	1.00 (0.98; 1.01)	0.99 (0.98; 1.01)
Symptoms in previous 3 months ^a			
Itching on the face or neck	1.00 (0.97, 1.01)	1.00 (0.97; 1.01)	0.99 (0.96; 1.02)
Eye irritation	0.99 (0.97, 1.01)	0.99 (0.97; 1.01)	0.99 (0.97; 1.01)
Swollen eyes	0.98 (0.94, 1.01)	0.98 (0.94; 1.01)	0.99 (0.94; 1.01)
Runny nose	1.00 (0.99, 1.01)	1.00 (0.99; 1.02)	1.00 (0.99; 1.01)
Nasal obstruction	1.01 (1.00, 1.02)	1.01 (1.00; 1.02)	1.01 (1.00; 1.03)
Dry throat	1.00 (0.98, 1.01)	1.00 (0.98; 1.01)	0.99 (0.98; 1.01)
Sore throat	1.00 (0.99, 1.01)	1.00 (0.99; 1.01)	1.00 (0.99; 1.01)
Irritative cough	1.00 (0.99, 1.01)	1.00 (0.99; 1.01)	0.99 (0.98; 1.01)
Breathing difficulties	1.00 (0.97, 1.01)	1.00 (0.97; 1.01)	0.99 (0.98; 1.01)
BMI ^b			
z-score CDC*	-0.002 (-0.006, 0.002)	-0.002 (-0.006; 0.001)	-0.003 (-0.008; 0.001)
z-score BMI*	-0.002 (-0.006, 0.002)	-0.002 (-0.007; 0.002)	-0.003 (-0.008; 0.002)
CDC			
Underweight	Reference	Reference	Reference
Normal weight	0.99 (0.97, 1.02)	0.99 (0.97; 1.02)	0.99 (0.97; 1.01)
Overweight	0.99 (0.97, 1.02)	0.99 (0.97; 1.02)	0.99 (0.97; 1.02)
Obese	1.00 (0.97, 1.02)	0.99 (0.97; 1.02)	0.99 (0.97; 1.02)
WHO			

Underweight	Reference	Reference	Reference
Normal weight	1.00 (0.96, 1.04)	1.00 (0.96; 1.04)	0.99 (0.95; 1.04)
Overweight	0.99 (0.95, 1.04)	0.99 (0.95; 1.04)	0.99 (0.95; 1.03)
Obese	1.00 (0.96, 1.04)	1.00 (0.96; 1.04)	0.99 (0.95; 1.03)
<i>IOTF</i>			
Underweight	Reference	Reference	Reference
Normal weight	0.99 (0.98, 1.01)	0.99 (0.98; 1.01)	0.99 (0.98; 1.01)
Overweight	0.99 (0.97, 1.01)	0.99 (0.97; 1.01)	0.99 (0.97; 1.01)
Obese	1.00 (0.98, 1.02)	1.00 (0.98; 1.02)	0.99 (0.97; 1.02)
<i>Percentage of body mass</i>			
Underfat	Reference	Reference	Reference
Normal	1.03 (0.92, 1.14)	1.03 (0.92; 1.14)	1.03 (0.91; 1.16)
Overfat	1.02 (0.91, 1.13)	1.02 (0.91; 1.14)	1.02 (0.90; 1.15)
Obese	1.02 (0.91, 1.14)	1.02 (0.91; 1.14)	1.02 (0.91; 1.16)
<i>Body composition*^b</i>			
Lean body mass	-0.002 (-0.02; 0.01)	-0.004 (-0.02; 0.01)	-0.005 (-0.02; 0.01)
Total body water	-0.001 (-0.01; 0.01)	-0.002 (-0.01; 0.08)	-0.003 (-0.01; 0.009)
Body fat (%)	-0.005 (-0.02; 0.01)	-0.01 (-0.03; 0.01)	-0.01 (-0.03; 0.01)
Body fat (Kg)	0.001 (-0.01; 0.01)	-0.001 (-0.015; 0.01)	-0.002 (-0.02; 0.014)
<i>Pupillometry*^c</i>			
Baseline pupil diameter	-0.004 (-0.01; -0.001)	-0.004 (-0.01; -4.78E-4)	-0.003 (-0.007; 1.91E-4)
Final pupil diameter	-0.002 (-0.004; 5.45E-4)	-0.002 (-0.004; 7.36E-4)	-9.70E-4 (-0.003; 0.001)
MCV	-0.004 (-0.01; -7.79E-4)	-0.004 (-0.01; -4.17E-4)	0.005 (8.00E-4; 0.009)
ACV	-0.003 (-0.006; -7.14E-4)	-0.003 (-0.006; -4.70E-4)	0.004 (0.001; 0.007)
Constriction amplitude	-0.02 (-0.04; 6.51E-4)	-0.02 (-0.04; 9.76E-4)	-0.02 (-0.04; -0.004)
ADV	-0.001 (-0.003; -2.18E-4)	-0.001 (-0.003; -1.51E-4)	-0.002 (-0.003; -2.00E-4)
T75	-0.002 (-0.006; 5.03E-4)	-0.003 (-0.006; 3.08E-4)	-0.002 (-0.006; 9.02E-4)
EBC pH ^d	8.68E-4 (-0.002; 0.004)	6.70E-4 (-0.003; 0.004)	-9.89E-6 (-0.003; 0.003)
EBC pH ^d			

≥7.4	1.00 (0.99; 1.01)	1.00 (0.99; 1.01)	0.99 (0.99; 1.01)
o-xylene			
Asthma ^{Ta}			
Medical diagnosis asthma	1.03 (0.98; 1.07)	1.03 (0.97; 1.07)	1.03 (0.97; 1.08)
BD+	1.01 (0.95; 1.06)	1.01 (0.95; 1.06)	1.01 (0.95; 1.06)
Medical diagnosis asthma and symptoms or BD+	1.03 (0.98; 1.07)	1.02 (0.98; 1.06)	1.02 (0.98; 1.07)
Medical diagnosis asthma or BD+	1.03 (0.99; 1.06)	1.02 (0.98; 1.06)	1.02 (0.98; 1.06)
Symptoms in previous 3 months ^a			
Itching on the face or neck	1.01 (0.95, 1.06)	1.01 (0.94; 1.06)	1.01 (0.93; 1.06)
Eye irritation	1.00 (0.95, 1.04)	1.00 (0.94; 1.04)	1.00 (0.94; 1.04)
Swollen eyes	1.02 (0.96, 1.06)	1.02 (0.96; 1.06)	1.01 (0.95; 1.07)
Runny nose	1.00 (0.97, 1.03)	1.00 (0.97; 1.03)	1.00 (0.97; 1.04)
Nasal obstruction	1.03 (1.00-1.07)	1.03 (0.99; 1.07)	1.04 (1.01; 1.08)
Dry throat	1.00 (0.96, 1.04)	1.00 (0.96; 1.03)	1.00 (0.95; 1.03)
Sore throat	1.01 (0.98, 1.05)	1.02 (0.99; 1.05)	1.01 (0.98; 1.05)
Irritative cough	1.00 (0.97, 1.03)	1.00 (0.97; 1.03)	0.99 (0.96; 1.03)
Breathing difficulties	1.02 (0.98, 1.06)	1.02 (0.98; 1.06)	1.02 (0.98; 1.07)
BMI ^b			
z-score CDC*	-0.001 (-0.01, 0.01)	-1.20E-2 (-0.01; 0.01)	-0.005 (-0.02; 0.007)
z-score BMI*	-0.001 (-0.01, 0.01)	-7.40E-4 (-0.01; 0.01)	-0.005 (-0.02; 0.009)
<i>CDC</i>			
Underweight	Reference	Reference	Reference
Normal weight	1.00 (0.93, 1.08)	1.00 (0.93; 1.08)	0.99 (0.92; 1.07)
Overweight	1.00 (0.92, 1.08)	1.00 (0.92; 1.08)	0.98 (0.90; 1.07)
Obese	1.01 (0.93, 1.09)	1.01 (0.93; 1.10)	0.99 (0.91; 1.08)
<i>WHO</i>			
Underweight	Reference	Reference	Reference
Normal weight	0.97 (0.89, 1.07)	0.98 (0.89; 1.07)	0.98 (0.88; 1.09)
Overweight	0.96 (0.87, 1.06)	0.96 (0.87; 1.06)	0.96 (0.86; 1.08)
Obese	0.99 (0.89, 1.09)	0.99 (0.89; 1.09)	0.98 (0.87; 1.10)

<i>IOTF</i>			
Underweight	Reference	Reference	Reference
Normal weight	1.00 (0.95, 1.05)	1.00 (0.95; 1.05)	0.99 (0.94; 1.05)
Overweight	1.00 (0.94, 1.06)	0.99 (0.94; 1.06)	0.98 (0.91; 1.04)
Obese	1.00 (0.94, 1.08)	1.01 (0.94; 1.08)	1.00 (0.93; 1.08)
<i>Percentage of body mass</i>			
Underfat	Reference	Reference	Reference
Normal	1.03 (0.83, 1.27)	1.03 (0.84; 1.26)	1.03 (0.84; 1.27)
Overfat	1.02 (0.82, 1.27)	1.02 (0.83; 1.25)	1.01 (0.82; 1.25)
Obese	1.03 (0.83, 1.27)	1.03 (0.84; 1.26)	1.03 (0.83; 1.26)
<i>Body composition*^b</i>			
Lean body mass	-0.03 (-0.07; 0.02)	-0.02 (-0.07; 0.02)	-0.03 (-0.08; 0.01)
Total body water	-0.02 (-0.06; 0.01)	-0.02 (-0.05; 0.01)	-0.03 (-0.06; 0.008)
Body fat (%)	-0.01 (-0.07; 0.05)	-0.01 (-0.07; 0.05)	-0.02 (-0.08; 0.05)
Body fat (Kg)	-0.01 (-0.05; 0.03)	-0.008 (-0.05; 0.03)	-0.01 (-0.06; 0.03)
<i>Pupillometry*^c</i>			
Baseline pupil diameter	-0.01 (-0.02; -3.06E-4)	-0.01 (-0.02; -1.02E-4)	-0.008 (-0.02; 0.002)
Final pupil diameter	-0.005 (-0.01; 0.002)	-0.004 (-0.01; 0.002)	-0.003 (-0.01; 0.004)
MCV	-0.01 (-0.02; -0.002)	-0.01 (-0.02; -0.003)	0.01 (0.002; 0.02)
ACV	-0.01 (-0.02; -0.003)	-0.01 (-0.02; -0.003)	0.01 (0.003; 0.02)
Constriction amplitude	-0.03 (-0.09; 0.02)	-0.04 (-0.09; 0.01)	-0.05 (-0.10; 0.01)
ADV	-0.003 (-0.007; 8.84E-4)	-0.003 (-0.007; 7.28E-4)	-0.003 (-0.007; 8.12E-4)
T75	-0.002 (-0.01; 0.006)	-0.003 (-0.01; 0.006)	-0.004 (-0.01; 0.005)
EBC pH ^d	0.003 (-0.006; 0.01)	0.002 (-0.007; 0.01)	-4.78E-4 (-0.01; 0.009)
<i>EBC pH^d</i>			
≥7.4	1.00 (0.97; 1.03)	1.00 (0.96; 1.03)	0.99 (0.96; 1.03)
m/p-xylene			
<i>Asthma^{†a}</i>			
Medical diagnosis asthma	1.00 (0.99, 1.02)	1.00 (0.98; 1.02)	1.00 (0.98; 1.02)
BD+	1.00 (0.98, 1.02)	1.00 (0.98; 1.02)	1.00 (0.98; 1.02)

Medical diagnosis asthma and symptoms or BD+	1.01 (0.99, 1.02)	1.00 (0.99; 1.02)	1.00 (0.98; 1.02)
Medical diagnosis asthma or BD+	1.01 (0.99, 1.02)	1.00 (0.99; 1.02)	1.00 (0.99; 1.02)
Symptoms in previous 3 months ^a			
Itching on the face or neck	1.00 (0.98, 1.02)	1.00 (0.98; 1.02)	1.00 (0.98; 1.02)
Eye irritation	1.00 (0.98, 1.01)	1.00 (0.98; 1.01)	1.00 (0.98; 1.01)
Swollen eyes	1.00 (0.98, 1.02)	1.00 (0.98; 1.02)	1.00 (0.98; 1.02)
Runny nose	1.00 (0.99, 1.02)	1.00 (0.99; 1.01)	1.00 (0.99; 1.01)
Nasal obstruction	1.01 (1.00, 1.02)	1.01 (1.00; 1.02)	1.01 (1.00; 1.03)
Dry throat	1.00 (0.99, 1.01)	1.00 (0.99; 1.01)	0.99 (0.98; 1.01)
Sore throat	1.00 (0.99, 1.01)	1.00 (0.99; 1.01)	1.00 (0.99; 1.02)
Irritative cough	1.00 (0.99, 1.01)	1.00 (0.99; 1.01)	1.00 (0.99; 1.01)
Breathing difficulties	1.00 (0.99, 1.02)	1.00 (0.99; 1.02)	1.00 (0.99; 1.02)
BMI ^b			
z-score CDC*	-0.001 (-0.004, 0.002)	-9.83E-4 (-4.41E-3; 0.002)	-0.02 (-0.006; 0.002)
z-score BMI*	-0.001 (-0.005, 0.003)	-9.79E-4 (-4.91E-3; 0.003)	-0.02 (-0.007; 0.02)
CDC			
Underweight	Reference	Reference	Reference
Normal weight	1.00 (0.98, 1.02)	1.00 (0.98; 1.02)	0.99 (0.97; 1.41)
Overweight	1.00 (0.98, 1.03)	1.00 (0.97; 1.03)	0.99 (0.96; 1.02)
Obese	1.00 (0.98, 1.03)	1.00 (0.98; 1.03)	0.99 (0.97; 1.02)
WHO			
Underweight	Reference	Reference	Reference
Normal weight	0.99 (0.96, 1.02)	0.99 (0.96; 1.02)	0.99 (0.96; 1.03)
Overweight	0.99 (0.96, 1.02)	0.99 (0.96; 1.02)	0.99 (0.95; 1.02)
Obese	0.99 (0.96, 1.02)	0.99 (0.96; 1.03)	0.99 (0.95; 1.03)
IOTF			
Underweight	Reference	Reference	Reference
Normal weight	1.00 (0.98, 1.01)	1.00 (0.98; 1.01)	0.99 (0.98; 1.01)
Overweight	1.00 (0.98, 1.02)	1.00 (0.98; 1.02)	0.99 (0.97; 1.01)
Obese	1.00 (0.98, 1.02)	1.00 (0.98; 1.02)	1.00 (0.98; 1.02)

<i>Percentage of body mass</i>			
Underfat	Reference	Reference	Reference
Normal	1.02 (0.93, 1.11)	1.02 (0.94; 1.10)	1.02 (0.93; 1.10)
Overfat	1.01 (0.93, 1.11)	1.01 (0.93; 1.10)	1.01 (0.92; 1.10)
Obese	1.01 (0.93, 1.10)	1.01 (0.93; 1.10)	1.01 (0.93; 1.10)
Body composition* ^b			
Lean body mass	-0.01 (-0.02; 0.005)	-0.007 (-0.02; 0.006)	-0.01 (-0.03; 0.005)
Total body water	-0.01 (-0.02; 0.004)	-0.005 (-0.01; 0.004)	-0.008 (-0.02; 0.003)
Body fat (%)	-0.004 (-0.02; 0.01)	-0.005 (-0.02; 0.01)	-0.008 (-0.03; 0.01)
Body fat (Kg)	-0.004 (-0.02; 0.01)	-0.003 (-0.01; 0.01)	-0.005 (-0.02; 0.01)
Pupillometry* ^c			
Baseline pupil diameter	-0.004 (-0.007; -0.001)	-0.004 (-0.007; -0.001)	-0.003 (-0.006; -4.14E-5)
Final pupil diameter	-0.002 (-0.004; -1.30E-5)	-0.002 (-0.004; 3.93E-5)	-0.001 (-0.003; 8.52E-4)
MCV	-0.005 (-0.008; -0.001)	-0.005 (-0.008; -0.002)	0.005 (0.001; 0.008)
ACV	-0.004 (-0.006; -0.001)	-0.004 (-0.006; -0.001)	0.004 (0.001; 0.006)
Constriction amplitude	-0.01 (-0.03; 0.006)	-0.01 (-0.03; 0.005)	-0.01 (-0.03; 0.004)
ADV	-7.85E-4 (-0.002; 3.96E-4)	-8.39E-4 (-0.002; 3.68E-4)	-0.001 (-0.002; 2.68E-4)
T75	-0.001 (-0.004; 0.002)	-0.001 (-0.004; 0.001)	-0.001 (-0.004; 0.002)
EBC pH ^d	9.13E-4 (-0.002; 0.004)	6.57E-4 (-0.002; 0.003)	-7.79E-4 (-0.004; 0.002)
EBC pH ^d			
≥7.4	1.00 (0.99; 1.01)	1.00 (0.99; 1.01)	0.99 (0.98; 1.01)
Hexane			
Asthma ^{Ta,c}			
Medical diagnosis asthma	1.00 (0.99, 1.01)	1.00 (0.99; 1.01)	1.00 (0.99; 1.01)
BD+	1.00 (0.99, 1.01)	1.00 (0.99; 1.01)	1.00 (0.99; 1.01)
Medical diagnosis asthma and symptoms or BD+	1.00 (0.99, 1.00)	1.00 (0.99; 1.01)	1.00 (0.99; 1.01)
Medical diagnosis asthma or BD+	1.00 (0.99, 1.01)	1.00 (0.99; 1.01)	1.00 (0.99; 1.01)
Symptoms in previous 3 months ^a			
Itching on the face or neck	1.00 (0.99, 1.01)	1.00 (0.99; 1.01)	1.00 (0.99; 1.01)
Eye irritation	1.00 (0.99, 1.01)	1.00 (0.99; 1.01)	1.00 (0.99; 1.01)

Swollen eyes	1.00 (0.99, 1.01)	1.00 (0.99; 1.01)	1.00 (0.99; 1.01)
Runny nose	1.00 (0.99, 1.01)	1.00 (0.99; 1.01)	1.00 (0.99; 1.01)
Nasal obstruction	1.00 (0.99, 1.01)	1.00 (0.99; 1.01)	1.00 (0.99; 1.01)
Dry throat	1.00 (0.99, 1.01)	1.00 (0.99; 1.01)	1.00 (0.99; 1.01)
Sore throat	1.00 (0.99, 1.01)	1.00 (0.99; 1.01)	1.00 (0.99; 1.01)
Irritative cough	1.00 (0.99, 1.01)	1.00 (0.99; 1.01)	1.00 (0.99; 1.00)
Breathing difficulties	1.00 (0.99, 1.01)	1.00 (0.99; 1.01)	1.00 (0.99; 1.01)
BMI ^b			
z-score CDC*	4.03E-4 (-7.28E-4, 0.001)	3.53E-4 (-7.91E-4; 0.001)	1.87E-4 (-0.001; 0.001)
z-score BMI*	4.51E-4 (-8.53E-4, 0.002)	3.72E-4 (9.41E-4; 0.002)	1.97E-4 (-0.001; 0.002)
<i>CDC</i>			
Underweight	Reference	Reference	Reference
Normal weight	1.00 (0.99, 1.02)	1.00 (0.99; 1.02)	1.00 (0.99; 1.01)
Overweight	1.00 (0.99, 1.02)	1.00 (0.99; 1.02)	1.00 (0.99; 1.01)
Obese	1.00 (0.99, 1.02)	1.00 (0.99; 1.02)	1.00 (0.99; 1.01)
<i>WHO</i>			
Underweight	Reference	Reference	Reference
Normal weight	1.10 (0.47, 2.58)	1.55 (1.54; 1.56)	1.18 (1.17; 1.19)
Overweight	1.10 (0.47, 2.58)	1.55 (1.54; 1.56)	1.18 (1.17; 1.19)
Obese	1.10 (0.47, 2.58)	1.55 (1.54; 1.56)	1.18 (1.17; 1.19)
<i>IOTF</i>			
Underweight	Reference	Reference	Reference
Normal weight	1.00 (0.99, 1.01)	1.00 (0.99; 1.01)	1.00 (0.99; 1.01)
Overweight	1.00 (0.99, 1.01)	1.00 (0.99; 1.01)	1.00 (0.99; 1.01)
Obese	1.00 (0.99, 1.01)	1.00 (0.99; 1.01)	1.00 (0.99; 1.01)
<i>Percentage of body mass</i>			
Underfat	Reference	Reference	Reference
Normal	1.00 (0.96, 1.04)	1.00 (0.97; 1.04)	1.00 (0.97; 1.03)
Overfat	1.00 (0.96, 1.05)	1.00 (0.97; 1.04)	1.00 (0.97; 1.03)
Obese	1.00 (0.96, 1.05)	1.00 (0.96; 1.04)	1.00 (0.97; 1.03)

Body composition* ^b			
Lean body mass	0.004 (-3.51E-4; 0.01)	0.002 (-0.002; 0.006)	0.002 (-0.003; 0.006)
Total body water	0.003 (-2.52E-4; 0.01)	0.001 (-0.002; 0.005)	0.001 (-0.002; 0.005)
Body fat (%)	-5.59E-5 (-0.01; 0.01)	0.001 (-0.004; 0.007)	0.001 (-0.005; 0.007)
Body fat (Kg)	0.001 (-0.003; 0.005)	0.001 (-0.003; 0.005)	7.61E-4 (-0.004; 0.005)
Pupillometry* ^c			
Baseline pupil diameter	-5.20E-4 (-0.001; 4.78E-4)	-5.95E-4 (-0.001; 4.09E-4)	-4.05E-4 (-0.001; 6.32E-4)
Final pupil diameter	-4.92E-4 (-0.001; 2.11E-4)	-5.11E-4 (-0.001; 2.00E-4)	-3.58E-4 (-0.001; 3.60E-4)
MCV	4.70E-5 (-0.001; 0.001)	-1.09E-4 (-0.001; 0.001)	1.48E-4 (-0.001; 0.001)
ACV	-3.30E-5 (-8.16E-4; 7.50E-4)	-1.25E-4 (-9.15E-4; 6.64E-4)	1.57E-4 (-6.79E-4; 0.001)
Constriction amplitude	0.003 (-0.002; 0.009)	0.003 (-0.003; 0.008)	0.002 (-0.004; 0.008)
ADV	-8.17E-5 (-4.35E-4; 2.71E-4)	-2.04E-5 (-3.82E-4; 3.41E-4)	6.68E-5 (-3.24E-4; 4.58E-4)
T75	5.00E-4 (-3.08E-4; 0.001)	3.77E-4 (-4.48E-4; 0.001)	3.16E-4 (-5.44E-4; 0.001)
EBC pH ^d	-3.17E-4 (-0.001; 7.25E-4)	-4.54E-4 (-0.001; 5.96E-4)	-1.55E-4 (-0.001; 9.34E-4)
EBC pH ^d			
≥7.4	1.00 (0.99; 1.01)	1.00 (0.99; 1.01)	1.00 (0.99; 1.01)
Ethylbenzene			
Asthma ^{†a}			
Medical diagnosis asthma	1.02 (0.95, 1.06)	1.01 (0.94; 1.06)	1.01 (0.94; 1.07)
BD+	1.01 (0.94, 1.06)	1.01 (0.94; 1.06)	1.01 (0.93; 1.06)
Medical diagnosis asthma and symptoms or BD+	1.02 (0.96, 1.06)	1.01 (0.96; 1.05)	1.01 (0.95; 1.06)
Medical diagnosis asthma or BD+	1.02 (0.97, 1.06)	1.01 (0.97; 1.05)	1.01 (0.96; 1.07)
Symptoms in previous 3 months ^a			
Itching on the face or neck	1.00 (0.93, 1.06)	1.00 (0.93; 1.06)	1.00 (0.92; 1.07)
Eye irritation	0.99 (0.94, 1.04)	0.99 (0.93; 1.04)	0.99 (0.93; 1.04)
Swollen eyes	1.00 (0.92, 1.05)	0.99 (0.91; 1.05)	0.99 (0.90; 1.05)
Runny nose	0.99 (0.96, 1.02)	0.99 (0.96; 1.02)	0.99 (0.96; 1.02)
Nasal obstruction	1.03 (1.00, 1.08)	1.03 (1.01; 1.08)	1.04 (1.01; 1.09)
Dry throat	1.00 (0.95, 1.03)	0.99 (0.95; 1.03)	0.99 (0.94; 1.03)

Sore throat	1.02 (0.98, 1.05)	1.02 (0.98; 1.05)	1.01 (0.98; 1.05)
Irritative cough	1.00 (0.96, 1.03)	1.00 (0.96; 1.03)	0.99 (0.95; 1.03)
Breathing difficulties	1.01 (0.95, 1.05)	1.01 (0.96; 1.05)	1.01 (0.95; 1.06)
BMI^b			
z-score CDC*	-0.007 (-0.02, 0.005)	-0.007 (-0.02; 0.005)	-0.01 (-0.02; 0.002)
z-score BMI*	-0.007 (-0.02, 0.006)	-0.007 (-0.02; 0.006)	-0.01 (-0.03; 0.004)
<i>CDC</i>			
Underweight	Reference	Reference	Reference
Normal weight	1.00 (0.93, 1.07)	1.00 (0.93; 1.08)	0.99 (0.92; 1.06)
Overweight	0.99 (0.91, 1.08)	0.99 (0.91; 1.08)	0.97 (0.89; 1.07)
Obese	0.99 (0.91, 1.08)	1.00 (0.91; 1.09)	0.98 (0.89; 1.07)
<i>WHO</i>			
Underweight	Reference	Reference	Reference
Normal weight	0.97 (0.89, 1.07)	0.98 (0.89; 1.07)	0.97 (0.88; 1.08)
Overweight	0.95 (0.86, 1.06)	0.95 (0.86; 1.06)	0.95 (0.85; 1.07)
Obese	0.97 (0.88, 1.08)	0.98 (0.88; 1.08)	0.96 (0.86; 1.07)
<i>IOTF</i>			
Underweight	Reference	Reference	Reference
Normal weight	0.99 (0.94, 1.04)	0.99 (0.94; 1.05)	0.99 (0.94; 1.04)
Overweight	0.98 (0.93, 1.05)	0.98 (0.92; 1.05)	0.97 (0.90; 1.04)
Obese	0.99 (0.92, 1.08)	0.99 (0.92; 1.07)	0.99 (0.92; 1.07)
<i>Percentage of body mass</i>			
Underfat	Reference	Reference	Reference
Normal	1.03 (0.82, 1.30)	1.03 (0.83; 1.29)	1.04 (0.83; 1.32)
Overfat	1.01 (0.80, 1.28)	1.01 (0.81; 1.27)	1.01 (0.79; 1.28)
Obese	1.02 (0.80, 1.29)	1.02(0.81; 1.28)	1.02 (0.80; 1.29)
Body composition*^b			
Lean body mass	-0.03 (-0.08; 0.02)	-0.03 (-0.07; 0.02)	-0.03 (-0.08; 0.02)
Total body water	-0.02 (-0.06; 0.01)	-0.02 (-0.05; 0.01)	-0.03 (-0.06; 0.01)
Body fat (%)	-5.59E-5 (-0.01; 0.01)	-0.03 (-0.10; 0.02)	-0.04 (-0.11; 0.02)

Body fat (Kg)	-0.02 (-0.06; 0.03)	-0.02 (-0.06; 0.02)	-0.02 (-0.07; 0.02)
Pupillometry*^c			
Baseline pupil diameter	-0.01 (-0.02; -0.002)	-0.01 (-0.02; -0.002)	-0.01 (-0.02; 0.001)
Final pupil diameter	-0.006 (-0.01; 0.001)	-0.006 (-0.01; 0.001)	-0.004 (-0.01; 0.003)
MCV	-0.01 (-0.02; -0.002)	-0.01 (-0.02; -0.002)	0.01 (0.002; 0.03)
ACV	-0.01 (-0.02; -0.003)	-0.01 (-0.02; -0.003)	0.01 (0.003; 0.02)
Constriction amplitude	-0.03 (-0.09; 0.02)	-0.03 (-0.09; 0.02)	-0.04 (-0.11; 0.02)
ADV	-0.004 (-0.008; -1.55E-4)	-0.004 (-0.009; -1.93E-4)	-0.005 (-0.01; -1.00E-4)
T75	-0.003 (-0.01; 0.006)	-0.004 (-0.01; 0.006)	-0.004 (-0.01; 0.006)
EBC pH ^d	0.001 (-0.008; 0.01)	5.73E-4 (-0.009; 0.01)	-0.03 (-0.01; 0.08)
EBC pH ^d			
≥7.4	1.00 (0.96; 1.03)	0.99 (0.96; 1.03)	0.99 (0.95; 1.03)
Styrene			
Asthma^{Ta,c}			
Medical diagnosis asthma	1.10 (0.79, 1.41)	1.09 (0.78; 1.40)	1.06 (0.73; 1.40)
BD+	1.00 (0.68, 1.31)	1.01 (0.68; 1.33)	1.05 (0.70; 1.41)
Medical diagnosis asthma and symptoms or BD+	1.06 (0.79, 1.32)	1.06 (0.79; 1.47)	1.09 (0.82; 1.39)
Medical diagnosis asthma or BD+	1.08 (0.85, 1.32)	1.08 (0.85; 1.33)	1.09 (0.84; 1.37)
Symptoms in previous 3 months^a			
Itching on the face or neck	0.98 (0.64, 1.30)	0.96 (0.61; 1.29)	0.90 (0.52; 1.26)
Eye irritation	1.03 (0.78, 1.28)	1.02 (0.77; 1.28)	0.97 (0.70; 1.25)
Swollen eyes	1.17 (0.89, 1.47)	1.19 (0.89; 1.51)	1.13 (0.81; 1.47)
Runny nose	0.98 (0.83, 1.16)	0.99 (0.83; 1.17)	1.01 (0.83; 1.21)
Nasal obstruction	1.02 (0.86, 1.22)	1.02 (0.86; 1.22)	1.06 (0.88; 1.29)
Dry throat	1.08 (0.88, 1.30)	1.09 (0.88; 1.32)	1.10 (0.88; 1.36)
Sore throat	0.96 (0.80, 1.14)	0.97 (0.81; 1.15)	0.98 (0.81; 1.18)
Irritative cough	0.97 (0.79, 1.16)	0.97 (0.79; 1.16)	0.95 (0.76; 1.16)
Breathing difficulties	1.05 (0.79, 1.32)	1.09 (0.82; 1.18)	1.07 (0.78; 1.38)
BMI^b			

z-score CDC*	0.06 (2.16E-5, 0.12)	0.06 (-0.002; 0.12)	-0.27 (-0.02; 0.12)
z-score BMI*	0.07 (-0.002, 0.13)	0.07 (-0.003; 0.14)	-0.25 (-0.02; 0.14)
<i>CDC</i>			
Underweight	Reference	Reference	Reference
Normal weight	1.20 (0.69, 2.06)	1.19 (0.70; 2.01)	1.08 (0.67; 1.76)
Overweight	1.20 (0.67, 2.13)	1.18 (0.67; 2.06)	1.10 (0.65; 1.86)
Obese	1.34 (0.76, 2.37)	1.37 (0.78; 2.38)	1.21 (0.72; 2.03)
<i>WHO</i>			
Underweight	Reference	Reference	Reference
Normal weight	1.59 (0.38, 6.59)	1.59 (0.39; 6.52)	1.65 (1.45; 1.88)
Overweight	1.54 (0.37, 6.43)	1.53 (0.37; 6.34)	1.54 (1.30; 1.83)
Obese	1.78 (0.43, 7.45)	1.81 (0.44; 7.51)	2.53 (2.41; 2.65)
<i>IOTF</i>			
Underweight	Reference	Reference	Reference
Normal weight	1.32 (0.83, 2.07)	1.28 (0.83; 1.97)	1.20 (0.79; 1.83)
Overweight	1.39 (0.87, 2.23)	1.36 (0.86; 2.15)	1.24 (0.79; 1.95)
Obese	1.30 (0.76, 2.22)	1.28 (0.76; 2.16)	1.24 (0.75; 2.06)
<i>Percentage of body mass</i>			
Underfat	Reference	Reference	Reference
Normal	1.38 (0.30, 6.21)	1.38 (0.29; 6.50)	1.12 (0.98; 1.27)
Overfat	1.56 (0.34, 7.09)	1.53 (0.32; 7.27)	1.18 (0.99; 1.38)
Obese	1.40 (0.31, 6.39)	1.42 (0.30; 6.77)	1.15 (0.97; 1.37)
<i>Body composition*^b</i>			
Lean body mass	-0.24 (-0.50; 0.01)	-0.14 (-0.37; 0.10)	-0.19 (-0.46; 0.07)
Total body water	-0.18 (-0.37; 2.98E-4)	-0.11 (-0.29; 0.06)	-0.16 (-0.35; 0.04)
Body fat (%)	0.09 (-0.23; 0.42)	0.17 (-0.14; 0.49)	0.19 (-0.18; 0.56)
Body fat (Kg)	-0.05 (-0.28; 0.18)	0.02 (-0.20; 0.25)	0.02 (-0.24; 0.29)
<i>Pupillometry*^c</i>			
Baseline pupil diameter	-0.02 (-0.07; 0.03)	-0.02 (-0.07; 0.03)	-0.01 (-0.07; 0.04)
Final pupil diameter	-0.008 (-0.04; 0.03)	-0.01 (-0.05; 0.02)	-0.006 (-0.04; 0.03)

MCV	-0.01 (-0.07; 0.04)	-0.02 (-0.07; 0.04)	0.02 (-0.04; 0.08)
ACV	-0.003 (-0.04; 0.04)	-0.005 (-0.04; 0.03)	0.009 (-0.03; 0.05)
Constriction amplitude	-0.05 (-0.33; 0.24)	-0.05 (-0.33; 0.24)	-0.04 (-0.36; 0.27)
ADV	0.002 (-0.02; 0.02)	-0.003 (-0.02; 0.02)	4.15E-4 (-0.02; 0.02)
T75	-0.03 (-0.07; 0.01)	-0.03 (-0.07; 0.01)	-0.03 (-0.08; 0.02)
EBC pH ^d	0.06 (0.01; 0.11)	0.06 (0.008; 0.11)	0.04 (-0.02; 0.09)
EBC pH ^d			
≥7.4	1.12 (0.95; 1.33)	1.12 (0.94; 1.32)	1.07 (0.88; 1.30)
Cyclohexanone			
Asthma ^{Ta}			
Medical diagnosis asthma	0.98 (0.82, 1.07)	0.98 (0.82; 1.07)	0.99 (0.83; 1.09)
BD+	1.01 (0.89, 1.08)	0.98 (0.81; 1.07)	0.98 (0.81; 1.09)
Medical diagnosis asthma and symptoms or BD+	0.94 (0.77, 1.04)	0.94 (0.77; 1.04)	0.95 (0.78; 1.06)
Medical diagnosis asthma or BD+	1.00 (0.91, 1.06)	0.98 (0.87; 1.06)	0.99 (0.88; 1.07)
Symptoms in previous 3 months ^a			
Itching on the face or neck	0.98 (0.82, 1.07)	0.98 (0.82; 1.07)	0.99 (0.83; 1.08)
Eye irritation	0.96 (0.82, 1.04)	0.96 (0.82; 1.04)	0.97 (0.83; 1.07)
Swollen eyes	1.00 (0.88, 1.08)	1.00 (0.88; 1.09)	1.01 (0.89; 1.10)
Runny nose	1.05 (0.99, 1.12)	1.05 (0.99; 1.12)	1.05 (0.99; 1.12)
Nasal obstruction	1.01 (0.96, 1.07)	1.01 (0.96; 1.07)	1.01 (0.96; 1.07)
Dry throat	1.02 (0.96, 1.08)	1.02 (0.96; 1.08)	1.02 (0.95; 1.09)
Sore throat	1.00 (0.95, 1.05)	1.01 (0.95; 1.06)	1.01 (0.95; 1.06)
Irritative cough	1.00 (0.94, 1.05)	1.00 (0.94; 1.05)	1.01 (0.94; 1.06)
Breathing difficulties	1.00 (0.90, 1.07)	1.01 (0.91; 1.08)	1.01 (0.91; 1.09)
BMI ^b			
z-score CDC*	0.02 (0.005, 0.04)	0.02 (0.001; 0.04)	0.03 (0.01; 0.05)
z-score BMI*	0.03 (0.007, 0.05)	0.02 (0.002; 0.04)	0.03 (0.01; 0.06)
CDC			
Underweight	Reference	Reference	Reference

Normal weight	1.02 (0.88, 1.20)	1.02 (0.88; 1.19)	1.05 (0.85; 1.30)
Overweight	1.04 (0.88, 1.22)	1.03 (0.88; 1.21)	1.08 (0.87; 1.35)
Obese	1.06 (0.90, 1.24)	1.04 (0.89; 2.98)	1.09 (0.88; 1.36)
<i>WHO</i>			
Underweight	Reference	Reference	Reference
Normal weight	1.67 (0.003; 7.94E2)	1.59 (0.01; 159E2)	2.45 (2.36; 2.55)
Overweight	1.70 (0.003; 8.06E2)	1.61 (0.01; 1.61E2)	2.54 (2.43; 2.65)
Obese	1.71 (0.004; 8.14E2)	1.61 (0.01; 1.61E2)	2.53 (2.41; 2.65)
<i>IOTF</i>			
Underweight	Reference	Reference	Reference
Normal weight	1.03 (0.92, 1.15)	1.03 (0.92; 1.15)	1.06 (0.90; 1.25)
Overweight	1.03 (0.91, 1.16)	1.01 (0.90; 1.15)	1.07 (0.90; 1.27)
Obese	1.06 (0.93, 1.21)	1.05 (0.92; 1.20)	1.10 (0.92; 1.31)
<i>Percentage of body mass</i>			
Underfat	Reference	Reference	Reference
Normal	2.11 (4.32E-12; 1.03E12)	2.71 (6.1E-40; 1.20E40)	3.40 (3.27; 3.54)
Overfat	2.14 (4.37E-12; 1.05E12)	2.74 (6.18E-40; 1.21E40)	3.49 (3.32; 3.67)
Obese	2.23 (4.55E-12; 1.09E12)	2.82 (6.35E-40; 1.25E40)	3.62 (3.47; 3.77)
Body composition* ^b			
Lean body mass	-0.04 (-0.11; 0.04)	-0.05 (-0.13; 0.02)	-0.02 (-0.10; 0.05)
Total body water	-0.03 (-0.08; 0.03)	-0.04 (-0.09; 0.01)	-0.02 (-0.08; 0.04)
Body fat (%)	0.18 (0.08; 0.27)	0.17 (0.07; 0.26)	0.21 (0.10; 0.32)
Body fat (Kg)	0.07 (-5.14E-4; 0.14)	0.04 (-0.02; 0.12)	0.08 (-0.002; 0.16)
Pupillometry* ^c			
Baseline pupil diameter	-0.009 (-0.02; 0.007)	-0.006 (-0.02; 0.01)	-0.01 (-0.02; 0.006)
Final pupil diameter	-0.002 (-0.01; 0.009)	-5.31E-4 (-0.01; 0.01)	-0.001 (-0.01; 0.01)
MCV	-0.009 (-0.02; 0.008)	-0.008 (-0.02; 0.009)	0.01 (-0.007; 0.03)
ACV	-0.01 (-0.02; 7.69E-4)	-0.01 (-0.02; 0.001)	0.01 (0.002; 0.03)
Constriction amplitude	-0.09 (-0.17; -0.002)	-0.08 (-0.17; 0.04)	-0.10 (-0.20; -0.01)
ADV	3.42E-4 (-0.005; 0.006)	5.75E-4 (-0.006; 0.007)	-1.13E-4 (-0.007; 0.007)

T75	-0.006 (-0.02; 0.007)	-0.003 (-0.02; 0.01)	-0.009 (-0.02; 0.006)
EBC pH ^d	-0.003 (-0.02; 0.01)	-0.006 (-0.02; 0.01)	-0.007 (-0.02; 0.01)
EBC pH ^d			
≥7.4	1.00 (0.94; 1.05)	0.99 (0.92; 1.04)	0.98 (0.91; 1.04)
Butylated hydroxytoluene			
Asthma ^{†a,c}			
Medical diagnosis asthma	1.00 (0.86, 1.09)	1.00 (0.86; 1.10)	1.01 (0.87; 1.11)
BD+	0.91 (0.67, 1.05)	0.92 (0.67; 1.06)	0.94 (0.70; 1.08)
Medical diagnosis asthma and symptoms or BD+	0.97 (0.83, 1.06)	0.97 (0.84; 1.07)	0.98 (0.85; 1.08)
Medical diagnosis asthma or BD+	0.97 (0.86, 1.05)	0.98 (0.86; 1.06)	0.99 (0.87; 1.07)
Symptoms in previous 3 months ^a			
Itching on the face or neck	1.00 (0.86, 1.10)	1.01 (0.86; 1.11)	1.02 (0.87; 1.12)
Eye irritation	1.04 (0.97, 1.11)	1.04 (0.95; 1.11)	1.04 (0.95; 1.12)
Swollen eyes	1.04 (0.93, 1.12)	1.04 (0.94; 1.12)	1.05 (0.94; 1.14)
Runny nose	0.99 (0.94, 1.05)	0.99 (0.93; 1.05)	0.99 (0.93; 1.05)
Nasal obstruction	0.97 (0.91, 1.02)	0.96 (0.89; 1.02)	0.95 (0.89; 1.02)
Dry throat	0.91 (0.77, 1.00)	0.92 (0.78; 1.01)	0.92 (0.77; 1.02)
Sore throat	0.96 (0.90, 1.02)	0.95 (0.87; 1.01)	0.94 (0.85; 1.01)
Irritative cough	1.02 (0.95, 1.08)	1.01 (0.94; 1.07)	1.01 (0.94; 1.08)
Breathing difficulties	0.94 (0.78, 1.05)	0.90 (0.68; 1.03)	0.90 (0.63; 1.04)
BMI ^b			
z-score CDC*	-0.008 (-0.03, 0.01)	-0.01 (-0.03; 0.01)	-0.008 (-0.03; 0.01)
z-score BMI*	-0.009 (-0.03, 0.01)	-0.01 (-0.04; 0.01)	-0.008 (-0.03; 0.02)
CDC			
Underweight	Reference	Reference	Reference
Normal weight	0.98 (0.88, 1.09)	0.97 (0.87; 1.09)	0.96 (0.85; 1.07)
Overweight	0.98 (0.87, 1.11)	0.98 (0.86; 1.11)	0.98 (0.85; 1.11)
Obese	0.96 (0.84, 1.10)	0.96 (0.83; 1.10)	0.95 (0.83; 1.10)
WHO			

Underweight	Reference	Reference	Reference
Normal weight	1.35 (0.43, 4.18)	1.36 (0.4; 4.26)	1.23 (1.18; 1.29)
Overweight	1.33 (0.43, 4.14)	1.35 (0.43; 4.22)	1.25 (1.18; 1.32)
Obese	1.33 (0.43, 4.13)	1.35 (0.43; 4.22)	1.23 (1.16; 1.31)
<i>IOTF</i>			
Underweight	Reference	Reference	Reference
Normal weight	0.98 (0.90, 1.08)	0.98 (0.89; 1.07)	0.96 (0.87; 1.06)
Overweight	1.01 (0.92, 1.11)	1.01 (0.91; 1.11)	1.01 (0.91; 1.11)
Obese	0.88 (0.68, 1.13)	0.85 (0.62; 1.26)	0.86 (0.64; 1.15)
<i>Percentage of body mass</i>			
Underfat	Reference	Reference	Reference
Normal	0.94 (0.78, 1.14)	0.95 (0.79; 1.14)	0.94 (0.78; 1.13)
Overfat	0.96 (0.79, 1.16)	0.95 (0.79; 1.16)	0.96 (0.79; 1.16)
Obese	0.93 (0.77, 1.14)	0.93 (0.77; 1.14)	0.94 (0.77; 1.14)
<i>Body composition*^b</i>			
Lean body mass	0.10 (0.02; 0.19)	0.09 (0.01; 0.17)	0.10 (0.01; 0.19)
Total body water	0.08 (0.01; 0.14)	0.06 (0.006; 0.12)	0.07 (0.01; 0.14)
Body fat (%)	-0.08 (-0.19; 0.03)	-0.07 (-0.18; 0.04)	-0.05 (-0.17; 0.07)
Body fat (Kg)	-0.007 (-0.08; 0.07)	-0.006 (-0.08; 0.07)	0.004 (-0.08; 0.09)
<i>Pupillometry*^c</i>			
Baseline pupil diameter	0.005 (-0.01; 0.02)	0.006 (-0.01; 0.03)	0.005 (-0.01; 0.03)
Final pupil diameter	0.002 (-0.01; 0.01)	0.002 (-0.01; 0.01)	6.19E-4 (-0.01; 0.01)
MCV	0.004 (-0.02; 0.02)	0.008 (-0.01; 0.03)	-0.01 (-0.03; 0.01)
ACV	0.008 (-0.007; 0.02)	0.01 (-0.004; 0.03)	-0.01 (-0.03; 0.004)
Constriction amplitude	0.05 (-0.06; 0.15)	0.07 (-0.04; 0.18)	0.08 (-0.03; 0.20)
ADV	0.003 (-0.004; 0.01)	0.004 (-0.003; 0.01)	0.004 (-0.004; 0.01)
T75	-0.005 (-0.02; 0.01)	-0.004 (-0.02; 0.01)	2.28E-4 (-0.02; 0.02)
EBC pH ^d	0.007 (-0.01; 0.02)	0.007 (-0.01; 0.02)	0.007 (-0.01; 0.03)
<i>EBC pH^d</i>			
≥7.4	1.00 (0.94; 1.05)	1.00 (0.94; 1.06)	1.01 (0.94; 1.08)

Benzene			
Asthma ^{†a}			
Medical diagnosis asthma	0.91 (0.49, 1.56)	0.90 (0.48; 1.55)	0.88 (0.43; 1.62)
BD+	1.67 (1.02, 2.66)	1.64 (1.00; 2.65)	1.49 (1.01; 2.53)
Medical diagnosis asthma and symptoms or BD+	1.13 (0.71, 1.74)	1.11 (0.70; 1.71)	1.13 (0.67; 1.81)
Medical diagnosis asthma or BD+	1.36 (0.92, 1.98)	1.32 (0.89; 1.94)	1.26 (0.80; 1.95)
Symptoms in previous 3 months ^a			
Itching on the face or neck	1.58 (0.95, 2.55)	1.56 (0.93; 2.56)	1.50 (0.84; 2.60)
Eye irritation	1.21 (0.80, 1.79)	1.21 (0.80; 1.79)	1.26 (0.80; 1.95)
Swollen eyes	1.21 (0.71, 1.96)	1.18 (0.69; 1.93)	1.19 (0.66; 2.04)
Runny nose	1.21 (0.91, 1.60)	1.20 (0.91; 1.61)	1.16 (0.85; 1.59)
Nasal obstruction	1.28 (0.96, 1.70)	1.27 (0.95; 1.69)	1.27 (0.93; 1.75)
Dry throat	1.05 (0.74, 1.47)	1.03 (0.72; 1.44)	1.01 (0.67; 1.48)
Sore throat	1.13 (0.85, 1.50)	1.16 (0.87; 1.54)	1.18 (0.86; 1.62)
Irritative cough	1.14 (0.84, 1.53)	1.14 (0.84; 1.54)	1.11 (0.79; 1.55)
Breathing difficulties	1.14 (0.73, 1.74)	1.15 (0.73; 1.76)	1.17 (0.71; 1.86)
BMI ^b			
z-score CDC*	0.04 (-0.06, 0.14)	0.03 (-0.07; 0.14)	0.01 (-0.12; 0.15)
z-score BMI*	0.04 (-0.07, 0.16)	0.04 (-0.08; 0.16)	0.02 (-0.13; 0.17)
CDC			
Underweight	Reference	Reference	Reference
Normal weight	1.02 (0.53, 1.97)	1.02 (0.53; 1.96)	0.96 (0.73; 1.25)
Overweight	0.93 (0.45, 1.94)	0.93 (0.45; 1.94)	0.89 (0.62; 1.28)
Obese	1.14 (0.54, 2.38)	1.12 (0.53; 2.35)	0.97 (0.68; 1.40)
WHO			
Underweight	Reference	Reference	Reference
Normal weight	1.05 (0.33, 3.40)	1.08 (0.34; 3.48)	0.94 (0.73; 1.22)
Overweight	1.03 (0.31, 3.43)	1.05 (0.32; 3.45)	0.95 (0.69; 1.31)
Obese	1.07 (0.32, 3.61)	1.11 (0.33; 3.74)	0.88 (0.62; 1.25)
IOTF			

Underweight	Reference	Reference	Reference
Normal weight	1.05 (0.64, 1.71)	1.02 (0.63; 1.67)	0.95 (0.71; 1.28)
Overweight	0.96 (0.55, 1.68)	0.94 (0.54; 1.65)	0.81 (0.56; 1.18)
Obese	1.17 (0.61, 2.27)	1.14 (0.58; 2.25)	1.09 (0.74; 1.60)
<i>Percentage of body mass</i>			
Underfat	Reference	Reference	Reference
Normal	0.80 (0.22, 2.92)	0.83 (0.23; 3.07)	0.91 (0.70; 1.19)
Overfat	0.69 (0.18, 2.61)	0.73 (0.19; 2.81)	0.77 (0.53; 1.11)
Obese	0.97 (0.26, 3.66)	0.99 (0.26; 3.75)	1.10 (0.79; 1.53)
Body composition* ^b			
Lean body mass	-0.18 (-0.60; 0.25)	-0.29 (-0.69; 0.10)	-0.32 (-0.83; 0.18)
Total body water	-0.16 (-0.47; 0.16)	-0.24 (-0.53; 0.05)	-0.26 (-0.63; 0.11)
Body fat (%)	0.42 (-0.12; 0.96)	0.44 (-0.08; 0.97)	0.51 (-0.17; 1.20)
Body fat (Kg)	0.14 (-0.24; 0.52)	0.09 (-0.28; 0.46)	0.11 (-0.38; 0.61)
Pupillometry* ^c			
Baseline pupil diameter	-0.08 (-0.17; 0.01)	-0.05 (-0.14; 0.03)	-0.06 (-0.17; 0.03)
Final pupil diameter	-0.03 (-0.10; 0.03)	-0.02 (-0.08; 0.04)	-0.01 (-0.08; 0.05)
MCV	-0.15 (-0.24; -0.05)	-0.12 (-0.22; -0.02)	0.15 (0.04; 0.26)
ACV	-0.13 (-0.20; -0.06)	-0.12 (-0.19; -0.04)	0.14 (0.06; 0.22)
Constriction amplitude	-0.59 (-1.10; -0.09)	-0.50 (-1.01; 0.005)	-0.74 (-1.30; -0.18)
ADV	-0.03 (-0.06; 0.002)	-0.03 (-0.07; 0.003)	-0.05 (-0.09; -0.007)
T75	0.03 (-0.05; 0.11)	0.04 (-0.04; 0.12)	0.02 (-0.07; 0.10)
EBC pH ^d	-0.03 (-0.11; 0.60)	-0.04 (-0.13; 0.05)	-0.09 (-0.20; 1.45)
EBC pH ^d			
≥7.4	0.98 (0.73; 1.31)	0.94 (0.69; 1.28)	0.86 (0.58; 1.26)
Benzaldehyde			
Asthma ^{†a}			
Medical diagnosis asthma	0.98 (0.93, 1.02)	0.98 (0.93; 1.03)	0.99 (0.93; 1.03)
BD+	1.02 (0.98, 1.06)	1.01 (0.97; 1.05)	1.02 (0.97; 1.06)
Medical diagnosis asthma and symptoms or BD+	1.00 (0.96, 1.03)	1.00 (0.96; 1.04)	1.00 (0.97; 1.04)

Medical diagnosis asthma or BD+	1.00 (0.97, 1.03)	1.00 (0.97; 1.03)	1.01 (0.97; 1.04)
Symptoms in previous 3 months ^a			
Itching on the face or neck	1.01 (0.97, 1.05)	1.01 (0.97; 1.05)	1.01 (0.97; 1.06)
Eye irritation	1.02 (0.99, 1.05)	1.02 (0.99; 1.06)	1.02 (0.99; 1.06)
Swollen eyes	1.00 (0.96, 1.04)	1.00 (0.96; 1.04)	1.00 (0.95; 1.04)
Runny nose	1.00 (0.98, 1.02)	1.00 (0.98; 1.02)	1.00 (0.98; 1.02)
Nasal obstruction	1.00 (0.98, 1.03)	1.00 (0.98; 1.03)	1.00 (0.98; 1.03)
Dry throat	0.99 (0.97, 1.02)	0.99 (0.96; 1.02)	0.99 (0.96; 1.02)
Sore throat	0.99 (0.97, 1.02)	0.99 (0.97; 1.02)	1.00 (0.98; 1.02)
Irritative cough	1.00 (0.98, 1.03)	1.00 (0.98; 1.03)	1.00 (0.98; 1.03)
Breathing difficulties	1.00 (0.96, 1.03)	1.00 (0.96; 1.04)	1.00 (0.96; 1.04)
BMI ^b			
z-score CDC*	0.006 (-0.002, 0.01)	0.005 (-0.003; 1.01)	-0.005 (-0.02; 0.006)
z-score BMI*	0.006 (-0.002, 0.01)	0.006 (-0.004; 0.01)	-0.006 (-0.02; 0.006)
CDC			
Underweight	Reference	Reference	Reference
Normal weight	1.01 (0.96, 1.06)	1.01 (0.96; 1.06)	0.99 (0.93; 1.05)
Overweight	1.01 (0.95, 1.07)	1.01 (0.95; 1.07)	0.98 (0.92; 1.05)
Obese	1.01 (0.95, 1.07)	1.01 (0.95; 1.07)	0.97 (0.90; 1.04)
WHO			
Underweight	Reference	Reference	Reference
Normal weight	1.06 (0.94, 1.19)	1.06 (0.94; 1.19)	1.02 (0.90; 1.16)
Overweight	1.08 (0.96, 1.22)	1.08 (0.96; 1.22)	1.03 (0.90; 1.17)
Obese	1.06 (0.94, 1.20)	1.06 (0.94; 1.20)	1.01 (0.88; 1.15)
IOTF			
Underweight	Reference	Reference	Reference
Normal weight	1.00 (0.97, 1.04)	1.00 (0.97; 1.04)	0.98 (0.94; 1.02)
Overweight	1.00 (0.96, 1.05)	1.00 (0.96; 1.04)	0.97 (0.92; 1.02)
Obese	1.01 (0.96, 1.06)	1.00 (0.95; 1.06)	0.97 (0.91; 1.04)
Percentage of body mass			

Underfat	Reference	Reference	Reference
Normal	0.97 (0.88, 1.06)	0.97 (0.88; 1.06)	0.96 (0.87; 1.07)
Overfat	0.98 (0.89, 1.08)	0.98 (0.89; 1.08)	0.96 (0.86; 1.07)
Obese	0.97 (0.88, 1.07)	0.97 (0.88; 1.07)	0.96 (0.86; 1.06)
Body composition* ^b			
Lean body mass	0.01 (-0.01; 0.05)	0.01 (-0.02; 0.04)	-0.01 (-0.05; 0.03)
Total body water	0.009 (-0.01; 0.03)	0.006 (-0.02; 0.03)	-0.01 (-0.04; 0.02)
Body fat (%)	0.002 (-0.04; 0.04)	0.002 (-0.04; 0.04)	-0.03 (-0.09; 0.02)
Body fat (Kg)	0.004 (-0.03; 0.03)	0.001 (-0.03; 0.03)	-0.02 (-0.06; 0.02)
Pupillometry* ^c			
Baseline pupil diameter	-0.01 (-0.02; -0.005)	-0.01 (-0.02; -0.003)	-0.01 (-0.02; -0.004)
Final pupil diameter	-0.007 (-0.01; -0.002)	-0.006 (-0.01; -0.001)	-0.008 (-0.01; -0.03)
MCV	-0.01 (-0.02; -0.003)	-0.007 (-0.01; 0.001)	0.007 (-0.001; 0.01)
ACV	-0.008 (-0.01; -0.002)	-0.005 (-0.01; 2.83E-4)	0.005 (-3.80E-4; 0.01)
Constriction amplitude	-0.04 (-0.07; 0.003)	-0.01 (-0.06; 0.02)	-0.01 (-0.06; 0.03)
ADV	-0.001 (-0.004; 0.001)	-0.001 (-0.004; 0.002)	-8.47E-4 (-0.004; 0.002)
T75	1.68E-4 (-0.006; 0.006)	3.64E-5 (-0.006; 0.006)	-7.46E-4 (-0.007; 0.006)
EBC pH ^d	8.61E-4 (-0.006; 0.008)	0.001 (-0.005; 0.009)	-5.53E-4 (-0.01; 0.009)
EBC pH ^d			
≥7.4	1.01 (0.98; 1.03)	1.01 (0.99; 1.03)	1.00 (0.97; 1.03)
4-chloroethylene			
Asthma ^{†a}			
Medical diagnosis asthma	1.04 (0.69, 1.38)	0.99 (0.63; 1.35)	1.05 (0.66; 1.47)
BD+	1.01 (0.67, 1.35)	1.04 (0.69; 1.40)	1.08 (0.52; 1.77)
Medical diagnosis asthma and symptoms or BD+	1.00 (0.71, 1.30)	0.97 (0.66; 1.28)	0.93 (0.60; 1.29)
Medical diagnosis asthma or BD+	1.05 (0.80, 1.31)	1.04 (0.77; 1.31)	1.05 (0.75; 1.37)
Symptoms in previous 3 months ^a			
Itching on the face or neck	1.07 (0.74, 1.40)	1.04 (0.70; 1.38)	1.11 (0.74; 1.52)
Eye irritation	0.88 (0.61, 1.16)	0.85 (0.57; 1.14)	0.87 (0.55; 1.19)
Swollen eyes	1.10 (0.78, 1.43)	1.08 (0.75; 1.42)	1.11 (0.76; 1.51)

Runny nose	1.03 (0.87, 1.23)	1.04 (0.87; 1.25)	1.07 (0.87; 1.32)
Nasal obstruction	1.12 (0.94, 1.35)	1.12 (0.93; 1.36)	1.17 (0.95; 1.47)
Dry throat	1.03 (0.82, 1.25)	1.01 (0.79; 1.24)	1.02 (0.77; 1.29)
Sore throat	1.01 (0.84, 1.21)	1.04 (0.86; 1.25)	1.10 (0.90; 1.36)
Irritative cough	1.05 (0.87, 1.26)	1.07 (0.88; 1.30)	1.13 (0.91; 1.39)
Breathing difficulties	0.99 (0.71, 1.28)	1.00 (0.70; 1.30)	1.02 (0.70; 1.37)
BMI^b			
z-score CDC*	-0.001 (-0.06, 0.06)	0.007 (-0.06; 0.07)	-0.07 (-0.04; 0.23)
z-score BMI*	-0.01 (-0.09, 0.06)	-0.001 (-0.08; 0.07)	-0.02 (-0.06; 0.25)
<i>CDC</i>			
Underweight	Reference	Reference	Reference
Normal weight	1.12 (0.68, 1.84)	1.11 (0.68; 1.83)	--
Overweight	1.23 (0.73, 2.07)	1.24 (0.74; 2.08)	--
Obese	0.77 (0.39, 1.53)	0.80 (0.40; 1.58)	--
<i>WHO</i>			
Underweight	Reference	Reference	Reference
Normal weight	0.86 (0.49, 1.51)	0.86 (0.49; 1.51)	--
Overweight	0.91 (0.51, 1.61)	0.92 (0.51; 1.64)	--
Obese	0.68 (0.35, 1.30)	0.70 (0.37; 1.36)	--
<i>IOTF</i>			
Underweight	Reference	Reference	Reference
Normal weight	1.02 (0.74, 1.40)	1.01 (0.73; 1.39)	--
Overweight	1.08 (0.76, 1.52)	1.08 (0.76; 1.53)	--
Obese	0.65 (0.30, 1.43)	0.68 (0.31; 1.47)	--
<i>Percentage of body mass</i>			
Underfat	Reference	Reference	Reference
Normal	187.2 (165.1, 212.3)	10.5 (9.74E-13; 1.12E14)	--
Overfat	203.0 (174.1, 236.8)	11.3 (1.05E-12; 1.21E14)	--
Obese	171.5 (142.9, 205.8)	9.84 (9.15E-13; 1.06E14)	--

Body composition*^b

Lean body mass	-0.21 (-0.48; 0.06)	-0.04 (-0.29; 0.21)	-0.03 (-0.54; 0.48)
Total body water	-0.18 (-0.38; 0.01)	-0.07 (-0.25; 0.12)	-0.16 (-0.53; 0.22)
Body fat (%)	-0.09 (-0.44; 0.25)	-0.007 (-0.35; 0.33)	0.37 (-0.31; 1.07)
Body fat (Kg)	-0.16 (-0.40; 0.08)	-0.06 (-0.30; 0.18)	0.13 (-0.37; 0.63)
Pupillometry* ^c			
Baseline pupil diameter	-0.06 (-0.12; -0.005)	-0.07 (-0.13; -0.01)	-0.06 (-0.12; 0.002)
Final pupil diameter	-0.05 (-0.08; -0.006)	-0.05 (-0.09; -0.01)	-0.04 (-0.08; 0.003)
MCV	-0.06 (-0.12; 0.001)	-0.07 (-0.14; -0.01)	0.07 (0.005; 0.14)
ACV	-0.04 (-0.09; -5.46E-4)	-0.05 (-0.10; -0.007)	0.05 (-0.003; 0.10)
Constriction amplitude	0.11 (-0.21; 0.43)	0.08 (-0.24; 0.41)	0.01 (-0.34; 0.37)
ADV	0.007 (-0.01; 0.03)	0.006 (-0.02; 0.03)	-9.00E-4 (-0.03; 0.02)
T75	-2.01E-4 (-0.05; 0.05)	0.001 (-0.05; 0.05)	0.006 (-0.05; 0.06)
EBC pH ^d	0.02 (-0.03; 0.08)	0.03 (-0.04; 0.08)	0.008 (-0.10; 0.12)
EBC pH ^d			
≥7.4	1.09 (0.90; 1.31)	1.11 (0.91; 1.34)	1.09 (0.73; 1.58)
2-butoxyethanol			
Asthma ^{†a}			
Medical diagnosis asthma	0.99 (0.96, 1.00)	0.99 (0.97; 1.00)	0.99 (0.95; 1.01)
BD+	1.00 (0.99, 1.01)	1.00 (0.99; 1.01)	0.99 (0.95; 1.02)
Medical diagnosis asthma and symptoms or BD+	1.00 (0.99, 1.01)	1.00 (0.99; 1.01)	1.00 (0.99; 1.01)
Medical diagnosis asthma or BD+	1.00 (0.99, 1.01)	1.00 (0.99; 1.01)	1.00 (0.99; 1.01)
Symptoms in previous 3 months ^a			
Itching on the face or neck	1.00 (0.99, 1.01)	1.00 (0.99; 1.01)	1.00 (0.99; 1.01)
Eye irritation	1.01 (0.99, 1.01)	1.01 (0.99; 1.02)	1.00 (0.99; 1.01)
Swollen eyes	1.00 (0.99, 1.01)	1.00 (0.99; 1.01)	1.00 (0.99; 1.01)
Runny nose	1.00 (0.99, 1.01)	1.00 (0.99; 1.01)	1.00 (0.99; 1.01)
Nasal obstruction	1.00 (0.99, 1.01)	1.00 (0.99; 1.01)	1.00 (0.99; 1.01)
Dry throat	1.00 (0.99, 1.01)	1.00 (0.99; 1.01)	1.00 (0.99; 1.01)
Sore throat	1.00 (0.99, 1.01)	1.00 (0.99; 1.01)	1.00 (0.99; 1.01)
Irritative cough	1.00 (0.99, 1.01)	1.00 (0.99; 1.01)	1.00 (0.99; 1.01)

Breathing difficulties	0.99 (0.98, 1.00)	0.99 (0.98; 1.01)	0.99 (0.97; 1.00)
BMI ^b			
z-score CDC*	2.77E-4 (-0.002, 0.002)	1.27E-4 (-0.002; 0.002)	-0.001 (-0.005; 0.002)
z-score BMI*	8.69E-5 (-0.002, 0.002)	-1.06E-4 (-0.002; 0.002)	-0.002 (-0.005; 0.002)
CDC			
Underweight	Reference	Reference	Reference
Normal weight	1.01 (0.98, 1.04)	1.01 (0.98; 1.04)	1.00 (0.98; 1.03)
Overweight	1.01 (0.98, 1.04)	1.01 (0.98; 1.04)	1.00 (0.97; 1.03)
Obese	1.01 (0.98, 1.04)	1.01 (0.98; 1.04)	0.99 (0.95; 1.03)
WHO			
Underweight	Reference	Reference	Reference
Normal weight	1.04 (0.90, 1.20)	1.04 (0.90; 1.19)	1.02 (0.92; 1.13)
Overweight	1.04 (0.90, 1.20)	1.04 (0.90; 1.19)	1.02 (0.92; 1.13)
Obese	1.03 (0.89, 1.20)	1.03 (0.89; 1.19)	1.00 (0.90; 1.12)
IOTF			
Underweight	Reference	Reference	Reference
Normal weight	1.01 (0.99, 1.03)	1.01 (0.95; 1.03)	1.00 (0.98; 1.02)
Overweight	1.01 (0.99, 1.03)	1.01 (0.59; 2.28)	1.00 (0.98; 1.02)
Obese	1.00 (0.97, 1.03)	0.99 (0.36; 3.00)	0.95 (0.82; 1.11)
Percentage of body mass			
Underfat	Reference	Reference	Reference
Normal	1.81 (0.08, 43.1)	4.36 (4.34; 4.38)	3.90 (3.85; 3.95)
Overfat	1.81 (0.07, 43.1)	4.35 (4.33; 4.38)	3.90 (3.85; 3.96)
Obese	1.80 (0.07, 42.9)	4.33 (4.30; 4.36)	3.81 (3.72; 3.91)
Body composition* ^b			
Lean body mass	-0.001 (-0.01; 0.01)	-0.002 (-0.01; 0.005)	-0.004 (-0.02; 0.009)
Total body water	-0.002 (-0.01; 0.004)	-0.003 (-0.009; 0.003)	-0.006 (-0.01; 0.003)
Body fat (%)	-0.005 (-0.01; 0.01)	-0.005 (-0.01; 0.006)	-0.01 (-0.03; 0.003)
Body fat (Kg)	-0.005 (-0.01; 0.003)	-0.005 (-0.01; 0.002)	-0.01 (-0.02; 0.002)
Pupillometry* ^c			

Baseline pupil diameter	0.002 (2.20E-4; 0.004)	0.002 (-8.02E-5; 0.004)	0.001 (-6.43E-4; 0.003)
Final pupil diameter	7.31E-4 (-5.77E-4; 0.002)	5.17E-4 (8.22E-4; 0.002)	-1.53E-5 (-0.001; 0.001)
MCV	0.001 (-9.03E-4; 0.003)	9.89E-4 (-0.001; 0.003)	-0.001 (-0.004; 8.50E-4)
ACV	9.93E-4 (-4.62E-4; 0.002)	8.45E-4 (-6.38E-4; 0.002)	-0.001 (-0.003; 3.93E-4)
Constriction amplitude	0.01 (0.002; 0.02)	0.01 (0.003; 0.02)	0.02 (0.005; 0.03)
ADV	1.82E-4 (-4.85E-4; 8.48E-4)	1.58E-4 (-5.32E-4; 8.48E-4)	2.12E-4 (-5.55E-4; 9.79E-4)
T75	0.001 (6.45E-5; 0.003)	0.001 (-9.99E-5; 0.003)	0.001 (-4.97E-4; 0.003)
EBC pH ^d	5.96E-4 (-0.001; 0.002)	6.79E-4 (-0.001; 0.002)	-0.001 (-0.004; 0.002)
EBC pH ^d			
≥7.4	1.00 (0.99; 1.01)	1.00 (0.99; 1.01)	0.99 (0.98; 1.00)
2-ethyl-1-hexanol			
Asthma ^{†a}			
Medical diagnosis asthma	1.04 (0.98, 1.08)	1.04 (0.98;1.09)	1.04 (0.98; 1.10)
BD+	1.01 (0.94, 1.06)	1.00 (0.92; 1.06)	1.00 (0.92; 1.06)
Medical diagnosis asthma and symptoms or BD+	1.00 (0.95, 1.06)	1.01 (0.95; 1.06)	1.01 (0.94; 1.06)
Medical diagnosis asthma or BD+	1.02 (0.97, 1.06)	1.02 (0.97; 1.06)	1.02 (0.97; 1.07)
Symptoms in previous 3 months ^a			
Itching on the face or neck	1.00 (0.91, 1.05)	1.00 (0.91; 1.06)	1.00 (0.90; 1.06)
Eye irritation	1.02 (0.96, 1.06)	1.02 (0.96; 1.06)	1.01 (0.96; 1.06)
Swollen eyes	1.02 (0.96, 1.07)	1.02 (0.96; 1.07)	1.02 (0.95; 1.07)
Runny nose	1.02 (0.98, 1.06)	1.02 (0.98; 1.06)	1.02 (0.98; 1.06)
Nasal obstruction	1.01 (0.97, 1.05)	1.01 (0.98; 1.05)	1.01 (0.98; 1.06)
Dry throat	1.00 (0.96, 1.04)	1.01 (0.96; 1.05)	1.01 (0.96; 1.05)
Sore throat	0.98 (0.94, 1.02)	0.98 (0.94; 1.02)	0.98 (0.94; 1.02)
Irritative cough	1.02 (0.99, 1.06)	1.02 (0.99; 1.06)	1.03 (0.99; 1.07)
Breathing difficulties	1.04 (0.99, 1.08)	1.04 (0.99; 1.08)	1.04 (0.99; 1.08)
BMI ^b			
z-score CDC*	0.003 (-0.01, 0.01)	0.002 (-0.010; 0.016)	0.008 (-0.007; 0.02)

z-score BMI*	0.003 (-0.01, 0.02)	0.003 (-0.01; 0.02)	0.009 (-0.09; 0.03)
<i>CDC</i>			
Underweight	Reference	Reference	Reference
Normal weight	1.02 (0.92, 1.14)	1.02 (0.92; 1.13)	1.03 (0.91; 1.16)
Overweight	1.03 (0.93, 1.16)	1.03 (0.92; 1.15)	1.05 (0.92; 1.19)
Obese	1.02 (0.91, 1.14)	1.01 (0.90; 1.14)	1.03 (0.90; 1.17)
<i>WHO</i>			
Underweight	Reference	Reference	Reference
Normal weight	1.03 (0.84, 1.25)	1.03 (0.84; 1.26)	1.03 (0.78; 1.35)
Overweight	1.03 (0.85, 1.26)	1.04 (0.84; 1.27)	1.05 (0.79; 1.38)
Obese	1.02 (0.83, 1.25)	1.01 (0.82; 1.25)	1.02 (0.77; 1.35)
<i>IOTF</i>			
Underweight	Reference	Reference	Reference
Normal weight	1.01 (0.94, 1.09)	1.01 (0.94; 1.09)	1.02 (0.94; 1.12)
Overweight	1.03 (0.95, 1.11)	1.02 (0.95; 1.11)	1.04 (0.94; 1.15)
Obese	0.98 (0.88, 1.10)	0.97 (0.85; 1.10)	0.99 (0.86; 1.14)
<i>Percentage of body mass</i>			
Underfat	Reference	Reference	Reference
Normal	1.01 (0.82, 1.24)	1.01 (0.82; 1.25)	1.02 (0.78; 1.33)
Overfat	1.02 (0.83, 1.25)	1.03 (0.83; 1.27)	1.06 (0.81; 1.39)
Obese	1.02 (0.82, 1.25)	1.02 (0.82; 1.26)	1.03 (0.78; 1.35)
Body composition* ^b			
Lean body mass	0.01 (-0.04; 0.07)	-0.004 (-0.05; 0.04)	0.006 (-0.05; 0.06)
Total body water	0.01 (-0.03; 0.05)	-0.003 (-0.04; 0.03)	0.005 (-0.004; 0.05)
Body fat (%)	0.01 (-0.06; 0.07)	0.01 (-0.06; 0.08)	0.03 (-0.04; 0.11)
Body fat (Kg)	0.005 (-0.04; 0.05)	-0.001 (-0.05; 0.05)	0.01 (-0.04; 0.07)
Pupillometry* ^c			
Baseline pupil diameter	0.009 (-0.002; 0.02)	0.009 (-0.003; 0.02)	0.009 (-0.004; 0.02)
Final pupil diameter	0.002 (-0.005; 0.01)	0.003 (-0.006; 0.01)	0.004 (-0.005; 0.01)
MCV	0.01 (-0.002; 0.02)	0.01 (-0.002; 0.02)	-0.01 (-0.02; 0.005)

ACV	0.006 (-0.003; 0.01)	0.007 (-0.003; 0.02)	-0.009 (-0.02; 0.001)
Constriction amplitude	0.03 (-0.03; 0.10)	0.04 (-0.03; 0.11)	0.01 (-0.07; 0.09)
ADV	7.93E-4 (-0.003; 0.005)	0.002 (-0.003; 0.006)	3.44E-4 (-0.005; 0.006)
T75	0.003 (-0.008; 0.01)	0.003 (-0.01; 0.01)	0.004 (-0.009; 0.02)
EBC pH ^d	0.009 (-0.002; 0.02)	0.009 (-0.002; 0.02)	0.01 (-0.002; 0.03)
EBC pH ^d			
≥7.4	1.02 (0.98; 1.05)	1.02 (0.98; 1.06)	1.03 (0.98; 1.07)
Formaldehyde			
Asthma ^{Ta,c}			
Medical diagnosis asthma	1.00 (0.94, 1.05)	0.99 (0.94; 1.05)	0.99 (0.93; 1.05)
BD+	0.98 (0.92, 1.03)	0.98 (0.93; 1.04)	0.99 (0.92; 1.05)
Medical diagnosis asthma and symptoms or BD+	1.00 (0.95, 1.04)	1.00 (0.95; 1.05)	1.00 (0.95; 1.05)
Medical diagnosis asthma or BD+	0.99 (0.95, 1.03)	0.99 (0.95; 1.03)	0.99 (0.94; 1.04)
Symptoms in previous 3 months ^a			
Itching on the face or neck	1.01 (0.96, 1.06)	1.01 (0.95; 1.06)	1.01 (0.95; 1.07)
Eye irritation	1.01 (0.97, 1.05)	1.01 (0.97; 1.05)	1.01 (0.97; 1.06)
Swollen eyes	1.00 (0.95, 1.05)	1.00 (0.95; 1.06)	1.00 (0.94; 1.06)
Runny nose	0.99 (0.97, 1.02)	0.99 (0.96; 1.02)	0.99 (0.96; 1.02)
Nasal obstruction	0.99 (0.96, 1.01)	0.99 (0.96; 1.01)	0.98 (0.95; 1.01)
Dry throat	0.99 (0.96, 1.03)	1.00 (0.96; 1.03)	1.00 (0.96; 1.04)
Sore throat	0.98 (0.96, 1.01)	0.98 (0.96; 1.01)	0.98 (0.95; 1.01)
Irritative cough	0.99 (0.96, 1.02)	0.99 (0.96; 1.02)	0.98 (0.95; 1.02)
Breathing difficulties	0.98 (0.94, 1.03)	0.98 (0.93; 1.03)	0.97 (0.92; 1.02)
BMI ^b			
z-score CDC*	0.004 (-0.005, 0.01)	0.007 (-0.003; 0.02)	0.007 (-0.006; 0.02)
z-score BMI*	0.003 (-0.008, 0.014)	0.007 (-0.005; 0.02)	0.007 (-0.008; 0.02)
CDC			
Underweight	Reference	Reference	Reference
Normal weight	1.02 (0.96, 1.09)	1.02 (0.95; 1.09)	1.00 (0.93; 1.08)

Overweight	1.03 (0.96, 1.10)	1.03 (0.96; 1.11)	1.02 (0.94; 1.12)
Obese	1.00 (0.93, 1.08)	1.00 (0.93; 1.08)	0.99 (0.90; 1.08)
<i>WHO</i>			
Underweight	Reference	Reference	Reference
Normal weight	1.03 (0.92, 1.16)	1.03 (0.92; 1.16)	1.03 (0.90; 1.17)
Overweight	1.03 (0.92, 1.17)	1.04 (0.92; 1.17)	1.04 (0.92; 1.19)
Obese	1.01 (0.90, 1.14)	1.02 (0.90; 1.15)	1.01 (0.89; 1.16)
<i>IOTF</i>			
Underweight	Reference	Reference	Reference
Normal weight	1.02 (0.97, 1.07)	1.02 (0.97; 1.08)	1.02 (0.96; 1.08)
Overweight	1.04 (0.98, 1.10)	1.05 (0.99; 1.11)	1.05 (0.98; 1.12)
Obese	0.99 (0.92, 1.06)	0.99 (0.92; 1.06)	0.99 (0.90; 1.08)
<i>Percentage of body mass</i>			
Underfat	Reference	Reference	Reference
Normal	1.06 (0.91, 1.22)	1.05 (0.91; 1.22)	1.07 (0.91; 1.25)
Overfat	1.07 (0.92, 1.24)	1.07 (0.92; 1.24)	1.09 (0.93; 1.28)
Obese	1.04 (0.89, 1.21)	1.04 (0.89; 1.21)	1.04 (0.89; 1.22)
<i>Body composition*^b</i>			
Lean body mass	0.007 (-0.03; 0.05)	0.04 (0.001; 0.08)	0.05 (-0.001; 0.10)
Total body water	-0.006 (-0.04; 0.02)	0.02 (-0.01; 0.04)	0.01 (-0.02; 0.05)
Body fat (%)	-0.02 (-0.07; 0.03)	0.006 (-0.05; 0.06)	-0.002 (-0.07; 0.06)
Body fat (Kg)	-0.02 (-0.05; 0.02)	0.008 (-0.03; 0.04)	0.007 (-0.04; 0.05)
<i>Pupillometry*^c</i>			
Baseline pupil diameter	0.01 (0.001; 0.02)	0.01 (-1.10E-4; 0.02)	0.007 (-0.003; 0.02)
Final pupil diameter	0.003 (-0.003; 0.01)	0.002 (-0.004; 0.01)	-2.49E-4 (-0.007; 0.006)
MCV	0.01 (-0.002; 0.02)	0.01 (-0.002; 0.02)	-0.009 (-0.02; 0.001)
ACV	0.01 (0.003; 0.02)	0.01 (0.003; 0.02)	-0.01 (-0.02; -0.003)
Constriction amplitude	0.08 (0.03; 0.13)	0.08 (0.03; 0.13)	0.10 (0.05; 0.16)
ADV	0.003 (1.68E-4; 0.01)	0.003 (-7.06E-4; 0.01)	0.003 (-1.67E-4; 0.007)
T75	-0.002 (-0.01; 0.005)	-0.002 (-0.01; 0.01)	-0.003 (-0.01; 0.005)

EBC pH ^d	0.01 (0.004; 0.02)	0.01 (0.004; 0.02)	0.008 (-0.003; 0.02)
EBC pH ^d			
≥7.4	1.02 (0.99; 1.05)	1.02 (0.99; 1.06)	1.01 (0.98; 1.05)
Acetaldehyde			
Asthma ^{†a}			
Medical diagnosis asthma	0.97 (0.84, 1.13)	0.97 (0.84; 1.13)	0.95 (0.80; 1.14)
BD+	1.04 (0.90, 1.21)	1.04 (0.90; 1.22)	1.04 (0.88; 1.23)
Medical diagnosis asthma and symptoms or BD+	1.00 (0.89, 1.13)	1.01 (0.89; 1.15)	1.01 (0.88; 1.17)
Medical diagnosis asthma or BD+	1.00 (0.90, 1.12)	1.00 (0.90; 1.12)	0.99 (0.87; 1.13)
Symptoms in previous 3 months ^a			
Itching on the face or neck	1.05 (0.91, 1.23)	1.05 (0.90; 1.23)	1.04 (0.88; 1.25)
Eye irritation	1.04 (0.93, 1.17)	1.03 (0.92; 1.16)	1.03 (0.90; 1.17)
Swollen eyes	0.98 (0.86, 1.13)	0.99 (0.86; 1.14)	1.00 (0.86; 1.18)
Runny nose	1.00 (0.92, 1.07)	0.99 (0.92; 1.07)	0.98 (0.90; 1.07)
Nasal obstruction	0.96 (0.89, 1.03)	0.96 (0.89; 1.03)	0.94 (0.97; 1.03)
Dry throat	0.99 (0.90, 1.08)	1.00 (0.91; 1.10)	1.00 (0.90; 1.12)
Sore throat	0.99 (0.92, 1.07)	1.00 (0.92; 1.08)	0.98 (0.89; 1.06)
Irritative cough	0.98 (0.91, 1.06)	0.98 (0.90; 1.07)	0.97 (0.88; 1.06)
Breathing difficulties	0.93 (0.83, 1.05)	0.93 (0.83; 1.06)	0.93 (0.81; 1.07)
BMI ^b			
z-score CDC*	0.01 (-0.01, 0.04)	0.01 (-0.01; 0.04)	0.02 (-0.01; 0.06)
z-score BMI*	0.01 (-0.01, .04)	0.02 (-0.01; 0.05)	0.03 (-0.02; 0.07)
CDC			
Underweight	Reference	Reference	Reference
Normal weight	1.02 (0.86, 1.21)	1.02 (0.86; 1.22)	1.04 (0.85; 1.28)
Overweight	1.05 (0.87, 1.27)	1.07 (0.88; 1.30)	1.14 (0.90; 1.44)
Obese	1.04 (0.86, 1.26)	1.04 (0.85; 1.27)	1.05 (0.83; 1.33)
WHO			
Underweight	Reference	Reference	Reference
Normal weight	1.06 (0.79, 1.43)	1.06 (0.79; 1.43)	1.07 (0.83; 1.38)

Overweight	1.07 (0.79, 1.44)	1.08 (0.79; 1.47)	1.14 (0.88; 1.49)
Obese	1.06 (0.78, 1.44)	1.06 (0.78; 1.45)	1.06 (0.82; 1.39)
<i>IOTF</i>			
Underweight	Reference	Reference	Reference
Normal weight	1.04 (0.92, 1.18)	1.04 (0.91; 1.18)	1.08 (0.92; 1.25)
Overweight	1.05 (0.91, 1.21)	1.07 (0.92; 1.24)	1.11 (0.93; 1.33)
Obese	1.11 (0.93, 1.33)	1.11 (0.92; 2.41)	1.17 (0.94; 1.47)
<i>Percentage of body mass</i>			
Underfat	Reference	Reference	Reference
Normal	1.04 (0.72, 1.50)	1.04 (0.72; 1.50)	1.10 (0.84; 1.45)
Overfat	1.04 (0.72, 1.51)	1.04 (0.71; 1.52)	1.19 (0.89; 1.58)
Obese	1.08 (0.74, 1.56)	1.07 (0.73; 1.55)	1.13 (0.85; 1.50)
Body composition* ^b			
Lean body mass	0.07 (-0.04; 0.18)	0.10 (-0.001; 0.21)	0.16 (0.02; 0.30)
Total body water	0.03 (-0.05; 0.11)	0.05 (-0.02; 0.13)	0.07 (-0.03; 0.18)
Body fat (%)	0.05 (-0.09; 0.19)	0.08 (-0.06; 0.22)	0.11 (-0.08; 0.29)
Body fat (Kg)	0.04 (-0.06; 0.14)	0.07 (-0.03; 1.17)	0.08 (-0.06; 0.22)
Pupillometry* ^c			
Baseline pupil diameter	0.03 (0.002; 0.05)	0.02 (0.001; 0.05)	0.02 (-0.002; 0.05)
Final pupil diameter	0.01 (-0.005; 0.03)	0.01 (-0.01; 0.03)	0.01 (-0.009; 0.03)
MCV	0.02 (-0.002; 0.05)	0.03 (4.65E-4; 0.05)	-0.02 (-0.05; 0.007)
ACV	0.03 (0.01; 0.05)	0.04 (0.02; 0.05)	-0.03 (-0.05; -0.01)
Constriction amplitude	0.14 (0.003; 0.28)	0.17 (0.03; 0.31)	0.16 (0.004; 0.31)
ADV	0.003 (-0.005; 0.01)	0.002 (-0.01; 0.01)	0.004 (-0.006; 0.01)
T75	0.01 (-0.01; 0.03)	0.01 (-0.01; 0.03)	0.005 (-0.02; 0.03)
EBC pH ^d	0.02 (-0.001; 0.04)	0.02 (-0.003; 0.04)	0.01 (-0.01; 0.04)
EBC pH ^d			
≥7.4	1.04 (0.96; 1.12)	1.03 (0.95; 1.13)	1.03 (0.93; 1.14)
PC1			
Asthma ^{Ta}			

Medical diagnosis asthma	1.12 (0.87, 1.38)	1.10 (0.84; 1.36)	1.10 (0.82; 1.40)
BD+	1.08 (0.83, 1.33)	1.07 (0.82; 1.42)	1.05 (0.79; 1.31)
Medical diagnosis asthma and symptoms or BD+	1.12 (0.91, 1.34)	1.08 (0.88; 1.27)	1.09 (0.87; 1.33)
Medical diagnosis asthma or BD+	1.14 (0.95, 1.35)	1.21 (0.93; 1.32)	1.11 (0.91; 1.33)
Symptoms in previous 3 months ^a			
Itching on the face or neck	1.08 (0.83, 1.33)	1.06 (0.80; 1.33)	1.06 (0.78; 1.36)
Eye irritation	0.98 (0.78, 1.18)	0.97 (0.76; 1.18)	0.97 (0.75; 1.20)
Swollen eyes	1.06 (0.81, 1.31)	1.04 (0.79; 1.29)	1.04 (0.77; 1.32)
Runny nose	1.00 (0.87, 1.14)	0.99 (0.86; 1.13)	1.02 (0.88; 1.17)
Nasal obstruction	1.25 (1.09; 1.47)	1.24 (1.08; 1.45)	1.32 (1.13; 1.58)
Dry throat	1.01 (0.85; 1.19)	1.00 (0.84; 1.17)	0.99 (0.81; 1.17)
Sore throat	1.01 (0.85, 1.18)	1.12 (0.98; 1.28)	1.11 (0.96; 1.28)
Irritative cough	1.00 (0.86, 1.16)	1.00 (0.87; 1.16)	0.97 (0.82; 1.13)
Breathing difficulties	1.08 (0.88, 1.30)	1.08 (0.88; 1.29)	1.10 (0.88; 1.34)
BMI ^b			
z-score CDC*	-0.02 (-0.09, 0.06)	-0.02 (-0.09; 0.06)	-0.04 (-0.12; 0.04)
z-score BMI*	-0.01 (-0.10, 0.07)	-0.01 (-0.10; 0.07)	-0.04 (-0.14; 0.06)
<i>CDC</i>			
Underweight	Reference	Reference	Reference
Normal weight	1.01 (0.73 (1.39))	1.01 (0.74; 1.40)	0.94 (0.68; 1.30)
Overweight	0.98 (0.69, 1.40)	0.98 (0.68; 1.41)	0.88 (0.60; 1.28)
Obese	1.03 (0.72, 1.48)	1.05 (0.73; 1.50)	0.92 (0.64; 1.33)
<i>WHO</i>			
Underweight	Reference	Reference	Reference
Normal weight	0.89 (0.57, 1.39)	0.90 (0.57; 1.41)	0.89 (0.80; 1.01)
Overweight	0.79 (0.49, 1.27)	0.79 (0.49; 1.27)	0.80 (0.69; 0.92)
Obese	0.92 (0.58, 1.47)	0.94 (0.59; 1.51)	0.85 (0.73; 0.98)
<i>IOTF</i>			
Underweight	Reference	Reference	Reference
Normal weight	0.98 (0.78, 1.23)	0.98 (0.78; 1.23)	0.95 (0.74; 1.21)

Overweight	0.96 (0.74, 1.24)	0.96 (0.74; 1.24)	0.85 (0.63; 1.14)
Obese	1.01 (0.74, 1.38)	1.02 (0.75; 1.40)	1.01 (0.73; 1.39)
<i>Percentage of body mass</i>			
Underfat	Reference	Reference	Reference
Normal	1.40 (0.46, 4.32)	1.39 (0.47; 4.14)	1.39 (1.23; 1.57)
Overfat	1.29 (0.42, 4.03)	1.27 (0.42; 3.84)	1.17 (0.97; 1.40)
Obese	1.34 (0.43, 4.15)	1.33 (0.44; 4.01)	1.29 (1.10; 1.51)
<i>Body composition*^b</i>			
Lean body mass	-0.18 (-0.46; 0.10)	-0.18 (-0.46; 0.10)	-0.22 (-0.54; 0.10)
Total body water	-0.17 (-0.39; 0.06)	-0.14 (-0.35; 0.06)	-0.18 (-0.42; 0.06)
Body fat (%)	-0.07 (-0.46; 0.33)	-0.08 (-0.46; 0.29)	-0.12 (-0.56; 0.31)
Body fat (Kg)	-0.07 (-0.35; 0.21)	-0.06 (-0.33; 0.21)	-0.08 (-0.39; 0.24)
<i>Pupillometry*^c</i>			
Baseline pupil diameter	-0.08 (-0.14; -0.01)	-0.07 (-0.14; -0.01)	-0.06 (-0.13; 0.007)
Final pupil diameter	-0.04 (-0.08; 0.007)	-0.04 (-0.08; 0.009)	-0.02 (-0.07; 0.02)
MCV	-0.09 (-0.16; -0.02)	-0.09 (-0.16; -0.02)	0.10 (0.02; 0.18)
ACV	-0.07 (-0.12; -0.02)	-0.07 (-0.12; -0.02)	0.08 (0.03; 0.14)
Constriction amplitude	-0.26 (-0.62; 0.10)	-0.27 (-0.62; 0.09)	-0.35 (-0.74; 0.04)
ADV	-0.02 (-0.05; 0.003)	-0.02 (-0.05; 0.002)	-0.03 (-0.06; 6.49E-4)
T75	-0.03 (-0.08; 0.03)	-0.03 (-0.09; 0.03)	-0.03 (-0.09; 0.03)
EBC pH ^d	0.02 (-0.04; 0.09)	0.02 (-0.04; 0.08)	-0.008 (-0.07; 0.06)
<i>EBC pH^d</i>			
≥7.4	1.02 (0.82; 1.25)	1.00 (0.80; 1.23)	0.98 (0.75; 1.23)
PC2			
<i>Asthma^{†a}</i>			
Medical diagnosis asthma	0.99 (0.74, 1.30)	0.97 (0.73; 1.29)	0.94 (0.67; 1.29)
BD+	0.84 (0.63, 1.10)	0.90 (0.67; 1.19)	0.93 (0.67; 1.27)
Medical diagnosis asthma and symptoms or BD+	1.01 (0.80, 1.27)	1.03 (0.81; 1.25)	1.04 (0.80; 1.34)
Medical diagnosis asthma or BD+	0.90 (0.73, 1.11)	0.93 (0.75; 1.16)	0.94 (0.73; 1.19)
Symptoms in previous 3 months ^a			

Itching on the face or neck	1.07 (0.81, 1.41)	1.07 (0.80; 1.41)	1.08 (0.79; 1.47)
Eye irritation	1.14 (0.92, 1.41)	1.10 (0.89; 1.36)	1.10 (0.87; 1.39)
Swollen eyes	1.05 (0.80, 1.36)	1.07 (0.82; 1.40)	1.07 (0.79; 1.43)
Runny nose	0.92 (0.80, 1.07)	0.91 (0.79; 1.06)	0.89 (0.76; 1.04)
Nasal obstruction	0.86 (0.74, 0.99)	0.85 (0.73; 0.99)	0.83 (0.71; 0.98)
Dry throat	0.92 (0.77; 1.10)	0.96 (0.80; 1.15)	0.97 (0.79; 1.19)
Sore throat	0.91 (0.79, 1.06)	0.91 (0.78; 1.06)	0.87 (0.74; 1.02)
Irritative cough	0.92 (0.79, 1.07)	0.92 (0.78; 1.07)	0.89 (0.75; 1.06)
Breathing difficulties	0.80 (0.63, 1.01)	0.78 (0.61; 1.00)	0.74 (0.55; 0.97)
BMI^b			
z-score CDC*	-0.005 (-0.08, 0.07)	0.005 (-0.07; 0.08)	0.006 (-0.09; 0.10)
z-score BMI*	-0.01 (-0.10, 0.07)	-8.21E-5 (-0.09; 0.09)	0.004 (-0.11; 0.11)
<i>CDC</i>			
Underweight	Reference	Reference	Reference
Normal weight	1.09 (0.78, 1.52)	1.09 (0.78; 1.53)	1.00 (0.87; 1.14)
Overweight	1.11 (0.77, 1.60)	1.16 (0.80; 1.68)	1.14 (0.96; 1.36)
Obese	0.98 (0.68, 1.43)	1.01 (0.69; 1.49)	0.93 (0.78; 1.11)
<i>WHO</i>			
Underweight	Reference	Reference	Reference
Normal weight	1.19 (0.66, 2.15)	1.18 (0.65; 2.13)	1.18 (1.04; 1.33)
Overweight	1.12 (0.61, 2.05)	1.15 (0.63; 2.11)	1.24 (1.06; 1.45)
Obese	1.08 (0.58, 1.98)	1.12 (0.60; 2.48)	1.10 (0.93; 1.30)
<i>IOTF</i>			
Underweight	Reference	Reference	Reference
Normal weight	1.15 (0.90, 1.47)	1.15 (0.89; 1.48)	1.11 (0.82; 1.48)
Overweight	1.25 (0.95, 1.65)	1.31 (0.99; 1.75)	1.31 (0.94; 1.84)
Obese	0.95 (0.67, 1.35)	0.96 (0.67; 1.38)	0.98 (0.64; 1.50)
<i>Percentage of body mass</i>			
Underfat	Reference	Reference	Reference
Normal	1.35 (0.65, 2.82)	1.33 (0.63; 2.78)	1.31 (1.15; 1.48)

Overfat	1.41 (0.67, 2.97)	1.37 (0.65; 2.92)	1.51 (1.28; 1.79)
Obese	1.16 (0.55, 2.45)	1.17 (0.55; 2.48)	1.10 (0.93; 1.30)
Body composition ^{*b}			
Lean body mass	0.33 (0.03; 0.63)	0.33 (0.03; 0.63)	0.40 (0.04; 0.76)
Total body water	0.05 (-0.19; 0.28)	0.17 (-0.05; 0.39)	0.19 (-0.08; 0.46)
Body fat (%)	-0.31 (-0.72; 0.10)	-0.17 (-0.57; 0.24)	-0.22 (-0.71; 0.28)
Body fat (Kg)	-0.13 (-0.42; 0.15)	0.001 (-0.28; 0.29)	-0.006 (-0.37; 0.35)
Pupillometry ^{*c}			
Baseline pupil diameter	0.11 (0.04; 0.17)	0.09 (0.02; 0.16)	0.09 (0.01; 0.16)
Final pupil diameter	0.04 (-0.004; 0.09)	0.03 (-0.02; 0.08)	0.02 (-0.03; 0.07)
MCV	0.09 (0.02; 0.17)	0.09 (0.01; 0.17)	-0.10 (-0.19; -0.02)
ACV	0.11 (0.06; 0.17)	0.11 (0.06; 0.17)	-0.12 (-0.18; -0.06)
Constriction amplitude	0.70 (0.32; 1.09)	0.72 (0.33; 1.12)	0.86 (0.44; 1.29)
ADV	0.02 (-0.002; 0.05)	0.02 (-0.008; 0.04)	0.03 (-0.002; 0.06)
T75	0.002 (-0.06; 0.06)	0.003 (-0.06; 0.06)	0.003 (-0.06; 0.07)
EBC pH ^d	0.08 (0.02; 0.15)	0.09 (0.02; 0.15)	0.05 (-0.02; 0.13)
EBC pH ^d			
≥7.4	1.12 (0.90; 1.40)	1.14 (0.90; 1.43)	1.09 (0.82; 1.43)

*Data reported as β (95% CI); ^TThe following asthma definitions were adopted: i) *Medical diagnosis of asthma*: self-reported medical diagnosis; ii) *Positive bronchodilatation (BD+)*: at least a 12% and over 200mL increase in FEV1 after bronchodilation; iii) *Medical diagnosis of asthma and symptoms or BD+*: at least a 12% and over 200mL increase in forced expiratory volume in 1 second (FEV1) after bronchodilation or self-reported medical diagnosis with reported symptoms (wheezing, dyspnea or dry cough) occurring in the past 12 months; iv) *Medical diagnosis of asthma or BD+*: at least a 12% and over 200mL increase in FEV1 after bronchodilation or self-reported medical diagnosis; CI: confidence interval; BMI: body mass index; CDC: US Centres for Disease Control; WHO: World Health Organization; IOTF: International Obesity Task Force; MCV: maximum constriction velocity; ACV: average constriction velocity; ADV: average dilation velocity; T75: total time taken by the pupil to recover 75% of the initial resting pupil size after it reached the peak of constriction; EBC: exhaled breath condensate.

Model 0 is null model; Model 1 is adjusted for age and sex; Model 2 is additionally adjusted for: ^aBMI (according to CDC criteria), atopy and parental education; ^basthma (according to medical diagnosis asthma and symptoms or BD+ criteria), parental education, physical activity, energy intake.

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