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The inflammatory potential of diet impacts the association between air pollution and childhood asthma

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Abstract

Background: Inhalation of fine particulate matter (PM) can cause systematic inflammation and oxidative stress, which may further aggravate the development and progression of asthma. Although nutritional intake of fatty acids and antioxidants may attenuate some effects of fine PM, the role of the inflammatory potential of diet has not been addressed. Therefore, we aimed to investigate possible modulatory effects of dietary inflammatory potential on the association of indoor air pollution and childhood asthma-related outcomes.

Methods: In a sample of 501 children (48.1% males, aged 7 to 12 years) from 20 public schools located in Porto, Portugal, we evaluated airway reversibility, exhaled nitric oxide levels, atopy and current respiratory symptoms. Dietary inflammatory index was calculated based on information collected through a reported 24-hour recall questionnaire, and participants were categorized as having an anti-inflammatory or pro-inflammatory diet. Concentrations of indoor PM_{2.5} and PM₁₀ were measured to assess indoor air quality. Generalized linear mixed models were used to investigate the proportion of effects explained by the exposures to PM_{2.5} and PM₁₀.

Results: After adjustment, the exposure effect of PM_{2.5} and PM₁₀ levels on children with asthma was higher for those having a pro-inflammatory diet (OR= 1.44, 95% CI: 1.01 to 2.21 and OR=1.29, 95% CI: 1.03 to 1.68, respectively) compared to those having an anti-inflammatory diet.

Conclusion: These findings suggest that the quality of diet might affect the association of indoor pollution and asthma in children, highlighting the relevance of children's diet as a potential protective factor to pollutants exposure in childhood asthma.

Key words: dietary inflammatory index, asthma, school exposure, indoor pollution

Introduction

Currently there is a progressive understanding of the negative health impacts derived from the exposure to air pollutants. According to previous studies, ozone, nitrogen dioxide, and particulate matter (PM) 2.5 can induce airway inflammation and airway hyper-responsiveness two characteristic features of asthma [1-3]. Additionally, a recent meta-analysis showed significant associations between exposure to nitrogen dioxide, PM 2.5 and PM 10 and asthma onset [4].

Fine particles, namely PM_{2.5}, represent one of the main pollutants of the industrialized countries [1, 5]. In fact, these pollutants, also present in indoor environments, frequently contain various immunogenic substances, such as fungal spores and pollen, which have been independently associated with exacerbation of asthma symptoms [1]. This can be explained by the fact that the first route of exposure to these pollutants to be through inhalation with consequent deep penetration into the airways that directly induces inflammation and oxidative stress caused by the depletion of intracellular glutathione with consequent decrease in the oxidized glutathione / glutathione ratio [6, 7]. Accordingly, oxidative stress can induce the production of pro-inflammatory cytokines, chemokines and adhesion receptors [7].

Research on mechanisms underlying the adverse health effects of air pollution suggest a potential role for dietary interventions showing that diet and some of its components with antioxidant or anti-inflammatory properties could protect against pollution effects on asthma [8]. Trials showed that there was a significant difference in impact of ozone exposure on lung function parameters between children with asthma supplemented with vitamins C and E in relation to non-supplemented (β ; SE= -12.03, 3.44, $p < 0.05$ and β ; SE= -13.25, 6.60, $p < 0.05$ for FEF₅₋₇₅ and PEF, respectively) [9]. More recently, fish oil supplementation was mentioned as having a protective effect against related air pollution on allergic sensitization (RR=1.74, CI_{95%} 1.22, 2.48 and RR=1.03, CI_{95%} 0.76, 1.41 for control and supplemented group, respectively) [10]. Accordingly, dietary components such as antioxidants seems to assume an important role for the oxidative stress in pathways that include the adversely effects of air pollution on asthma [1].

Although an unhealthy diet or nutritional inadequacy with low levels of antioxidant nutrients seems to interact with air pollution to cause or worsen asthma, there is no previous studies addressing the interaction of inflammatory potential of diet in the association of asthma and air pollution. The dietary inflammatory index was developed to provide an overall score that

accounts for the consumption of food components known for their anti- or pro-inflammatory capacity and has been associated with several outcomes including cancer, metabolic syndrome and asthma [11, 12]. Therefore, we aimed to investigate the interaction of the dietary inflammatory index on the association of indoor air pollution and childhood asthma-related outcomes.

Methods

Study design and participants

1602 children aged 7 to 12 years, attending 71 classrooms from 20 public schools located in the Portuguese city of Porto, were invited to participate in a cross-sectional study examining the association of PM levels in classrooms and asthma [13]. Children who did not provided informed consent (n=686), who refused to perform clinical procedures (n=58), who were unable to comply with study procedures (n=242), or took food supplements in the past 12 months (n=115) were excluded. A final sample of 501 children was considered for this analysis (Figure 1).

Outcome assessments

Information on respiratory symptoms was assessed by questionnaire and participants had their atopic status, airway inflammation and lung function evaluated, considering the lung function as a primary outcome.

Symptoms: A self-administered Portuguese translation of the International Study of Asthma and Allergy in Children (ISAAC) study questionnaire was completed by the child's parent or caregiver, and reviewed by a research nurse [14]. The questionnaire enquired about social, demographic and behavioral characteristics as well as about respiratory/allergic health and current respiratory symptoms in the previous 3 months. Medical asthma diagnosis was defined by a positive answer to the question "Has your child ever been diagnosed with asthma by a physician?". Maternal smoking during pregnancy was obtained from a positive answer to the question "Did the mother smoke during pregnancy?". Exposure to tobacco at home was defined by a positive answer to the questions "Is your child exposed to tobacco smoke at home?".

Lung function and airway reversibility: Spirometry was used to assess lung function and airway reversibility according to the official ATS/ERS guidelines [15] and were recorded before and after the inhalation of 400µg of salbutamol. Positive bronchodilation (+BD) was defined by at least a 12% and over 200mL increase in forced expiratory volume in 1 second (FEV1). Different asthma definitions were considered as follows [13]: i) Ever: self-reported medical diagnosis; ii) Medical diagnosis with asthma symptoms OR +BD: self-reported medical diagnosis with reported symptoms (wheezing, dyspnea or dry cough) occurring in the past 12

months OR positive bronchodilation; and iii) Medical diagnosis and under asthma treatment: self-reported medical diagnosis and currently under anti-asthma medication.

Assessment of diet and dietary inflammatory index (DII) calculation

Dietary inflammatory index (DII): Dietary data was obtained from a single 24-hour recall questionnaire answered by children, without parents and using a photo atlas to estimate portion sizes. This questionnaire aimed to obtain detailed information about all foods and beverages consumed in the previous 24 hours [16]. The DII allows the consumption categorization of a list with 45 possible food items, which range from maximally anti-inflammatory to maximally pro-inflammatory potential [11, 17]. The macro- and micronutrients in this study were corrected for total energy intake by normalizing all intakes of macro and micronutrients to a diet of 2208 kcal by regression analysis of the residual method [18]. From the 45 possible food parameters, 29 were used to calculate DII in our participants. The children consumed no alcohol. Although, various macro and micronutrients were included, data on eugenol, garlic, ginger, onion, saffron, turmeric, flavan-3-ol, flavones, flavonols, flavonones, anthocyanidins, isoflavones, pepper, thyme/oregano and rosemary were not available in our study, because no information was available for these components in the Food Processor nutritional database neither those herbs or spices were possible to collect from 24-hour recall questionnaire.

Collection and analysis of indoor air sampling

Measurements of indoor PM_{2.5}, PM₁₀, ultrafine particles (UFP), carbon dioxide (CO₂), ozone (O₃) and nitrogen dioxide (NO₂) concentrations were performed to assess air quality. These measurements levels were performed in classrooms during a 5-day period (from Monday morning until Friday afternoon) on winter season. A portable TSI DustTrak DRX photometer (model 8533; TSI Inc.) was used for the analysis of PM_{2.5} and PM₁₀, measuring particles with a laser photometer based on light scattering principle. This equipment had a $\pm 0.1\%$ accuracy reading of $1\mu\text{g}/\text{m}^3$ and the measuring range was $1\text{--}150\times 10^3\mu\text{g}/\text{m}^3$. An internal battery powered a built-in diaphragm pump that allowed a flow rate of 3.0 L/min. The measures were continuously collected for at least 8 hours. One minute was set between each sample to the logging intervals. The monitors are zeroed automatically using the external zeroing module to minimize the zero-drift effect [19].

Statistical analyses

The normality distribution of continuous variables was tested by the Kolmogorov–Smirnov test. The Mann–Whitney test was used for inferential analysis when non-Gaussians distributions were observed. In the absence of normality, the data are expressed as medians (25th–75th percentile). The proportion of effects explained by the exposures to PM_{2.5} and PM₁₀ were

measured by generalized linear mixed effect model with LOGIT LINK FUNCTION. The magnitude of the effect was estimated by Odds Ratio (OR) and 95% confidence interval (95% CI). Additionally, β and 95% CI was estimated for continuous variables. Lung function parameters, exhaled NO and all subjective and objective measures of asthma were included as outcomes, considering “medical diagnosis” and “under asthma treatment” as primary outcomes while “positive bronchodilation” and “asthma symptoms” as secondary. The values of DII were grouped in one of two categories according to the inflammatory potential of the diet: anti-inflammatory, when the values were below zero, and pro-inflammatory, when the values were higher. Shivappa *et al.* review pointed 45 food parameters and they were scored with +1, -1 or 0 according to their inflammatory effects: pro, anti or null, respectively. Accordingly, we aggregated children based on their pro or anti-inflammatory individual DII score [17]. No children obtained an individual score equal to 0. The estimates were assessed in several models: a model for main effects (model 1); a model considering an interaction between PM2.5 or 10 and dietary inflammatory index (model 2); and a model adjusted for age, sex, exposure to tobacco at home, maternal smoking during pregnancy, atopy, body mass categories and school (model 3). Model 3 only considered the interaction if this interaction was significant in model 2. A 0.05 level of significance and 95 % confidence interval (CI) was considered. R software was used to carry out all the analyses.

Ethical standards

The Ethical Committee of the University Hospital São João approved the study. Every procedure was in accordance with Helsinki Declaration, and written consent was obtained from each child’s legal guardian or parent.

Results

Asthma prevalence was 6.8, 9.2 and 6.0% (Table 1) for ever asthma, medical diagnosis with asthma symptoms or positive bronchodilation, and medical diagnosis under asthma treatment, respectively. The prevalence of both overweight and obesity according to CDC classification was 27.8% and atopy was 36.8%. The mean DII score (0.1 ± 1.5) indicated an overall pro-inflammatory diet intake. Significant differences ($p < 0.05$) between participants of each school regarding age, body mass categories, forced expiratory flow middle portion of FVC (FEF25-75), exhaled NO, atopy, DII score, exposure to tobacco at home and maternal smoking during pregnancy were found. The characteristics of the children not included in the study were similar to those included (Table S1). Lastly, the indoor levels of PM2.5, PM10, UFP, CO₂, O₃ and NO₂ were also significantly different among schools (Table S2).

After adjusting for age, sex, body mass categories, exposure to tobacco at home, maternal smoking during pregnancy and school, the exposure effect of PM 2.5 levels on children with medical diagnosis and under asthma treatment was 42% higher when diets were pro-inflammatory (Table 2, model 3 OR = 1.44, 95%CI: 1.01 to 2.21). Moreover, it was found a negative association between PM 2.5 levels and medical diagnosis and under asthma treatment (OR=0.76, 95% CI 0.46; 0.92) in children with an anti-inflammatory potential of diet. No additional significant results were found for the other asthma criteria/ definitions.

Regarding lung function parameters, crude and adjusted models revealed no significant interactions between PM2.5 levels and dietary inflammatory index (Table S3). However, after adjustment, a significant association between PM 2.5 levels and FVC reversibility (β = 0.34, CI 95% 0.16; 0.52) was found.

Similarly, the exposure effect of PM10 levels on children with ever asthma and with medical diagnosis and under asthma treatment were, respectively, 25 % and 30% higher when diets were pro-inflammatory (Table 3, model 3 OR= 1.25, 95%CI 1.02, 1.56 and OR=1.29, 95%CI 1.03, 1.68, respectively). Additionally, in children with anti-inflammatory potential of diet, a negative association between PM10 levels and medical diagnosis and under asthma treatment (OR=0.75, 95% CI 0.59; 0.91) was found.

There were not significant interactions between PM10 levels and lung function parameters (Table S4). Furthermore, PM 10 levels were positively associated with FVC reversibility (β = 0.23, CI 95% 0.09; 0.37) and FEV1 reversibility (β = 0.16, CI 95% 0.03; 0.29).

Discussion

In our study, we have shown that the effect of to PM2.5 and PM10 on children with asthma, defined by medical diagnosis and under asthma treatment, was significantly higher in those who have a pro-inflammatory compared to a more anti-inflammatory diet. Although two previously studies have suggested that pro-inflammatory diets assessed by DII were associated with current wheeze [12], asthma [11] and decreased FEV1 [11, 12] and FVC [12] in adults, and current wheeze in children [12], there is a scarcity of studies investigating the effects of nutrition and food intake on rapidly rising air pollution. These are difficult to design due to the confounding factors of diet, obesity, co-morbid illness, medication and environmental exposure [20].

The idea that diet can help to reduce some of the effects of pollution on asthma has gained interest and certain vitamins seems to attenuate the effects of air pollution on asthma [8]. A few years ago, Romieu *et al.*, observed that when exposed to ozone, children with daily supplementation of vitamins C and E, maintain their lung function levels, while lung function

levels of children not taking supplements decreased [9]. In Mexico, 117 children with asthma were assigned to either receive a daily supplement of vitamins C and E or placebo, in a double-blinded manner. Exposure assessment, namely particulates and ambient ozone, was obtained from Mexican government's air monitoring stations. In response to ozone exposure, IL-6 from nasal lavage, was significantly increased in placebo group contrary to supplemented children whose IL-6 did not decrease (1.07 pg/mL, CI 95% 0.48 to 1.65 *versus* 0.04 pg/mL, CI 95% - 0.50 to 0.64, $p=0.02$) [21]. More recently, Hansell *et al.* randomized children to receive supplement of fish oil or placebo from birth to 5 years of age [10]. Weight road density at place of residence was measured to reflect the exposure to traffic related air pollution. In this study, significant interactions between the supplementation of fish oil from birth to 5 years of age and traffic related air pollution was found for house dust mite, inhalant and all-allergen SPT at age of 5. The relative risk (RR) of positive SPT to house dust mite was significantly lower in supplemented group (RR=1.03, CI 95% 0.76 to 1.41) compared to control (RR=1.74, CI 95% 1.22 to 2.48), suggesting that supplementation eliminated the risk's increase [10].

Although studies have been conducted under ozone exposure, it was recently described that high ozone concentrations with strong atmospheric oxidation could promote the secondary particle formation enhancing ambient PM_{2.5} levels [22]. Moreover, the synergic effect when considering all dietary components seems to have larger impact on disease pathogenesis than individual nutrients and bioactive compounds [12]. Therefore, we used the DII to describe the overall intake of food for each child, considering the combination, frequency, quantity, and variety of the diet. Indeed, our results support the current evidence, revealing that an unhealthy (pro-inflammatory) diet may interact with air pollution to worsen asthma.

Our study has a few limitations. Firstly, the cross-sectional design does not allow establishing causal relationships between indoor PM levels and dietary inflammatory index and asthma. However, it is unlikely that the most of the children with respiratory disease differentially adopt a pro-inflammatory dietary pattern [12]. Furthermore, the dietary inflammatory index was previously used in Portuguese children [23, 24]. Secondly, although dietary inflammatory index, has been calculated using the 24-hour recall, not accounting for daily or seasonal variability in dietary patterns, this index was designed to be used with dietary data collected from different assessment methods, including the 24-hour-recall [17]. Moreover, since methods to estimate the food supplements contribution to habitual intakes of micronutrients are not standardized, children taking food supplements were excluded [25]. Thirdly, it was not possible to assess all the forty-five parameters of the dietary inflammatory index. Considering that all the 16 parameters excluded were all anti-inflammatory, this may have increased the DII scores of the diet. However, other studies investigating the association between DII and asthma had similar exclusions related to anti-inflammatory components [11, 12]. Nonetheless, not all parameters

that DII encompasses, such as alcohol, are appropriate when performed in children [26]. Fourthly, even though the avoidance of air pollution measurements during the summer, end-of-term vacations and at weekends, the indoor assessment was limited to 5 days, which restricted the identification of potential differences in the previous months and years of exposure. However, as already proposed by Annesi-Maesano *et al.* [27], despite the limited period of time evaluating indoor exposure, these results emphasized the potential role of school air quality on asthma. Fifthly, although we fail in evaluating the type and dose of asthma medication we considered the current under anti-asthma medication as a different asthma definition. Similarly to previous studies, addressing the role of diet on asthma medication use, asthma medication includes both inhaled corticosteroids and short acting bronchodilators [28]. Sixthly, comorbidities of asthma during childhood, namely allergic rhinitis and food allergies, were not taken into account in our study. However, the evidence of the impact of comorbidities on childhood asthma is poor [29]. Seventhly, atopy was defined based on positivity to skin prick test extract that did not include any tree pollen. Nevertheless, in the area and for this age, mites and grass pollens account for the vast majority of allergic subjects, being tree monosensitization a rare event. Lastly, we only have considered the classroom effect but children spend 8 hours per day at school environment, especially indoors. Therefore, it is expected that air quality in schools will play an important role in assessing the effects of PM exposure [13].

The present study has also important strengths. To our knowledge, this is the first community-based survey evaluating the modification of the association between air pollution and childhood asthma by the effect of the inflammatory potential of diet. Moreover, the detailed collection of health data, from a large number of children, performed by the same research team guarantees a relatively unbiased estimate of the prevalence of asthma, allergic sensitization and respiratory symptoms. Additionally, the clinical and physical assessments including a large number of participants and the measurements of indoor levels were performed in a considerable number of classrooms, accounting for several confounding factors namely the exposure to tobacco at home and maternal smoking during pregnancy. Although ultrafine particles, carbon dioxide, ozone and nitrogen dioxide had been measured indoors, we only found significant associations between PM_{2.5}, PM₁₀ and asthma. In addition, it was addressed that total mass concentration PM_{2.5} serves as an indicator that “greatly oversimplifies complex biological phenomena” [30]. Furthermore, dietary patterns have been increasingly studied as a tool to characterize the diet since they are able to express the effects of the interactions between the whole food matrixes, instead of individual dietary components [31]. Accordingly, we considered the all-dietary components available from 24h-recall, using the dietary inflammatory index to classify children dietary patterns as anti-inflammatory or pro-inflammatory. In addition, we controlled our models for body mass categories. Lastly, to estimate the effect of particulate matter on different

asthma diagnosis criteria, we used a robust statistical tool that allowed a multilevel approach, considering the complex relationship between the different levels of variables.

Particulate matter can induce oxidative stress and inflammation on respiratory airways and nutrition plays an important role in decreasing severity and managing asthma. One of the possible ways that diet can help is through the modulation of PM toxicity. Therefore, dietary components with a positive overall inflammatory effect score, such as, saturated fatty acids, can lead to the stimulation of the innate immunity through the activation of receptors, namely the TLR-4 which initiates the NF-kB inflammatory cascade [28]. In its turn, dietary components with a negative overall inflammatory effect, namely unsaturated fatty acids and antioxidants, seem to decrease the levels of C-reactive protein, IL-6 and intracellular adhesion molecule-1 in plasma. Therefore, dietary patterns should include foods that provide several antioxidants, namely fruit, vegetables and legumes, (rich in carotenoids, ascorbic acid, tocopherols and flavonoids), fatty fish (high in omega-3 PUFA) and whole grain, an important source of fibre. Moreover, micro-nutrient energy dense foods, high in trans and saturated fatty acids, sugar and salt, such those commonly found in Westernized dietary patterns, should be avoided.

In summary, the present study provide further support to the role of diet's inflammatory characteristics modulating the effects of indoor air pollution on asthma.

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Authors' Contributions: All authors were involved in investigation and gave constructive criticism of the study manuscript. IP, JCR, MF, DS and PC participated in the data collection, database construction and contributed to the interpretation of the results. FCM, MS, IP and AM contributed to the statistical analysis. LD and VGL contributed to the interpretation of the results and reviewed the manuscript. FCM, AM and PM wrote the manuscript with input from all authors.

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Tables.

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Table 1 Characteristics of the participants by attending school

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School number	Total	1	2	3	4	5	6	7	8	9	10
Participants [n(%)]	501	12 (2.4)	34 (6.8)	47 (9.4)	47 (9.4)	48 (9.6)	30 (6.0)	28 (5.6)	12 (2.4)	31 (6.2)	46 (9.2)
Classrooms [n(%)]	71	2 (2.8)	4 (5.6)	4 (5.6)	4 (5.6)	4 (5.6)	4 (5.6)	4 (5.6)	2 (2.8)	3 (4.2)	3 (4.2)
Age (years, mean $\pm$ SD)	8.7 $\pm$ 0.8	9.1 $\pm$ 0.9	8.7 $\pm$ 1.0	8.5 $\pm$ 0.7	8.6 $\pm$ 0.7	8.9 $\pm$ 0.8	8.8 $\pm$ 0.7	9.0 $\pm$ 0.9	8.9 $\pm$ 0.7	8.9 $\pm$ 0.9	8.6 $\pm$ 0.8
Female [n(%)]	241 (48.1)	5 (2.07)	13 (5.4)	26 (10.8)	22 (9.13)	28 ()	15 (50.0)	10 (35.7)	6 (50.0)	18 (58.1)	23 (50.0)
Body Mass categories† [n(%)]											
Underweight	23 (4.6)	1 (8.3)	0 (0.0)	3 (6.4)	2 (4.3)	2 (4.2)	2 (6.7)	3 (10.7)	0 (0.0)	1 (3.2)	2 (4.3)
Normalweight	339 (67.7)	7 (58.3)	19 (55.9)	36 (76.6)	35 (74.5)	37 (77.1)	17 (56.7)	13 (46.4)	7 (58.3)	20 (64.5)	33 (71.7)
Overweight	75 (15.0)	4 (33.3)	5 (14.7)	4 (8.5)	6 (12.8)	5 (10.4)	9 (30.0)	5 (17.9)	1 (8.3)	7 (22.6)	6 (13.0)
Obese	64 (12.8)	0 (0.0)	10 (29.4)	4 (8.5)	4 (8.5)	4 (8.3)	2 (6.7)	7 (25.0)	4 (33.3)	3 (9.7)	5 (10.9)
Lung function											

FVC (L, mean ± SD)	1.9 ± 0.4	2.00 ± 0.2	1.9 ± 0.4	1.8 ± 0.3	2.00 ± 0.4	1.9 ± 0.3	1.9 ± 0.3	2.1 ± 0.3	2.1 ± 0.4	2.0 ± 0.4	1.9 ± 0.3
FEV1 (L, mean ± SD)	1.8 ± 0.3	1.8 ± 0.2	1.7 ± 0.3	1.7 ± 0.3	1.9 ± 0.3	1.8 ± 0.3	1.8 ± 0.3	1.9 ± 0.3	1.9 ± 0.3	1.8 ± 0.3	1.8 ± 0.2
FEV1 reversibility (%, mean ± SD)	4.2 ± 6.3	4.6 ± 5.1	5.1 ± 5.7	3.4 ± 5.1	3.1 ± 4.5	2.4 ± 6.2	4.9 ± 5.6	4.5 ± 5.9	6.2 ± 6.2	1.7 ± 5.7	3.9 ± 5.7
FEF 25 – 75 (L/s, mean ± SD)	2.3 ± 0.5	2.3 ± 0.8	2.2 ± 0.5	2.3 ± 0.5	2.4 ± 0.6	2.4 ± 0.5	2.3 ± 0.5	2.4 ± 0.6	2.3 ± 0.5	2.4 ± 0.7	2.3 ± 0.5
FEF 25 – 75 reversibility (%, mean ± SD)	12.3 ± 15.6	16.0 ± 21.2	13.3 ± 15.3	13.5 ± 13.1	6.5 ± 11.4	6.8 ± 16.7	8.6 ± 9.9	17.2 ± 14.1	10.8 ± 16.0	7.91 ± 10.9	15.5 ± 16.7
+BD [n (%)]	28 (5.6)	0 (0.0)	2 (7.1)	2 (7.1)	1 (3.6)	2 (7.1)	2 (7.1)	1 (3.6)	1 (3.6)	1 (3.6)	2 (7.1)
Asthma definitions [n (%)]											
Ever	34 (6.8)	3 (8.8)	4 (11.8)	4 (11.8)	3 (8.8)	3 (8.8)	2 (5.9)	0 (0.0)	0 (0.0)	2 (5.9)	1 (2.9)
Medical diagnosis with asthma	46 (9.2)	2 (4.3)	5 (10.9)	5 (10.9)	4 (8.7)	4 (8.7)	4 (8.7)	1 (2.2)	1 (2.2)	3 (6.5)	2 (4.3)

symptoms or
+BD

Medical diagnosis and under asthma treatment	30 (6.0)	3 (10.0)	3 (10.0)	4 (13.3)	3 (10.0)	2 (6.7)	2 (6.7)	0 (0.0)	0 (0.0)	2 (6.7)	1 (3.3)
Exhaled NO (ppb)	11 (0.0; 137.0)	10.5 (8.3; 42.5)	11.0 (5.0; 23.3)	8.0 (4.0; 20.0)	10.0 (5.0; 22.0)	8.0 (2.0; 14.0)	10.5 (6.0; 15.8)	9.5 (4.5; 14.8)	14.8 (6.5; 18.8)	6.0 (3.0; 13.0)	10.0 (4.0; 23.3)
Atopy‡ [n(%)]	183 (36.8%)	3 (1.6)	13 (7.1)	8 (4.4)	17 (9.3)	16 (8.7)	6 (3.3)	12 (6.6)	6 (3.3)	17 (9.3)	24 (13.1)

Current
symptoms§
[n(%)]

Breathing difficulties	51 (10.5)	1 (1.9)	6 (11.8)	3 (5.9)	3 (5.9)	5 (9.8)	2 (3.9)	3 (5.9)	2 (3.9)	5 (9.8)	2 (3.9)
Irritative cough	144 (29.6)	3 (2.1)	10 (6.9)	9 (6.3)	19 (13.2)	11 (7.6)	6 (4.2)	5 (3.5)	2 (1.4)	11 (7.6)	10 (6.9)
DII score (mean ± SD)	3.7 ± 1.5	0.8 ± 1.1	0.4 ± 1.4	0.5 ± 1.4	0.0 ± 1.5	0.2 ± 1.4	-0.1 ± 1.0	-0.2 ± 1.4	0.5 ± 1.0	0.0 ± 1.4	-0.1 ± 0.3
Tobacco at home [n(%)]	168 (36.4)	7 (4.2)	16 (9.5)	14 (8.3)	16 (9.5)	22 (13.1)	9 (5.4)	11 (6.5)	5 (3.0)	10 (6.0)	17 (10.1)
Maternal	129	4 (3.1)	15 (11.6)	12 (9.3)	12 (9.3)	22 (17.1)	5 (3.9)	7 (5.4)	4 (3.1)	6 (4.7)	10 (21.7)

smoking during pregnancy [n(%)]	(26.3)										
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394 Data are expressed as medians (25th-75th percentile) unless otherwise stated

395 †: according to US Centres for Disease Control

396 ‡: defined by a positive skin prick test to at least one of the allergens

397 §: symptoms in the previous 3 months

398 +BD: positive bronchodilation defined by at least a 12% and over 200mL increase in forced expiratory volume in 1 second (FEV1)

399 Ever asthma: self-reported medical diagnosis

400 Medical diagnosis or +BD: self-reported medical diagnosis OR positive bronchodilation

401 Medical diagnosis with asthma symptoms or +BD: self-reported medical diagnosis with reported symptoms (wheezing, dyspnea or dry cough) occurring in the past 12 months

402 OR positive bronchodilation

403 Medical diagnosis and under asthma treatment: self-reported medical diagnosis and currently under anti-asthma medication

404 FVC: forced vital capacity

405 FEV1: forced expiratory volume in the first second

406 FEF25-75: forced expiratory flow middle portion of FVC

407 FEV1 reversibility: forced expiratory volume in the first second after bronchodilation

408 FEF25-75 reversibility: forced expiratory flow middle portion of FVC after bronchodilation

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411 **Table 1** Characteristics of the participants by attending school (cont.)

School number	11	12	13	14	15	16	17	18	19	20	p-value
Participants [n(%)]	26 (5.2)	12 (2.4)	22 (4.4)	15 (3.0)	8 (1.6)	7 (1.4)	15 (3.0)	15 (3.0)	23 (4.6)	23 (4.6)	
Classrooms [n(%)]	4 (5.6)	4 (5.6)	3 (4.2)	3 (4.2)	2 (2.8)	3 (4.2)	2 (2.8)	4 (5.6)	4 (5.6)	4 (5.6)	
Age (years)	8.5 ± 0.7	8.6 ± 0.5	8.4 ± 0.7	8.3 ± 0.5	7.9 ± 0.4	9.0 ± 1.0	8.3 ± 0.8	8.7 ± 0.8	8.9 ± 0.7	8.5 ± 0.6	<0.01
Female [n(%)]	11 (4.6)	7 (3.0)	4 (1.7)	4 (1.7)	6 (2.5)	3 (1.2)	6 (2.5)	8 (3.3)	14 (5.8)	12 (5.0)	0.21
Body Mass categories [†] [n(%)]											0.343
Underweight	2 (8.7)	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	1 (4.3)	1 (4.3)	1 (4.3)	
Normalweight	15 (4.4)	9 (2.7)	16 (4.7)	11(3.2)	7 (2.1)	5 (1.47)	9 (2.7)	9 (2.7)	16 (4.7)	18 (5.3)	
Overweight	2 (2.7)	2 (2.7)	2 (2.7)	4 (5.3)	1 (1.3)	1 (1.3)	2 (2.7)	3 (4.0)	4 (5.3)	2 (2.7)	
Obese	7 (10.9)	0 (0.0)	4 (6.3)	0 (0.0)	0 (0.0)	11 (17.2)	3 (4.7)	2 (3.1)	2 (3.1)	2 (3.1)	
Lung function											
FVC (L, mean ± SD)	1.8 ± 0.3	2.0 ± 0.3	2.0 ± 0.5	1.9 ± 0.2	1.8 ± 0.2	2.00 ± 0.3	1.8± 0.4	1.9 ± 0.5	2.0 ± 0.3	1.9 ± 0.3	0.21
FEV1 (L, mean ± SD)	1.6 ± 0.3	1.8 ± 0.3	1.8 ± 0.4	1.8 ± 0.2	1.7 ± 0.2	1.8 ± 0.2	1.6 ± 0.2	1.8 ± 0.4	1.9 ± 0.3	1.8 ± 0.3	0.24
FEV1 reversibility (%, mean ± SD)	6.0 ± 7.9	5.8 ± 3.3	5.2 ± 6.1	2.5 ± 5.5	1.7 ± 8.0	5.4 ± 9.8	6.6 ± 7.0	6.4 ± 12.5	5.0 ± 6.3	4.0 ± 4.2	0.32
FEF 25 – 75	2.1 ± 0.4	2.3 ± 0.5	2.3 ± 0.5	2.4 ± 0.6	2.2 ± 0.4	2.1 ± 0.6	2.2 ± 0.5	2.4 ± 0.9	2.6 ± 0.5	2.4 ± 0.5	0.58

(L/s, mean $\pm$ SD)											
FEF 25 – 75 reversibility (% , mean $\pm$ SD)	17.2 $\pm$ 17.9	16.4 $\pm$ 16.4	8.6 $\pm$ 16.8	10.6 $\pm$ 13.3	14.4 $\pm$ 6.82	18.6 $\pm$ 11.2	18.4 $\pm$ 18.8	12.5 $\pm$ 30.9	11.6 $\pm$ 12.6	14.3 $\pm$ 12.7	0.04
+BD [n (%)]	3 (10.7)	0 (0.0)	1 (3.6)	1 (3.6)	1 (3.6)	2 (7.1)	3 (10.7)	1 (3.6)	2 (7.1)	0 (0.0)	0.33
Asthma defenitions [n (%)]											
Ever	4 (11.8)	0 (0.0)	1 (2.9)	1 (2.9)	1 (2.9)	0 (0.0)	1 (2.9)	1 (2.9)	2 (5.9)	1 (2.9)	0.54
Medical diagnosis with asthma symptoms or +BD	4 (8.7)	0 (0.0)	1 (2.2)	1 (2.2)	1 (2.2)	2 (4.3)	2 (4.3)	2 (4.3)	2 (4.3)	0 (0.0)	0.75
Medical diagnosis and under asthma treatment	3 (10.0)	0 (0.0)	1 (3.3)	1 (3.3)	1 (3.3)	0 (0.0)	0 (0.0)	1 (3.3)	2 (6.7)	1 (3.3)	0.55
Exhaled NO (ppb)	16.0 (11.0; 24.3)	15.0 (7.0; 19.5)	19.5 (7.0; 38.0)	10.0 (8.0; 17.0)	17.0 (11.0; 30.3)	21.0 (5.0; 32.0)	16.0 (9.0; 20.0)	11.0 (6.00; 15.0)	10.0 (6.0; 23.0)	12.0 (7.0; 15.0)	<0.01

Atopy ‡ [n(%)]	6 (23.1)	1 (8.3)	6 (28.6)	1 (7.1)	5 (62.5)	5 (71.4)	9 (60.0)	9 (60.0)	13 (56.5)	6 (26.1)	<0.01
Current symptoms§											
Breathing difficulties [n (%)]	3 (5.9)	2 (3.9)	2 (3.9)	1 (2.0)	1 (2.0)	0 (0.0)	1 (2.0)	2 (3.9)	4 (7.8)	3 (5.9)	0.91
Irritative cough [n (%)]	9 (6.3)	6 (4.2)	7 (4.9)	4 (2.8)	3 (2.1)	2 (1.4)	5 (3.5)	5 (3.5)	10 (6.9)	7 (4.9)	0.64
DII score (mean ± SD)	-0.3 ± 1.5	0.7 ± 1.4	-0.2 ± 2.1	0.1 ± 1.7	-0.1 ± 1.6	0.5 ± 0.7	-1.9 ± 1.5	5.3 ± 1.2	0.6 ± 1.4	0.1 ± 2.2	<0.01
Tobacco at home [n(%)]	13 (7.7)	2 (1.2)	6 (3.6)	2 (1.2)	0 (0.00)	2 (1.2)	5 (3.0)	1 (0.6)	5 (3.0)	5 (3.0)	0.03
Maternal smoking during pregnancy [n(%)]	12 (9.3)	3 (2.3)	3 (2.3)	1 (0.8)	0 (0.0)	0 (0.0)	4 (3.1)	6 (4.7)	2 (1.6)	1 (0.8)	<0.001

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413 Data are expressed as medians (25th-75th percentile) unless otherwise stated

414 †: according to US Centres for Disease Control

415 ‡: defined by a positive skin prick test to at least one of the allergens

416 §: symptoms in the previous 3 months

417 +BD: positive bronchodilation defined by at least a 12% and over 200mL increase in forced expiratory volume in 1 second (FEV1)

418 Ever asthma: self-reported medical diagnosis
419 Medical diagnosis or +BD: self-reported medical diagnosis OR positive bronchodilation
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421 OR positive bronchodilation
422 Medical diagnosis and under asthma treatment: self-reported medical diagnosis and currently under anti-asthma medication
423 FVC: forced vital capacity
424 FEV1: forced expiratory volume in the first second
425 FEF25-75: forced expiratory flow middle portion of FVC
426 FEV1 reversibility: forced expiratory volume in the first second after bronchodilation
427 FEF25-75 reversibility: forced expiratory flow middle portion of FVC after bronchodilation
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Table 2 Multilevel model analysis for the association between Particulate Matter 2.5 and asthma definitions

	Model 1	Model 2	Model 3
Ever asthma			
PM2.5	0.92 (0.78; 1.04)	0.77 (0.56; 0.98)	0.91 (0.78; 1.03)
DII	1.17 (0.56; 2.44)	0.34 (0.06; 1.71)	1.01 (0.47; 2.13)
PM2.5 x DII		1.28 (0.96; 1.83)	--
Medical diagnosis with asthma symptoms or +BD			
PM2.5	0.95 (0.86; 1.05)	0.89 (0.72; 1.04)	0.95 (0.85; 1.05)
DII	1.11 (0.59; 2.06)	0.59 (0.16; 2.06)	1.12 (0.58; 2.12)
PM2.5 x DII	--	1.12 (0.92; 1.42)	--
Medical diagnosis and under asthma treatment			
PM2.5	0.89 (0.74; 1.02)	0.68 (0.46; 0.92)	0.68 (0.46; 0.91)
DII	1.20 (0.55; 2.57)	0.23 (0.04; 1.35)	0.20 (0.03; 1.15)
PM2.5 x DII	--	1.43 (1.01; 2.20)	1.44 (1.01; 2.21)

PM2.5: Particulate Matter 2.5 represented per 100 units

DII: Dietary Inflammatory Index categories

PM2.5 x DII: Dietary inflammatory index categories as an interaction term

+BD: positive bronchodilation defined by at least a 12% and over 200mL increase in forced expiratory volume in 1 second (FEV1)

Ever asthma: self-reported medical diagnosis

Medical diagnosis with asthma symptoms or +BD: self-reported medical diagnosis with reported symptoms (wheezing, dyspnea or dry cough) occurring in the past 12 months OR positive bronchodilation

Medical diagnosis and under asthma treatment: self-reported medical diagnosis and currently under anti-asthma medication

Model 1: Main effects

Model 2: considering an interaction between PM2.5 and DII

Model 3: Additionally adjusted for age, sex, exposure to tobacco at home, maternal smoking during pregnancy, atopy, body mass categories according to CDC and school

Significant associations in **bold**

Table 3 Multilevel model analysis for the association between Particulate Matter 10 and asthma definitions

	Model 1	Model 2	Model 3
Ever asthma			
PM10	0.95 (0.85; 1.04)	0.82 (0.66; 0.97)	0.81 (0.66; 0.95)
DII	1.19 (0.57; 2.49)	0.23 (0.04; 1.28)	0.19 (0.03; 1.01)
PM10 x DII	---	1.23 (1.01; 1.55)	1.25 (1.02; 1.56)
Medical diagnosis with asthma symptoms or +BD			
PM10	0.98 (0.91; 1.05)	0.93 (0.82; 1.05)	0.97 (0.90; 1.04)
DII	1.12 (0.59; 2.07)	0.61 (0.15; 2.41)	1.13 (0.59; 2.16)
PM10 x DII	---	1.07 (0.93; 1.25)	---
Medical diagnosis and under asthma treatment			
PM10	0.91 (0.81; 1.00)	0.76 (0.60; 0.93)	0.76 (0.59; 0.92)
DII	1.24 (0.57; 2.67)	0.20 (0.03; 1.17)	0.16 (0.02; 1.00)
PM10 x DII	---	1.28 (1.03; 1.67)	1.29 (1.03; 1.68)

PM10: Particulate Matter 10 represented per 100 units

DII: Dietary Inflammatory Index categories

PM10 x DII: Dietary inflammatory index categories as an interaction term

+BD: positive bronchodilation defined by at least a 12% and over 200mL increase in forced expiratory volume in 1 second (FEV1)

Ever asthma: self-reported medical diagnosis

Medical diagnosis with asthma symptoms or +BD: self-reported medical diagnosis with reported symptoms (wheezing, dyspnea or dry cough) occurring in the past 12 months OR positive bronchodilation

Medical diagnosis and under asthma treatment: self-reported medical diagnosis and currently under anti-asthma medication

Model 1: Main effects

Model 2: considering an interaction between PM10 and DII

Model 3: Additionally adjusted for age, sex, exposure to tobacco at home, maternal smoking during pregnancy, atopy, body mass categories according to CDC and school

Significant associations in **bold**

468 **Figures.**

469 **Figure 1** Flow chart of the study participants.

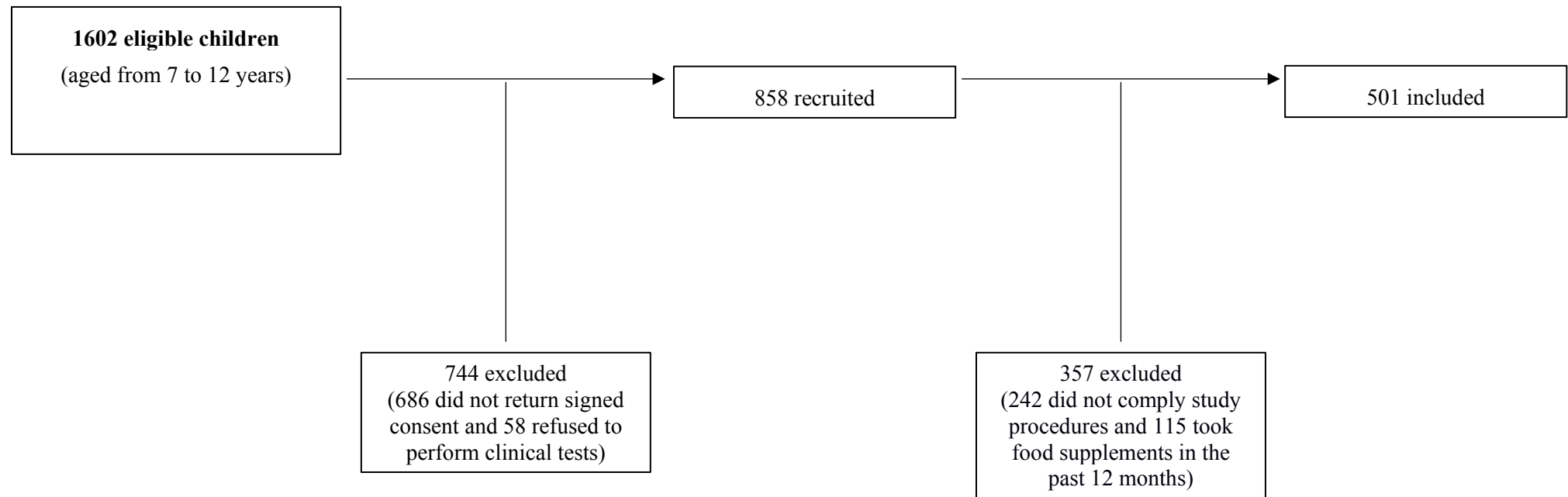


FIG 1. Flow chart of the participants in the study.