



18-year evolution of asthma and allergic diseases in French urban schoolchildren in relation to indoor air pollutant levels

Fabien Sasso^a, Mathieu Izard^b, Thomas Beneteau^c, Thierry Rakotozandry^a, Myriam Ramadour^d, Isabella Annesi-Maesano^c, Dominique Robin^b, Denis Charpin^{a,*}

^a Pulmonology Unit, La Timone Hospital, Marseille and Aix-Marseille University, France

^b Atmo-Sud, Marseille, France

^c EPAR, IPLESP, UMR S, 1136, INSERM & UPMC Paris 6, Sorbonne University, Medical School Saint-Antoine, France

^d Central Services, Luminy Campus, Marseille, France

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ABSTRACT

Background: An initial epidemiological study carried out 18 years ago in Marseilles indicated that the air quality in schools was poor and that there was an association between the level of fine particulates and the occurrence of asthma in children. The aim of the present study was to evaluate the change in the prevalence of childhood asthma and allergic diseases and their link with the levels of air pollutants and other factors of potential risk. **Methods:** In 2016, using a questionnaire identical to the one used for the 1st survey in 1998–1999, we collected information regarding the symptoms, the diagnosis, and the potential confounding factors. We measured the main indoor and outdoor pollutants at the schools.

Results: Overall, the prevalence of asthma and of allergic diseases exhibited an increasing trend in the time interval between the two studies, significant only for dry cough and pollen allergy. The level of air pollutants decreased significantly indoors. In spite of this, we found a correlation and a dose-effect relationship between the level of PM_{2.5} and the prevalence of asthma. A family history of asthma and allergies, the insalubrity of the place of residence, and a non-Mediterranean diet were also associated with the risk of these diseases.

Conclusion: In the time interval between the two studies, which were 18 years apart, despite a reduction in the level of air pollutants in classrooms, asthma was still related to PM_{2.5}. Other potentially causative or contributing environmental factors were also related to asthma and allergies.

1. Introduction

Stage 2 of the ISAAC-France survey, which was undertaken in 1998–1999, concluded that the air quality was poor in a third of the scholastic facilities of six large cities that had participated in the study, and revealed the existence of a relationship between pollution by fine particles and the risk of asthma [1]. Due to the absence of a thorough epidemiological survey since this time in France, and in light of the interest that has been generated to date regarding atmospheric pollution and its long-term effects, it struck us that it would be useful to perform a new epidemiological study of schools in the Marseille metropolitan area in 2016 based on a protocol similar to the one used in 1998–1999 in terms of the measurements of pollutants and the questionnaire, although without the other paraclinical examinations.

2. Aims

2.1. The main objective

The main objective of this epidemiological study was to reevaluate the prevalence of asthma and allergic diseases in children in the Marseille metropolitan area in 2016, so as to assess the change, over a period of approximately seventeen years (1999–2016), of this prevalence for a sample of children that can be considered to be representative of pupils in grades CM₁ and CM₂.

2.2. The secondary objective

The secondary objective of this survey was to reevaluate the level of indoor pollution in primary school classrooms in 2016, to compare this with the levels of pollution recorded in 1999, and to assess its impact on

* Corresponding author. Pulmonology Unit, Groupe Hospitalier de la Timone, 264, rue Saint-Pierre, 13385, Marseille, cedex 05, France.

E-mail address: denis-andre.charpin@ap-hm.fr (D. Charpin).

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asthma and allergic diseases.

3. Materials and methods

3.1. The studied group

We selected in 2016 the same 17 schools in the Marseille metropolitan area as the ones that had participated in phase 2 of the ISAAC survey in 1999, so as to repeat the same protocol.

The schools' selection was based on their exposure to outdoor air contaminants found in the Marseille metropolitan area. Thus, a small number of these schools were located in the Marseille city center, while the remainder were located in the outskirts south of town. Seventeen of the 18 schools participating in stage 2 of the ISAAC survey in 1999 also participated in the 2016 survey. The eighteenth school in stage 2 of the ISAAC survey could not be located and was therefore not included in the 2016 survey. All of the children in grades CM₁ and CM₂ at each school were included in the survey.

For logistical reasons, we only had the parents of the pupils filling out the standardized questionnaire, which was identical to the one filled out by the parents of the children participating in survey in 1999. The clinical examinations, urine analyses, cutaneous allergological tests and a standardized 6 min running test performed in 1999 were not repeated in 2016.

3.2. Methodology

3.2.1. The questionnaire

We repeated in 2016 the distribution of the standardized questionnaire already used in 1999, which was based on the international ISAAC 2 questionnaire regarding asthmatic, rhinitis, and prior or current cutaneous, symptoms, the diagnosis of asthma, allergic rhinitis and eczema, as well as potential confounding factors. These anonymous questionnaires were exhaustive and they were in the form of a booklet of seventeen pages comprising 25 items. After having met with each school principal, scheduling of the distribution was established according to each school's intake. The questionnaires were distributed in person to the pupils of every CM₁ and CM₂ grade at each school. The questionnaires had to be filled out by the parent(s) of the pupil or their legal guardian, and they were collected at each school approximately 15 days later.

3.2.2. Logistics

Authorization for the survey was obtained from the Institutional Review Board (IRB N° 2016/03) and the French Data Protection Agency (CNIL N° 1990795).

A few months before the start of the study, we scheduled a meeting with the doctor responsible for the Aix-Marseille Academy, in order to inform them of the objectives of our survey, as well as its practical modalities. Once the medical nature of the project was approved, a meeting was held with the deputy director of the Aix-Marseille Academy and the Academy Inspectors concerned with the schools that we wished to study. A letter written by the deputy director of the Aix-Marseille Academy in support of our request was also sent to the school principals. We then met with each school principal so as to inform them of our project either through individual meetings or through joint meetings with the relevant Academy Inspectors. A member of the AirPACA team, which was an associated entity responsible for monitoring air quality in the Provence-Alpes-Côte-d'Azur (PACA) region attended each meeting so as to show the school principals the metrological modalities. After having obtained their approval, the parents of the children were informed in writing regarding the modalities of the survey.

After handing out the questionnaires, meetings were held in the schools in order to provide assistance to families who had difficulty understanding and/or completing it. In parallel, certain school

principals held meetings with parents of the children so as to implement a hotline aimed at assisting families as much as possible with completing the questionnaires. Associations of parents of the pupils also became involved. Furthermore, in "Urban Policy" neighborhoods, corresponding with areas where promoting education is a priority, additional assistance was offered to the school principals of the areas concerned so as to assist families with correctly completing the questionnaires.

3.2.3. Metrology

AirPACA performed the metrological measurements in 1999, and this entity was commissioned to repeat the measurements in 2016. A member of AirPACA participated in all of the meetings with the school principals in order to present the project to them, along with presentation of the study and distribution of the questionnaires. Meetings were then held for the AirPACA member and the principals so as to identify the rooms to be monitored and to assess their availability in 2016 compared to in 1999.

The objective was to repeat the measurements in the same classrooms as in 1999. AirPACA was therefore instructed to carry out measurements of nitrogen dioxide (NO₂), fine particulate matter (PM_{2.5}), aldehydes, benzene and carbon monoxide (CO) and of the comfort parameter CO₂ at each school, while seeking to adhere as much as possible with the chronological order in which the measurements were made in 1999.

The sampling cartridges used for aldehydes, NO₂ (Passam), and benzene were identical to those used in 1999.

The technique for measuring PM_{2.5} (gravimetry) was identical to the one used in 1999.

The measurements were started in February of 2016 and they ended at the start of July of 2016. The collection of pollutants was undertaken at each school over the course of a school week (4.5 days). The measuring equipment was put in place on the Monday morning before 08h30 and it was recovered on the Friday at about 16h30. It was placed at a height in each classroom that precluded being within reach of the children and, if possible, sufficiently away from all of the windows.

Measuring devices were placed in each classroom, and measurements under the roof of the schoolyard were also taken in the case of NO₂ and benzene; the measurement under the roof of the schoolyard was considered to be representative of the nearby exposure of the children, as the primary schools were generally within no more than a 500 m radius of the pupils' homes.

For aldehydes, the technicians used Radiello™ 165 passive diffusion cartridge samplers. Nitrogen dioxide was measured using specific diffusion cartridge samplers (Passam). The samplings and analyses of other families of volatile organic compounds (VOCs) were carried out using Radiello™ 145 passive diffusion cartridges. Measurement of low-molecular weight VOCs (equivalent to formaldehyde) and Total VOCs (equivalent to toluene) were carried out using Fireflies® sensors (AZIMUT Monitoring) equipped with electrochemical detection micro-sensors.

3.2.4. Measurements of the concentrations of PM_{2.5} were performed in two ways

The average mass concentration over the measurement period was obtained by gravimetry. The sampling was carried by an active method with pre-weighed Teflon filters. The air was aspirated at a flow rate of 1.8 L/min through a sampling head specific for the PM_{2.5} fraction (H-PEM) over the period that the classrooms were occupied. The filters were then weighed for quantification of the mass of the particles. Additionally, measurements in real-time were performed with a pDR-1500 optical counter of fine particles. This was a portable nephelometer allowing real-time measurement of the mass concentration of dust suspended in the air. For logistical reasons, only two classrooms per school could undergo measurement of PM_{2.5} by gravimetry. These classrooms were selected randomly.

Table 1

The relevance of respiratory symptoms over the course of the past 12 month of the child's life (upper part of the table) and over the course of their entire life (lower part).

Respiratory symptoms (year)	2016	1999	p
Dry nocturnal cough without indication of a respiratory infection	249 (20.8%)	152 (14.9%)	< 0.001
Chest wheezing during or after exertion	74 (6.2%)	49 (4.8%)	0.323
Chest wheezing at any time	97 (8.1%)	67 (6.6%)	0.421
Respiratory symptoms (life)	2016	1999	p
Already awoken by a feeling of chest tightness	186 (15.6%)	152 (14.9%)	0.752
Already awoken by shortness of breath	92 (7.7%)	68 (6.7%)	0.667
Chest wheezing	261 (21.8%)	195 (19.1%)	0.535

Lastly, the measurement of CO₂ levels was carried out by means of a nondispersive infrared detector, while CO levels were determined using an electrochemical detector.

3.2.5. Statistical analyses

The first stage of our epidemiological study was descriptive, and it assessed the changes in the prevalence of asthma, childhood allergic diseases, and atmospheric pollution for the period in question (1999–2016). The second stage was analytical, and its aim was to study the impact of atmospheric pollution and other risk factors on the prevalence of asthma and childhood allergic diseases.

For the dichotomous variables, we determined the percentage of positive, negative, or absent answers. For the continuous variables, the average and the maximal and minimal values for the distribution were calculated. A p-value < 0.05 was taken to indicate statistical significance.

For the dichotomous variables, the analysis comprised comparison of the percentages of the positive answers to the various questions, by the Chi-square test, after adjustment for potential confounding factors for which the distribution between the two surveys, also evaluated by the Chi-square test, yielded a p-value of less than 0.10. For the continuous variables, we performed a Student's t-test, again after adjustment for potential confounding factors.

After adjustment for potential confounding factors, an odds-ratio was calculated for the logistic regression model so as to express a possible statistical association between two variables, with a confidence interval of 95%. The following potential confounding factors were considered: age, gender, the neighborhood, a prior family history of asthma or allergic reactions, the socioeconomic level, passive smoking, diet, the condition of the home and particularly its level of insalubrity, the presence of domestic animals, prematurity, the body mass index and a low birth weight, the childcare arrangement, and maternal breast feeding beyond four months of age.

The confounding factors for which the p-value was below 0.10 were selected and they were included in the statistical analysis.

The notion of insalubrity was defined by an affirmative answer to at least one of the following items: “Is, or was, the home's paint peeling?; Is, or was, there often condensation in the home?; Is, or was, there water damage in one of the main rooms in the home?; Are, or were, there damp patches or mildew on the surface of any of the main rooms in home?”.

We then performed a semi-individual approach, given that the statistical unit for the clinical data was individual (questionnaire) while for the parameters for pollution of the unit was the classroom. The exposures to airborne contaminants of the air were regrouped as tertiles and a new logistic regression model was calculated after adjustment for potential confounding factors. Three tertiles were defined: “low”, whereby the lowest exposure was the reference; the values obtained for the “medium” and “high” tertiles were compared to the “low” tertile.

4. Results

4.1. Characteristics of the studied population

Of the 1587 questionnaires that were distributed, 1228 were collected. The rate of return was therefore 77.4%. Of the 1228 questionnaires that were collected, 29 were not interpretable. The study was therefore based on the 1199 questionnaires that had been collected and that were interpretable. These were compared to the 1019 children that were studied in 1999. In our study, boys comprised 51.9% and girls 48.1%. The average age was 10.3 years.

4.2. Change in the prevalence of allergic diseases

4.2.1. Prevalence of asthma symptoms

The prevalence of the main symptoms of asthmatic disease is summarized in Table 1, which compares the results with those of the first survey. There was an increasing trend in the symptoms suggestive of asthma. This trend was significant only for the prevalence of a dry nocturnal cough over the course of the last 12 months. Some (i.e. 21.8%) of the parents who were questioned indicated that their child had experienced chest wheezing at some stage in their life. Of these 261 children, 37.2% had experienced chest wheezing at some time in the last 12 months. Out of these 97 children who had already exhibited chest wheezing in the last 12 months, 10 (i.e. 10.3% of this population), experienced a wheezing attack in the past year that was sufficiently serious to prevent them from saying more than one or two words in the attack's aftermath.

4.2.2. Prevalence of allergic rhinitis symptoms

In the present study, 399 children, or 33.3% of the studied population, indicated that they had experienced allergic rhinitis symptoms in their life, such as sneezing, a runny nose, or nasal congestion that did not coincide with a respiratory infection. In 1999, 264 children, or 25.9% of the studied population exhibited such symptoms (p < 0.02). In the 2016 survey, 90% of these children had exhibited symptoms in the past year. This percentage was 85.6% in 1999, a difference that was not statistically significant.

Only 64.8% of the parents of children exhibiting symptoms of allergic rhinitis thought that these symptoms were allergic. Of the parents who answered in the affirmative to this question, 54.2% said so because their child has already undergone cutaneous tests and 45.8% since they had been provided the diagnosis by their family doctor.

4.2.3. Prevalence of eczema symptoms

Two hundred and seventy-two children, or 23% of the studied population, indicated that they had already experienced an intermittent pruritic skin rash for a period of at least six months in their lives, while in 1999 there were 262 such children, or 23.7% of the studied population (a difference that was not statistically significant).

In 2016, two hundred children (16.7%) had a pruritic rash in the last year versus 152 children (14.9%) in 1999 (p < 0.001).

Table 2

Change in the prevalence of the diagnosis of asthma, allergic rhinitis, and eczema for the 1999–2016 period.

Diagnosis	2016	1999	p
Asthma	153 (12.8%)	106 (10.4%)	0.260
Allergy to pollen	278 (23.3%)	129 (12.7%)	< 0.001
Eczema	294 (24.5%)	233 (22.9%)	0.893

Table 3

Change in the level of atmospheric pollutants measured over 5 days in each classroom and in the school playground, in 1998–1999 and in 2016.

Indoor pollutants	2016	1999	p
NO ₂	22.4 ± 9.2	29.9 ± 14.9	0.0013
PM _{2.5}	10.4 ± 3.6	15.7 ± 4.9	< 0.001
Formaldehyde	16.7 ± 9.2	24.0 ± 13.5	< 0.001
Acetaldehyde	5.4 ± 1.9	8.1 ± 4.5	< 0.001
Benzene	1.55 ± 0.4	Not measured	/
Outdoor pollutants	2016	1999	p
NO ₂	26.5 ± 8.1	37.5 ± 15.3	< 0.001
Benzene	1.21 ± 0.38	NC	/

The comparison of the prevalence of the diagnoses between 1999 and 2016 is presented in Table 2.

4.3. Change in atmospheric pollution and relationship to asthma and allergies

The average levels of indoor NO₂, PM_{2.5}, formaldehyde, and acetaldehyde in all of the classrooms assessed in 2016 were compared to those obtained in 1999 (Table 3). The overall change in outdoor NO₂ is also presented in Table 3. Both indoor and outdoor air pollutants levels decreased significantly.

Fig. 1 shows the association between the diagnosis of asthma and the exposure to PM_{2.5}, organized according to tertiles, as defined previously, according to a regression model with adjustment for the numerous confounding factors, and exhibiting a significant dose-effect relationship. This association was not found for the other pollutants, or in regard to allergic rhinitis and eczema.

4.4. Investigation of other risk factors of childhood asthma and allergic diseases

Using this logistic regression model, we sought to show a statistically significant association between exposure to a risk for asthma or childhood allergic diseases, and the occurrence of one of these pathologies in the pupils who participated in the survey of 2016.

Apart from the deleterious effect already mentioned of pollution by fine particles, should also be mentioned the role of genetic factors, insalubrity, and nutritional factors. It should be noted that the number of insalubrious homes went from 20% to 35% in the time interval between the two surveys. A role for genetic factors can be seen with the presence of asthma in the father and of allergic rhinitis or dietary allergies in the mother. Insalubrity and nutritional factors, such as eating fast-food, had a relative risk of allergic rhinitis of 1.18 ($p = 0.05$), while white fish and raw vegetables had a protective factor of 0.38 ($p = 0.09$).

Applying a logistic regression model yielded an association between a maternal and paternal history of eczema and the answer to the following question: “Has your child already has a skin rash and that appeared and disappeared intermittently over a period of six months?” The consumption of citrus appeared to be protective, with a relative risk of 0.38 ($p < 0.001$).

5. Discussion

Overall, we observed a slight increase in the rate of occurrence for asthma, rhinitis, and eczema over the course of the time period in question. However, these trends were not statistically significant, with the exception of a dry cough occurring in the last 12 months, the diagnosis of allergy to pollen, and the prevalence of a rash indicative of eczema in the last 12 months. This result is in keeping with the increase in the prevalence of asthma that has been documented at the national level in children at the end of preschool for the 2012–2013 period compared to 2005–2006 [2].

The measurements of indoor pollution carried out in 2016 revealed a statistically significant decrease between 1999 and 2016 in the pollutants measured indoors, that is to say NO₂, PM_{2.5}, formaldehyde, and acetaldehyde. This finding is in keeping with an overall improvement in the air quality in schools, even if other pollutants present in the air that can have an impact on the occurrence of asthma and allergic diseases, such as VOCs other than aldehydes, for example phthalates, or also ultrafine particles and polycyclic aromatic hydrocarbons, were not measured. Outdoor NO₂ was also diminishing in line with the recent conclusions from the report by the central air quality monitoring laboratory comparing the 2005–2006 and 2012–2013 periods [3].

Overall, there was a trend although not significant for an increase in the prevalence of symptoms and the diagnosis of asthma and allergic diseases in children over the course of this 18 year period, while the level of indoor air pollutants decreased. However, just like in the first survey PM_{2.5} was still significantly related to asthma in our second survey in spite of its lower concentrations. Other risk factors will therefore have to be identified, although this descriptive survey cannot provide clues to explain the relationship between increasing trends in asthma and allergic diseases and environmental and lifestyle changes.

The logistic regression model used in our study after adjustment for confounding factors allowed a statistically significant association to be shown between the exposure to indoor PM_{2.5} and the risk of asthma, with a dose-response curve. This is in keeping with the experimental and epidemiological results for a good number of other studies. Thus, Bowatte et al. in a meta-analysis of studies of birth cohorts, showed a statistically significant risk of asthma in relation to exposure to fine particles, and an association with allergic rhinitis and eczema [4]. They also showed that, after adjustment for confounding factors, the insalubrity of the children's homes was associated with the occurrence of respiratory symptoms. Numerous international studies [5–7] have shown a link between insalubrity and the occurrence of asthma and even aggravation of the respiratory condition of asthmatic patients, particularly for children. The prior ISAAC study performed in France identified nutritional factors, that is to say the consumption of “fast-food” as a risk factor, and the consumption of fish and of raw vegetables as protective factors at the national level [8]. The role of genetic factors is clearly well known.

Our study has some limitations. The time frame in which the metrological measurements were performed was short (4.5 days), although the teachers and the children did not change their habits during this measurement period. Furthermore, the school environment was not the only source of pollution for the children, as it can also be present in the children's homes. The level of domestic pollutants was not measured, although their presence was indicated by the answers to the questionnaire.

The main strength of the present study lies with the large sample size. Furthermore, the ISAAC method that it employs is a reliable methodology that has been used in numerous publications since the early 2000s. Measurement of the various pollutants was also done in a reliable and objective manner by the AirPACA teams according to a strict and rigorous methodology, while trying to closely reproduce what had already been done in 1999. The level of participation was very satisfactory, and this may have been due to involvement of the inspectors of the academy, the principals and the teachers, as well as the

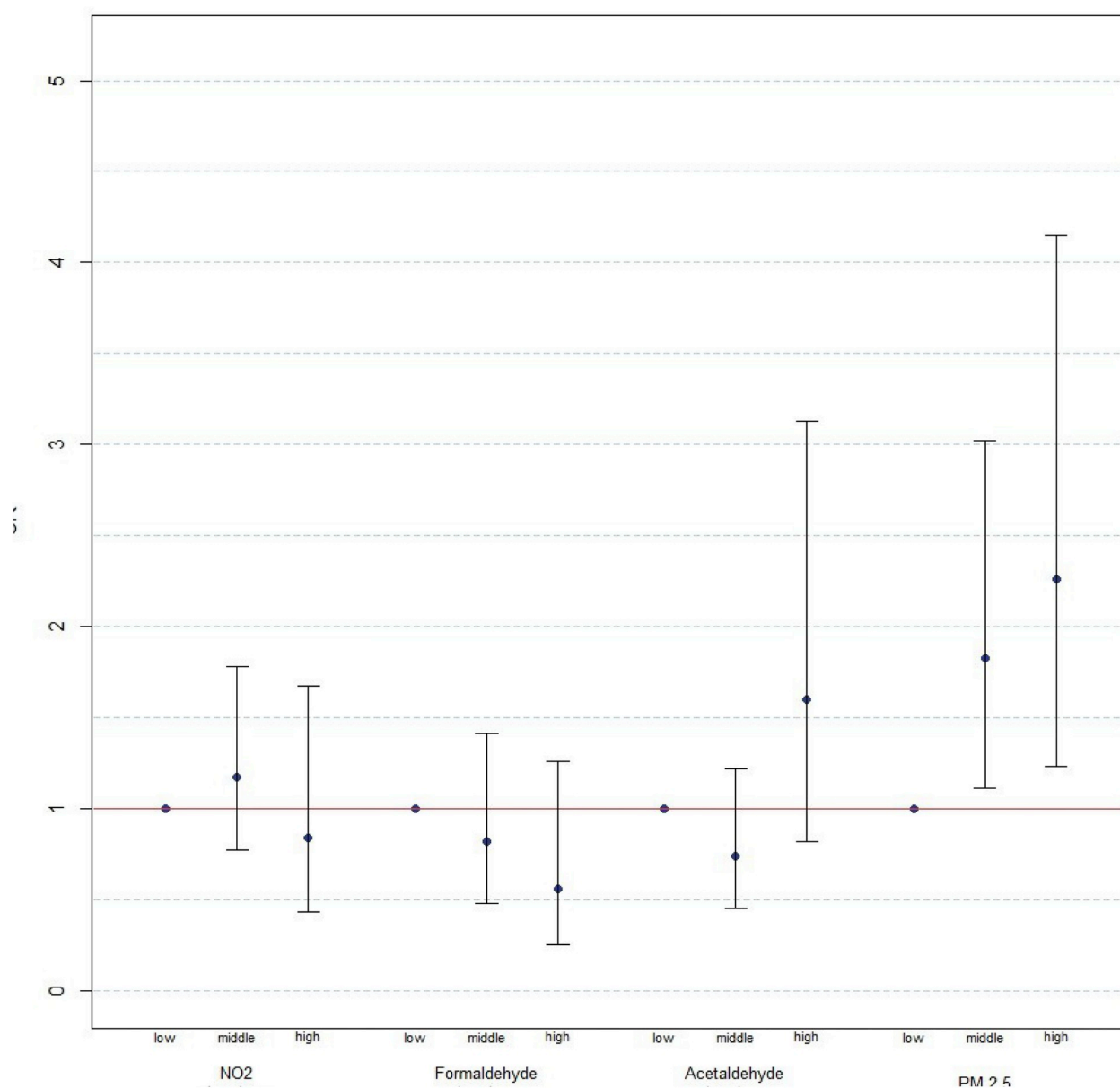


Fig. 1. Odds-ratios between exposure to indoor atmospheric pollutants (tertiles) and the diagnosis of asthma in the set of pupils who were studied.

distribution and collection of the questionnaires in person.

6. Conclusion

An increasing trend in the prevalence of asthma and allergies appears in schoolchildren of our survey over the course of the 1999–2016 period. Simultaneously, the levels of the main tracers of atmospheric pollution decreased in the classrooms. However, we found a significant dose-effect relationship between $PM_{2.5}$ and asthma diagnosis. As asthma and allergies are multifactorial diseases, this indicates that other risk factors warrant being considered to explain asthma and allergies increase, such as insalubrity and dietary habits, even though there is still an association in regard to the level of fine particles.

Conflicts of interest

The authors declare that they have no competing interests.

Conflicts of interest

None.

Author contributions

F. Sasso organized the onsite study and handled the distribution and collection of the questionnaires, M. Izard and D. Robin were in charge of measuring air pollution, T. Beneteau and I. Annnesi-Maesano conducted the statistical analysis, M. Ramadour performed the basic statistical analysis, T. Rakotozandry was in charge of the data management, and D. Charpin designed the study and wrote the manuscript.

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