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# Modifiable exposures to air pollutants related to asthma phenotypes in the first year of life in children of the EDEN mother-child cohort study

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## Abstract

**Background:** Studies have shown diverse strength of evidence for the associations between air pollutants and childhood asthma, but these associations have scarcely been documented in the early life. The purpose of this study was to evaluate the impacts of various air pollutants on the development of asthma phenotypes in the first year of life.

**Methods:** Adjusted odds ratios were estimated to assess the relationships between exposures to air pollutants and single and multi-dimensional asthma phenotypes in the first year of life in children of the EDEN mother-child cohort study (n = 1,765 mother-child pairs). The Generalized Estimating Equation (GEE) model was used to determine the associations between prenatal maternal smoking and *in utero* exposure to traffic-related air pollution and asthma phenotypes (data were collected when children were at birth, and at 4, 8 and 12 months of age). Adjusted Population Attributable Risk (aPAR) was estimated to measure the impacts of air pollutants on health outcomes.

**Results:** In the first year of life, both single and multi-dimensional asthma phenotypes were positively related to heavy parental smoking, traffic-related air pollution and dampness, but negatively associated with contact with cats and domestic wood heating. Adjusted odds ratios (aORs) for traffic-related air pollution were the highest [1.71 (95% Confidence Interval (CI): 1.08-2.72) for ever doctor-diagnosed asthma, 1.44 (95% CI: 1.05-1.99) for bronchiolitis with wheezing, 2.01 (95% CI: 1.23-3.30) for doctor-diagnosed asthma with a history of bronchiolitis]. The aPARs based on these aORs were 13.52%, 9.39%, and 17.78%, respectively. Results persisted for prenatal maternal smoking and *in utero* exposure to traffic-related air pollution, although statistically significant associations were observed only with the asthma phenotype of ever bronchiolitis.

**Conclusions:** After adjusting for potential confounders, traffic-related air pollution *in utero* life and in the first year of life, had a greater impact on the development of asthma phenotypes compared to other factors.

**Keywords:** Environment, Traffic-related air pollution, Environmental Tobacco Smoke (ETS), Pets, Moulds, Asthma, Children

## Background

The prevalence of asthma has increased constantly in recent decades [1-3] and different factors have been implicated in its aetiology. Although genetic factors are important determinants of asthma [4], exposures to certain environmental factors play an essential role in the

phenotypic expression of this condition [5,6] thus contributing substantially to the risk of its development [7].

The strength of evidence for the associations between exposures to various air pollutants and the development of childhood asthma is diverse [8]. Robust data casually related asthma to allergens including aero-allergens such as house dust mite [9]. Studies consistently demonstrated that Environmental Tobacco Smoke (ETS) increases the risk of asthma in children [10-12]. Other investigations showed an independent effect of dampness and moulds on the development of childhood asthma [13,14], although

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some investigations argued that the relationship may be partly explained by reporting bias [15]. Conversely, a protective effect was suggested for early life exposure to pets [16,17], exposure to domestic wood heating and rural living [18]. In contrast with initial findings [19], recent investigations, including birth cohort studies, have indicated a link between exposure to outdoor air pollution and subsequent asthma development [20-22]. Indoor air pollutants have also been related to asthma [23], but there is a lack of longitudinal data in this respect.

The aim of our study is to investigate the impacts of exposures to passive smoking, traffic-related air pollution, dampness, visible moulds, bleaching agents, house dust mites, pets and domestic heating on the development of asthma in the first year of life, which is a period of life when the lung is still developing. For passive smoking and traffic-related air pollution, *in utero* exposures were taken into account to better understand the development of childhood asthma. The health outcomes we considered in this study included both single and multi-dimensional asthma phenotypes at 0-4 months, 4-8 months, and 8-12 months respectively as well as their evolution during the first year of life. To this extent, we used data from a birth cohort to study the impacts of the *in utero* and first year of life exposures on asthma phenotypes in the first year of life.

## Methods

### Study population

The EDEN mother-child cohort study (Study of pre- and post-natal determinants of children's growth and development) is an on-going investigation in two study centres, Nancy and Poitiers, in France. This study enrolled 2,002 women during pregnancy and was described in more detail previously [24]. This study was approved by the ethical committee (*Comité Consultatif pour la Protection des Personnes dans la Recherche Biomédicale*, CCPPRB) of Kremlin Bicêtre and by the Data Protection Authority (*Commission Nationale de l'Informatique et des Libertés*, CNIL). Two hundred and thirty-seven children failed to be followed-up at 1 year of age.

### Data collection

Data were collected when children were at birth, and at 4, 8 and 12 months of age respectively, by standardised questionnaires that allowed the investigation of socio-demographic characteristics, *in utero* and first year of life environmental exposures and respiratory health of the children throughout the first year of life. At birth and 12 months of age, the questionnaires were completed by mothers with the assistance of the midwives in the hospitals. When children were at 4 and 8 months of age, the questionnaires sent by mail were completed and returned back by the parents within 1 month after the

distribution. If needed, parents could ask for assistance to complete the questionnaire by telephoning the midwives. The response rate of our study was 90%. At the age of 12 months, the children were offered a clinical examination.

### Assessment of exposures to air pollutants

Table 1 describes *in utero* and first year of life exposures to air pollutants assessed by standardised questionnaires and their temporal sequence with asthma phenotypes, namely, prenatal maternal smoking and *in utero* exposure to traffic-related air pollution and exposures to heavy parental smoking, traffic-related air pollution, dampness, visible moulds, bleaching agents, house dust mites, pets and domestic heating in the first year of life.

### Assessment of asthma phenotypes

An enriched version of the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire was used to define asthma phenotypes. In order to cover the spectrum of asthma outcomes fully in the first year of life, both single and multi-dimensional asthma phenotypes (as defined in Table 2) were assessed.

### Statistical analysis

This included 3 steps: 1) classical descriptive analysis; 2) analytical analysis for the estimation of the adjusted odds ratios between exposures and asthma phenotypes; 3) the estimation of the adjusted population attributable risk for exposures having statistically significant relationships with the prevalences of asthma phenotypes.

### Descriptive analysis

The population characteristics were presented by means and percentages. Chi-square test was used to analyze differences of proportion of exposures and asthma phenotypes between boys and girls. Morbidity associated with asthma phenotypes was defined in terms of prevalence (number of cases/number of children at risk at the considered period) and incidence (number of new cases/number of children at risk at the considered period after having excluded those that developed the same asthma phenotype in the previous periods).

### Analytical analysis

The investigation of the relationships between exposures and asthma phenotypes was conducted using two different models according to whether exposure was assessed simultaneously with health outcome or whether it preceded the health outcome.

- 1) Exposure assessed simultaneously with asthma  
Multivariable logistic regression was implemented to estimate odds ratios (OR) of the relationships

**Table 1 *In utero* and first year of life exposures to air pollutants sources and their temporal sequence with asthma phenotypes in children of the EDEN mother-child cohort study**

| Period of life/Air pollutant and related sources    | Corresponding questions   | Temporal sequence of asthma phenotypes in relation to exposure        |  |
|---|---|---|--|
|   |   | Exposure assessed in the first of life (at the period of the outcome) | <i>In utero</i> exposure (preceding the outcome) |
| <b><i>In utero</i> life</b>                         |   |   |  |
| Prenatal maternal smoking                           | 1. Did you smoke during the first trimester of pregnancy?   | No  | Yes  |
|   | 2. Did you smoke during the second trimester of pregnancy?  |   |  |
|   | 3. Did you smoke during the third trimester of pregnancy?   |   |  |
| Traffic-related air pollution                       | 1. Does your house located near a bus stop or a passageway of trucks?   | No  | Yes  |
|   | 2. Does the cars often or continuously pass by your house?  |   |  |
| <b>First year of life</b>                           |   |   |  |
| Heavy parental smoking in the last 12 months        | 1. Did you smoke at present?  | Yes   | No   |
|   | 2. An answer of "more than 20" to the question "How many cigarettes do you smoke every day?"  |   |  |
| Traffic-related air pollution in the last 12 months | 1. Do you live less than 200 meters away from a road with heavy traffic?  | Yes   | No   |
|   | 2. Notably, Google Earth was used to check the validity of maternal reporting by taking into account a 200 m circular buffer and more than 10,000 vehicles per day (traffic volumes were provided by local authorities) using the home address as reference.. |   |  |
| Dampness in the last 12 months                      | Are there any problems of dampness, moisture or condensation that have often, or permanently, existed in the house since the birth of the child?  | Yes   | No   |
| Visible moulds in the past 12 months                | Are there any visible moulds that have often, or permanently, existed in the house of the child since the birth of the child?   | Yes   | No   |
| Bleaching agents in the past 12 months              | Do you often clean with or use the bleaching agents in the presence of the child?   | Yes   | No   |
| House dust mites in the past 12 months              | Has your child frequently been in contact with carpets, or glazing, or curtains?  | Yes   | No   |
| Contact with cats in the past 12 months             | 1. Was there a new cat in your house and (or) did you let the cat enter the sleeping room of the child?   | Yes   | No   |
|   | 2. Did your child contact with cats outside your house at least once per week?  |   |  |
| Contact with dogs in the past 12 months             | 1. Was there a new dog in your house and (or) did you let the dog enter the sleeping room of the child?   | Yes   | No   |
|   | 2. Did your child contact with dogs outside your house at least once per week?  |   |  |
| Type of domestic heating in the past 12 months      | Which is your main type of heating in the house: gas, petroleum, wood or others?  | Yes   | No   |

between all exposure variables together and the prevalence of each asthma phenotype during the first year of life after adjusting for confounders. Potential confounders included study centre, maternal occupation, maternal age at recruitment, maternal pre-pregnancy body mass index (BMI) as

estimated by weight in kilograms divided by the square of the height ( $\text{kg}/\text{m}^2$ ), child's birth weight, cesarean delivery, preterm birth, breastfeeding, siblings, gender and family history of asthma, eczema, allergic rhinitis or food allergy.

2) Exposure assessed before asthma development

**Table 2 Asthma phenotypes in the first year of life in the children of the EDEN mother-child cohort study**

| Asthma phenotypes  | Corresponding questions   | Periods                                |
|--|---|--|
| <b>Single phenotypes</b>   |   |  |
| Ever bronchiolitis   | Question 1: Did your child suffer from bronchiolitis during the last 4 months?  | 0-4 months, 4-8 months and 8-12 months |
| Ever wheezing  | Question 2: Did your child ever have wheezing or whistling in the chest after the birth?<br>Question 3: Did your child ever have wheezing or whistling in the chest during the last 4 months? | 0-8 months, 8-12 months                |
| Ever doctor-diagnosed asthma   | Question 4: Did your child have a diagnosed asthma during the last 4 months?  | 0-4 months, 4-8 months and 8-12 months |
| <b>Multi-dimensional phenotypes</b>                                  |   |  |
| Bronchiolitis and wheezing   | Questions 1, 2, 3   | 0-8 months, 8-12 months                |
| Doctor-diagnosed asthma with a history of bronchiolitis              | Questions 1, 4  | 0-4 months, 4-8 months and 8-12 months |
| Doctor-diagnosed asthma with wheezing                                | Questions 2, 3, 4   | 0-8 months, 8-12 months                |
| Doctor-diagnosed asthma with wheezing and a history of bronchiolitis | Questions 1, 2, 3, 4  | 0-8 months, 8-12 months                |

The marginal model [25] was used to analyze the associations of prenatal maternal smoking and *in utero* exposure to traffic-related air pollution together with the prevalence of each asthma phenotype at 3 survey time points (at 4, 8 and 12 months of age) after adjustment for confounders. The parameters of the marginal models were estimated by the Generalized Estimating Equation (GEE) approach, using exchangeable working correlation matrices. In order to study the relationships between the exposures, i.e., prenatal maternal smoking and *in utero* exposure to traffic-related air pollution, and each health outcome in the GEE model, we introduced a variable of time and tested the statistical significance of the presence of interactions between this time variable (=1 if at the age of 4 months, =2 if at the age of 8 months, =3 if at the age of 12 months) and each exposure, adjusting for confounders. As the interaction terms were not significant ( $P$ -value > 0.05) in the models, they were consequently dropped. In the next step, we studied the associations of all exposures together with each health outcome, including the time variable and confounders. This enabled to estimate the impact of time on the associations between the exposures and each health outcome.

#### Adjusted population attributable risk

The impact of each exposure on asthma phenotypes was estimated by the adjusted Population Attributable Risk (aPAR), the fraction of the total disease experienced in the population that would not have occurred if the effect associated with the risk factor of interest was absent

[26]. The aPARs were calculated with the formula provided by Bruzzi [26]:

$$\text{aPAR} = 1 - \sum (\rho_j / RR_j)$$

$\rho_j$  is the proportion of an asthma phenotype within the stratum  $j$ . The multivariable logistic regression or GEE model-based odds ratios were used to estimate the relative risk for stratum  $j$  compared with the baseline stratum ( $RR_j$ ). When the model-based odds ratio was less than 1.0, the aPAR estimate was negative, representing a potentially protective effect. The lower and upper 95% confidence interval (95% CI) of odds ratios for each stratum was used to estimate the lower and upper bounds of aPAR.

Confounders had been identified when the addition of a covariate to the model changed the odds ratio (OR) by 10%, without considering statistical significance. Effect modifiers had been identified when a covariate had a statistically significant interaction ( $P$ -value < 0.05) with the exposure as tested with the logistic model or the statistic of Wald chi-square in the case of the GEE model.

All statistical tests were performed using SAS® statistical software version 9.2 (SAS® Institute Inc, Cary, North Carolina). All  $P$ -values were two-tailed.  $P$  < 0.05 was considered statistically significant.

## Results

### Characteristics of study population

The characteristics of the study population and the potential confounders are described in Table 3. The number of children was equally distributed between two study centres and according to gender. There were no differences for the characteristics between boys and girls

( $P > 0.05$ ), except for study centre, cesarean delivery and birth weight.

#### Exposures to air pollutants

Table 4 describes the frequency of the exposures to air pollutants in the study population. During *in utero* life, 25% of the children had been exposed to maternal smoking and 28% of their mothers had lived close to a road with heavy traffic. Similar figures were found for

exposure to traffic-related air pollution in the first year of life (21%), but not for passive smoking (13% exposed to heavy parental smoking). Exposures did not differ between boys and girls ( $P > 0.05$ ).

#### Asthma phenotypes in the first year of life

The prevalences and incidences of each asthma phenotype at the 3 survey time points (at ages of 4, 8 and 12 months, respectively) are presented in Table 5. In terms of single

**Table 3 Characteristics of the study population according to gender in the children of the EDEN mother-child cohort study**

| Variables   | All (N = 1765)   | Boys (n = 918)   | Girls (n = 847)  | P*    |
|---|------------------|------------------|------------------|-------|
| <b>Study centre, n (%)</b>  |                  |                  |                  |       |
| Poitiers  | 866(49.07)       | 490(53.38)       | 376(44.39)       | <0.01 |
| Nancy   | 899(50.93)       | 428(46.62)       | 471(55.61)       |       |
| <b>Family income (€/month), n (%)</b>   |                  |                  |                  |       |
| Low(≤1500)  | 262(14.84)       | 140(15.25)       | 122(14.40)       | 0.15  |
| Middle(1501–3000)   | 1001(56.71)      | 534(58.17)       | 467(55.14)       |       |
| High(>3001)   | 492(27.88)       | 237(25.82)       | 255(30.11)       |       |
| <b>Maternal education attainment, n (%)</b>   |                  |                  |                  |       |
| Less than high school   | 104(5.89)        | 55(5.99)         | 49(5.79)         | 0.97  |
| High school   | 683(38.70)       | 352(38.34)       | 331(39.08)       |       |
| College/University or more  | 950(53.82)       | 492(53.59)       | 458(54.07)       |       |
| <b>Maternal occupation, n (%)</b>   |                  |                  |                  |       |
| Blue-collar (laborers)  | 81(4.59)         | 49(5.34)         | 32(3.78)         | 0.24  |
| White-collar (occupations of intermediate, administrative, sales and customers and personal services) | 1339(75.86)      | 688(74.95)       | 651(76.86)       |       |
| Professional (professional occupations, managers and senior officials)                                | 217(12.29)       | 108(11.76)       | 109(12.87)       |       |
| <b>Maternal age at recruitment (years), (Mean ± SD<sup>†</sup>)</b>                                   | 30.64 ± 4.81     | 30.70 ± 4.81     | 30.58 ± 4.81     | 0.61  |
| <b>Maternal pre-pregnancy body mass index, n (%)</b>  |                  |                  |                  |       |
| Underweight (<18.50 kg/m <sup>2</sup> )   | 136(7.71)        | 74(8.06)         | 62(7.32)         | 0.80  |
| Normal (18.50–24.99 kg/m <sup>2</sup> )   | 1139(64.53)      | 597(65.03)       | 542(63.99)       |       |
| Overweight (25.00–29.99 kg/m <sup>2</sup> )   | 305(17.28)       | 156(16.99)       | 149(17.59)       |       |
| Obese (≥30.00 kg/m <sup>2</sup> )   | 149(8.44)        | 73(7.95)         | 76(8.97)         |       |
| <b>Cesarean delivery, n (%)</b>   | 278(15.75)       | 162(17.65)       | 116(13.70)       | 0.02  |
| <b>Preterm birth<sup>‡</sup>, n (%)</b>   | 428(24.25)       | 231(25.16)       | 197(23.26)       | 0.35  |
| <b>Birth weight (grams), (Mean ± SD)</b>  | 3285.56 ± 506.65 | 3350.52 ± 529.41 | 3214.89 ± 470.89 | <0.01 |
| <b>Breastfeeding, n (%)</b>   |                  |                  |                  |       |
| Never   | 795(45.04)       | 436(47.49)       | 359(42.38)       | 0.07  |
| ≤ 4 months  | 550(31.16)       | 279(30.39)       | 271(32.00)       |       |
| > 4 months  | 420(23.80)       | 203(22.11)       | 217(25.62)       |       |
| <b>Siblings, n (%)</b>  | 962(54.50)       | 505(55.01)       | 457(53.96)       | 0.68  |
| <b>Family history of asthma, eczema, allergic rhinitis or food allergy, n (%)</b>                     | 912(51.67)       | 484(52.72)       | 428(50.53)       | 0.33  |

\* P, the P-value for t-test or chi-square test between boys and girls;

<sup>†</sup> SD, standard deviation;

<sup>‡</sup>Maternal gestational age < 37 weeks.

asthma phenotypes, ever bronchiolitis was the commonest condition at each survey, followed by ever wheezing and then ever doctor-diagnosed asthma. The most frequent multi-dimensional phenotype was constituted by bronchiolitis with wheezing. Almost 6% of children had suffered from all the 3 single phenotypes (ever bronchiolitis, ever wheezing and ever doctor-diagnosed asthma) in the first year of life.

### Associations between exposures to air pollutants and asthma phenotypes

#### Exposure assessed simultaneously with asthma

Applying the multivariable logistic regression models yielded that various asthma phenotypes were positively associated with heavy parental smoking, traffic-related air pollution and dampness in the last 12 months and negatively associated with contact with cats and domestic wood heating in the last 12 months (see Additional file 1: Table S1). No statistically significant associations ( $P > 0.05$ ) were found between asthma outcomes and visible moulds, bleaching agents, house dust mites, contact with dogs, domestic gas heating, or domestic petroleum heating in the last 12 months (data not showed). A statistically significant interaction between gender and traffic-related air pollution in the last 12 months was

found in the multivariable logistic model with ever wheezing as the dependent variable ( $P < 0.01$ ).

#### Exposure preceding asthma development

The application of the marginal model, taking into account the evolution of asthma phenotypes, indicated that prenatal maternal smoking and *in utero* exposure to traffic-related air pollution were associated with ever bronchiolitis (aOR = 1.39 (95% CI: 1.10-1.76) for prenatal maternal smoking, aOR = 1.51 (95% CI: 1.18-1.92) for *in utero* exposure to traffic-related air pollution), but only a trend (with aOR > 1) was found between *in utero* exposures and other asthma phenotypes (data not shown). There was no statistical significance ( $P > 0.05$ ) for the interaction term between exposure to the risk factors and time in the models. The aOR for time was 2.43 (95% CI: 2.28-2.60) for the model describing the relationships between *in utero* exposures and ever bronchiolitis.

#### Adjusted population attributable risk

aPARs varied from 17.78% for exposure to traffic air pollution in the last 12 months to -14.41% for contact with cats in the last 12 months, both in the case of doctor-diagnosed asthma with a history of bronchiolitis (see Additional file 1: Table S1). When considering *in utero* life, aPAR was 7.60%

**Table 4 *In utero* and first year of life exposures to air pollutants sources in the children of the EDEN study population according to gender**

| Variables   | All (N = 1765) |       | Boys (n = 918) |       | Girls (n = 847) |       | P*   |
|---|----------------|-------|----------------|-------|-----------------|-------|------|
|   | n              | (%)   | n              | (%)   | n               | (%)   |      |
| <b><i>In utero</i> life</b>                         |                |       |                |       |                 |       |      |
| Prenatal maternal smoking                           | 450            | 25.50 | 228            | 24.84 | 222             | 26.21 | 0.48 |
| Traffic-related air pollution                       | 501            | 28.39 | 246            | 26.80 | 255             | 30.11 | 0.10 |
| <b>First year of life</b>                           |                |       |                |       |                 |       |      |
| Heavy parental smoking in the last 12 months        | 227            | 12.86 | 113            | 12.31 | 114             | 13.46 | 0.75 |
| Traffic-related air pollution in the last 12 months | 372            | 21.08 | 201            | 21.90 | 171             | 20.19 | 0.61 |
| Dampness in the last 12 months                      | 86             | 4.87  | 46             | 5.01  | 40              | 4.72  | 0.90 |
| Visible moulds in the last 12 months                | 76             | 4.31  | 41             | 4.47  | 35              | 4.13  | 0.84 |
| Bleaching agents in the last 12 months              | 102            | 5.78  | 50             | 5.45  | 52              | 6.14  | 0.46 |
| House dust mites in the last 12 months              | 209            | 11.84 | 117            | 12.75 | 92              | 10.86 | 0.29 |
| Cats in the past 12 months                          | 156            | 8.84  | 79             | 8.61  | 77              | 9.09  | 0.75 |
| Dogs in the past 12 months                          | 117            | 6.63  | 65             | 7.08  | 52              | 6.14  | 0.45 |
| Domestic heating in the last 12 months              |                |       |                |       |                 |       |      |
| Electricity   | 353            | 20.00 | 187            | 20.37 | 166             | 19.60 | 0.24 |
| Gas   | 736            | 41.70 | 383            | 41.72 | 353             | 41.68 |      |
| Petroleum   | 314            | 17.79 | 160            | 17.43 | 154             | 18.18 |      |
| Wood  | 79             | 4.48  | 47             | 5.12  | 32              | 3.78  |      |
| Others  | 45             | 2.55  | 30             | 3.27  | 15              | 1.77  |      |

\* P, the P-value for chi-square test between boys and girls.

**Table 5 Prevalence and incidence of asthma phenotypes in the children of the EDEN study population in the first year of life**

| Variables  | 4 months survey |                  | 8 months survey |                  | 12 months survey |                  |
|--|-----------------|------------------|-----------------|------------------|------------------|------------------|
|  | Incidence (n,%) | Prevalence (n,%) | Incidence (n,%) | Prevalence (n,%) | Incidence (n,%)  | Prevalence (n,%) |
| <b>Single phenotypes</b>   |                 |                  |                 |                  |                  |                  |
| Ever bronchiolitis   | 197(11.16)      | 197(11.16)       | 359(22.90)      | 556(31.50)       | 156(12.90)       | 712(40.34)       |
| Ever wheezing  | —               | —                | —               | 294(16.66)       | 91(6.19)         | 385(21.81)       |
| Ever doctor-diagnosed asthma   | 17(0.96)        | 17(0.96)         | 101(5.72)       | 118(6.69)        | 17(1.03)         | 135(7.65)        |
| <b>Multi-dimensional phenotypes</b>                                  |                 |                  |                 |                  |                  |                  |
| Bronchiolitis with wheezing  | —               | —                | —               | 148(8.39)        | 44(2.49)         | 301(17.05)       |
| Doctor-diagnosed asthma with a history of bronchiolitis              | 11(0.62)        | 11(0.62)         | 50(2.86)        | 61(3.46)         | 4(0.24)          | 112(6.35)        |
| Doctor-diagnosed asthma with wheezing                                | —               | —                | —               | 92(5.22)         | 5(0.28)          | 118(6.69)        |
| Doctor-diagnosed asthma with wheezing and a history of bronchiolitis | —               | —                | —               | 48(2.72)         | 3(0.17)          | 103(5.84)        |

for prenatal maternal smoking and 10.81% for *in utero* exposure to traffic-related air pollution, both in relation to the asthma phenotype of ever bronchiolitis.

## Discussion

In our study, passive smoking and exposure to traffic-related air pollution, both *in utero* life and in the first year of life, and dampness were found to be risk factors for various asthma phenotypes in the first year of life, while contact with cats and domestic wood heating were found to be protective against asthma in the first year of life. Some studies had observed the effects of air pollutants and related sources that we considered in our study. Results of the SIDIRA-2 study (Italian Studies on Respiratory Disorders in Children and the Environment-2nd phase) had showed that passive smoking, high traffic and dampness were risk factors for asthma in children aged 6–7 years [27]. Our data further support the associations in the first year of life.

Evidence for the association between asthma and prenatal and postnatal parental smoking is fairly consistent [10,28–30]. Recently, a systematic review of prospective studies published between 1997 and February 2011 indicated that both prenatal maternal smoking and postnatal maternal smoking were associated with wheezing in the first 2 years of life (OR = 1.41 (95% CI: 1.19–1.67) and OR = 1.70 (95% CI: 1.24–2.35), respectively) [30]. In our study, prenatal maternal smoking had a greater impact on childhood asthma than postnatal heavy parental smoking. This could be explained by the fact that the proportion of prenatal maternal smoking (25%) is higher than that of heavy parental smoking in the last 12 months (13%) in our population. Notably, results of a recent French national prenatal survey showed that 24% of women smoked during pregnancy [31], which is in agreement with our data. Furthermore, compared to

postnatal passive smoking, prenatal maternal smoking is more likely to reduce respiratory function after birth [32], which would consequently have a greater impact on the development of asthma.

The association between asthma and traffic-related air pollution has been well documented in the literature [21,27,33–37], but few studies have investigated the association between traffic-related air pollution and asthma in the first year of life. In a previous case–control study in 5 French metropolitan areas, results indicated that traffic related pollutants might be associated with the incidence of asthma in children aged 0–3 years old [37]. In our study, results showed that there were robust associations between *in utero* and first year of life exposure to traffic-related air pollution and asthma phenotypes in the first year of life. Furthermore, the impact of traffic-related air pollution on asthma phenotypes in the first year of life was greater than that of other risk factors even after adjustment for potential confounders, which is consistent with the results of the SIDIRA-2 study previously described [27]. One asset of our study is that we used Google Earth® and traffic volume provided by local authorities at mothers' address to check the validity of the subjectively measured exposure to traffic and thus minimise the exposure misclassification. The subjectively measured variable of traffic-related air pollution showed high concordance with the Google Earth®-derived variable, with up to 92% of children were well classified. Only 5% of the children whose mother reported traffic-related air pollution were not exposed according to the Google Earth®-derived variable, whereas 3% of the children that did not declare to be exposed were exposed according to this objectively assessed variable. Some studies have compared the subjectively measured exposure to traffic with objectively assessed exposures, implying that both have their own advantages and no method

could be *per se* considered as the gold standard [38]. In the USA, Gauderman *et al.* reported that the simple and widely available indicator of the distance between living house and freeway was as strongly and precisely associated with childhood asthma as were more complex objective estimates based on dispersion models [34].

Interestingly, our data further confirmed the findings from previous studies having related bronchiolitis to passive smoking [39] and air pollution [40,41]. This is important in terms of public health because bronchiolitis is an important phenotype of asthma in early life [42].

More consistently, several investigations showed a positive association between dampness and asthma, although very few have considered it in the first year of life. In the DRIAS study (Respiratory Symptoms in children and the Environment in Sardegna, Italy), results showed that exposure to dampness during the first year of life was associated with increased prevalence of current wheeze for primary school children (OR = 1.96; 95% CI: 1.34-2.88) [14]. Similarly, a more recent review implied that dampness was the risk factor for respiratory and allergic health in birth cohorts [43]. However, because of recall bias in the case of questionnaire investigation, the relationship between dampness in the last 12 months and asthma phenotypes in the first year of life needs to be further confirmed. Contrarily to other investigations [9], we did not find any relationship between exposure to house dust mite and the prevalences of asthma phenotypes, probably because the sources (carpets, or glazing, or curtains) we considered were not sufficient.

Our data showed that contact with cats in the last 12 months may be protective against asthma in the first year of life. This is in agreement with previous studies [17]. A potential mechanism was proposed by Platts-Mills *et al.* who indicated that contact with cats could induce IgG and IgG4 antibody responses, which is protective against the development of asthma [44].

In our study, domestic wood heating in the last 12 months was found to be negatively associated with asthma phenotypes in the first year of life. Among other authors, Kilpeläinen *et al.* investigated the association between early life exposure to wood stove heating and subsequent asthma development, results showed that a farm environment was the main confounding factor for the association between wood stove heating and asthma [45]. However, in the present study, the associations between domestic wood heating and asthma phenotypes were not confounded by the rural environment. This is in agreement with the fact that in France wood begins to be widely used for heating even in the urban and peri-urban settings because of its low cost. In addition, it is publicly supported in terms of tax reductions.

The major limitation of our study is that exposures and health outcomes were assessed by questionnaires, without

objective assessments. However, our data collection was prospective and the mothers replied for well-standardised questionnaires that were previously validated. In addition, our findings are consistent with those of other studies conducted in other Western European countries and based on questionnaire investigation [14,36,37]. Another limitation of our study is that the exposure to risk factors was assessed simultaneously with asthma outcomes except for prenatal maternal smoking and *in utero* exposure to traffic-related air pollution. Therefore, the causal link implied by our study should be interpreted with caution. Lastly, the questions for assessing *in utero* and first year of life exposure to traffic-related air pollution were different (as showed in Table 1). This is because, after the survey time point of at birth, in order to take results from recent studies into account [46,47], we modified the questionnaire and assessed distances of the dwellings to major road, and in particular the 200 m circular buffer with which a risk of asthma had been associated. As a consequence, responses for *in utero* and first year of life exposure to traffic were not exactly comparable. In addition, the response rates varied from one survey to the other. Indeed, for some mothers, it was difficult to figure out the exact circular buffer and there were more missing values for the variable of first year of life exposure to traffic-related air pollution than for the variable of *in utero* exposure to traffic-related air pollution. Notably, some mother-child pairs changed their residences after the birth of the child. However, in spite of these differences, the associations between asthma phenotypes and the exposure to traffic-related air pollution *in utero* life and in the first year of life are consistent.

The strength of our investigation lies in the fact that the sample is large and drawn from the general population and that we use standardised instruments for the assessment of both exposure and asthma phenotypes. The fact that our investigation focuses on the first year of life which is crucial for the development of asthma using the data of a birth cohort constitutes an added value. In addition, we used different models to analyse the relationships between asthma outcomes and *in utero* and first year of life exposures respectively, taking into account the temporal sequence in relation to asthma outcomes. We also considered the potential confounders and effect modifiers in the models to show the independent effects of exposures *in utero* life and in the first year of life. Lastly, several asthma phenotypes covering a large spectrum of asthma outcomes in early childhood were included thus reducing misclassification of asthmatic cases.

## Conclusions

In our study, asthma outcomes in the first year of life were found to be positively related to maternal smoking, traffic-related air pollution and dampness, but negatively



associated with contact with cats and domestic wood heating. Furthermore, *in utero* exposures to passive smoking and traffic-related air pollution were both related to the development of asthma phenotypes in the first year of life. After adjusting for potential confounders, traffic-related air pollution had a greater impact on the development of asthma phenotypes compared to other factors. Interventional studies need to be implemented to evaluate the consequences of the avoidance or the promotion of these factors.

## Consent

Written informed consent was obtained from all participating women for publication of this report and any accompanying images.

## Additional file

**Additional file 1: Table S1.** Association between exposures to air pollutants sources and asthma phenotypes in the first year of life in children of the EDEN mother-child cohort study.

## Abbreviations

OR: Odds ratio; aOR: Adjusted odds ratio; aPAR: Adjusted Population Attributable Risk; BMI: Body mass index; SD: Standard deviation; NO<sub>2</sub>: Nitrogen dioxide; PM<sub>10</sub>: Particulate matter with an aerodynamic diameter below 10 μm.

## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

IAM conceived the study. NB and IAM participated in the data collection. CZ performed statistical analysis and data interpretation with the assistance of NB and SB. CZ wrote the manuscript with the co-supervision of IAM and TZ. All authors read and approved the final manuscript.

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