Long-term exposure to ambient air pollution and asthma symptom score in the CONSTANCES cohort

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ABSTRACT

Background  The asthma symptom score allows to consider asthma as a continuum and to investigate its risk factors. One previous study has investigated the association between asthma score and air pollution and only for nitrogen dioxide (NO2). We aimed to study the associations between particulate matter with an aerodynamic diameter lower than 2.5 µm (PM2.5), black carbon (BC) and NO2 and the asthma symptom score in adults from CONSTANCES, a French population-based cohort.

Methods  Asthma symptom score (range: 0–5) was based on the number of five self-reported symptoms of asthma in the last 12 months. Annual individual exposure to PM2.5, BC and NO2 was estimated at participants’ residential address using hybrid land-use regression models. Cross-sectional associations of each pollutant with asthma symptom score were estimated using negative binomial regressions adjusted for age, sex, smoking status and socioeconomic position. Associations with each symptom were estimated using logistic regression. The effect of BC independent of total PM2.5 was investigated with a residual model.

Results  Analyses were conducted on 135 165 participants (mean age: 47.2 years, 53.3% women, 19.0% smokers, 13.5% ever asthma). The ratio of mean score was 1.12 (95% CI 1.10 to 1.14), 1.14 (95% CI 1.12 to 1.16) and 1.12 (95% CI 1.10 to 1.14) per one IQR increase of PM2.5 (4.86 µg/m3), BC (0.88 10−5 m−3) and NO2 (17.3 µg/m3). Positive and significant associations were also found for each asthma symptom separately. BC effect persisted independently of total PM2.5.

Conclusion  Exposure to each pollutant was associated with increased asthma symptom score in adults. This study highlights that BC could be one of the most harmful particulate matter components.

INTRODUCTION

Asthma is a chronic disease that affects around 270 million people worldwide.1 The prevalence of ever asthma in adults was recently estimated at 13% in France.2,3 Asthma is a heterogeneous disease characterised by reversible airflow limitation manifest by respiratory symptoms, particularly at night or early morning, and usually associated with chronic airway inflammation.4 There are different epidemiological definitions of asthma. Although the dichotomous definition based on the presence or absence of asthma is one of the most widely used, asthma could be viewed as a continuum in light of the current knowledge on its pathophysiology and natural history.5 The asthma symptom score based on the main symptoms of asthma is a continuous measure that offers the advantage of not being dependent on the heterogeneity of asthma labelling by healthcare professionals and of characterising and quantifying asthma symptoms in participants who have never been labelled as asthmatics.5,6 The use of this asthma symptom score has been advocated to identify the risk factors of asthma symptoms,5,6 for which it provides increased statistical power and decreased misclassification risk, as compared with dichotomous definitions of asthma.

Asthma is a multifactorial disease in which environmental factors play an important role.7 Among these, air pollution is particularly relevant as, in 2019, more than 90% of the world’s population are exposed to air pollution levels that are above the 2005 WHO recommended guidelines.8 While numerous studies on the link between air pollution and asthma have been conducted in the paediatric population,10 fewer are available in adult population.11 In a meta-analysis, exposure to nitrogen dioxide (NO2) and particulate matter with an aerodynamic diameter lower than 2.5 µm (PM2.5) was borderline associated with incidence of asthma12 and its exacerbations,13 while no association with asthma prevalence was found.14 Despite the growing literature on the harmful effects of black carbon (BC),15 a component of particulate matter...
arising from incomplete combustion, very few studies have analysed its effects on asthma. In a European study including six cohorts, exposure to PM2.5 absorbance (a proxy of BC) was not associated with incident asthma. A recent study showed a significant association between annual BC exposure (estimated the year before the study) and asthma attacks but not with physician-diagnosed asthma. Within the Effects of Low-Level of Air Pollution: A Study in Europe (ELAPSE), pooled data from Danish and Swedish cohorts, long-term exposure to BC was significantly associated with an increased incidence of asthma. To our knowledge, there is one study that has investigated the association between NO2 exposure and asthma symptom score, finding a positive association. Associations between long-term exposure to PM2.5 and BC and the asthma symptom score have never been studied.

In the present paper, we aimed to study the association between long-term exposure to air pollution focusing on PM2.5, BC and NO2 and the asthma symptom score. We also aimed to study the association of air pollution with each of the symptom included in the asthma symptom score to capture different dimensions of the disease. This work was carried out using detailed individual characteristics and air pollution exposure estimates available in the large French population-based cohort CONSTANCES.

METHODS
Population study
CONSTANCES is a population-based cohort designed as a sample of French adults as previously described. Briefly, between 2012 and 2019, more than 200,000 adults aged 18–69 years at baseline were selected randomly from the database of the National Pension Insurance Fund (CNAV; Caisse Nationale d’Assurance Vieillesse) and invited to participate in the CONSTANCES cohort. At inclusion, participants completed several questionnaires and attended one of the 24 participating health prevention centres (HPCs; Centre d’examens de santé) located in 21 cities throughout metropolitan France (online supplemental figure S1) for a comprehensive health examination. Our study population included all participants with complete data on asthma symptom score, air pollution and adjustment variables, included between 2012 and 2017. All participants signed a written informed consent.

Asthma symptom score
At inclusion, participants completed a questionnaire on asthma and respiratory symptoms based on the validated and standardized European Community Respiratory Health Survey (ECRHS) questionnaires.

The asthma symptom score was developed by Sunyer et al and was shown to increase both specificity and power against self-reports of ever having asthma and bronchial responsiveness. The asthma score has good predictive ability for outcomes related with asthma and also good ability to detect environmental risk factors. This score can be calculated in participants with asthma and also into those who have never been identified as having asthma. Ranging from 0 to 5, the score is calculated as the sum of positive answers to respiratory symptoms during the past 12 months. The symptoms were (1) breathlessness while wheezing, (2) woken up with chest tightness, (3) attack of shortness of breath at rest, (4) attack of shortness of breath after exercise and (5) woken up by attack of shortness of breath.

Air pollution exposure
Long-term exposure to PM2.5, BC and NO2 was assigned at each participant’s residential address at inclusion using the 100×100 m hybrid land-use regression (LUR) models developed in the ELAPSE project. Measurement data for PM2.5 and NO2 were obtained for 2010 from the European Environment Agency (EEA) AirBase database; for BC the annual mean concentrations measured as PM2.5 absorbance in the ESCAPE study were used. All LUR models included satellite-derived and/or chemical transport model estimates, and a number of geographic information system (GIS)-derived predictor variables including road density, altitude, population density and land use. The LUR models explained 54.4%, 58.8% and 72.2% of spatial variation of BC, NO2 and PM2.5, respectively.

Statistical analysis
The sociodemographic and clinical characteristics and air pollution exposure were described in all participants and according to the five levels of the asthma symptom score: p trends corresponding to Cochran-Mantel-Haenszel’s $\chi^2$ tests for categorical variables and univariate linear regression tests for continuous variable are presented. To determine the correlation between pollutants, Spearman correlation coefficients were performed. Cross-sectional associations between long-term exposure to air pollutants and asthma symptom score were estimated using negative binomial regressions. The estimates were expressed as the ratio of mean score (RMS) with 95% CI. Estimates were calculated for each pollutant separately, for an increase of their IQR: 4.86 $\mu$g/m3 for PM2.5, 0.88 $10^{-3}$ m$^{-1}$ for BC and 17.3 $\mu$g/m3 for NO2.

First, we performed univariate analyses (model M0) and then multivariate analyses with several levels of adjustments: first adjusting for age, sex, smoking status and educational level (model M1), and then further adjusting for French Deprivation Index to also consider socioeconomic factors at the contextual level (model M2, the main model) (see online supplemental material I for further information on the adjustment variables).

Since BC is a component of PM2.5 and both are highly correlated, we used the residual method described previously by Mostofsky et al to assess the association of BC independently from that of total PM2.5. This approach consists of regressing BC against PM2.5 and using the residuals of this regression as
exposure in the negative binomial regression provided that these residuals were not correlated with PM$_{2.5}$.

Supplementary analyses using the main model (model 2) were carried out. A marginal model was performed using the generalised estimating equations to take into account the HPCs participating in CONSTANCES. Analyses were also carried out after multiple imputations (n=10) for missing data on smoking status (3%) and diploma (1%) using the SAS procedures MI and MIANALYZE. As high body mass index (BMI) was also described as a risk factor for asthma, a further adjustment for BMI was performed. As air pollution and tobacco may share similar mechanisms of action, the main analysis was also conducted among never-smoker participants only. A sex stratification was conducted to consider the potential difference in susceptibility to air pollution between men and women. As some participants had not answered the ever asthma question, analyses were also stratified according to missing or not missing answer to the question on ever asthma.

Finally, we investigated the associations between long-term exposure to air pollutants and each symptom of the asthma symptom score by logistic regression. All analyses were performed using SAS software (V9.4).

**RESULTS**

The study was based on the 150,231 participants included between 2012 and 2017. Participants with missing data on any of the five questions on asthma symptoms (n=7,208), diploma (n=2032) or tobacco status (n=5104) were excluded. We also excluded 722 participants without data on air pollution exposure due to a lack of geocoded addresses (see flow chart in figure 1).

The main analyses included 135,165 participants. Their mean (SD) age at inclusion was 47.2 years (13.7), 53.3% were women and 13.5% had ever asthma. Some significant but small differences in individual characteristics were found between included and non-included participants (online supplemental table S1).

Table 1 presents the characteristics of all participants and according to the asthma symptom score level: 68.5% of the participants had a score equal to 0 and 12.2% had a score of 2 or more, and the most prevalent symptoms were attacks of shortness of breath after exercise (22.7% of the total population) and woken up with a feeling of chest tightness (12.1% of the total population). The higher the asthma symptom score, the

| Table 1 | Characteristics of participants at baseline according to the level of asthma symptom score |
|---------|--------------------------------------------------------------------------------------------|
| **All** | **Score=0** | **Score=1** | **Score=2** | **Score=3** | **Score=4** | **Score=5** |
| N=135165 | n=92582 (68.5%) | n=26029 (19.3%) | n=9280 (6.87%) | n=4016 (2.97%) | n=2061 (1.52%) | n=1197 (0.8%) |
| Women, % | 53.3 | 51.9 | 56.3 | 56.6 | 56.8 | 56.3 | 53.2 | <10$^{-4}$ |
| Age, mean (SD) | 47.2 (13.7) | 47.5 (13.5) | 47.1 (14.0) | 45.2 (14.1) | 44.6 (13.8) | 45.2 (13.7) | 46.0 (13.0) | <10$^{-4}$ |
| Smoking status, % | | | | | | | | |
| Never | 47.3 | 50.4 | 42.1 | 38.3 | 37.8 | 37.3 | 35.9 | <10$^{-4}$ |
| Past | 33.8 | 34.0 | 34.4 | 31.8 | 30.9 | 32.3 | 31.8 | |
| Current | 19.0 | 15.6 | 23.5 | 29.9 | 31.4 | 30.4 | 32.3 | |
| BMI, kg/m², mean (SD) | 24.9 (4.46) | 24.6 (4.09) | 25.6 (4.90) | 25.9 (5.17) | 26.2 (5.39) | 26.3 (5.61) | 26.6 (5.34) | <10$^{-4}$ |
| Education, % | | | | | | | | |
| No diploma or grade school | 8.87 | 8.35 | 8.76 | 10.7 | 12.2 | 14.0 | 17.5 | <10$^{-4}$ |
| High school | 34.0 | 33.4 | 34.0 | 36.7 | 37.3 | 37.5 | 43.2 | |
| University | 57.1 | 58.2 | 57.2 | 52.6 | 50.6 | 48.5 | 39.3 | |
| Asthma, % | | | | | | | | <10$^{-4}$ |
| Never asthma | 86.5 | 91.7 | 83.8 | 70.0 | 57.1 | 47.9 | 33.1 | |
| Ever asthma | 13.5 | 8.31 | 16.2 | 30.0 | 42.9 | 52.1 | 66.9 | |
| Asthma confirmed by a physician, % | | | | | | | | <10$^{-4}$ |
| Never asthma | 88.0 | 92.8 | 85.8 | 72.2 | 59.8 | 50.1 | 35.2 | |
| Ever asthma confirmed by a physician | 12.0 | 7.22 | 14.2 | 27.8 | 40.2 | 49.9 | 64.8 | |
| Asthma symptoms in the last 12 months, % | | | | | | | | |
| Attack of short breath after activity | 22.7 | 0 | 67.0 | 73.6 | 83.1 | 90.5 | 100 | <10$^{-4}$ |
| Woken up with a feeling of chest tightness | 12.1 | 0 | 19.9 | 49.7 | 83.9 | 98.2 | 100 | <10$^{-4}$ |
| Wheeze and breathlessness | 8.67 | 0 | 8.51 | 44.1 | 64.9 | 78.3 | 100 | <10$^{-4}$ |
| Attack of short breath while at rest | 5.58 | 0 | 3.47 | 22.8 | 43.0 | 77.8 | 100 | <10$^{-4}$ |
| Woken up by shortness of breath | 3.38 | 0 | 1.19 | 9.81 | 25.2 | 55.2 | 100 | <10$^{-4}$ |
| Air pollution exposure, median (IQR) | | | | | | | | |
| PM$_{2.5}$, μg/m³ | 16.2 (4.86) | 16.2 (4.76) | 16.3 (4.97) | 16.3 (5.05) | 16.4 (4.96) | 16.4 (5.24) | 16.3 (4.72) | <10$^{-4}$ |
| BC, 10$^{-3}$ m$^{-1}$ | 1.66 (0.88) | 1.64 (0.87) | 1.68 (0.91) | 1.68 (0.91) | 1.71 (0.91) | 1.71 (0.93) | 1.70 (0.92) | <10$^{-4}$ |
| NO$_x$, μg/m³ | 23.5 (17.3) | 23.3 (16.9) | 23.9 (18.1) | 24.0 (18.5) | 24.1 (18.4) | 24.4 (19.9) | 24.3 (17.9) | <10$^{-4}$ |

*P trend in bold are <0.05.

BC, black carbon; BMI, body mass index; NO$_x$, nitrogen dioxide; PM$_{2.5}$, particulate matter with an aerodynamic diameter lower than 2.5 μm.

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more participants reported current smoking, higher BMI and lower educational level. Similarly to the ever asthma variable, the percentage of participants with ever asthma confirmed by a physician increased with the number of symptoms: from 7.22% for participants with no symptoms to 64.8% for participants with five symptoms. The distribution of the asthma symptom score was homogeneous across centres (online supplemental table S2).

The median (IQR) in exposure level was 16.2 (4.86) µg/m³ for PM₁₀, which is above the 2021 WHO air quality guideline level of 5 µg/m³ (100% of participants were exposed to levels higher than the new recommendation), 1.66 (0.88) 10⁻⁵ m⁻¹ for BC and 23.5 (17.3) µg/m³ for NO₂, which is also above the 2021 WHO air quality guideline level of 10 µg/m³ (96.2% of participants were exposed to levels higher than the new recommendation). Air pollution exposures were higher in Paris, and Lyon (online supplemental table S2). Air pollutants were highly correlated together; the Spearman correlation coefficients were 0.87 between PM₁₀ and NO₂, 0.80 between PM₂·₅ and BC, and 0.93 between NO₂ and BC.

For all studied air pollutants, an increase in exposure was associated with an increase in the asthma symptom score whatever the level of adjustment. For the main model M2, the RMS were 1.12 (95% CI 1.10 to 1.14) per IQR increase of PM₂·₅; 1.14 (95% CI 1.12 to 1.16) per IQR increase of BC; and 1.12 (95% CI 1.10 to 1.14) per IQR increase in NO₂ (table 2). BC residuals regressed on PM₂·₅ were also significantly associated with an increase in the asthma symptom score: RMS=1.03 (95% CI 1.02 to 1.04) for an IQR increase of BC residuals. Similar results to those of the main model were obtained using the imputed data sets, with the supplemental adjustment for BMI or by restricting the analyses to never-smokers (figure 2, online supplemental table S3). Slightly lower but still significant associations were found with marginal models.

After stratifying by sex, RMS were similar in men and women. After stratifying by asthma status, slightly lower but still significant RMS were found in the ever asthma strata compared with never asthma strata. After stratification on missing data for ever asthma, RMS were similar in each category, although the RMS had larger CI and were not significant in participants with ever asthma missing.

Finally, each of the three air pollutants was significantly associated with each one of the five asthma symptoms (figure 3, online supplemental table S4). The results varied according to the symptom: the lowest ORs were estimated for ‘attack of shortness of breath after exercise’ and the two highest were observed for ‘attack of shortness of breath at rest’ and ‘woken up by shortness of breath’.

### DISCUSSION

In the present study, we found that long-term exposure to PM₂·₅, BC and NO₂ was associated with increased asthma symptom score; the results were confirmed in several supplementary analyses. The association for BC exposure was independent of the total PM₁₀ mass. When considering each asthma symptom separately, we found positive and significant associations with all pollutants.

Our findings were observed in a large population-based cohort in France. The participants were highly characterised and the asthma symptom score is based on validated and standardised questions on five main respiratory symptoms in the last 12 months. This score is an alternative to the classic dichotomous definition of asthma allowing to consider recent asthma activity and also some asthma heterogeneity, and could be of relevance as asthma is often underdiagnosed. Indeed, in an international study in 70 countries, one-third of French participants aged 18–45 years with asthma symptoms (attacks of wheezing or whistling breath in the past 12 months) were not diagnosed.

### Table 2   Associations between long-term exposure to PM₁₀, BC and NO₂ and asthma symptom score

|          | PM₁₀ | BC    | NO₂   |
|----------|------|-------|-------|
|          | RMS  | 95% CI| RMS   | 95% CI| RMS   | 95% CI|
| Model 0  | 1.06 | 1.05 to 1.08 | 1.07  | 1.06 to 1.09 | 1.06  | 1.05 to 1.08 |
| Model 1  | 1.07 | 1.06 to 1.09 | 1.08  | 1.07 to 1.10 | 1.07  | 1.06 to 1.09 |
| Model 2  | 1.12 | 1.10 to 1.14 | 1.14  | 1.12 to 1.16 | 1.12  | 1.10 to 1.14 |

All p values were <10⁻⁴. RMS were calculated for an increase of IQR (4.86 µg/m³ for PM₁₀, 0.88 10⁻⁵ m⁻¹ for BC and 17.3 µg/m³ for NO₂).

Model 0: univariate; model 1: adjusted for age, sex, smoking status and educational level; model 2 (main model): adjusted for age, sex, smoking status, educational level and French Deprivation Index.

BC, black carbon; NO₂, nitrogen dioxide; PM₁₀, particulate matter with a mean diameter ≤ 2.5 µm; RMS, ratio mean score.
with asthma. In addition, in a recent paper by Delmas et al, with participants from the CONSTANCES cohort, 64.4% of participants with airflow limitation did not report a previous diagnosis of obstructive lung disease (asthma, COPD or bronchiectasis). This score has the advantage of characterising and quantifying asthma symptoms in participants who have never been labelled as asthmatics.

Air pollution exposure was estimated using validated LUR models for 2010. One strength of this analysis is the individual exposure at the participant’s residential address, predicted at a fine scale. The performance of the LUR models was good for PM$_{2.5}$ and adequate for BC and NO$_2$. We hypothesised that the exposure at the inclusion address reflects long-term exposure at least for participants who did not move shortly before the inclusion. Furthermore, we considered the annual mean of exposure, which is coherent with the timeframe of the questions on asthma symptoms (ie, the last 12 months). Air pollution exposure was modelled prior to baseline for all individuals, which we also observed an independent effect of BC. These results suggest that the association between air pollution exposure and asthma symptoms could reflect common biological mechanisms and the asthma symptom score may incorporate different phenotypes of asthma, such as non-asthma symptom related to smoking. For these reasons we performed supplementary analyses among participants who had never smoked in their lifetime and the RMS were very similar to those in the main model, suggesting that the effects of air pollution on asthma symptom score are independent of those of smoking status.

Studies on the prevalence or incidence of asthma and air pollution suggested the role of traffic-related pollution on asthma in adults. To our knowledge, this study is the first to investigate the association between PM$_{2.5}$ and BC exposure and asthma symptom score. Our results are in line with those from a previous paper in the European ECRHS study, which indicated significant associations between NO$_2$ exposure and asthma symptom score. Our results were observed at average NO$_2$ levels below the 2005 WHO guidelines of 40 µg/m$^3$, in agreement with the recent results of the ELAPSE project showing that exposure to low levels of NO$_2$ was associated with asthma incidence. The ELAPSE study also showed that long-term exposure to low levels of PM$_{2.5}$ and BC was associated with an increased risk of incident asthma. Following the recent update of the WHO air quality guidelines in 2021, in which the annual exposure levels for NO$_2$ and PM$_{2.5}$ have been substantially reduced, our study 96.9% and 100% of the participants were exposed to an average level above the NO$_2$ and PM$_{2.5}$ new recommended values, respectively. Environmental health policies are now facing new challenges as it is well established that previous air quality guidelines were not protective enough for the population. The 2021 WHO air quality guidelines also pointed out the harmful effect of BC below the 2005 WHO guidelines of 40 µg/m$^3$, in agreement with the recent results of the ELAPSE project showing that exposure to low levels of NO$_2$ was associated with asthma incidence. The ELAPSE study also showed that long-term exposure to low levels of PM$_{2.5}$ and BC was associated with an increased risk of incident asthma.
The exact underlying biological mechanisms linking air pollution and asthma are not fully identified. Three main interconnected mechanisms have been proposed: oxidative stress, inflammation and immunological responses. Exposure to air pollutants, including PM2.5, BC and NO2, can activate these pathways, leading to airway and systemic damages, increased asthma symptoms and exacerbation risk, and increased allergic sensitisation. They also could act as an adjuvant and stimulate the allergic response by enhancing production of IgE and stimulating dendritic cells to enhance T helper cell type 2 (Th2) responses. The immune response could subsequently induce a local inflammatory response in the airway epithelium. In addition, air pollution may also promote T2 inflammation that could be independent of allergic pathways. It is therefore difficult to disentangle the exact role of each pollutant in these mechanisms. Studying inflammatory asthma phenotypes or endotypes may help to better understand the mechanisms involved.

In conclusion, this study adds some evidence on the effect of long-term exposure to PM2.5, BC and NO2 on asthma in adults. Individual exposure to each pollutant was associated with asthma symptom score. These findings contribute to a better understanding of air pollution-related respiratory disease and demonstrate that air pollution, even at relatively low levels, remains a public health issue.

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**Ethics approval** This study involves human participants. Approvals were obtained from the National Data Protection Authority on 3 March 2011 (Commission Nationale de l’Informatique et des Libertés - CNIL, French National Data Protection Authority; authorisation number 910486), the National Council for Statistical Information (Conseil National de l’Information Statistique - CNIS), the National Medical Council (Conseil National de l’Ordre des Médecins - CNOM), and the Institutional Review Board of the National Institute for Medical Research-INSERM (authorisation number 01-011). Participants gave informed consent to participate in the study before taking part.

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**Data availability statement** Data may be obtained from a third party and are not publicly available. French researchers wishing to make use of the CONSTATES cohort infrastructure must submit an application. Projects may only use the available data or biological materials and/or collect additional data for a specific purpose. Cohort data access applications are submitted in the context of a permanent call for proposals (CFPs). Access to the infrastructure is governed by the CONSTATES Charter, which specifies the rights and responsibilities of the research teams whose projects have been accepted. Applicants are invited to draft a scientific protocol of their research project specifying the scientific objectives, the method, the expected results, the data requested (and the justification for their use) and, if applicable, the elements related to the additional data collection envisaged. The projects are then examined by the CONSTATES International Scientific Committee and where applicable by its Ethics Review Board. The foundations are issued by the Institutional Steering Committee, which comprised CONSTATES partner organisations. Applications must be submitted to the French legal authority for personal data processing before the required data are sent to the researcher in charge of the project. These steps must be carried out in close collaboration with the PI of CONSTATES. For further information: https://www.constances.fr/conduct-project-ongoing.php.

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