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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 association between asthma score and air pollution, and only for NO₂. We aimed to study the associations between PM_{2.5}, black carbon (BC) and NO₂ and the asthma symptom score in adults from CONSTANCES, a French population-based cohort.

Methods: Asthma symptom score (ranging: 0 to 5) was based on the number of five self-reported symptoms of asthma in the last 12 months. Annual individual exposure to PM_{2.5}, BC and NO₂ was estimated at the 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 PM_{2.5} 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). Ratio of mean score were 1.12 (95%CI 1.10–1.14), 1.14 (95%CI 1.12–1.16) and 1.12 (95%CI 1.10–1.14) per one interquartile range increase of PM_{2.5} (4.86 µg/m³), BC (0.88 10⁻⁵m⁻¹) and NO₂ (17.3 µg/m³). Positive and significant associations were also found for each asthma symptom separately. BC effect persisted independently of total PM_{2.5}.

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 PM components.

Key Messages:

What is already known on this topic: The evidence for the association between long-term exposure to air pollution and asthma is still limited in adults. Only one previous study has investigated association between asthma score and air pollution, and only for NO₂.

What this study adds: Our research provides for the first-time evidence on the association between air pollution exposure and asthma symptom score, using validated data in large population-based cohort.

How this study might affect research, practice or policy: 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.

Introduction

Asthma is a chronic disease that affects around 270 million of people worldwide.[1] The prevalence of ever asthma in adults was recently estimated at 13% in France.[2,3] Asthma is a heterogeneous disease characterized by reversible airflow limitation manifested 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 characterizing 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 risk factors of asthma symptoms,[5,6] for which it provides increased statistical power and decreased misclassification risk, as compared to dichotomous definitions of asthma.

Asthma is a multifactorial disease in which environmental factors play an important role.[7,8] Among these, air pollution is particularly relevant as, in 2019, more than 90% of the world's population is exposed to air pollution levels that are above 2005 WHO recommended guidelines.[9] 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 NO₂ and PM_{2.5} was borderline associated with incidence of asthma [12] 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 (PM) arising from incomplete combustion, very few studies have analysed its effects on asthma. In a European study including 6 cohorts, the exposure to PM_{2.5} absorbance (a proxy of BC) was not associated with incident asthma.[16] 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.[17] In the ELAPSE study of pooled data from Danish and Swedish cohorts, long-term exposure to BC was significantly associated with an increased incidence of asthma.[18] To our knowledge, there is one study that has investigated the association between NO₂ exposure and asthma symptom score, founding a positive association.[19] Associations between long-term exposure to PM_{2.5} 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 PM_{2.5}, 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 the 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 the French adults as previously described[20,21] 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 to the CONTANCES 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 (Figure S1) for a comprehensive health examination. Our study population included all participants with complete data for asthma symptom score, air pollution and adjustment variables, included between 2012 and 2017.

Approvals were obtained from the National Data Protection Authority on March 3, 2011 (Commission Nationale de l'Informatique et des Libertés—CNIL, French National Data Protection Authority (authorisation no. 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 no. 01-011). 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 standardised 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-report of ever having asthma and bronchial responsiveness.[6] The asthma score has good predictive ability for outcomes related with asthma and also good ability to detect environmental risk factors.[6] 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) breathless 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 PM_{2.5}, BC, and NO₂ was assigned at each participant's residential address at inclusion using the 100x100 m hybrid Land-Use-Regression models (LUR) developed in the ELAPSE project.[22] Measurement data for PM_{2.5} and NO₂ were obtained for 2010 from the European Environment Agency (EEA) AirBase database; for BC the annual mean concentrations measured as PM_{2.5} absorbance in the ESCAPE study were used. All LUR models included satellite derived and/or chemical transport model estimates, and a number of 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 PM_{2.5} respectively.[22]

Statistical analysis

The sociodemographic and clinical characteristics and air pollution exposure were described in all participants and according to the five levels of asthma symptom score: p trends corresponding to Cochran-Mantel-Haenszel's Chi² 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 ratio of mean score (RMS) with their 95% confidence interval (CI). Estimates were calculated for each pollutant separately, for an increase of their interquartile range (IQR): 4.86 µg/m³ for PM_{2.5}, 0.88 10⁻⁵.m⁻¹ for BC and 17.3 µg/m³ for NO₂.

First, we performed univariate analyses (Model M0), then multivariate analyses with several levels of adjustments: first adjusting for age, sex, smoking status and education level (Model M1), and then further adjusting for French Deprivation Index (Fdep) to also consider socio-economic factors at contextual level (Model M2, the main model). See the online supplement for further information on the adjustment variables.

Since BC is a component of PM_{2.5} and both are highly correlated, we used the residual method described previously by Mostofsky *et al.* [23] to assess the association of BC independently from that of total PM_{2.5}. This approach consists in regressing BC against PM_{2.5} 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 Generalized Estimating Equations (GEE) 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 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.[24] Analyses were stratified according to the ever asthma status (never asthma/ever asthma). 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 (version 9.4).

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 ($n = 2,032$) or tobacco status ($n = 5,104$) 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 (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 two or more, the most prevalent symptoms were attacks of shortness of breath after exercise (22.7% of total population) and woken up with a feeling of chest tightness (12.1% of total population). The higher the asthma symptom score, the more participants reported current smoking, higher BMI and lower education 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 (supplementary Table S2).

Table 1: Characteristics of participants at baseline according to the level of asthma symptom score

	All n = 135,165	Score = 0 n = 92,582 (68.5%)	Score = 1 n = 26,029 (19.3%)	Score = 2 n = 9,280 (6.87%)	Score = 3 n = 4,016 (2.97%)	Score = 4 n = 2,061 (1.52%)	Score = 5 n = 1,197 (0.8%)	P trend
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 confirmed by a physician	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 whilst 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. med (IQR)

PM _{2.5} , µg/m ³	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 ⁻⁵ 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 ₂ , µg/m ³	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

BC: black carbon; BMI: body mass index; IQR: interquartile range; med: median; NO₂: nitrogen dioxide; PM_{2.5} particulate matter with an aerodynamic diameter lower than 2.5 µm; SD: standard deviation. P-trend in bold are < 0.05.

The median (interquartile range) in exposure levels were 16.2 (4.86) $\mu\text{g}/\text{m}^3$ for $\text{PM}_{2.5}$ which is above the 2021 World Health Organization (WHO) air quality guideline level of 5 $\mu\text{g}/\text{m}^3$ (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) $\mu\text{g}/\text{m}^3$ for NO_2 which is also above the 2021 WHO air quality guideline level of 10 $\mu\text{g}/\text{m}^3$ (96.2% of participants were exposed to levels higher than the new recommendation). Air pollution exposures were higher in Paris, Lyon and Marseille (Table S2). Air pollutants were highly correlated together, the Spearman correlation coefficient was 0.87 between $\text{PM}_{2.5}$ and NO_2 , 0.80 between $\text{PM}_{2.5}$ and BC and 0.93 between NO_2 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, RMS (ratio mean score) were: 1.12 (95% CI 1.10 – 1.14) per IQR increase in $\text{PM}_{2.5}$; 1.14 (95% CI 1.12 – 1.16) per IQR increase in BC; and 1.12 (95% CI 1.10 – 1.14) per IQR increase in NO_2 (Table 2). BC residuals regressed on $\text{PM}_{2.5}$ were also significantly associated with an increase in the asthma symptom score: RMS = 1.03 (95% CI 1.02 - 1.04) for an IQR increase of BC residuals. Similar results to those of the main model were obtained using the imputed datasets, with the supplemental adjustment for BMI, or by restricting the analyses to never-smokers (Figure 2, supplementary Table S3). Slightly lower but still significant associations were found with marginal models.

Table 2: Associations between long-term exposure to $\text{PM}_{2.5}$, BC and NO_2 and asthma symptom score

	$\text{PM}_{2.5}$		BC		NO_2	
	RMS	(CI 95%)	RMS	(CI 95%)	RMS	(CI 95%)
Model 0	1.06	(1.05, 1.08)	1.07	(1.06, 1.09)	1.06	(1.05, 1.08)
Model 1	1.07	(1.06, 1.09)	1.08	(1.07, 1.10)	1.07	(1.06, 1.09)
Model 2	1.12	(1.10, 1.14)	1.14	(1.12, 1.16)	1.12	(1.10, 1.14)

$\text{PM}_{2.5}$: particulate matter with a mean diameter $\leq 2.5 \mu\text{m}$; NO_2 : nitrogen dioxide; BC: black carbon; RMS: ratio mean score; CI: confidence interval, IQR: interquartile range. All P-values were $<10^{-4}$.

RMS were calculated for an increase of an interquartile range (4.86 $\mu\text{g}/\text{m}^3$ for $\text{PM}_{2.5}$, 0.88 10^{-5} m^{-1} for BC and 17.3 $\mu\text{g}/\text{m}^3$ for NO_2). Model 0: univariate, Model 1: adjusted for age, sex, smoking status, educational level; Model 2=main model: adjusted for age, sex, smoking status, educational level, fdep (French Deprivation Index).

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 never asthma strata compared to ever 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, supplementary 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 PM_{2.5}, BC, and NO₂ was associated with an increased asthma symptom score, the results were confirmed in several supplementary analyses. The association for BC exposure was independent of the total PM_{2.5} 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 characterized and the asthma symptom score is based on validated and standardized questions on five main respiratory symptoms in the last 12 months. This score is an alternative to the classical 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 with asthma.[25] In addition, in a recent paper by Delmas *et al.*, with data from the Constances cohort, 64.4% of participants with airflow limitation did not report a previous diagnosis of obstructive lung disease (asthma, chronic obstructive pulmonary disease or bronchiectasis).[26] This score has the advantage of characterizing 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 NO₂. [22] We hypothesized 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 annual means of exposure, which is coherent with the timeframe of the questions on asthma symptoms (i.e., the last 12 months). Air pollution exposure was modelled prior to baseline for all individuals though not at the exact year of inclusion, but pollution levels from year to year are highly correlated in a given geographical area.[27] Exposure measurement did not take into account time activity patterns leading to the absence of data on exposure at the workplace or during commuting. Uncertainties in the exposure of participants and potential measurement errors are very likely non-differential, probably leading to an underestimation of the association between air pollution exposure and asthma.[28]

Our results showed robust and consistent associations for the three pollutants studied, PM_{2.5}, BC and NO₂, whatever the model, but causality cannot be studied because temporality is not defined. Analyses were adjusted for potential confounders identified in the literature, and as recommended by Teman *et al.*, [29] SES variables were considered at the individual and at the contextual level

along with age, sex, and tobacco habits in the main analysis. In the literature, potential sex-related differences in the effect of air pollution have been investigated.[24] Our analysis stratified according to sex showed similar effects in men and women, in line with a previous review [30] suggesting that the discordant results of adult studies do not support sex-related differential effects of air pollution on asthma. It is possible that smoking and air pollution share common biological mechanisms [31] and the asthma symptom score may incorporate different phenotypes of asthma, such as non-asthma symptom related to smoking.[6] 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 is 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 than those from a previous paper in the European ECRHS study,[19] which indicated significant associations between NO₂ exposure and asthma symptom score. Our results were observed at average NO₂ levels below the 2005 WHO guidelines of 40 µg/m³, in agreement with the recent results of the ELAPSE project showing that exposure to low levels of NO₂ was associated with asthma incidence.[18] 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.[18] Following the recent update of the WHO air quality guidelines in 2021, in which the annual exposure levels for NO₂ and PM_{2.5} have been substantially reduced,[9] in our study 96.9% and 100% of the participants were exposed to an average level above the NO₂ 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 but could not provide guideline levels due to insufficient quantitative evidence.[9] Exposure to NO₂, PM_{2.5}, and BC the year before study participation was reported increased the risk of asthma attack in the last 12 months in a Northern European population,[17] and our results are also in line with this study. Furthermore, the analysis based on BC residuals using the method of Mostofsky *et al.*, [23] suggests associations of BC independent from those of total PM_{2.5} mass – even if these BC associations could also be due to other PM_{2.5} components correlated with BC. We conducted another study, using data from the Constances cohort, on the association between air pollution and rhinitis, in which we also observed an independent effect of BC.[32] These findings for BC exposure add to increasing evidence of a health effect related to this specific PM_{2.5} component [9,15] and provide quantitative evidence .

Regarding each asthma symptom, the highest effects of air pollutants were observed for the two less prevalent but most severe symptoms of asthma, being attacks of shortness of breath at rest and woken up by shortness of breath. In contrast, the post-exercise symptom, for which the association is lower, is less specific of asthma. These results suggest that the association between air pollution and asthma symptoms could reflect effects of air pollution exposure on the activity and the severity of asthma.[5,6]

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.[11] Exposure to air pollutants, including PM_{2.5}, BC and NO₂, can activate these pathways leading to airway and systemic damages, increased asthma symptoms and exacerbation risk,[33] and increased allergic sensitization.[11,34,35] They also could act as an adjuvant and stimulate the allergic response by enhancing production of immunoglobulin [Ig]E and stimulating dendritic cells to enhance Th2 responses.[34,36] 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 allergy pathways.[36] It is therefore difficult to disentangle the exact role of each pollutant in these mechanisms.[37] Studying inflammatory asthma phenotypes [38] or endotypes [39] may help to better understand the mechanisms involved.

In conclusion, this study adds some evidence on the effect of long-term exposure to PM_{2.5}, 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.

Competing interest

No competing interests for all authors that are related to the content of our manuscript.

Contributors

MK, MS: Conceptualization, Methodology, Formal analysis, Writing – Original Draft, Visualization. EL: Methodology, Resources, Writing – Review & Editing. JC, KdH, DV: Methodology, Resources, Writing – Review & Editing. MG, MZ: Resources, Writing – Review & Editing. NR: Writing – Review & Editing. RN, BJ: Conceptualization, Methodology, Writing – Review & Editing, Supervision.

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References

- 1 GBD Chronic Respiratory Disease Collaborators. Prevalence and attributable health burden of chronic respiratory diseases, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Respir Med* 2020;**8**:585–96. doi:10.1016/S2213-2600(20)30105-3
- 2 Delmas M-C, Bénézet L, Ribet C, *et al.* Prévalence de l'asthme chez l'adulte en France, données de la cohorte Constances. *Revue des Maladies Respiratoires* 2021;**38**:797–806. doi:10.1016/j.rmr.2021.05.007
- 3 Raheison-Semjen C, Izadifar A, Russier M, *et al.* Prévalence et prise en charge de l'asthme de l'adulte en France en 2018: enquête ASTHMAPOP. *Revue des Maladies Respiratoires* 2019;**36**:A7. doi:10.1016/j.rmr.2018.10.018
- 4 Mims JW. Asthma: definitions and pathophysiology: Asthma: definitions and pathophysiology. *International Forum of Allergy and Rhinology* 2015;**5**:S2–6. doi:10.1002/alr.21609
- 5 Pekkanen J, Sunyer J, Anto JM, *et al.* Operational definitions of asthma in studies on its aetiology. *Eur Respir J* 2005;**26**:28–35. doi:10.1183/09031936.05.00120104
- 6 Sunyer J, Pekkanen J, Garcia-Esteban R, *et al.* Asthma score: predictive ability and risk factors. *Allergy* 2007;**62**:142–8. doi:10.1111/j.1398-9995.2006.01184.x
- 7 Le Moual N, Jacquemin B, Varraso R, *et al.* Environment and asthma in adults. *La Presse Médicale* 2013;**42**:e317–33. doi:10.1016/j.lpm.2013.06.010
- 8 Leynaert B, Le Moual N, Neukirch C, *et al.* Facteurs environnementaux favorisant le développement d'un asthme. *La Presse Médicale* 2019;**48**:262–73. doi:10.1016/j.lpm.2019.02.022
- 9 World Health Organization. *WHO global air quality guidelines: particulate matter (PM_{2.5} and PM₁₀), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide*. Geneva: : World Health Organization 2021.
- 10 Khreis H, Kelly C, Tate J, *et al.* Exposure to traffic-related air pollution and risk of development of childhood asthma: A systematic review and meta-analysis. *Environment International* 2017;**100**:1–31. doi:10.1016/j.envint.2016.11.012
- 11 Chatkin J, Correa L, Santos U. External Environmental Pollution as a Risk Factor for Asthma. *Clin Rev Allergy Immunol* Published Online First: 12 January 2021. doi:10.1007/s12016-020-08830-5

- 12 Anderson HR, Favarato G, Atkinson RW. Long-term exposure to air pollution and the incidence of asthma: meta-analysis of cohort studies. *Air Qual Atmos Health* 2013;**6**:47–56. doi:10.1007/s11869-011-0144-5
- 13 Orellano P, Quaranta N, Reynoso J, *et al.* Effect of outdoor air pollution on asthma exacerbations in children and adults: Systematic review and multilevel meta-analysis. *PLoS ONE* 2017;**12**:e0174050. doi:10.1371/journal.pone.0174050
- 14 Anderson HR, Favarato G, Atkinson RW. Long-term exposure to outdoor air pollution and the prevalence of asthma: meta-analysis of multi-community prevalence studies. *Air Qual Atmos Health* 2013;**6**:57–68. doi:10.1007/s11869-011-0145-4
- 15 French Agency for Food, Environmental and Occupational Health & Safety. Particulate matter in ambient air Health effects according to components, sources and particle size Impact on air pollution of the technologies and composition of the motor vehicle fleet operating in France. ANSES Opinion. Amended summary report and recommendations from the collective expert appraisal. <https://www.anses.fr/fr/system/files/AIR2014SA0156RaEN.pdf>
- 16 Jacquemin B, Siroux V, Sanchez M, *et al.* Ambient air pollution and adult asthma incidence in six European cohorts (ESCAPE). *Environ Health Perspect* 2015;**123**:613–21. doi:10.1289/ehp.1408206
- 17 Nordeide Kuiper I, Svanes C, Markevych I, *et al.* Lifelong exposure to air pollution and greenness in relation to asthma, rhinitis and lung function in adulthood. *Environ Int* 2020;**146**:106219. doi:10.1016/j.envint.2020.106219
- 18 Liu S, Jørgensen JT, Ljungman P, *et al.* Long-term exposure to low-level air pollution and incidence of asthma: the ELAPSE project. *Eur Respir J* 2021;**57**. doi:10.1183/13993003.03099-2020
- 19 Jacquemin B, Sunyer J, Forsberg B, *et al.* Association between modelled traffic-related air pollution and asthma score in the ECRHS. *Eur Respir J* 2009;**34**:834–42. doi:10.1183/09031936.00138208
- 20 Zins M, Goldberg M, CONSTANCES team. The French CONSTANCES population-based cohort: design, inclusion and follow-up. *Eur J Epidemiol* 2015;**30**:1317–28. doi:10.1007/s10654-015-0096-4
- 21 Henny J, Nadif R, Got SL, *et al.* The CONSTANCES Cohort Biobank: An Open Tool for Research in Epidemiology and Prevention of Diseases. *Front Public Health* 2020;**8**:605133. doi:10.3389/fpubh.2020.605133
- 22 de Hoogh K, Chen J, Gulliver J, *et al.* Spatial PM_{2.5}, NO₂, O₃ and BC models for Western

Europe – Evaluation of spatiotemporal stability. *Environment International* 2018;**120**:81–92. doi:10.1016/j.envint.2018.07.036

23 Mostofsky E, Schwartz J, Coull BA, *et al.* Modeling the Association Between Particle Constituents of Air Pollution and Health Outcomes. *American Journal of Epidemiology* 2012;**176**:317–26. doi:10.1093/aje/kws018

24 Clougherty JE. A Growing Role for Gender Analysis in Air Pollution Epidemiology. *Environmental Health Perspectives* 2010;**118**:10.

25 To T, Stanojevic S, Moores G, *et al.* Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC Public Health* 2012;**12**:204. doi:10.1186/1471-2458-12-204

26 Delmas M-C, Bénézet L, Ribet C, *et al.* Underdiagnosis of obstructive lung disease: findings from the French CONSTANCES cohort. *BMC Pulm Med* 2021;**21**:319. doi:10.1186/s12890-021-01688-z

27 Hansell A, Ghosh RE, Blangiardo M, *et al.* Historic air pollution exposure and long-term mortality risks in England and Wales: prospective longitudinal cohort study. *Thorax* 2016;**71**:330–8. doi:10.1136/thoraxjnl-2015-207111

28 Basagaña X, Aguilera I, Rivera M, *et al.* Measurement error in epidemiologic studies of air pollution based on land-use regression models. *Am J Epidemiol* 2013;**178**:1342–6. doi:10.1093/aje/kwt127

29 Temam S, Burte E, Adam M, *et al.* Socioeconomic position and outdoor nitrogen dioxide (NO₂) exposure in Western Europe: A multi-city analysis. *Environ Int* 2017;**101**:117–24. doi:10.1016/j.envint.2016.12.026

30 Burte E, Nadif R, Jacquemin B. Susceptibility Factors Relevant for the Association Between Long-Term Air Pollution Exposure and Incident Asthma. *Curr Environ Health Rep* 2016;**3**:23–39. doi:10.1007/s40572-016-0084-1

31 Ni Y, Shi G, Qu J. Indoor PM_{2.5}, tobacco smoking and chronic lung diseases: A narrative review. *Environ Res* 2020;**181**:108910. doi:10.1016/j.envres.2019.108910

32 Savouré M, Lequy É, Bousquet J, *et al.* Long-term exposures to PM_{2.5}, black carbon and NO₂ and prevalence of current rhinitis in French adults: The Constances Cohort. *Environ Int* 2021;**157**:106839. doi:10.1016/j.envint.2021.106839

33 Tiotiu AI, Novakova P, Nedeva D, *et al.* Impact of Air Pollution on Asthma Outcomes. *Int J Environ Res Public Health* 2020;**17**. doi:10.3390/ijerph17176212

34 Niranjana R, Thakur AK. The Toxicological Mechanisms of Environmental Soot (Black

Carbon) and Carbon Black: Focus on Oxidative Stress and Inflammatory Pathways. *Front Immunol* 2017;**8**:763. doi:10.3389/fimmu.2017.00763

35 Rouadi PW, Idriss SA, Naclerio RM, *et al.* Immunopathological features of air pollution and its impact on inflammatory airway diseases (IAD). *World Allergy Organ J* 2020;**13**:100467. doi:10.1016/j.waojou.2020.100467

36 Pfeffer PE, Mudway IS, Grigg J. Air Pollution and Asthma: Mechanisms of Harm and Considerations for Clinical Interventions. *Chest* 2021;**159**:1346–55. doi:10.1016/j.chest.2020.10.053

37 Bush A. Pathophysiological Mechanisms of Asthma. *Front Pediatr* 2019;**7**:68. doi:10.3389/fped.2019.00068

38 Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. *Nat Med* 2012;**18**:716–25. doi:10.1038/nm.2678

39 Berdine G, Alexander R, Nugent K. Clinical entities, phenotypes, causation, and endotypes based on selected asthma publications. *Baylor University Medical Center Proceedings* 2020;**33**:580–5. doi:10.1080/08998280.2020.1793444

Figures:

Figure 1: Flow chart

Figure 2: Associations between exposure to air pollution and asthma symptom score

RMS (95% CI) were calculated:

◆: For an increase of an IQR of PM_{2.5} (4.86 µg/m³)

●: For an increase of an IQR of BC (0.88 10⁻⁵m⁻¹)

▲: For an increase of an IQR of NO₂ (17.3 µg/m³)

£: RMS adjusted for age, sex, smoking status, education level, and fdep (French Deprivation Index)

§: RMS adjusted for age, sex, education level, and fdep.

*: RMS adjusted for age, sex, smoking status, education level, fdep and BMI

†: RMS adjusted for age, smoking status, education level, and fdep

BC: black carbon; CI: confidence interval; NO₂: nitrogen dioxide; RMS: Ratio of Mean Score; PM_{2.5} particulate matter with an aerodynamic diameter less than 2.5 µm. See Table S3 for corresponding numeric data.

Figure 3: Adjusted OR (95% CI) of the associations between PM_{2.5}, BC and NO₂ and each asthma symptom

OR (95% CI) were calculated:

◆: For an increase of an IQR of PM_{2.5} (4.86 µg/m³)

●: For an increase of an IQR of BC (0.88 10⁻⁵m⁻¹)

▲: For an increase of an IQR of NO₂ (17.3 µg/m³)

BC: black carbon; CI: confidence interval; NO₂: nitrogen dioxide; RMS: Ratio Mean Score; PM_{2.5} particulate matter with an aerodynamic diameter less than 2.5 µm.

Adjusted OR for age, sex, smoking status, education level, and French deprivation index. All p-values were < 0.05.

The symptoms of asthma symptom score are presented by decreasing prevalence.

See Table S4 for corresponding numeric data.

Participants included
between 2012 and 2017
n = 150,231

Asthma score missing
n = 7,208

Participants with asthma
score
n = 143,023

Air pollution missing
n = 722

- Diplomas missing:
n = 2,032
- Smoking habits missing:
n = 5,104

Final sample
n = 135,165



