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# Long-term exposures to $PM_{2.5}$, black carbon and $NO_2$ and prevalence of current rhinitis in French adults: The Constances Cohort

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ABSTRACT

*Background:* Rhinitis is one of the most common disease worldwide with a high and increasing prevalence. There is limited knowledge on the link between long-term exposure to air pollution and rhinitis.
*Objectives:* We aim to study the associations between long-term exposure to air pollutants and self-reported current rhinitis among adults from Constances, a large French population-based cohort.
*Methods:* Current rhinitis was defined at inclusion from questionnaire by the presence of sneezing, runny or blocked nose in the last 12 months without a cold or the flu. Annual concentrations of nitrogen dioxide ($NO_2$), particulate matter $\leq 2.5$ μm ($PM_{2.5}$) and black carbon (BC) were estimated at the participants' residential address by European land-use regression models. Cross-sectional associations between annual exposure to each air pollutant and current rhinitis were estimated using logistic models adjusted for age, sex, smoking, education level and French deprivation index. The health prevention centers were taken into account by marginal models with generalized estimating equations. Several supplementary analyses were performed.
*Results:* Analyses were performed on 127,108 participants (47 years old on average, 54% women, 19% current smokers). The prevalence of current rhinitis, allergic (AR) and non-allergic (NAR) rhinitis were 36%, 25% and 11% respectively. Adjusted ORs for current rhinitis were 1.13 (1.08, 1.17), 1.12 (1.07, 1.17), and 1.11 (1.06, 1.17) per one interquartile range increase of $PM_{2.5}$ (4.85 μg/m$^3$), BC ($0.88 \cdot 10^{-5}$ m$^{-1}$) and $NO_2$ (17.3 μg/m$^3$) respectively. Significant and positive associations were also found for both AR and NAR. Results were similar in men and women, and in the different smoking strata, and were consistent with meta-analysis or after imputing missing covariates.
*Discussion:* An increase of modeled annual average residential exposure to $PM_{2.5}$, BC, and $NO_2$ was significantly associated with an increase of prevalence of current rhinitis in adults in the French general population. The results suggest that among air pollutants, BC may be of special interest.

## 1. Introduction

Air pollution is a major risk factor for health in terms of both mortality and morbidity (Schraufnagel et al., 2019a). The respiratory tract is the first organ affected by air pollutants and it is commonly accepted that air pollution exposure has harmful effects on respiratory

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health (Schraufnagel et al., 2019b). There is a substantial body of literature on the long-term effects of pollution on lung function (Edginton et al., 2019) and respiratory diseases such as asthma (Thurston et al., 2020) or chronic obstructive pulmonary disease (Park et al., 2021). However, even if rhinitis is one of the most common medical conditions in the world (Bousquet et al., 2020), the literature on the association between long term exposure to air pollution and rhinitis remains scarce. In the pediatric population, exposures to nitrogen dioxide ($NO_2$), sulfur dioxide ($SO_2$), particulate matter $\leq$ 10 μm ($PM_{10}$) and particulate matter $\leq$ 2.5 μm ($PM_{2.5}$) were associated with the prevalence of allergic rhinitis (AR) (Zou et al., 2018). In adults, the association between long-term exposure to air pollution and rhinitis has been poorly investigated in population-based studies, and the results are inconsistent: exposure to traffic or specific pollutants such as fractions of particulate matter (PM), $NO_2$ or nitrogen oxide ($NO_x$) were significantly associated with an increased risk of current AR in some studies (de Marco et al., 2002; Lindgren et al., 2009; Nordeide Kuiper et al., 2020), while others found null or non-significant positive results (Heinrich et al., 2005; Wyler et al., 2000; Zhang et al., 2009). Although there is a growing body of literature showing the harmful effect of black carbon (BC) or soot, a component of PM, on health (Yang et al., 2019), to our knowledge, only one study has examined the association between BC exposure and the prevalence of current AR (Nordeide Kuiper et al., 2020). Furthermore, previous studies have focused solely on AR and have therefore omitted non-allergic rhinitis (NAR), except the paper by Lindgren et al. in which exposure to road traffic was studied in association with both AR and NAR (Lindgren et al., 2009).

The aim of the present study was to assess the associations between long-term exposures to $PM_{2.5}$, BC and $NO_2$ and the presence of rhinitis symptoms in the past 12 months among adults from Constances, a large French population-based cohort.

## 2. Material and methods

### 2.1. Study design

Constances (https://www.constances.fr) is a population-based cohort of more than 200,000 adults aged 18 to 69 at inclusion (2012 – 2019), randomly selected from social security affiliates in France. Recruited participants lived in administrative districts (departments) where one of the 24 participating health prevention centers (HPC) are located (www.constances.fr/centres-examens-sante, see Figure S1). At inclusion, each participant completed standardized questionnaires on occupational exposures, lifestyle and health including a detailed one on respiratory health, and had a complete medical examination (Goldberg et al., 2017; Henny et al., 2020; Ruiz et al., 2016; Zins et al., 2015).

All confidentiality, safety and security procedures were approved by the French legal authorities. According to the French regulations, the Constances Cohort project has obtained the authorization of the National Data Protection Authority (Commission Nationale de l'Informatique et des Libertés-CNIL). In addition, Constances was approved by 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), the Institutional Review Board of the National Institute for Medical Research-INSERM and the local Committee for Persons Protection (Comité de protection des personnes).

### 2.2. Definitions of rhinitis

The definitions of ever rhinitis and current rhinitis were based on the responses from the detailed questionnaire on respiratory health that were previously used and validated in the International study of asthma and allergies in childhood (ISAAC) (Asher et al., 1995). Participants who answered yes to "*Have you ever had a problem with sneezing, or a runny, or a blocked nose when you did not have a cold or the flu?*" were considered as having ever rhinitis, otherwise as never having rhinitis. Among participants with ever rhinitis, those who answered yes to "*Have you had these problems in the last 12 months*" were classified as having current rhinitis, otherwise as having non-current rhinitis.

In order to distinguish AR from NAR, we used an adaptation of the question used in the European Community Respiratory Health Survey (ECRHS) to define nasal allergies (ECRHS, 1996; Savouré et al., 2021). Participants with rhinitis who answered yes to "*Have you ever had nasal allergies in your lifetime, including hay fever?*" were classified as AR, otherwise as NAR.

### 2.3. Estimation of air pollution exposure

Exposure assessment for $PM_{2.5}$, BC and $NO_2$ was based on estimated annual concentration data from Land Use Regression (LUR) models developed for Western Europe using a supervised linear regression approach based on data from a large regulatory network (de Hoogh et al., 2018). The LUR models were calibrated and validated using annual average $PM_{2.5}$ and $NO_2$ concentration data derived for 2010 from the AirBase v8 dataset (de Hoogh et al., 2018). For BC, which is not available through AirBase, the annual mean BC concentrations, measured as $PM_{2.5}$ absorbance based on reflectance measurement of the filters, were obtained from the ESCAPE study (Eeftens et al., 2012). Predictors used in the LUR include satellite-derived and chemical transport modeled estimates, land use variables, population density, road density and altitude. The models were applied on a 100 × 100 m grid across Western Europe (de Hoogh et al., 2018). Modeled exposures were assigned at the participants' residential address at inclusion. We used annual averages for each pollutant from year 2010 models at the address of inclusion as a proxy for participants' long-term exposure to air pollution.

### 2.4. Statistical analyses

The main analyses were complete case analyses, i.e. after excluding participants with missing data for rhinitis, air pollution or adjustment variables. The general characteristics of participants who reported current rhinitis in the last 12 months were compared with those of the reference group, defined as participants with never or non-current rhinitis, with standard statistical tests: Chi2 for categorical variables and Student tests for continuous variables. Spearman correlation coefficients were performed to study the correlations between the different pollutants.

### 2.5. Main analyses

The cross-sectional associations between long-term exposure to air pollutants and current rhinitis were studied using logistic regression models. Estimates were calculated considering each pollutant separately for an increase of their interquartile range (IQR), thus is 4.85 μg/m$^3$ for $PM_{2.5}$, 0.88 $10^{-5}$ m$^{-1}$ for BC and 17.3 μg/m$^3$ for $NO_2$.

As recruited participants lived in departments where HPC are located, analyses were carried out using marginal models with generalized estimating equations (Heagerty and Zeger, 2000) to take into account potential clustering, i.e. that participants living in the same department were likely more similar than those living in other departments.

Associations between each air pollutant and current rhinitis were assessed with several single-pollutant models. Univariate analyses were first performed (model M0). A first level of adjustments for age, sex and smoking status (never smoker, ex-smoker, current smoker) was made on the basis of a priori hypothesis based on the literature (model M1). Further adjustment was made for educational level (no diploma/grade school, high school, university) as a proxy for socioeconomic status at the individual level (model M2). Finally, as the importance of taking both individual and contextual socioeconomic status into account in

studies on the health effects of air pollution (Hajat et al., 2021; Temam et al., 2017), a model with an additional adjustment on the contextual French Deprivation Index (Fdep) was used (model M3 = main model). The Fdep is a score calculated according to the participant's residential address from principal component analysis at the smallest geographical division in France (IRIS - Regrouped statistical information blocks with 2000 inhabitants in average) that considers an accumulation of material and social disadvantages (Rey et al., 2009).

### 2.6. Supplementary analyses

All supplementary analyses were performed with the main M3 model.

As BC is a component of $PM_{2.5}$, and as they are highly correlated, using a two-pollutant model mutually adjusting one pollutant for the other is precluded. As an alternative to isolate the effect of BC from that of total $PM_{2.5}$, we used the residuals method described by Mostofsky et al. (2012). Following this approach, we regressed BC as response variable on $PM_{2.5}$. These residuals were decorrelated from $PM_{2.5}$ and an increase in these residuals correspond to an increase in BC holding total $PM_{2.5}$ constant. We used these residuals as a new exposure variable in a single-pollutant model.

The analyses were carried out for current AR (reference group: never rhinitis and non-current AR) and current NAR (reference group: never rhinitis and non-current NAR) separately.

As air pollution could lead to different responses between men and women, stratification according to sex was performed. As air pollution and tobacco may share similar underlying biological mechanisms, stratification according to smoking was also performed. Heterogeneity between strata were tested using interaction tests.

As an alternative of the marginal model, models were also performed with HPC as an adjustment variable, in a meta-analysis on HPC or without considering the HPC.

As the main analyses were complete case analyses, additional analyses were also carried out after multiple imputations (n = 10) for missing data on smoking status and diploma using the SAS procedures MI and MIANALYZE.

We also performed analyses by changing the reference group, and by comparing current rhinitis to never rhinitis and current rhinitis to non-current rhinitis separately.

All analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC).

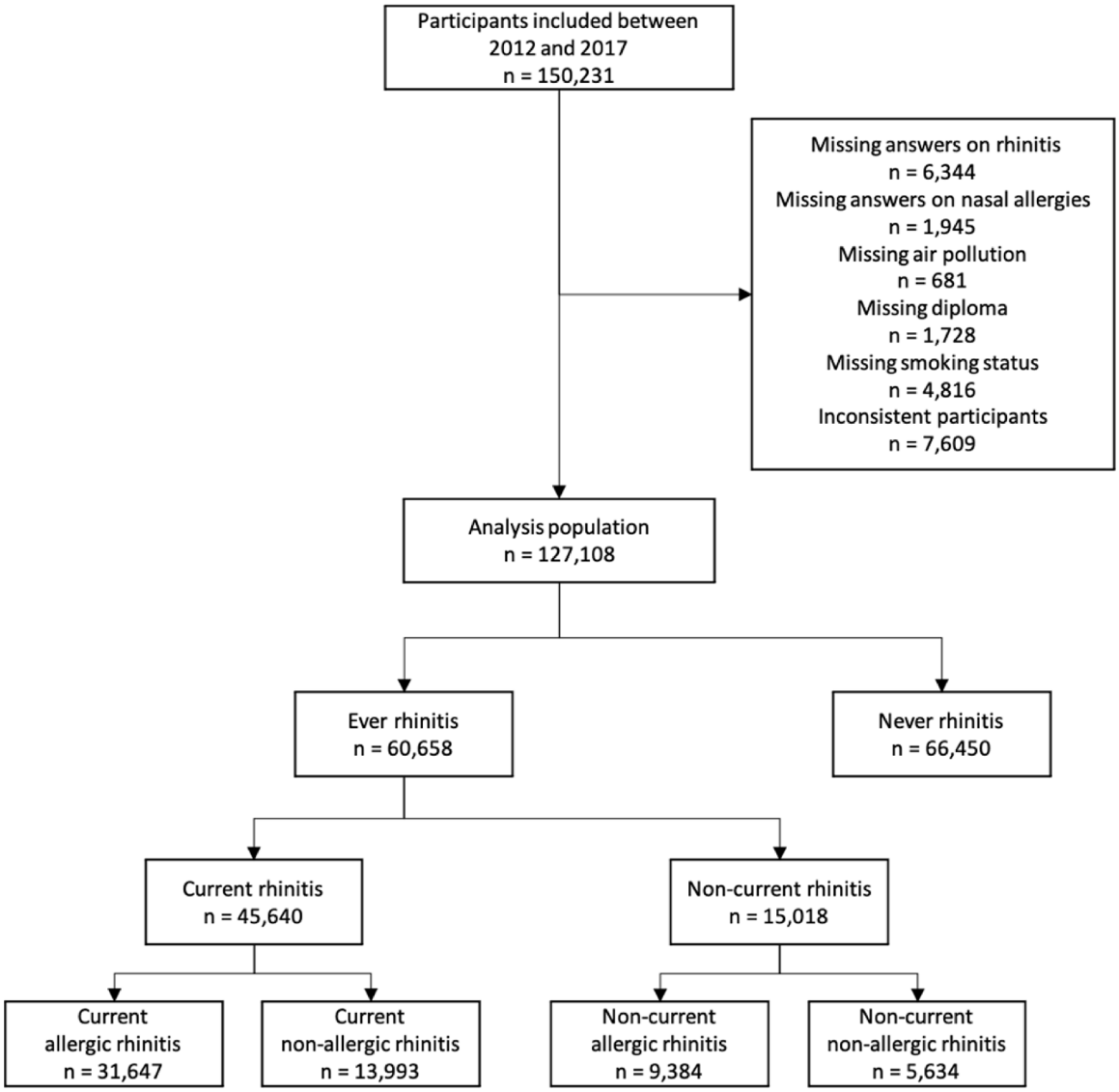


**Fig. 1.** Flow chart.

## 3. Results

We analyzed data from participants included in the cohort between 2012 and 2017 (n = 150,231). Participants with missing data regarding the definitions of rhinitis (n = 6344), the presence of nasal allergies (n = 1945), air pollution (n = 681), diploma (n = 1728) or tobacco status (n = 4816) were excluded from the main analyses. Participants who answered yes to "*Have you ever had any nasal allergies including hay fever?*" and no to "*Have you ever had a problem with sneezing, or a runny or a blocked nose when you did not have a cold or the flu?*" were considered inconsistent and were also excluded from the analyses (n = 7609). The flow chart is presented in Fig. 1.

A total of 127,108 adults were included in the main analyses. The differences regarding the main characteristics between participants included and those not included were small, although statistically significant due to the large number of participants (Table S1).

Characteristics of the participants included in the analyses are presented in Table 1. They were on average 47 years old and 53.8% were women. The prevalence of ever rhinitis and current rhinitis were 47.7% and 35.9% respectively. The prevalence of current AR and current NAR were 24.9% and 11.0% respectively. Compared to the reference group, the current rhinitis group comprised more women, a lower average age, higher education level and reported more ever asthma (Table 1). More details about the participants characteristics according to their rhinitis status are given in Table S2.

Pollutant levels were variable across HPC and within HCP (Figure S1). Table S3 shows the distribution of pollutants and their correlation coefficients. The annual mean concentration of $PM_{2.5}$ was 17.1 μg/m$^3$ which is above the World Health Organization (WHO) guideline of 10 μg/m$^3$, and the annual mean concentration of $NO_2$ was 26.5 μg/m$^3$ which is below the WHO guideline of 40 μg/m$^3$. The annual average concentration of BC was $1.82 \cdot 10^{-5}$ m$^{-1}$. Correlations between the three pollutants were high (0.80 between $PM_{2.5}$ and BC, 0.87 between $PM_{2.5}$ and $NO_2$, and 0.93 between BC and $NO_2$).

Table 2 shows the associations between $PM_{2.5}$, BC and $NO_2$ and current rhinitis. At all levels of covariate adjustment, an increase of $PM_{2.5}$, BC, or $NO_2$ was significantly associated with an increased risk of current rhinitis. Adjusted ORs for the main model M3 were 1.13 (95% CI: 1.08, 1.17) per IQR increase in $PM_{2.5}$, 1.12 (95% CI: 1.07, 1.17) per IQR increase in BC and 1.11 (95% CI: 1.06, 1.17) per IQR increase in $NO_2$.

BC residuals regressed on $PM_{2.5}$ were also significantly associated with an increase of current rhinitis (OR: 1.05, 95% CI: 1.02, 1.07 for an IQR increase of BC residuals).

The results of the supplementary analyses are shown in Fig. 2, Table S4, and Figure S2. Significant and positive associations were also found for both AR and NAR with similar effect estimates between AR and NAR for $PM_{2.5}$ and $NO_2$. For BC, the adjusted OR was slightly higher in AR compared to NAR (ORs: 1.15 vs 1.09 respectively). The ORs were similar between men and women and there were no significant interactions between each pollutant and sex. Stratification by smoking status yielded similar results for each stratum and there were no significant interactions between each pollutant and smoking status.

Similar results were obtained for $PM_{2.5}$ when not considering the HPC in the model, and the ORs were slightly higher for BC and $NO_2$. Adjusting on the HPC gave almost the same results as those from the marginal model for all pollutants. Similarly, the meta-analyses gave similar results to those of the main model for $PM_{2.5}$, BC and $NO_2$, for both fixed and random effects: the heterogeneity was not significant ($I^2$ = 0%, p = 0.58) for $PM_{2.5}$, and was significant for BC and $NO_2$ ($I^2$ = 48%, p = 0.01 and $I^2$ = 44%, p = 0.02 respectively).

Multiple imputations yielded significant and similar results as those of the main model.

Taking as a reference group only participants who never had rhinitis,

**Table 1**
Characteristics of the participants.

| | All n = 127,108 | Reference population[a] n = 81,468 | Current rhinitis n = 45,640 | P value |
|---|---|---|---|---|
| Women, n (%) | 68,354 (53.8%) | 42,883 (52.6%) | 25,471 (55.8%) | <0.0001 |
| Age, year, mean ± SD | 47.1 ± 13.6 | 47.9 ± 13.5 | 45.7 ± 13.8 | <0.0001 |
| BMI, kg/m$^2$, n (%) | | | | <0.0001 |
| <18.5 | 3,350 (2.8%) | 2,010 (2.6%) | 1,340 (3.1%) | |
| 18.5–25 | 66,309 (54.5%) | 41,561 (53.3%) | 24,748 (56.5%) | |
| 25–30 | 37,164 (30.5%) | 24,464 (31.4%) | 12,700 (29.0%) | |
| ≥ 30 | 14,936 (12.3%) | 9,911 (12.7%) | 5,025 (11.5%) | |
| Smoking status, n (%) | | | | <0.0001 |
| Never | 59,922 (47.1%) | 38,888 (47.7%) | 21,034 (46.1%) | |
| Ex-smoker | 42,943 (33.8%) | 27,437 (33.7%) | 15,506 (34.0%) | |
| Current | 24,243 (19.1%) | 15,143 (18.6%) | 9,100 (19.9%) | |
| Educational level, n (%) | | | | <0.0001 |
| No diploma or grade school | 11,355 (8.9%) | 7,723 (9.5%) | 3,632 (8.0%) | |
| High school | 43,290 (34.1%) | 28,888 (35.5%) | 14,402 (31.6%) | |
| University | 72,463 (57.0%) | 44,857 (55.1%) | 27,606 (60.5%) | |
| Ever asthma, n (%) | 17,148 (13.6%) | 7,014 (8.7%) | 10,134 (22.4%) | <0.0001 |
| Ever rhinitis, n (%) | 60,658 (47.7%) | 15,018 (18.4%) | 45,640 (100%) | <0.0001 |
| Current rhinitis, n (%) | 45,640 (35.9%) | / | 45,640 (100%) | |
| Current allergic rhinitis, n (%) | 31,647 (24.9%) | / | 31,647 (69.3%) | |
| Current non-allergic rhinitis, n (%) | 13,993 (11.0%) | / | 13,993 (30.7%) | |
| $PM_{2.5}$, μg/m$^3$, mean ± SD | 17.1 ± 3.35 | 17.0 ± 3.31 | 17.3 ± 3.40 | <0.0001 |
| BC, $10^{-5}$ m$^{-1}$, mean ± SD | 1.82 ± 0.59 | 1.79 ± 0.58 | 1.87 ± 0.59 | <0.0001 |
| $NO_2$, μg/m$^3$, mean ± SD | 26.5 ± 12.3 | 25.9 ± 12.2 | 27.4 ± 12.5 | <0.0001 |

BC: black carbon; BMI: body mass index; $NO_2$: nitrogen dioxide; $PM_{2.5}$ particulate matter with an aerodynamic diameter less than 2.5 μm; SD: standard deviation.
a: reference population = never rhinitis + non-current rhinitis

**Table 2**
OR (95% CI) of the associations between $PM_{2.5}$, BC and $NO_2$ and current rhinitis.

| | OR (95% CI) | | | | | |
|---|---|---|---|---|---|---|
| | $PM_{2.5}$ | | BC | | $NO_2$ | |
| M0 | 1.16 | (1.11,1.22) | 1.17 | (1.10,1.23) | 1.15 | (1.08,1.22) |
| M1 | 1.13 | (1.09,1.19) | 1.13 | (1.08,1.19) | 1.12 | (1.07,1.18) |
| M2 | 1.12 | (1.07,1.17) | 1.12 | (1.06,1.17) | 1.11 | (1.05,1.17) |
| M3 = main model | 1.13 | (1.08,1.17) | 1.12 | (1.07,1.17) | 1.11 | (1.06,1.17) |

BC: black carbon; CI: confidence interval; $NO_2$: nitrogen dioxide; OR: odds ratio; $PM_{2.5}$ particulate matter with an aerodynamic diameter less than 2.5 μm.
All estimates were from logistic regression models, OR (95% CI) were calculated for an increase of an interquartile range (4.85 μg/m$^3$ for $PM_{2.5}$, 0.88 $10^{-5}$ m$^{-1}$ for BC and 17.3 μg/m$^3$ for $NO_2$). The health prevention center was taken into account by marginal models with generalized estimating equations Current rhinitis was compared to never rhinitis + non-current rhinitis. M0: univariate analysis; M1: adjusted for age, sex, and smoking status; M2: adjusted for age, sex, smoking status, and educational level; M3: adjusted for age, sex, smoking status, educational level, and French deprivation index. All p-values were < $10^{-4}$.

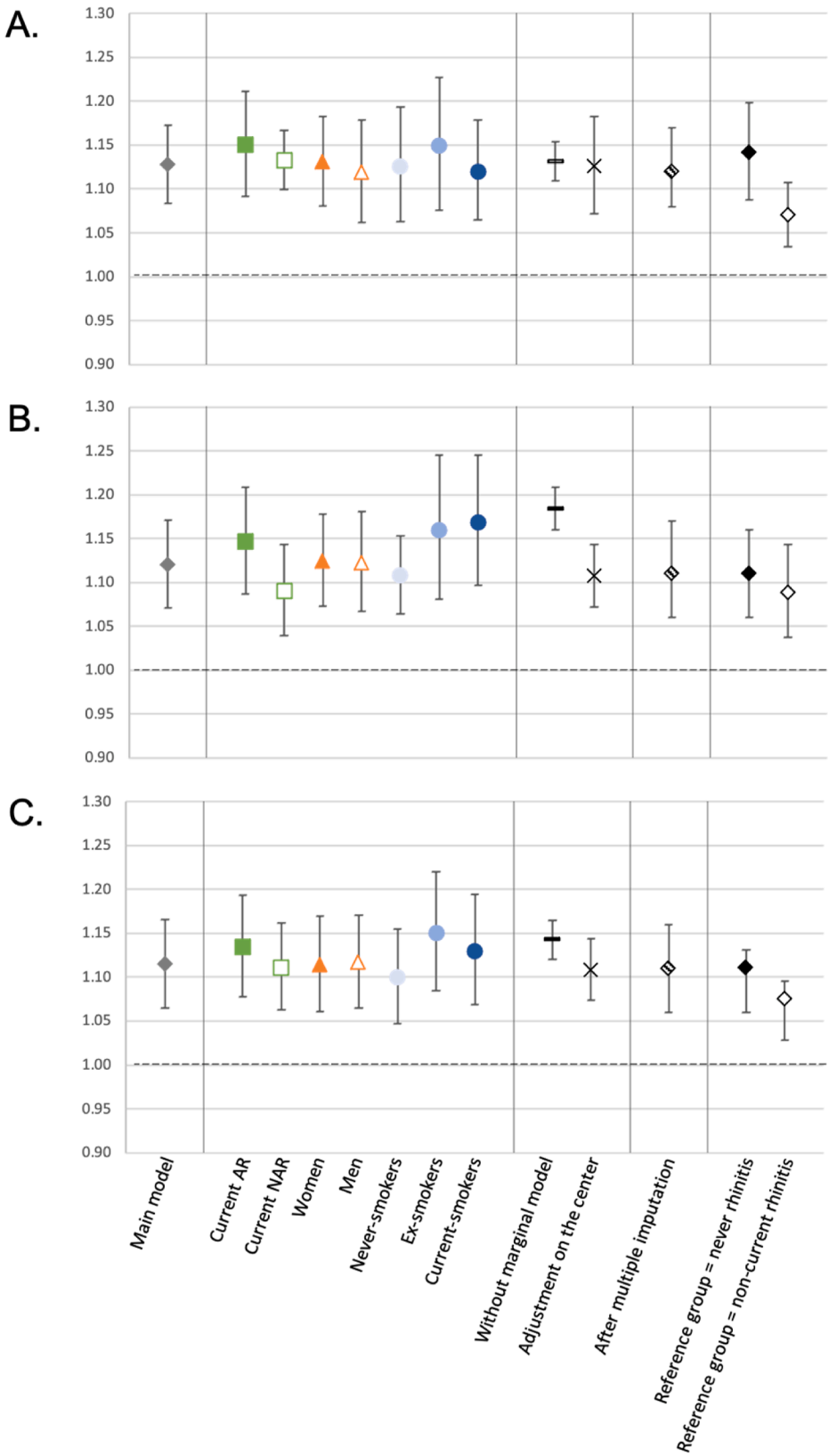


**Fig. 2.** Associations between exposure to air pollution and current rhinitis OR (95% CI) were calculated: (A) For an increase of an IQR of $PM_{2.5}$ (4.85 μg/m$^3$). (B) For an increase of an IQR of BC (0.88 $10^{-5}$ m$^{-1}$). (C) For an increase of an IQR of $NO_2$ (17.3 μg/m$^3$). ◆■□—X▨◆◇: adjusted ORs for age, sex, smoking status, educational level, and French deprivation index. ▲△: adjusted ORs for age, smoking status, educational level, and French deprivation index. ●●●: adjusted ORs for age, sex, educational level, and French deprivation index. AR: Allergic Rhinitis; BC: black carbon; CI: confidence interval; NAR: Non-Allergic Rhinitis; $NO_2$: nitrogen dioxide; OR: odds ratio; $PM_{2.5}$ particulate matter with an aerodynamic diameter less than 2.5 μm. The health prevention center was taken into account by marginal models with generalized estimating equations (except in the model adjusted on the center and in the model without marginal model). All p-values were $< 10^{-4}$.

the ORs were similar to those reported in the main model. In contrast, when only participants with non-current rhinitis were included as a reference group, ORs were still significant but lower than those in the main model.

## 4. Discussion

In this cross-sectional analysis, an increase of modeled annual average residential exposure to $PM_{2.5}$, BC, and $NO_2$ was significantly associated with an increased risk of current rhinitis in adults in a large population-based study. These results were consistent regardless of the adjustment, the stratification and the sensitivity analysis.

Our analyses were conducted in the largest French adult population-based cohort, which yielded very high statistical power. Our definition of rhinitis is self-reported and based on the answer to the validated and standardized questions that were used in the ISAAC study (Asher et al., 1995). These questions have the advantage of being based on the main symptoms of AR and NAR and are understandable to all participants which allows all rhinitis to be considered, even those that have not been diagnosed by a doctor. This is especially important as many patients with mild symptoms do not consult a doctor for their rhinitis. Thus taking into account only the medical diagnosis could lead to an underestimation of the actual number of cases of mild to moderate rhinitis (Bousquet et al., 2012; Wise et al., 2018). Skin Prick Tests and/or Immunoglobulin E (IgE) that are the gold standard to differentiate AR from NAR were not available in the Constances study. We have therefore distinguished AR from NAR based on the validated and standardized question of nasal allergies adapted from the ECRHS study (ECRHS, 1996) that has very often been used in the literature to define AR. This definition combined with the ISAAC definition has been shown to be a suitable proxy for AR and NAR (Savouré et al., 2021) even if classification errors cannot be excluded.

In this study, long-term exposure to air pollutants was estimated at the participants' residential address at inclusion using validated European LUR models that provide a fine-scale (100 × 100 m) estimate used to assign (de Hoogh et al., 2018). We considered outdoor pollution, and as participants are not always at home, we acknowledge that this can lead to exposure misclassification. We carried out cross-sectional analyses, so temporality is not defined, and causality cannot be studied. We hypothesize that the measurements performed in 2010 at the inclusion address reflect the long-term air pollution exposure of the participants. It has been shown that the pollution levels from one year to another for the same geographical area are very similar (Hansell et al., 2016). We assume that the annual mean of the pollutants reflects a long-term exposure, which is probably true for those who did not move for several years prior to outcome assessment; unfortunately we did not have the residential history of the participants to perform such a sensitivity analysis. We cannot exclude that the limitations presented above may lead to a non-differential measurement error suggesting that the actual effect of long-term exposure to air pollution on rhinitis may be higher than the one we have identified. Although we adjusted for the main confounders associated with both rhinitis and air pollution, we cannot exclude that a residual confound remains. In Constances, each participant is assigned to an HPC. The estimation of air pollution was based on the same LUR model and rhinitis was assessed by questionnaire which is the same for all participants, independently of the HPC. In our opinion, there is no center effect as classically defined in epidemiology, i.e. meaning that exposure or/and the outcome of interest are differentially assessed across centers. However, it is possible that participants living near the same HPC are more similar in terms of lifestyle or pollen exposure for example, than participants from different HPC. That is why we considered the HPC in a marginal model with generalized equations. The results were similar when considering the HPC in an adjusted model or with the meta-analyses. However, for the meta-analyses the coefficient of heterogeneity was significant for BC and $NO_2$. This heterogeneity is mainly due to the results for Paris HPC. The results for Paris could be explained by the fact that Parisian participants show less variability in air pollution exposure. Not considering the HPC gave similar results to those of the marginal model for $PM_{2.5}$ and slightly higher ORs for BC and $NO_2$. Overall, our analyses yielded significant results and the sensitivity analyses we have performed support the robustness of our results.

The existing literature is ambiguous as to which group current rhinitis is compared to, and previous studies have not consistently defined whether or not non-current rhinitis was included in the reference group. In our opinion, participants who have non-current rhinitis may be considered as a "special group" as they used to have rhinitis that is no longer active. Thus, we conducted an extra analysis excluding participants with non-current rhinitis, yielded results nearly identical to those of the main analysis. We also compared current rhinitis to non-current rhinitis. The research question behind the latter analysis was to determine if long-term exposure to air pollution could affect symptom activation among participants with a history of rhinitis. To our knowledge, our study is the first to report this type of comparison. Our results were significant and can be added to the growing literature on the association of air pollution with the severity and exacerbation of rhinitis (Burte et al., 2020; Li et al., 2020a; Naclerio et al., 2020). In addition, our analyses comparing current rhinitis to non-current rhinitis yielded lower ORs than analyses comparing current rhinitis to never rhinitis. This difference in the strength of the associations could be partly explained by the study population: indeed, the comparison between current rhinitis and non-current rhinitis was conducted in a more homogenous population of participants with a rhinitis during their lifetime. These results need to be explored further but they could suggest that air pollution may be associated not only with the presence of rhinitis symptoms but also with the activation of rhinitis symptoms in participants who previously have had rhinitis.

Our main results are difficult to compare with those in the literature as there are only few studies on the association between long-term exposure to air pollution and the prevalence of current rhinitis in adults in population-based cohorts. Three studies in Europe (de Marco et al., 2002; Lindgren et al., 2009; Nordeide Kuiper et al., 2020) have shown that exposure to $NO_2$ was associated with an increase in the prevalence of current AR in adults. In these studies, as in our results, associations were observed at annual mean concentrations of $NO_2$ below the WHO recommended value of 40 $\mu g/m^3$, which may suggest that air pollution could have effects on rhinitis even at low levels. To our knowledge only one study (Nordeide Kuiper et al., 2020) has examined the effects of $PM_{2.5}$ and BC on current AR in adults. In the study by Nordeide Kuiper et al., Swedish and Norwegian adults were included and the long-term exposures to $PM_{2.5}$, BC and $NO_2$ were estimated with the same European LUR as the one used in the present study (de Hoogh et al., 2018). Similarly to our study, long-term exposure to $PM_{2.5}$, BC or $NO_2$ in the year prior to the report of current AR was significantly associated with an increased risk of current AR (Nordeide Kuiper et al., 2020). Long-term exposures over the lifetime, the period of adolescence, or childhood, of participants were not significantly associated with current AR in adults (Nordeide Kuiper et al., 2020). This may suggest that recent exposure to air pollution may be more important in the occurrence of current rhinitis. To our knowledge, only one study (Lindgren et al., 2009) has considered both AR and NAR. The authors found that road traffic exposure in the adult population was associated with a higher prevalence of AR but not NAR, suggesting that rhinitis should not be treated as a homogeneous disease (Lindgren et al., 2009). In our results, we have observed significant associations between each of the three pollutants and both AR and NAR. The results were very similar between AR and NAR for $PM_{2.5}$ and $NO_2$, but interestingly for BC the OR was slightly higher for AR compared to NAR. AR and NAR present distinct physiopathological mechanisms, and it is therefore possible that the effect of pollutants is different according to the phenotypes of rhinitis. Given the limited literature that has considered AR and NAR, these hypotheses need to be further explored.

We performed analyses by stratifying according to sex, as air

pollution could lead to different responses between men and women (Clougherty, 2010). The interactions were non-significant between the different pollutants and sex, and the results were similar for women and men. Among adults, evidence of effect modification by sex remains uncertain but the role of biological factors such as hormones, of lung volume or of gender-related factors such as differential accuracy in residence-based exposure assignment could partly explain the greater effects of air pollution observed in women than in men (Clougherty, 2010). As tobacco and air pollutants may share similar underlying biological mechanisms on the onset of respiratory disease (Ni et al., 2020), we have also stratified according to smoking status. We did not observe any interactions between smoking status and the different pollutants, and the results were very similar according to the different strata suggesting that the effect of air pollution on rhinitis would be independent of smoking status.

Due to the high correlation between the three pollutants, we could not perform a two-pollutant or tri-pollutant model by adjusting for the other pollutants (Dominici et al., 2010). As BC is a component of PMs, we used the residual method proposed by Mostofsky et al. to take into account the confounding induced by $PM_{2.5}$ (Mostofsky et al., 2012). Our results with BC residuals were very similar to those of BC, suggesting that BC and closely-linked components are associated with rhinitis independently of total $PM_{2.5}$. Our results reinforce the hypothesis that BC is one of the most harmful components of PMs (Yang et al., 2019) even if further studies between exposure to BC and rhinitis are needed to confirm our findings.

We did not adjust for the different distribution of pollen species in France. However, the marginal model allowed us to consider indirectly, among other things, the differences in the distribution of pollens between the different HPC. The associations between long-term exposure to air pollution, greenspace and rhinitis is understudied. In the recent study by Nordeide Kuiper et al., no significant association was observed between greenspace and rhinitis (Nordeide Kuiper et al., 2020). However, in the study by Markevych et al., early life residence in places with many allergenic trees increased the prevalence of allergic rhinitis later in life. Exposure to greenspace could promote rhinitis by increasing exposure to pollens (Markevych et al., 2020). To our knowledge there is no study on the interaction between long-term exposure to air pollution, greenspace and rhinitis in adults. In their study in 2020, Nordeide Kuiper et al. simultaneously adjusted on greenspace and air pollution in their analyses, but potential interactions were not tested. Considering the relationships between greenspace, air pollution and rhinitis is an interesting research perspective, especially given climate change and its connection with air pollution and respiratory health (D'Amato et al., 2016).

Three major underlying biological pathways have been proposed to explain the link between long-term air pollution and rhinitis: inflammation, oxidative stress, and allergy. They are highly interrelated and can be local, by acting specifically on the nasal epithelium, and/or systemic. The inflammatory effect of air pollutants can be neutrophilic or eosinophilic (Ramanathan et al., 2017; Wei and Tang, 2018). Inflammation can lead to an increase in the permeability of the nasal epithelial barrier leading to an easier access of allergens to the immune system (De Grove et al., 2018). PM, BC and $NO_2$ can induce the production of reactive oxygen and nitrogen species in the airway epithelium and macrophages, which can subsequently maintain the inflammatory effect and augment immune response (Leikauf et al., 2020; Li et al., 2020b; Niranjan and Thakur, 2017; Rouadi et al., 2020). Finally, regarding AR, air pollutants, in particular diesel particles, could act as adjuvant in synergy with allergens to increase the allergic response which can subsequently induce inflammation (Joubert et al., 2020; Li et al., 2020a; Niranjan and Thakur, 2017). To date, the pathways involved in the association between air pollution and rhinitis have been poorly investigated. Studying the three pathways mentioned above could improve the characterization of the disease, and the understanding of its association with air pollution leading to a better management of rhinitis.

In conclusion, long-term exposure to air pollution was associated with current rhinitis in adults in a large French population-based study. The results suggest that among air pollutants, BC may be of special interest. In view of the high prevalence of rhinitis, these findings have an important public health impact and reinforce the need to reduce the population's exposure to air pollution.

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## CRediT authorship contribution statement

**Marine Savouré:** Conceptualization, Methodology, Formal analysis, Writing – original draft, Visualization. **Émeline Lequy:** Methodology, Resources, Writing – review & editing. **Jean Bousquet:** Writing – review & editing. **Jie Chen:** Methodology, Resources, Writing – review & editing. **Kees de Hoogh:** Methodology, Resources, Writing – review & editing. **Marcel Goldberg:** Resources, Writing – review & editing. **Danielle Vienneau:** Methodology, Resources, Writing – review & editing. **Marie Zins:** Resources, Writing – review & editing. **Rachel Nadif:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Bénédicte Jacquemin:** Conceptualization, Methodology, Writing – review & editing, Supervision.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary material

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