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Burte E, PhD[1,2,3,4], Leynaert B, PhD[5], Marcon A, PhD[6], Bousquet J, MD[1,2,7], Benmerad M, MSc [8], Bono R, PhD[9], Carsin AE, MSc[3,4,10,11], de Hoogh K, PhD[12,13], Forsberg B, PhD[14], Gormand F, MD[15], Heinrich J, PhD[16,17], Just J, MD[18,19], M Nieuwenhuijsen, PhD[3,4,10,11], Pin I, MD[8,20], Stempfelet M, MSc[21], Sunyer J, MD, PhD[3,4,10,11], Villani S, PhD[22], Künzli N, PhD[12,13], Siroux V, PhD[8], Jarvis D, MD, PhD [23,24], Nadif R, PhD[1,2*], Jacquemin B, MD, PhD[1,2,3,10*]

* These authors contributed equally to this study

1. INSERM, U1168, VIMA: Aging and chronic diseases. Epidemiological and public health approaches, Villejuif, France
2. Univ Versailles St-Quentin-en-Yvelines, UMR 1168, F-78180, Montigny le Bretonneux, France
3. ISGLobal, Barcelona, Spain.
4. Universitat Pompeu Fabra (UPF), Barcelona, Spain.
5. Inserm, UMR 1152, Pathophysiology and Epidemiology of Respiratory Diseases, Paris, France;
6. Unit of Epidemiology and Medical Statistics, Department of Diagnostics and Public Health, University of Verona, Verona;
7. University Hospital, Montpellier, France; MACVIA-France, Contre les MAladies Chroniques pour un Vieillissement Actif en France, European Innovation Partnership on Active and Healthy Ageing Reference Site, Montpellier;
8. Team of Environmental Epidemiology applied to Reproduction and Respiratory Health, Inserm U1209, CNRS, University Grenoble Alpes, Institute for Advanced Biosciences (IAB), Grenoble, France
9. Dept of Public Health and Pediatrics, University of Turin, Turin.
10. CIBER Epidemiología y Salud Pública (CIBERESP), Spain.
11. IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain.
12. Swiss Tropical and Public Health Institute, Basel, Switzerland
13. University of Basel, Basel, Switzerland
14. Dept of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden
15. CHU de Lyon, Pneumology Dept, Lyon, France.
16. Ludwig Maximilians University Munich, University Hospital Munich, Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, Munich, Germany
17. Comprehensive Pneumology Center Munich (CPC-M), Member of the German Center for Lung Research
18. Allergology Department, Assistance Publique-Hôpitaux de Paris, Hôpital Armand-Trousseau
19. Sorbonne Université Paris 6, Paris, France
20. Pediatrie, CHU de Grenoble Alpes, Grenoble, France.
21. Santé Publique France, 12, rue du Val d'Osne, 94415 Saint-Maurice, France.
22. Unit of Biostatistics and Clinical Epidemiology, Dept of Public Health, Experimental and Forensic Medicine University of Pavia, Pavia.
23. National Heart and Lung Institute, Imperial College London, London, United Kingdom
24. MRC Centre for Environment and Health, School of Public Health, London, United Kingdom

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Corresponding author:

Bénédicte Jacquemin,

INSERM, U1168, VIMA: Aging and chronic diseases, Epidemiological and Public health approaches, F-94807, Villejuif, France. Phone number: 33 (0) 145 59 50 22, Fax number: 33 (0) 145 59 51 69

E-mail: benedicte.jacquemin@inserm.fr

Abstract:

Background: Very few studies have examined the association between long-term outdoor air pollution and rhinitis severity in adults.

Objective: To assess the cross-sectional association between individual long-term exposure to air pollution and severity of rhinitis.

Methods: Participants with rhinitis from two multicentre European cohorts (EGEA and ECRHS) were included. Annual exposure to NO_2, PM_{10}, $PM_{2.5}$ and PMcoarse (calculated by subtracting $PM_{2.5}$ from PM_{10}) was estimated using land-use regression models derived from the ESCAPE project, at the participants' residential address. The score of rhinitis severity (range 0-12), based on intensity of disturbance due to symptoms reported by questionnaire, was categorized in low (reference), mild, moderate and high severity. Polytomous logistic regression models with a random intercept for city were used.

Results: 1408 adults with rhinitis (mean age: 52 years, 46% men, 81% from ECRHS) were included. The median [Q1-Q3] score of rhinitis severity was 4 [2-6]. Higher exposure to PM_{10} was associated with higher rhinitis severity (aOR[95% CI] for a 10 µg/m^3 increase of PM_{10}: for mild: 1.20[0.88-1.64], moderate: 1.53[1.07-2.19], and high severity: 1.72[1.23-2.41]). Similar results were found for $PM_{2.5}$. Higher exposure to NO_2 was associated with an increased severity of rhinitis, with similar aORs whatever the level of severity. aORs were higher among participants without allergic sensitization than in those with, but interaction was found only for NO_2.

Conclusions: People with rhinitis who live in areas with higher levels of pollution are more likely to report more severe nasal symptoms – further work is required to elucidate the mechanisms of this association.

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Capsule summary: People with rhinitis who live in areas with higher levels of pollution are more likely to report more severe nasal symptoms – further work is required to elucidate the mechanisms of this association.

Key messages:

- Very little is known about air pollution as risk factor for rhinitis and its phenotypes in adults
- Air pollution and particularly particulate matter is associated with an increase in rhinitis severity
- Air pollution needs to be controlled

Keywords: rhinitis, allergic sensitization, air pollution, environment, severity, respiratory disease

Abbreviations:

ARIA: Allergic Rhinitis and its Impact on Asthma

ECRHS: European Community Respiratory Health Survey

EGEA: Epidemiological Study on the Genetics and Environment on Asthma

ESCAPE: European Study of Cohorts for Air Pollution Effects

LUR: Land-Use Regression

NO_2: nitrogen dioxide

OR: Odds Ratio

PM: Particulate matter

SAR: Seasonal Allergic Rhinitis

Introduction

Rhinitis is a very frequent disease affecting between 20% and 50% of the population according to countries and definitions (Bousquet et al. 2008; Katelaris et al. 2012; Wang et al. 2014). The principal symptoms of rhinitis are sneezing and runny, blocked or itchy nose, in absence of a cold or the flu (Bousquet and Cauwenberge 2002). Often considered as a trivial disease, rhinitis does actually have an important impact on quality of life (Bousquet et al. 2013; Leynaert et al. 2000). Rhinitis is generally divided into allergic and non-allergic rhinitis, often differing in terms of symptoms, duration, treatment, seasonality and/or severity (Papadopoulos et al. 2015; Quillen and Feller 2006). Very little is known about the environmental risk factors of rhinitis and its different phenotypes, including air pollution (Heinrich 2018). As rhinitis is frequently associated with asthma (Shaaban et al. 2008) for which air pollution has been shown to strongly aggravate symptoms (Rage et al. 2009), and even induce the disease (Guarnieri and Balmes 2014), it is a genuine question to wonder about the effects of air pollution on rhinitis.

There are very few studies focusing on the association between air pollution and rhinitis in adults. Short-term exposure to air pollution has been associated with exacerbation of rhinitis leading to more daily clinical examinations (Hajat et al. 2001; Zhang et al. 2011). However, association between long-term air pollution and rhinitis severity has scarcely been studied. One large French study assessing the link between grass pollen counts, air pollution levels and severity of seasonal allergic rhinitis found a positive but not statistically significant association between air pollutant level and severe allergic rhinitis (Annesi-Maesano et al. 2012). However, this study only considered seasonal allergic rhinitis and no other phenotypes. Recently, an American study examined the relationship between $PM_{2.5}$ (airborne particles with an aerodynamic diameter $\leq$2.5 µm) and black carbon and rhinitis in 125 patients with chronic rhinosinusitis with and without polyps (Mady et al. 2018). They found significantly higher exposure levels of $PM_{2.5}$ and black carbon among participants without allergic sensitization compared to those with allergic sensitization, and also found an association between black carbon and non-allergic symptoms of rhinitis. In a previous study, we found no consistent evidence for an association between long-term exposure to air pollution and incidence of rhinitis, whether allergic or non-allergic (Burte et al. 2018). We hypothesized that air pollution may not induce rhinitis development, but may still be associated with an increase in severity of the disease.

In the present study, we aimed to examine the association between long term exposure to air pollution and severity of allergic and non-allergic rhinitis in two European studies.

Methods:

Study design and settings

Participants included in the analysis were those suffering from rhinitis at the second follow-up (2011-2013) of two large multicentre epidemiological European studies: the European Community Respiratory Health Survey (ECRHS) and the Epidemiological Study on the Genetics and Environment on Asthma (EGEA).

The EGEA ((Kauffmann 1999; Kauffmann et al. 1997), https://egeanet.vjf.inserm.fr/) is a French cohort of 2,047 participants (asthma patients –adults or children- enrolled from hospital chest clinics, their first-degree relatives, and controls who were recruited from other hospital wards or from electoral lists) enrolled between 1991 and 1995 from five French cities. A first follow-up was conducted between 2003 and 2007 (EGEA2, N=2121, (Kauffmann et al. 1997; Siroux et al. 2009)) and a second between 2011 and 2013 (EGEA 3, N=1558, (Bouzigon et al. 2015)).

The ECRHS (Burney et al. 1994) is a population-based cohort of young adults, enriched with participants with respiratory symptoms, recruited from 1992 to 1994 in 28 western European cities (ECRHS I, N=17880, http://www.ecrhs.org/) and followed up twice: between 2000 and 2002 (ECRHS II, n=10933, European Community Respiratory Health Survey II Steering Committee 2002) and between 2011 and 2013 (ECRHS III, N=7040).

Participants of both studies were extensively characterized with regard to their respiratory health and risk factors using similar standardized protocols and questionnaires. Ethical approval was obtained in each study from the appropriate institutional ethics committees and written informed consent was obtained from each participant.

Definition of rhinitis

In this cross-sectional analysis, report of ever rhinitis was defined by a positive response 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*?" in EGEA3 and ECRHS III.

Among those who had reported ever rhinitis, rhinitis in the last 12 months was defined by a positive response 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 in the last 12 months*?" in EGEA3 and ECRHS III.

Definition of score of severity of rhinitis (based on symptoms of rhinitis)

A numeric score of severity of rhinitis was assessed at EGEA3 and ECRHSIII, adapted from the Symptomatic Global Score for seasonal allergic rhinitis (Rouve et al. 2010). This score was calculated on the basis of the answers to question on severity of the four main symptoms of rhinitis (watery runny nose, blocked nose, itchy nose and sneezing). In case of missing data for severity of one or more symptoms, no imputation was done and these participants were not included in the analyses. For each of the four items, participants had to indicate how important the symptom had hampered their daily life in the last 12 months:

0. No problem (symptom not present)
1. A problem that is/was present but not disturbing
2. A disturbing problem but not hampering day time activities or sleep
3. A problem that hampers certain activities or sleep

Each question scored from 0 to 3 and thus summing the answers to these 4 questions, the overall score ranged from 0 to 12, the higher score indicating a higher severity. The overall score was further categorized into four levels according to the quartiles of the distribution: low severity (score <=2), mild severity (score = 3 or 4), moderate severity (score = 5 or 6) and high severity (score >=7). Low severity was considered as the reference in the analyses.

Additionally, severity was analysed symptom by symptom, using the following classification to approximate closely the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines (2): The category 0 was considered as the reference compared to mild rhinitis (1), and moderate/severe rhinitis (2/3 pooled together).

Definition of allergic sensitization

In EGEA2, allergic sensitization was defined using skin-prick test (SPT) for 12 aeroallergens (mean wheal diameter 3mm ≥ than the negative control to at least one of the following allergens:

cat, *Dermatophagoides pteronyssinus*, *Blattela germanica*, olive, birch, *Parieteria judaica*, timothy grass, ragweed pollen, *Aspergillus*, *Cladosporium herbarum*, *Alternaria tenuis*).

In ECRHS II, allergic sensitization was defined using specific Immunoglobulin E (IgE) to four allergens (specific IgE≥35kU/mL to at least one of the following allergens: cat, *Dermatophagoides pteronyssinus*, *Cladosporium,* and timothy grass).

Definition of asthma

Ever asthma was defined by a positive response to "*Have you ever had asthma?*" in ECRHS III; and by a positive response to one of the following questions "*Have you ever had attacks of breathlessness at rest with wheezing?*" or "*Have you ever had asthma attacks?*" at EGEA1, EGEA2 or EGEA3 or by being recruited as asthmatic cases in EGEA 1 (Siroux et al. 2011).

Estimation of air Pollution exposure

Long-term exposure to pollutants was estimated using land use regression models derived from the European Study of Cohorts for Air Pollution Effects (ESCAPE www.escapeproject.eu (Beelen et al. 2013; Eeftens et al. 2012)) project. The home addresses of the participants at EGEA2 and ECRHS II, living in ESCAPE cities were geocoded. As no exposure data at the same year of EGEA2 or ECRHS II was available, the exposure at the closest year was used. Therefore, geocodes were linked with ambient concentrations of air pollutants estimated using land-use regression (LUR) models between 2009 and 2010. Available air pollutants were: NO_2 (nitrogen dioxide), PM_{10} (airborne particles with an aerodynamic diameter $\leq$10 µm), $PM_{2.5}$ and PMcoarse (airborne particles with an aerodynamic diameter ranging from 2.5 to 10µm, calculated by subtracting $PM_{2.5}$ from PM_{10}). Estimates of NO_2 were available for all 17 cities (Umea, Norwich, Ipswich, Antwerp, Erfurt, Paris, Lyon, Grenoble, Marseille, Verona, Pavia, Turin, Oviedo, Galdakao, Barcelona, Albacete and Huelva) and estimates of all PM metrics for 6 cities (Norwich, Ipswich, Antwerp, Paris, Grenoble, Turin and Barcelona). Data on two traffic exposure indicators -traffic intensity (on the nearest road), and traffic load (in a 100m buffer)- were also available.

Statistical analysis

Associations between long-term exposure to air pollutants (estimated at participants' residential addresses at the first follow-up of each study, thus between 2000 and 2007) and the severity score of rhinitis (assessed at the second follow-up of each study, thus between 2011 and 2013) were analysed using polytomous logistic regression. To account for between-city heterogeneity, a random intercept for city was used (GLLAMM procedure in STATA14).

Models were carried out without any adjustment, and then adjusted on pre-selected variables based on previous literature: age, sex, smoking status, asthma and allergic sensitization. Analyses with traffic density or traffic load were further adjusted for NO_2 background level as described in the ESCAPE protocol. Results are presented as odds ratio (OR) with the associated 95% confidence interval associated. Estimates were reported for an increase of 10 $\mu g/m^3$ for NO_2 and PM_{10}, 5 $\mu g/m^3$ for $PM_{2.5}$ and PMcoarse, 4,000,000 vehicles*m/day for traffic load on all major roads in a 100m buffer and 5,000 vehicles/day for traffic density on the nearest road, following ESCAPE protocol.

Considering that air pollution may act differently according to allergic sensitization, a stratified analysis on allergic sensitization status was carried out. As air pollution is known to increase asthma severity and as asthma and rhinitis are strongly related, a stratified analysis on asthma status was also carried out. Smokers have a continual bombardment of the nasal cavities with PM and irritant gases from cigarette smoke, which could affect pollutant response and thus a stratified analysis on smoking status (current smokers vs. ex or never smokers) was carried out. Finally, since the design of ECRHS and EGEA differed, a stratified analysis on study was also carried out on the study. The interactions between each pollutant and each factor of stratification were tested by likelihood ratio tests in separate models.

To test if association between air pollution and severity of rhinitis differs according to the type of symptom, the association between air pollutants and severity of each of the four symptoms separately was estimated.

Sensitivity analyses were performed: as treatment may have lowered severity, analysis excluding participants with medication in the last 12 months (use of medication –pills or spray- to treat nasal disorder in the last 12 months) was performed. Given that the methods used to take into account the within-city (or centre) correlation is a complex issue (Basagaña et al. 2018), and to ensure robustness of our results, simple polytomous regressions without adding a city level intercept were also performed. As participants may have moved between the first and the second follow-up of both studies, we also performed the fully adjusted analysis among non-movers only to ensure robustness of the results. Since only half of the population has PM data and to ensure comparability of the results, analyses with NO_2 were also performed in the restricted population with PM exposure data.

Bi-pollutant models including NO_2 and each one of the PM metrics were also performed to test the independence of the results for each of the pollutant.

All analyses were carried out by Stata (Stata 14)).

Results:

This study included 1408 participants from EGEA3 and ECRHS III with symptoms of rhinitis in the last 12 months, having available data on rhinitis severity score and individual air pollution estimates (Flow-chart available in Figure 1).

A detailed description of the characteristics of the 1408 participants is reported in Table 1, for all participants and according to the four levels of severity of rhinitis. ECRHS contributed with 81% of the study population. Participants were on average 52.3 years old, 54.4% were women and 28% had asthma. The median severity score of rhinitis was 4 ([Q1-Q3]=[2-6]). When increasing in the severity category, participants were younger, more often from the EGEA study, and more often had asthma and allergic sensitization (from 18% in low severity to 39% in high severity and from 35% in low severity to 64% in high severity respectively). Participants with higher severity also reported allergic rhinitis or hay fever more often (from 34% for low severity to 81% for high severity) as well as more frequent symptoms of rhinitis.

An increase in air pollution exposure was associated with an increased in the severity of rhinitis (Figure 2, exact ORs in Table S2 in Supplementary material). Increased levels of PM_{10} and $PM_{2.5}$ were associated with higher levels of severity, with an exposure-response association. A similar pattern was found for PMcoarse with a slightly lower effect and reaching statistical significance only for high severity. For NO_2, there was no exposure-response relationship. ORs for mild, moderate and high severity were similarly estimated at around 1.15. No association was found between traffic load or traffic intensity and score of severity.

Stratified analyses

Stratification by allergic sensitization

Among participants with no allergic sensitization, increase in NO_2, PM metrics and traffic intensity exposure were associated with an increased severity score of rhinitis, with an exposure-response relationship (Figure 3 and Table S2 in Supplementary material). Among participants with allergic sensitization, increase in air pollution exposure was associated with an increased severity score of rhinitis only for $PM_{2.5}$. No association was found for the other pollutants. A statistically significant interaction was found between allergic sensitization and NO_2 (p-interaction of the likelihood-ratio test= 0.02), at borderline statistical significance for traffic load (p-interaction=0.05) and traffic intensity (p-interaction=0.08), and not statistically significant for PM_{10} (p-interaction=0.26), $PM_{2.5}$ (p-interaction=0.21) and PMcoarse (p-interaction=0.24).

Stratification by asthma status

Among the participants without asthma, an increase in air pollution exposure was associated with an increased severity score of rhinitis -similar to the results of the participants without allergic sensitization-(Table S2 in Supplementary material). In contrast, in the participants with asthma, an increase in air pollution exposure was not associated with an increased severity score of rhinitis – similar to the results of the participants with allergic sensitization. An interaction was found for NO_2 (p-interaction =0.007) and for traffic load (p-interaction=0.03) and no interaction was found between other pollutants and asthma (p-interactions>0.11).

Stratification by smoking status

Among non-smokers, a higher air pollution exposure was associated with an increased severity score of rhinitis (Table S3 in Supplementary material). In contrast, higher exposure was not associated with an increased severity score in smokers although all interaction tests were below conventional levels of significance (p-interactions <0.14)

Stratification by study

Among participants from the ECRHS study, higher air pollution exposure was associated with an increased severity score of rhinitis (Table S3 in Supplementary material). In contrast, a higher exposure was not associated with an increased severity score in participants from the EGEA study although all interaction tests were below conventional levels of significance (p-interactions <0.40).

Analyses of the association between air pollutants exposure and severity of each symptom of rhinitis

The associations between air pollutants exposure and the symptoms composing the score are shown in Table S1 of the Supplementary material. In summary, PM_{10} and $PM_{2.5}$ exposure increased the severity of blocked nose, itchy nose and sneezing, with an exposure-response relationship. NO_2 exposure increased the severity of runny and blocked nose when compared to no symptoms, with a similar effect size for moderate/severe or mild symptoms. No association was found between NO_2 exposure and severity of itchy nose and sneezing. No association was found between PMcoarse exposure and severity of any of the four symptoms. No association was found between traffic load or traffic intensity and severity of any of the four symptoms.

Sensitivity analyses

When considering only the participants who did not take medicine for rhinitis in the last 12 months, results were similar to those from the main analysis, with a dose-relationship for PM (Table S4 in Supplementary material). Analyses among non-movers only showed similar results to those from the main analysis, with even higher ORs for NO_2 and PM metrics (Table S5 in Supplementary material).

In the bi-pollutants models (Table S6 in Supplementary Material), results remained consistent for PM metrics, with higher OR but wider confidence intervals, leading to only two statistically significant ORs: for high level of severity for PM_{10} and $PM_{2.5}$ (Pearson correlation between NO_2 and $PM_{2.5}$=0.60, between NO_2 and PM_{10}=0.70, and NO_2 and PMcoarse=0.72). Interestingly, estimates for NO_2 in the bi-pollutant models with PM_{10} and PMcoarse were higher than those in the main model and were reaching statistical significance for almost all level of severity.

Unadjusted models or models without taking city level into account gave very similar results as those using adjusted model with a random intercept for city, without changing the statistical significance of the results (results not shown).

Analyses with NO_2 in the restricted population having PM exposure data gave similar results (results not shown).

Discussion

In 1,408 participants from two European studies with detailed characterization of rhinitis, we investigated the association between individual air pollution exposure and severity of rhinitis. An increase in PM_{10} and $PM_{2.5}$ exposure was associated with an increased severity of rhinitis. To a lesser extent, PMcoarse and NO_2 were also associated with severity of rhinitis, with no exposure-response relationship for NO_2. No association was found between traffic load or traffic intensity and severity of rhinitis.

Our study is one of the first to examine the long-term effects of air pollution on the severity of rhinitis, considering separately allergic and non-allergic rhinitis separately. Previously, a French study among 17,567 children and adults has modelled the risk of suffering from severe seasonal allergic rhinitis (SAR) as a function of both grass pollen count and outdoor air pollution evaluated by daily mean exposure over a period of a few months (Annesi-Maesano et al. 2012). They found a positive but not statistically significant association between NO_2 or PM_{10} exposure and SAR high severity, with a trend for PM $_{10}$, and with adjustment for pollen count. Findings from this study cannot be directly compared with our study given the differences in the phenotype studied, in the definition of severity as they considered high versus no, low or moderate severity, in the estimation of exposure to air pollution, and given the lack of results without adjustment on grass pollen. Nevertheless, our results for PM_{10} and $PM_{2.5}$ among participants with allergic sensitization seem to be in line with this previous study. Unfortunately, we did not have data on grass pollen to take into account their interrelation with air pollutants in the study of allergic rhinitis.

One of the weaknesses of our study is the time discrepancy between ESCAPE measurement and the follow-up dates of the two studies: individual addresses were collected between 2000 and 2007, air pollution was measured and modelled between 2009 and 2010 and severity of rhinitis was collected between 2011 and 2013. Although the temporality -exposure assessment before severity assessment- is respected, we did not have the annual exposure corresponding to the year before questionnaire completion. This is a common problem when dealing with estimation of long-term annual air pollution. We assume that spatial variability of that specific year also represents the spatial patterns during previous years (de Hoogh et al. 2016). Our results among non-movers were similar to those from the main analysis, with even higher ORs, strengthening the robustness of our results.

One of the strength of the present analysis is the appraisal of allergic and non-allergic rhinitis phenotypes, of rhinitis severity as well as the consideration of different types of symptoms. We found differences in the association between air pollution exposure and severity of rhinitis according to the phenotype studied. After stratification by allergic sensitization, the effect of pollutants seemed higher among participants without allergic sensitization than in those with, although that interaction was statistically significant only for NO_2. The interactions between PM metrics and allergic sensitization were not statistically significant. However, we may not have enough power to find an interaction, as the sample size is almost half for PM analyses compared to NO_2 analyses. The higher association among participants without allergic sensitization could be partly supported by the fact that allergic sensitization is already a risk factor for high severity: there are twice as many participants with allergic sensitization with a high severity of rhinitis compared to low severity. The effect of pollutants may have a lower impact on those with already severe rhinitis. However, as discussed before, no association was found in the study by Annesi-Maesano et al. (Annesi-Maesano et al. 2012) between air pollution levels and score of allergic rhinitis. In the study by Mady et al., a positive correlation was found between exposure to black carbon and some symptoms of rhinitis, regardless of allergic sensitization status, and no results were available for $PM_{2.5}$. Furthermore, this study was based on a small selected sample of patients with disease, without formal statistical analyses. We had no data on the seasonality of the symptoms, and thus we were not able to assess whether air pollution exposure had a different impact on severity of rhinitis, depending on seasonal or “all-over-the-year” symptoms. We had data on the long-term annual exposure of air pollution and this study was not designed to investigate short-term/ seasonal variation in nasal symptoms according to air pollutant levels.

Accounting for asthma when assessing the association between air-pollution and rhinitis is not trivial as rhinitis and asthma are strongly related, and air pollution is known to increase asthma severity and incidence. Our results were similar when adjusting or not adjusting for asthma. Stratified analyses on asthma showed a higher effect of air pollutant among participants without asthma, but the interaction was statistically significant only for NO_2, as for allergic sensitization. The similarity of results according to allergic sensitization and according to asthma is probably due to the fact that allergic sensitization is strongly interrelated to asthma. Anyway, the association between air pollution exposure and rhinitis severity is most likely not confused by asthma status.

We found that a higher exposure to air pollution was associated with an increased severity of rhinitis among non-smokers but not among smokers. However, the estimates were of comparable magnitude or even higher in smokers than in non-smokers, and no interaction was found. These results are probably due to the fact that less than 20% of individuals were current smokers and therefore the sample size was probably small for such an evaluation. Similarly, we found that a higher exposure in air pollution was associated with an increased severity in ECRHS but not in EGEA, which represent around 20% of the individuals of our study. However, as EGEA is originally a case-control on asthma and thus have a high proportion of participants with asthma, results from the stratified analyses by study are in line with those from the analyses stratified by asthma.

We found similar results whether or not taking into account the city or including a random intercept for the city level, suggesting that adding the city level did not provide more information for the model and thus that the association between air pollution and severity of rhinitis does not change according to the city. Generally, our results were quite robust as estimates were similar in crude and adjusted analysis, whether taking the city into account or not.

The ARIA classification on severity was initially built for allergic rhinitis, but it may be extended to other phenotypes of rhinitis such as non-allergic rhinitis. Indeed, questions used to define severity are not specifically related to the allergic facet of the disease. Rhinitis is usually not defined by only one symptom, but by a combination of several symptoms characterizing the disease as a whole (Bousquet et al. 2008). We have therefore considered the score of severity in order to appraise the general effect of long-term air pollution on rhinitis severity. However, some symptoms may be more frequent in allergic rhinitis or non-allergic (Quillen and Feller 2006), and the effect of air pollutant on rhinitis severity may depend of the type of symptom of rhinitis. In our study, results differed according to the symptom and even if results were slightly stronger for “blocked nose”, no clear allergic or non-allergic pattern stood out.

Our results also differed according to the pollutant studied. Association between PM metrics and rhinitis severity increased gradually with levels of severity, whereas in the association between NO_2 exposure, effect size was the same whatever the levels. Both NO_2 and PM metrics are pollutants related to traffic, but their size and mechanisms of action are different, as well as how they can interact with pollen (D’Amato et al. 2016, 2018; Diaz-Sanchez 2000). The interaction between allergic sensitization and asthma status and NO_2 also supports this hypothesis. The potential mechanisms of action suggested to explain the effects of air pollutants are related to oxidative stress (Bates et al. 2019), reactive oxygen species, apoptosis and inflammation (Jang et al. 2016). In our case, gaseous or particulate pollutants seem to both have a distinct effect on rhinitis severity, and this was confirmed by our bi-pollutant model. It is somehow surprising that associations were weaker or null for PMcoarse, given that this PM fraction would be expected to have a higher nasal fractional deposition than $PM_{2.5}$. Particulates of different aerodynamic diameters may lead to different inflammatory responses in the respiratory tract (Huang et al. 2017) and the mechanisms underlying the interaction between PM and the immune system still need to be elucidated and addressed clinically (Wu et al. 2018). Furthermore, the biological effects of particulates are based on their chemical compositions, which may depend on the diameter of particulates. We found no clear association between traffic metrics and severity of rhinitis, a result consistent with previous ESCAPE papers reporting associations between specific pollutants with asthma and lung function, but not with traffic metrics (Adam et al. 2015; Jacquemin et al. 2015). All these results bring up the hypothesis that biological mechanisms by which air pollution may affect rhinitis are not the same depending on the pollutant as well as on the phenotype of rhinitis studied, and in particular according to allergic sensitization. Further studies filling the gap between air pollution exposure, biological markers of inflammation and phenotype of rhinitis are needed to better understand the underlying mechanisms of the general association.

In conclusion, using data from the 1,408 adults with rhinitis from two European studies on respiratory health, the present study showed that annual air pollution exposure was associated with increased severity of rhinitis, in particular for PM metrics. These results bring new insights into the management of rhinitis, a hidden major public health challenge, associated with substantial daily impairment and high cost to society. Finally, our results contribute to a better understanding of the environmental risk factors of this disease and re-emphasize the evidence that air pollution needs to be better controlled.

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Table 1 Characteristics of the participants, overall and by levels of score of severity

Variable	ALL N=1408	low severity N= 418	mild severity N=417	moderate severity N=251	high severity N=322	p-value
Score of severity, median [q1-q3]	4[2-6]	2[1-2]	4[3-4]	6[5-6]	8[7-9]	
Age, mean±sd	52.3±10.3	54.2±9.53	52.8±10.3	50.5±10.8	50.5±10.6	<0.001
Study, % EGEA	19.0	12.0	18.5	23.1	25.5	<0.001
Sex=women, %	54.4	51.2	51.8	60.2	57.5	0.059
Smoking status, %						
current	18.3	19.9	17.3	23.8	13.0	0.004
ex-smoker	38.3	40.3	41.5	30.7	37.8	
never	43.4	39.8	41.2	45.6	49.2	
Educational level, %						0.386
low	21.4	21.8	17.8	22.2	25.2	
medium	29.7	29.8	31.2	27.8	29.0	
high	48.9	48.4	51.0	50.0	45.9	
Asthma ever, %	28.2	18.0	28.4	30.9	38.9	<0.001
Asthma age of onset, mean±sd	16.9±13.9	17.1±13.9	18.5±14.7	16.2±13.8	13.8±14.7	0.43
Report of allergic rhinitis or hay fever ever, %	58.8	34.6	58.7	69.9	81.6	<0.001
Allergic sensitization, %	47.2	35.4	46.2	46.7	64.3	<0.001
Frequency of the symptoms=persistent, %	29.4	21.9	26	30	43.3	<0.001
Medication for rhinitis in the last 12 months=yes, %	42.0	16.7	37.0	52.7	68.8	<0.001
NO_2, µg.m^{-3}, mean±sd	29.9±14.6	28.2±14.1	30.5±14.9	30.5±15.1	30.8±14.2	0.047
PM_{10}, µg.m^{-3}, mean±sd	25.2±6.95	24.1±6.34	24.8±7.09	26.1±7.09	26.7±7.21	0.0009
$PM_{2.5}$, µg.m^{-3}, mean±sd	15.3±3.79	14.6±3.37	15.3±4.10	15.7±3.74	15.9±3.81	0.0018
Pmcoarse, µg.m^{-3}, mean±sd	10.1±3.91	9.77±3.80	9.85±3.67	10.4±3.95	10.8±4.27	0.0231
Traffic load, mean	1600627	1460000	1510000	1790000	1750000	0.52
Traffic intensity, mean	5624	4328	5496	7227	6439	0.0109
Severity of runny nose						<0.001
no	26.6	57.7	23.0	11.6	2.80	
mild	37.1	37.8	59.5	35.1	37.1	
moderate/severe	36.2	4.60	17.5	53.4	88.2	
Severity of blocked nose						<0.001
no	32.5	72.7	26.6	14.3	2.20	
mild	25.3	21.8	44.4	20.3	9.00	
moderate/severe	42.2	5.50	29.0	65.3	88.8	
Severity of itchy nose						<0.001
no	44.7	82.5	46.8	27.9	6.20	

mild	31.6	16.5	49.2	45.0	17.7	
moderate/severe	23.7	1.00	4.10	27.1	76.1	
Severity of sneezing						<0.001
no	30.4	60.8	28.8	16.7	3.70	
mild	37.8	36.4	57.1	38.7	14.0	
moderate/severe	31.8	2.87	14.2	44.6	82.3	

q1= quartile 1, q3= quartile 3, sd= standard deviation, p-value of the overall difference between the 4 categories of severity of rhinitis, p-value overall

Figure 1: Flow-chart of the participants

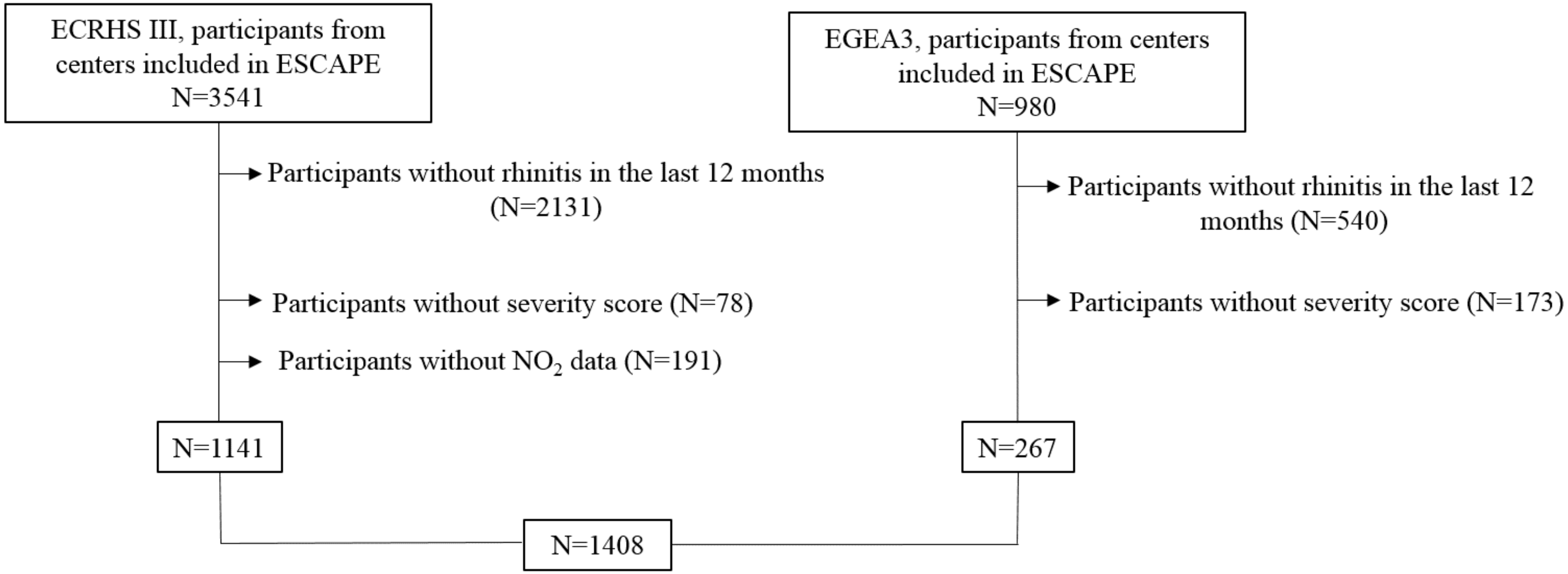


Figure 2: Associations between air pollutant metrics and severity of rhinitis

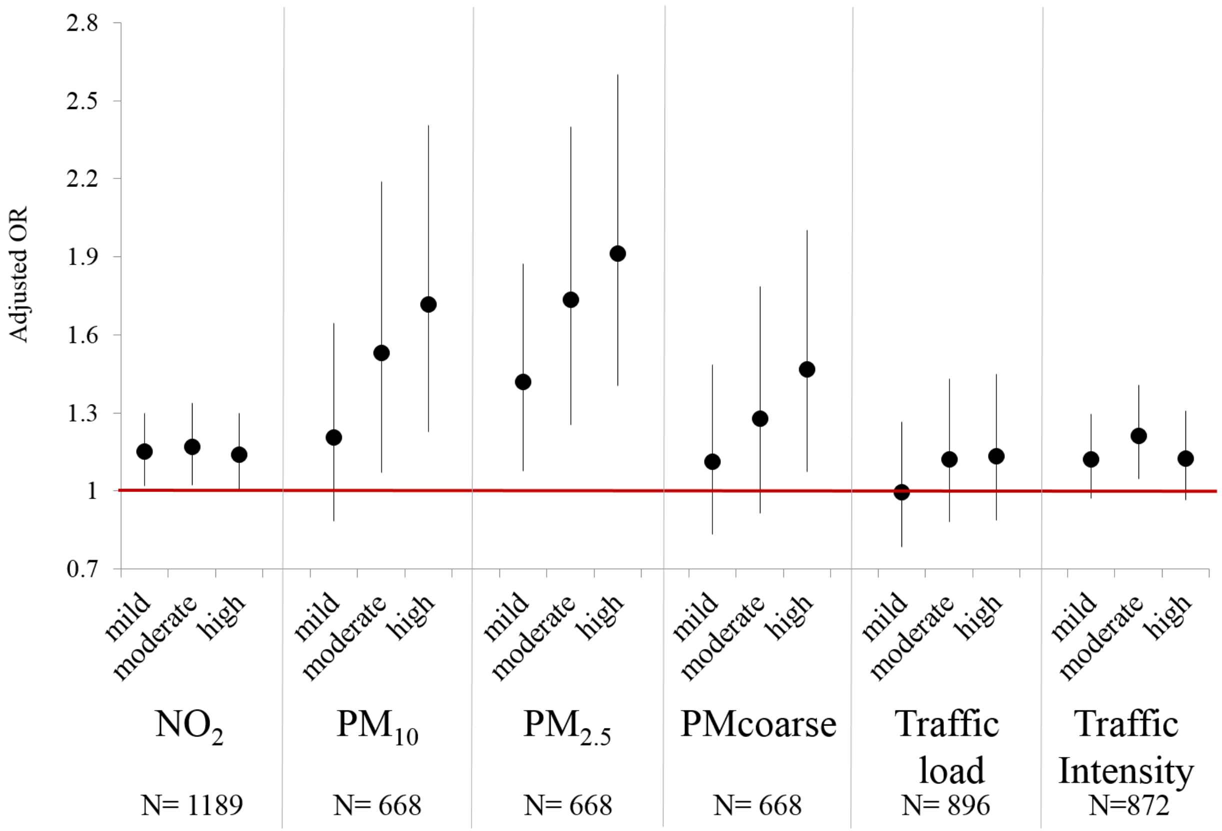
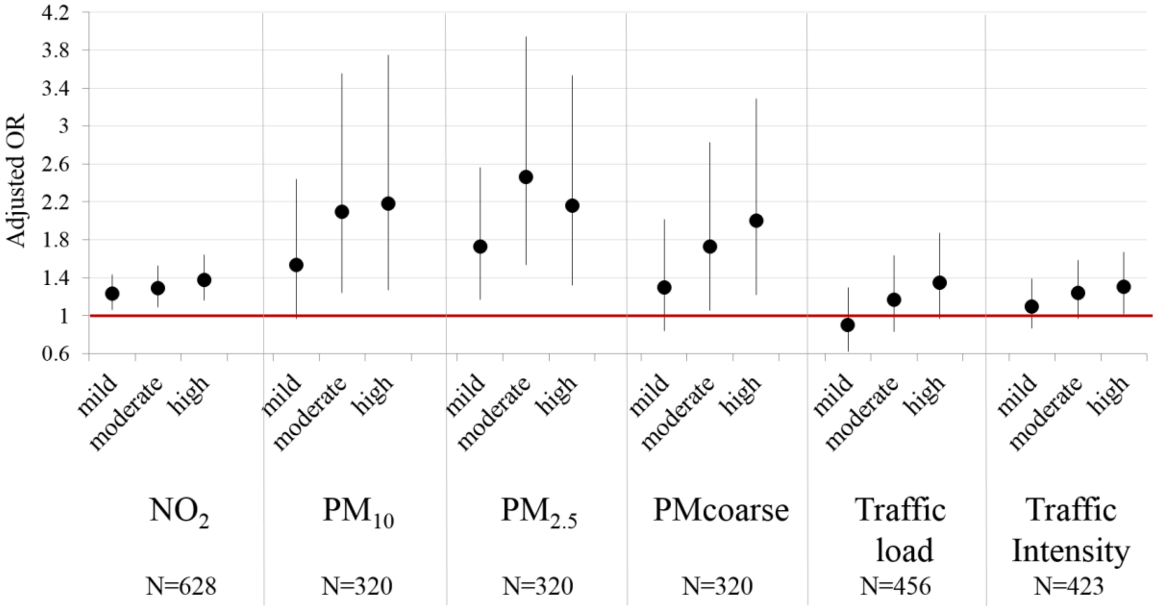


Figure 3: Associations between air pollutant metrics and levels of severity score of rhinitis, among participants without allergic sensitization (A) and among participants with allergic sensitization (B)

A



B

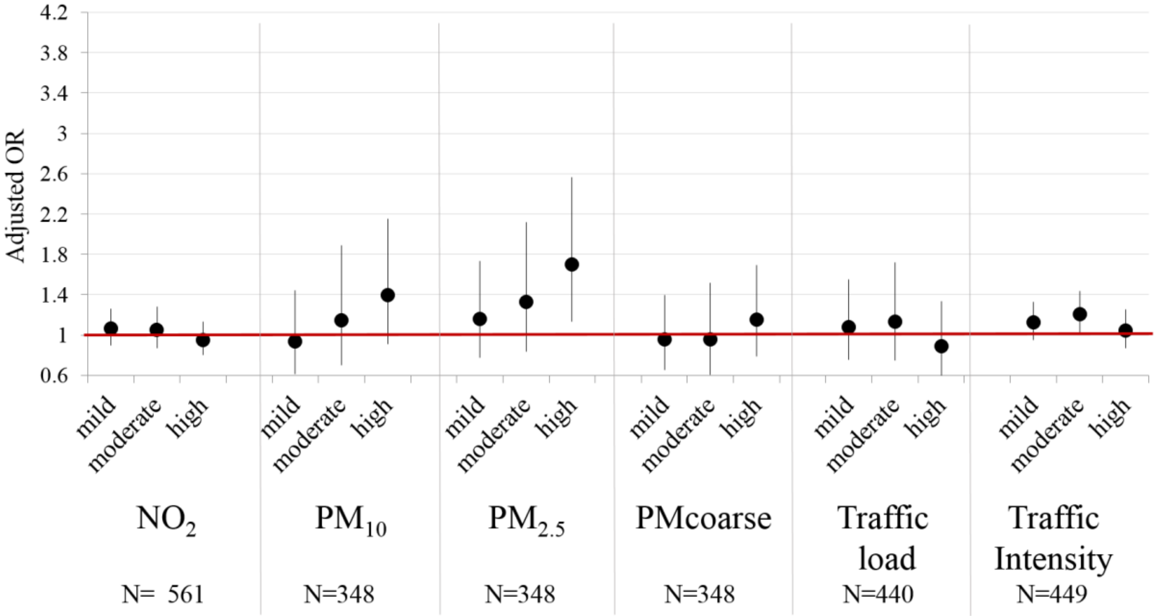


Figure legends

Figure 2: Associations between air pollutant metrics and severity of rhinitis

Reference : low severity, Odds Ratio adjusted for age, sex, smoking status, asthma, allergic sensitization (and NO_2 background for traffic load and traffic Intensity), with city as a random intercept. Estimates are presented for an increase of 10 μg/m^3 for NO_2 and PM_{10} and 5 μg/m^3 for $PM_{2.5}$ and PMcoarse, and of 4,000,000 vehicles*m/day for traffic load on all major roads in a 100m buffer and 5,000 vehicles/day for traffic density on the nearest road. Number reported below the pollutants correspond to the number of patients included in the adjusted analysis.

Figure 3: Associations between air pollutant metrics and levels of severity score of rhinitis, among participants without allergic sensitization (A) and among participants with allergic sensitization (B)

Reference: low severity, Odds Ratio adjusted for age, sex, smoking status, asthma (and NO_2 background for traffic load and traffic Intensity), with city as a random intercept. Estimates are presented for an increase of 10 μg/m^3 for NO_2 and PM_{10} and 5 μg/m^3 for $PM_{2.5}$ and PMcoarse, and of 4,000,000 vehicles*m/day for traffic load on all major roads in a 100m buffer and 5,000 vehicles/day for traffic density on the nearest road. Number reported below the pollutants corresponds to the number of patients included in the adjusted analysis