



## Association between air pollution and rhinitis incidence in two European cohorts

Emilie Burte, Bénédicte Leynaert, Roberto Bono, Bert Brunekreef, Jean Bousquet, Anne-Elie Carsin, Kees de Hoogh, Bertil Forsberg, Frédéric Gormand, Joachim Heinrich, et al.

### ► To cite this version:

Emilie Burte, Bénédicte Leynaert, Roberto Bono, Bert Brunekreef, Jean Bousquet, et al.. Association between air pollution and rhinitis incidence in two European cohorts. *Environment International*, 2018, 115, pp.257 - 266. 10.1016/j.envint.2018.03.021 . inserm-01814823

**HAL Id: inserm-01814823**

**<https://inserm.hal.science/inserm-01814823>**

Submitted on 13 Jun 2018

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# Association between air pollution and rhinitis incidence in two European cohorts

Burte Emilie<sup>1,2,3,4</sup>, Leynaert Bénédicte<sup>5</sup>, Bono Roberto<sup>6</sup>, Brunekreef Bert<sup>7</sup>, Bousquet Jean<sup>1,2,8</sup>, Carsin Anne-Elie<sup>3,9,10</sup>, De Hoogh Kees<sup>11,12</sup>, Forsberg Bertil<sup>13</sup>, Gormand Frédéric<sup>14</sup>, Heinrich Joachim<sup>15,16</sup>, Just Jocelyne<sup>17,18</sup>, Marcon Alessandro<sup>19</sup>, Künzli Nino<sup>11,12</sup>, Nieuwenhuijsen Mark<sup>3,4,9,10</sup>, Pin Isabelle<sup>20,21</sup>, Stempfelet Morgane<sup>22</sup>, Sunyer Jordi<sup>3,4,9,10</sup>, Villani Simona<sup>23</sup>, Siroux Valérie<sup>21</sup>, Jarvis Deborah<sup>24</sup>, Nadif Rachel<sup>1,2\*</sup>, Jacquemin Bénédicte<sup>1,2,3,4,9,10\*</sup>

1. INSERM, U1168, VIMA: Aging and chronic diseases. Epidemiological and public health approaches, Villejuif, France
2. Univ Versailles St-Quentin-en-Yvelines, UMR-S 1168, F-78180, Montigny le Bretonneux, France
3. ISGLoBAL, Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain;
4. Universitat Pompeu Fabra (UPF), Barcelona, Spain.
5. Inserm, UMR 1152, Pathophysiology and Epidemiology of Respiratory Diseases, Paris, France.
6. Dept of Public Health and Pediatrics, University of Turin, Turin.
7. Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands. Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands
8. 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;
9. CIBER Epidemiología y Salud Pública (CIBERESP), Spain.
10. IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain.
11. Swiss Tropical and Public Health Institute, Basel, Switzerland
12. University of Basel, Basel, Switzerland
13. Environmental and Occupational Medicine, Dept of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden.
14. CHU de Lyon, Pneumology Dept, Lyon, France.
15. Ludwig Maximilians University Munich, University Hospital Munich, Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, Munich, Germany
16. Comprehensive Pneumology Center Munich (CPC-M), Member of the German Center for Lung Research
17. Allergology Department, Assistance Publique-Hôpitaux de Paris, Hôpital Armand-Trousseau
18. Université Paris 6 Pierre et Marie Curie, Paris, France
19. Unit of Epidemiology and Medical Statistics, Dept of Diagnostics and Public Health, University of Verona, Verona, Italy.
20. CHU de Grenoble Alpes, Pédiatrie, Grenoble, France.
21. Univ. Grenoble Alpes, Inserm, CNRS, IAB, 38000 Grenoble, France
22. Santé Publique France, 12, rue du Val d'Osne, 94415 Saint-Maurice, France.
23. Unit of Biostatistics and Clinical Epidemiology Dept of Public Health, Experimental and Forensic Medicine University of Pavia, Pavia.
24. Faculty of Medicine, School of Public Health, Imperial College London, London, United Kingdom

\* These authors contributed equally to this study

## Acknowledgment and Funding:

### Funding:

ECRHS was supported by the European Commission, as part of their Quality of Life program.

The coordination of ECRHS II was supported by the European Commission, as part of their Quality of Life program.

The following bodies funded the local studies in ECRHS II in this article: **Albacete**-Fondo de Investigaciones Santarias (grant code: 97/0035-01, 99/0034-01, and 99/0034-02), Hospital Universitario de Albacete, Consejería de Sanidad. **Antwerp**-FWO (Fund for Scientific Research)-Flanders Belgium (grant code: G.0402.00), University of Antwerp, Flemish Health Ministry. **Barcelona**-Fondo de Investigaciones Sanitarias (grant code: 99/0034- 01, and 99/0034-02), Red Respira (RTIC 03/11 ISC IIF). Ciber of Epidemiology and Public Health has been established and founded by Instituto de Salud Carlos III. **Erfurt**-GSF–National Research Centre for Environment & Health, Deutsche Forschungsgemeinschaft (DFG) (grant code FR 1526/1-1). **Galdakao**-Basque Health Department. **Grenoble**-Programme Hospitalier de Recherche Clinique-DRC de Grenoble 2000 no.2610, Ministry of Health, Direction de la Recherche Clinique, Ministère de l’Emploi et de la Solidarité, Direction Générale de la Santé, CHU de Grenoble, Comité des Maladies Respiratoires de l’Isère. **Ipswich and Norwich** National Asthma Campaign (UK). **Huelva**-Fondo de Investigaciones Santarias (FIS) (grant code: 97/0035-01, 99/0034-01, and 99/0034-02). **Oviedo**-Fondo de Investigaciones Santarias (FIS) (grant code: 97/0035-01, 99/0034-01, and 99/0034-02). **Paris**-Ministère de l’Emploi et de la Solidarité, Direction Générale de la Santé, UCBPharma (France), Aventis (France), Glaxo France, Programme Hospitalier de Recherche Clinique-DRC de Grenoble 2000 no. 2610, Ministry of Health, Direction de la Recherche Clinique, CHU de Grenoble. **Pavia**-Glaxo, Smith & Kline Italy, Italian Ministry of University and Scientific and Technological Research 3 (MURST), Local University Funding for Research 1998 & 1999 (Pavia, Italy). **Turin**-ASL 4 Regione Piemonte (Italy), AO CTO/ICORMA Regione Piemonte (Italy), Ministero dell’Università e della Ricerca Scientifica (Italy), Glaxo Wellcome spa (Verona, Italy). **Umeå**- Swedish Heart Lung Foundation, Swedish Foundation for Health Care Sciences & Allergy Research, Swedish Asthma & Allergy Foundation, Swedish Cancer & Allergy Foundation. **Verona**-University of Verona; Italian Ministry of University and Scientific and Technological Research (MURST); Glaxo, Smith & Kline Italy.

EGEA is funded in part by PHRC-Paris, PHRC-Grenoble, ANR 05-SEST-020-02/05-9-97, ANR-06-CEBS, ANR-CES-2009, Région Nord Pas-de-Calais, Merck Sharp & Dohme (MSD)

#### Acknowledgment:

#### ECRHS

The ECRHS data incorporated in this analysis would not have been available without the collaboration of the following individuals and their research teams:

**ECRHS Co-ordinating centre:** P Burney, D Jarvis, S Chinn, J Knox (ECRHS II), C Luczynska+ , J Potts.

**Steering Committee for ECRHS II:** P Burney, D Jarvis, S Chinn, J.M Anto, I.Cerveri, R.deMarco ,  
T.Gislason, J.Heinrich, C. Janson, N. Kunzli, B. Leynaert, F. Neukirch, T. Rochat, J. Schouten, J.  
Sunyer; C. Svanes, P. Vermeire+ , M. Wjst.

**Principal Investigators and Senior Scientific Teams for ECRHS II:** Australia: Melbourne (M  
Abramson, R Woods, EH Walters, F Thien), Belgium: South Antwerp & Antwerp City (P Vermeire+ ,  
J Weyler, M Van Sprundel, V Nelen), Denmark: Aarhus (EJ Jensen), Estonia: Tartu (R Jogi, A Soon),  
France: Paris (F Neukirch, B Leynaert, R Liard, M Zureik), Grenoble (I Pin, J Ferran-Quentin),  
Bordeaux (A Taytard, C Raherison), Montpellier (J Bousquet, P Demoly)Germany: Erfurt (J Heinrich,  
M Wjst, C Frye, I Meyer) Hamburg (K Richter),Iceland: Reykjavik (T Gislason, E Bjornsson, D  
Gislason, T Blondal, A Karlsdottir), Italy: Turin (M Bugiani, R Bono, P Piccioni, E Caria, A Carosso,  
E Migliore, G Castiglioni), Verona (R de 5 Marco, G Verlato, E Zanolin, S Accordini, A Poli, V Lo  
Cascio, M Ferrari), Pavia (A Marinoni, S Villani, M Ponzio, F Frigerio, M Comelli, M Grassi, I  
Cerveri, A Corsico),Netherlands: Groningen & Geleen (J Schouten, M Kerkhof), Norway: Bergen (A  
Gulsvik, E Omenaas, C Svanes, B Laerum), Spain: Barcelona (JM Anto, J Sunyer, M Kogevinas, JP  
Zock, X Basagana, A Jaen, F Burgos), Huelva (J Maldonado, A Pereira, JL Sanchez), Albacete (J  
MartinezMoratalla Rovira, E Almar), Galdakao (N Muniozguren, I Urritia), Oviedo (F Payo), Sweden:  
Uppsala (C Janson, G Boman, D Norback, M Gunnbjornsdottir), Goteborg (K Toren, L Lillienberg,  
AC Olin, B Balder, A Pfeifer-Nilsson, R Sundberg), Umea (E Norrman, M Soderberg, K Franklin, B  
Lundback, B Forsberg, L Nystrom),Switzerland: Basel (N Kunzli, B Dibbert, M Hazenkamp, M  
Brutsche, U Ackermann-Liebrich); UK: Norwich (D Jarvis, B Harrison), Ipswich (D Jarvis, R Hall, D  
Seaton), USA: Portland (M Osborne, S Buist, W Vollmer, L Johnson)

#### EGEA:

**Coordination:** V Siroux (epidemiology, PI since 2013); F Dumenais (genetics); I Pin (clinical  
aspects); R Nadif (biology); F Kauffmann (PI 1992-2012). **Respiratory epidemiology:** Inserm U 700,  
Paris: M Korobaeff (Egea1), F Neukirch (Egea1); Inserm U 707, Paris: I Annesi-Maesano (Egea1-2);  
Inserm CESP/U 1018, Villejuif: F Kauffmann, N Le Moual, R Nadif, MP Oryszczyn (Egea1-2), R  
Varraso; Inserm U 823, Grenoble: V Siroux. **Genetics:** Inserm U 393, Paris: J Feingold; Inserm U  
946, Paris: E Bouzigon, F Dumenais, MH Dizier; CNG, Evry: I Gut (now CNAG, Barcelona, Spain),  
M Lathrop (now Univ McGill, Montreal, Canada). Clinical centers: Grenoble: I Pin, C Pison; Lyon: D  
Ecochard (Egea1), F Gormand, Y Pacheco; Marseille: D Charpin (Egea1), D Vervloet (Egea1-2);  
Montpellier: J Bousquet; Paris Cochin: A Lockhart (Egea1), R Matran (now in Lille); Paris Necker: E  
Paty (Egea1-2), P Scheinmann (Egea1-2); 6 Paris-Trousseau: A Grimfeld (Egea1-2), J Just. **Data and  
quality management:** Inserm exU155 (Egea1): J Hochez; Inserm CESP/U 1018, Villejuif: N Le  
Moual; Inserm ex-U780: C Ravault (Egea1-2); Inserm ex-U794: N Chateigner (Egea1-2); Grenoble: J  
Quentin-Ferran (Egea1-2).

Valerie Siroux has received speaker honorarium from TEVA, AstraZeneca and Novartis-France,  
outside the submitted work. No other relevant disclosure.

**Corresponding author:**

**Emilie Burte**

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

E-mail: [emilie.burte @inserm.fr](mailto:emilie.burte@inserm.fr)

**Short running title: Air pollution and incident rhinitis**

**Manuscript word count: 4243**

**Abstract word count: 220**

Abstract:

**Background:** The association between air pollution and rhinitis is not well established.

**Aim:** The aim of this longitudinal analysis was to study the association between modeled air pollution at the subjects' home addresses and self-reported incidence of rhinitis.

**Methods:** We used data from 1533 adults from two multicentre cohorts' studies (EGEA and ECRHS). Rhinitis incidence was defined as reporting rhinitis at the second follow-up (2011 to 2013) but not at the first follow-up (2000 to 2007). Annual exposure to NO<sub>2</sub>, PM<sub>10</sub> and PM<sub>2.5</sub> at the participants' home addresses was estimated using land-use regression models developed by the ESCAPE project for the 2009-2010 period. Incidence rate ratios (IRR) were computed using Poisson regression. Pooled analysis, analyses by city and meta-regression testing for heterogeneity were carried out.

**Results:** No association between long-term air pollution exposure and incidence of rhinitis was found (adjusted IRR (aIRR) for an increase of 10 µg.m<sup>-3</sup> of NO<sub>2</sub>: 1.00[0.91-1.09], for an increase of 5µg.m<sup>-3</sup> of PM<sub>2.5</sub>: 0.88[0.73-1.04]). Similar results were found in the two-pollutant model (aIRR for an increase of 10 µg.m<sup>-3</sup> of NO<sub>2</sub>: 1.01[0.87-1.17], for an increase of 5µg.m<sup>-3</sup> of PM<sub>2.5</sub>: 0.87[0.68-1.08]). Results differed depending on the city, but no regional pattern emerged for any of the pollutants.

**Conclusions:** This study did not find any consistent evidence of an association between long-term air pollution and incident rhinitis.

## Introduction:

The prevalence of rhinitis varies between 10 and 50% worldwide (Bousquet et al. 2008; Wang et al. 2014) and has strongly increased during the last decades, mostly in industrialized countries (de Marco et al. 2012; Zhang and Zhang 2014). Although rhinitis is usually considered as a minor respiratory condition, it is often associated with a strong impairment in daily life and has an important economical and societal impact (Bousquet et al. 2017; Leynaert and Soussan 2003; Linneberg et al. 2016). Although environmental determinants of rhinitis are not well-known, environmental changes are suspected to be a major driver in the rise of allergy. During the past years, the link between outdoor air pollution and allergy continues to strengthen, both in children and in adults (Carlsten and Rider 2017).

Rhinitis is a complex disease, frequently associated with asthma, whatever the allergic sensitization status (Shaaban et al. 2008). In adults there is growing evidence associating air pollution with asthma (Guarnieri and Balmes 2014). There are also evidences of the adverse effect of outdoor air pollution on allergic diseases (HEI 2010; Heinrich and Wichmann 2004), even if this association is not consistently reported (Lindgren et al. 2009). However, there are very few studies on the effect of air pollution on rhinitis (Deng et al. 2016; Jang et al. 2016; Rancière et al. 2016). It has been shown that air pollution and particularly diesel exhaust particles have the capability of enhancing immunological responses to allergens and elicit inflammatory reactions in the airways at relatively low concentrations and even with short exposure durations (Brunekreef and Sunyer 2003). Traffic-related air pollutants modify responses to allergens in the nasal mucosa (Peden 2001), and several studies have shown an increase in daily consultations for allergic rhinitis in general practitioners due to short-term air pollution exposure (Hajat et al. 2001; Zhang et al. 2011). Traffic-related air pollution has been consistently associated with prevalence of rhinitis among an Italian population, but only among non-smokers (Cesaroni et al. 2008). Furthermore, proximity to traffic has been

associated with allergic rhinitis prevalence among Swedish adults (Lindgren et al. 2009). However, no study has ever assessed the association between exposure to long-term air pollution and the incidence of rhinitis in adults.

The aim of the present study was to assess the association between long term modeled air pollution exposure at the participant's home addresses and the incidence of self-reported rhinitis among adults from two large European studies.

## Methods:

### *Study design and participants*

The data came from two multicentre epidemiological European studies: the French Epidemiological case-control and family-based study of the Genetics and Environment of Asthma (EGEA, (Kauffmann et al. 1997)), and the population-based study: the European Community Respiratory Health Survey (ECRHS, (Burney et al. 1994)).

EGEA is a cohort study based on an initial group of asthma cases recruited in chest clinics between 1991 and 1995 from 5 French cities (EGEA1, <https://egeanet.vjf.inserm.fr/>) along with their first-degree relatives, and a group of controls (n=2,047). A first follow-up (EGEA2, (Kauffmann 1999; Kauffmann et al. 1997)) was conducted between 2003 and 2007 (n=2121) and a second follow-up (EGEA3) between 2011 and 2013 using self-completed questionnaire (n=1558) (Bouzigon et al. 2015).

ECRHS is a random population-based multicentre cohort of young adults, aged 20 to 44 years at recruitment, 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 (Jarvis 2002; Kogevinas et al. 2007)) and between 2011 and 2013 (ECRHS III, n=7040).



Both cohort studies applied standardized protocols and comparable detailed questionnaires on respiratory health and risk factors for the two follow-up. Ethical approval was obtained in each cohort from the appropriate institutional ethics committees, and written consent was obtained from each participant.

The present longitudinal analysis includes a subsample of 1533 adults from 17 European cities who reported no rhinitis at the first follow-up (EGEA2, ECRHS II), and with available data on rhinitis and air pollution exposure at the second follow up (EGEA3, ECRHS III, Figure 1).

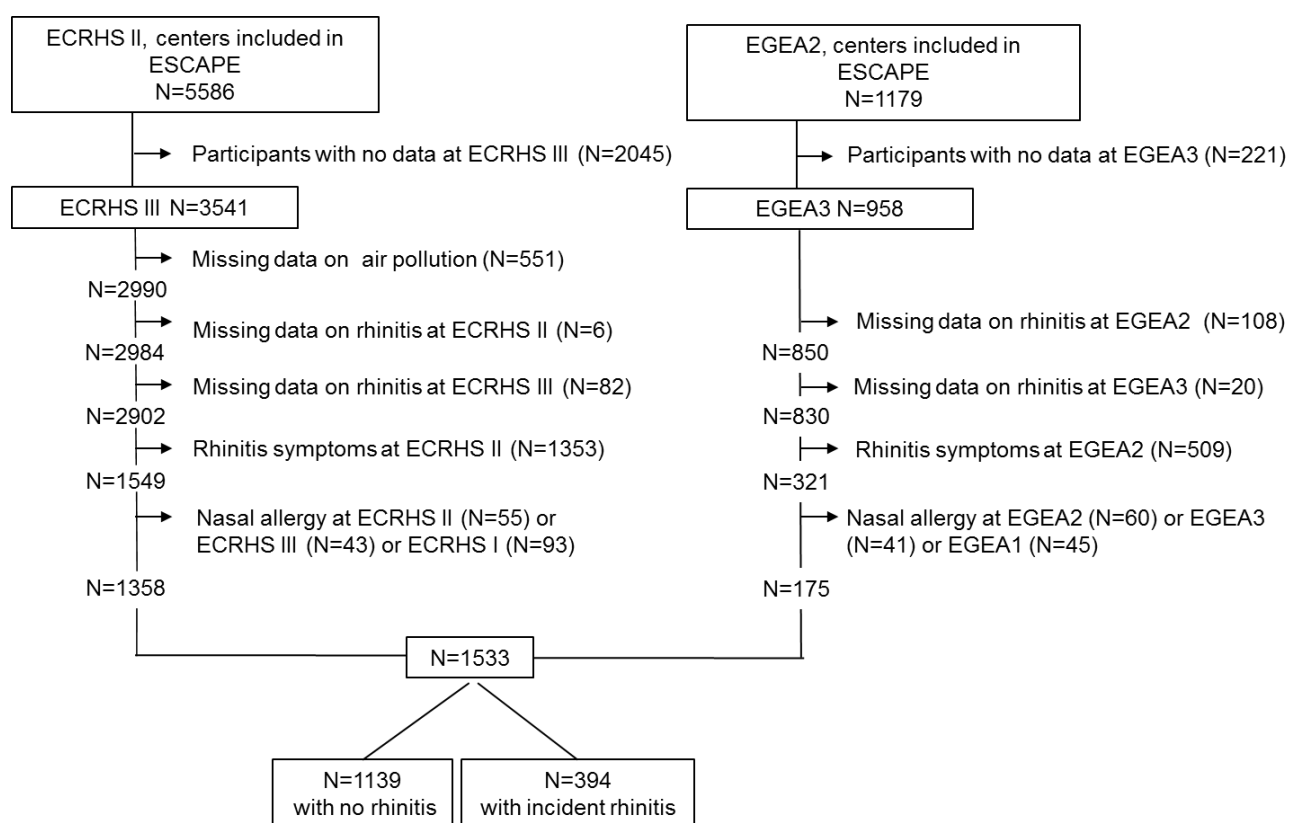


Figure 1 Flow-chart of the participants

## Estimation of air pollution exposure

Within the frame of the European Study of Cohorts for Air Pollution Effects (ESCAPE [www.escapeproject.eu](http://www.escapeproject.eu) (Beelen et al. 2013; Eeftens et al. 2012)), the place of residence of each subject at the first follow-up of the two studies (EGEA2 and ECRHS II) was geocoded

and linked with NO<sub>2</sub> (nitrogen dioxide), PM<sub>10</sub> (airborne particles with an aerodynamical diameter  $\leq 10 \mu\text{m}$ ) and PM<sub>2.5</sub> (airborne particles with an aerodynamical diameter  $\leq 2.5 \mu\text{m}$ ) model estimates developed between 2009 and 2010. Estimates of NO<sub>2</sub> are available for 17 cities (Umea, Norwich, Ipswich, Antwerp, Erfurt, Paris, Lyon, Grenoble, Marseille, Verona, Pavia, Turin, Oviedo, Galdakao, Barcelona, Albacete and Huelva). Given that PM were measured only in a subset of cities within ESCAPE, estimates of PM were available for 6 cities (Norwich, Ipswich, Antwerp, Paris, Grenoble, Turin and Barcelona). Annual averages – average of daily exposure over one year- of air pollutant concentrations were estimated at participants' residential addresses with land use regression models. Results are reported for an increase of  $10 \mu\text{g.m}^{-3}$  for PM<sub>10</sub> and NO<sub>2</sub> and  $5 \mu\text{g.m}^{-3}$  for PM<sub>2.5</sub>, following the ESCAPE protocol (Beelen et al. 2014). Assessment of air pollution exposure is detailed in the Supplementary material.

The main results for estimates of NO<sub>x</sub> (nitrogen oxides), PM<sub>2.5</sub> absorbance, PM<sub>coarse</sub> and two traffic exposure indicators - traffic intensity (on the nearest road), and traffic load (in a 100m buffer) - are available in the supplementary material.

### **Definition of rhinitis, asthma and allergic sensitization**

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 EGEA and ECRHS. Incident rhinitis was defined by a positive response at EGEA3/ECRHS III and a negative response at EGEA 2/ECRHS II. This definition does not distinguish between rhinitis subtypes; to differentiate between participants with nonallergic rhinitis and those with allergic rhinitis, stratified analyses by allergic sensitization were used. In order to ensure that incident cases were real incident cases of rhinitis, several steps of caution were taken: 1) participants that have declared nasal symptoms (EGEA1) or nasal allergy (ECRHS I) at inclusion were

excluded, 2) participants with a positive response to “*Have you ever had allergic rhinitis?*” or “*Have you ever had hay fever?*” at EGEA2 or ECRHS II were not considered in the analysis, 3) participants with no rhinitis at both first (EGEA2 or ECRHS II ) and second follow-up (EGEA3 or ECRHS III ) but who had answered yes to “*Have you ever had allergic rhinitis?*” or “*Have you ever had hay fever?*” at EGEA3 or ECRHS III were also excluded from the analyses. In a sensitivity analysis, incidence of allergic rhinitis, defined by a positive response to “*Have you ever had allergic rhinitis?*” or “*Have you ever had hay fever?*” was considered. “Asthma ever” was defined (Siroux et al. 2011) by a positive response to “*Have you ever had asthma?*” in ECRHS; 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?*” or by being recruited as an asthmatic case in EGEA.

Allergic sensitization was defined using the skin-prick test (SPT) for 12 aeroallergens in EGEA2 (a wheal diameter  $\geq 3$  mm and superior to the negative control wheal to at least one of the allergen among: cat, *Dermatophagoides pteronyssinus*, *Blattella germanica*, olive, birch, *Parietaria judaica*, timothy grass, ragweed pollen, *Aspergillus*, *Cladosporium herbarum*, *Alternaria tenuis*). Allergic sensitization was defined using specific Immunoglobulin E (IgE) to four allergens in ECRHS II (specific IgE  $\geq 35$  kU/ml to at least one of the allergen among: cat, *Dermatophagoides pteronyssinus*, *Cladosporium*, and timothy grass).

## **Statistical analysis**

The differences in general characteristics between the two studies were evaluated using the Student test for quantitative variables and the Chi-square test or Fisher exact test for qualitative variables.

Incident rates of rhinitis were estimated as the ratio between the number of new cases at ECRHS III/EGEA3 and the number of person-years at risk (per 1,000), which were considered to be equal to the length of the follow-up (between ECRHS II/EGEA2 and ECRHS III/EGEA3) (De Marco et al. 2011) for each participant of the cohort who was rhinitis-free at baseline. Exact 95% confidence intervals were computed using the Poisson distribution. Correlations between pollutants were assessed using the Spearman coefficient.

Associations between air pollutants and incident rhinitis were evaluated using incidence rate ratio (IRR) in a pooled dataset. The IRRs were computed using Poisson regression models, with a random-intercept at city level (level 2), and the follow-up time as an offset. Based on the ESCAPE protocol, estimates were calculated for an increase of  $10 \mu\text{g}/\text{m}^3$  for  $\text{NO}_2$  and  $\text{PM}_{10}$ ,  $5 \mu\text{g}/\text{m}^3$  for  $\text{PM}_{2.5}$  and  $\text{PM}_{\text{coarse}}$ ,  $10 \mu\text{g}/\text{m}^3$  for  $\text{NO}_X$ , 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. The estimates were adjusted for pre-selected variables -at ECRHS II/EGEA2- based on previous literature: age, sex, number of siblings, family history of allergy, smoking status, educational level -as a proxy of socio-economic status- and asthma status.

Analyses with traffic density or traffic load were also adjusted for  $\text{NO}_2$  background level. In a sensitivity analysis, the fully adjusted model was additionally adjusted for study (EGEA/ECRHS). Analyses were subsequently stratified according to pre-set subgroups, namely asthma status, allergic sensitization status, sex, smoking, and finally study (EGEA/ECRHS) because of the different recruitment criteria in EGEA and ECRHS.

In a second step, analysis by city and meta-regression were applied to study the association between air pollution and incident rhinitis for each city. The DerSimonian-Laird approach was used to estimate the between-study variance and heterogeneity was measured by  $I^2$ , which ranges from 0% to 100%. The  $I^2$  statistic describes the percentage of variation across studies that is due to heterogeneity rather than chance (Higgins and Thompson 2002; Higgins

et al. 2003). These meta-regressions were adjusted only for age as the number of incident cases was too small in some cities to adjust for other factors.

Analyses were done using R statistical software (R Core Team, 2012).

### Results:

A total of 1533 adults from 17 European cities (Table 1) were included in the analyses: 1358 from ECRHS (mean age=43.3 years, 51.4% female) and 175 from EGEA (mean age=44.4 years, 49.7% female). The crude incident rate at the 3<sup>rd</sup> follow-up was 23.4 per 1000 person-years (95% CI: [21.2-25.8]) with 394 participants reporting incident rhinitis and a median length of the follow-up of 11 years. Participants with incident rhinitis were younger and reported more often a history of asthma than those without rhinitis (Table 1).

<b>Variables</b>	<b>All (N=1533)</b>	<b>No rhinitis (N=1139)</b>	<b>Incident rhinitis (N=394)</b>	<b>p crude overall</b>
<b>Age, mean±sd</b>	43.4±8.9 (N=1533)	43.7±8.9	42.7±8.9	0.06
<b>Study, % EGEA</b>	11.4 (N=1533)	11.4	11.4	1
<b>Sex=women</b>	51.2 (N=1533)	50.1	54.3	0.17
<b>BMI, %</b>	(N=1374)			0.27
<b>&lt;18</b>	1.8	2.0	1.4	
<b>18-25</b>	49.6	48.1	54.1	
<b>25-30</b>	34.2	35.2	31.4	
<b>&gt;=30</b>	14.3	14.7	13.2	
<b>Smoking status, %</b>	(N=1520)			0.34
<b>current</b>	30.7	29.7	33.7	
<b>ex-smoker</b>	27.8	28.2	26.5	
<b>never</b>	41.5	42.1	39.8	
<b>Educational level, %</b>	(N=1529)			0.49
<b>low</b>	26.3	26.8	24.7	
<b>medium</b>	34.7	34.9	33.8	
<b>high</b>	39.0	38.2	41.5	
<b>Asthma ever, %</b>	5.1 (N=1533)	4.1	7.9	<0.01
<b>Asthma age of onset, mean±sd</b>	17.8±16.2 (N=75)	18.6±16.9	16.7±15.4	0.61
<b>Report of hay fever or AR ever, %</b>	5.6 (N=1522)	0	22.2	<0.01
<b>Allergic sensitization, %</b>	18.4 (N=1306)	17.6	22.2	0.25
<b>NO<sub>2</sub>, µg.m<sup>-3</sup>, mean±sd*</b>	29.3±15.1 (N=1533)	28.9±15.4	30.3±14.2	0.11
<b>PM<sub>10</sub>, µg.m<sup>-3</sup>, mean±sd*</b>	26.9±8.3 (N=738)	27.2±8.7	26.2±7.1	0.09

<b>PM<sub>2.5</sub>, <math>\mu\text{g}\cdot\text{m}^{-3}</math>, mean<math>\pm</math>sd*</b>	16.4 $\pm$ 4.9 (N=738)	16.6 $\pm$ 5.2	15.9 $\pm$ 4.4	0.08
<b>*Annual.averaged</b>				

*Table 1 General characteristics of all the participants at ECRHS II/EGEA2, and according to rhinitis status*

Correlations between the three pollutants were high (0.71 between NO<sub>2</sub> and PM<sub>10</sub>, 0.70 between NO<sub>2</sub> and PM<sub>2.5</sub> and 0.77 between PM<sub>10</sub> and PM<sub>2.5</sub>, Table 1 in Supplementary material).

#### *Main analysis*

Pooled analyses of the associations between NO<sub>2</sub>, PM<sub>10</sub> or PM<sub>2.5</sub> and incident rhinitis showed no statistically significant results (Table 2). In a two-pollutant model including NO<sub>2</sub> and PM<sub>2.5</sub>, results were very similar to those of the single pollutant-model. No association was found when considering other pollutants or traffic measures (NO<sub>x</sub>, PM<sub>2.5</sub> absorbance, PM coarse or traffic measures, Supplemental Material, Table 2). The sensitivity analysis studying incident allergic rhinitis showed similar results (Table 2).

#### *Stratifying by study*

When stratifying by study, estimates of the associations were positive in the EGEA study for the three air pollutants and statistically significant for NO<sub>2</sub> in the crude analysis (Table 2). In the adjusted model, this estimate was similar and borderline. No statistically significant association was found in ECRHS, where results were similar to those from the main analysis.

#### *Stratifying by asthma status*

When stratifying by asthma status, estimates were positive in participants with asthma and similar to the main analysis in those without asthma for the three air pollutants. However, none of the results were statistically significant (Table 2).

#### *Stratifying by allergic sensitization status*

Among the sensitized participants, estimates were negative for PM<sub>10</sub> and PM<sub>2.5</sub>. Results were statistically significant only for PM<sub>2.5</sub> (Table 2). The strength of the associations increases in the adjusted model. Among non-sensitized participants, no statistically significant association was found with any of the three pollutants.

#### *Stratifying by sex*

Among males only, estimates were negative for PM<sub>10</sub> and PM<sub>2.5</sub> and statistically significant only for PM<sub>2.5</sub> (Table 2). No statistically significant association was found among females or with NO<sub>2</sub>.

#### *Stratifying by smoking status*

Finally, when stratifying by smoking status, a borderline positive association of rhinitis with NO<sub>2</sub> was found among non-smokers, while an inverse significant relationship was found with PM<sub>10</sub> among smokers (Table 2).

Additionally, adjusting the results for study did not change any of the results (data not shown).

#### *Analysis by city and meta-regression*

Estimates for NO<sub>2</sub> were positive in 8 out of 17 cities but reached statistical significance only in Paris. Estimates were negative in 9 cities but not statistically significant (Figure 2).

Similarly, positive and negative estimates were found according to the city for PM<sub>10</sub> and PM<sub>2.5</sub>. However, no statistical heterogeneity between cities was found in the meta-regression, with I<sup>2</sup> values ranging from 0% for PM<sub>2.5</sub> to 36% for PM<sub>10</sub>. No significant association was found in the meta-regressions (Figure 2).

302 A sensitivity analysis considering participants separately from EGEA and ECRHS, and from  
303 Grenoble and Paris, showed that among the same city, results differed according to the study  
304 (Figure 1 in Online Repository)



Analyses	No of subjects (No of incident cases) in adjusted model		crude IRR (95%CI)			aIRR (95%CI)		
	NO <sub>2</sub>	PM <sub>10</sub> and PM <sub>2.5</sub>	NO <sub>2</sub>	PM <sub>10</sub>	PM <sub>2.5</sub>	NO <sub>2</sub>	PM <sub>10</sub>	PM <sub>2.5</sub>
<b>Main analyses</b>	1372(354)	645(187)	1.02[0.93-1.11]	0.90[0.73-1.10]	0.89[0.73-1.05]	1.00[0.91-1.09]	0.88[0.72-1.08]	0.88[0.73-1.04]
Two-pollutant model (NO <sub>2</sub> , PM <sub>2.5</sub> )			1.05[0.91-1.21]		0.84[0.66-1.05]	1.01[0.87-1.17]		0.87[0.68-1.08]
<b>Stratified analyses</b>								
By study						**		
EGEA	112(30)	80(21)	<b>1.42[1.12-1.82]</b>	1.77[0.67-4.35]	1.82[0.73-4.88]	1.38[0.99-2.06]	2.57[0.54-10.2]	2.22[0.55-9.14]
ECRHS	1260(324)	565(166)	0.98[0.89-1.07]	0.88[0.71-1.08]	0.87[0.70-1.03]	0.98[0.89-1.07]	0.87[0.70-1.08]	0.87[0.71-1.04]
By asthma status								
Asthmatics	65(25)	40(16)	1.16[0.94-1.39]	0.98[0.55-1.60]	0.90[0.51-1.43]	1.09[0.84-1.39]	1.15[0.54-2.22]	1.11[0.55-2.13]
Non-asthmatics	1307(329)	605(171)	1.00[0.91-1.09]	0.89[0.71-1.10]	0.89[0.72-1.07]	0.99[0.90-1.08]	0.86[0.69-1.07]	0.87[0.71-1.04]
By allergic sensitization status								
atopic	202(59)	112(37)	0.96[0.81-1.12]	0.76[0.49-1.11]	<b>0.66[0.35-0.95]</b>	0.95[0.77-1.14]	0.73[0.42-1.15]	<b>0.52[0.29-0.87]</b>
non-atopic	962(250)	442(132)	1.05[0.95-1.15]	0.93[0.76-1.17]	0.95[0.79-1.14]	1.05[0.95-1.15]	0.90[0.72-1.15]	0.93[0.76-1.14]
By smoking status						*		
smoker	803(212)	364(106)	0.98[0.88-1.09]	0.79[0.60-1.05]	0.83[0.62-1.07]	0.96[0.85-1.07]	<b>0.75[0.56-0.99]</b>	0.80[0.60-1.03]
non-smoker	569(142)	281(81)	1.09[0.99-1.20]	1.03[0.80-1.31]	0.96[0.77-1.16]	1.10[0.99-1.22]	1.10[0.84-1.41]	0.99[0.78-1.22]
By gender								
Male	659(159)	304(82)	1.01[0.90-1.11]	0.83[0.63-1.07]	<b>0.78[0.61-0.98]</b>	0.99[0.88-1.10]	0.83[0.61-1.08]	<b>0.76[0.57-0.98]</b>
Female	713(195)	341(105)	1.04[0.93-1.17]	0.95[0.70-1.28]	0.98[0.75-1.26]	1.04[0.92-1.16]	0.92[0.68-1.24]	0.96[0.74-1.25]
<b>Secondary analysis</b>								
Incidence of allergic rhinitis	1128	530	1.09[0.94-1.25]	0.91[0.70-1.17]	0.92[0.73-1.13]	1.07[0.92-1.23]	0.95[0.72-1.26]	0.94[0.73-1.17]

aIRR: Incidence Rate Ratio adjusted for age, sex, number of siblings, family history of allergy, smoking status, educational level and asthma status. IRR with duration of follow-up as offset and a random intercept at city level, for an increase of 10 µg.m<sup>-3</sup> for NO<sub>2</sub> and PM<sub>10</sub> and for an increase of 5 µg.m<sup>-3</sup> for PM<sub>2.5</sub>. \*\*: p-interaction= 0.047, \*: p-interaction=0.08, all other p-interaction>0.12.

305 Table 2 IRR of the associations between pollutants (NO<sub>2</sub>, PM<sub>10</sub>, PM<sub>2.5</sub>) and incident rhinitis, in all, and stratifying by study, asthma status, allergic sensitization and smoking

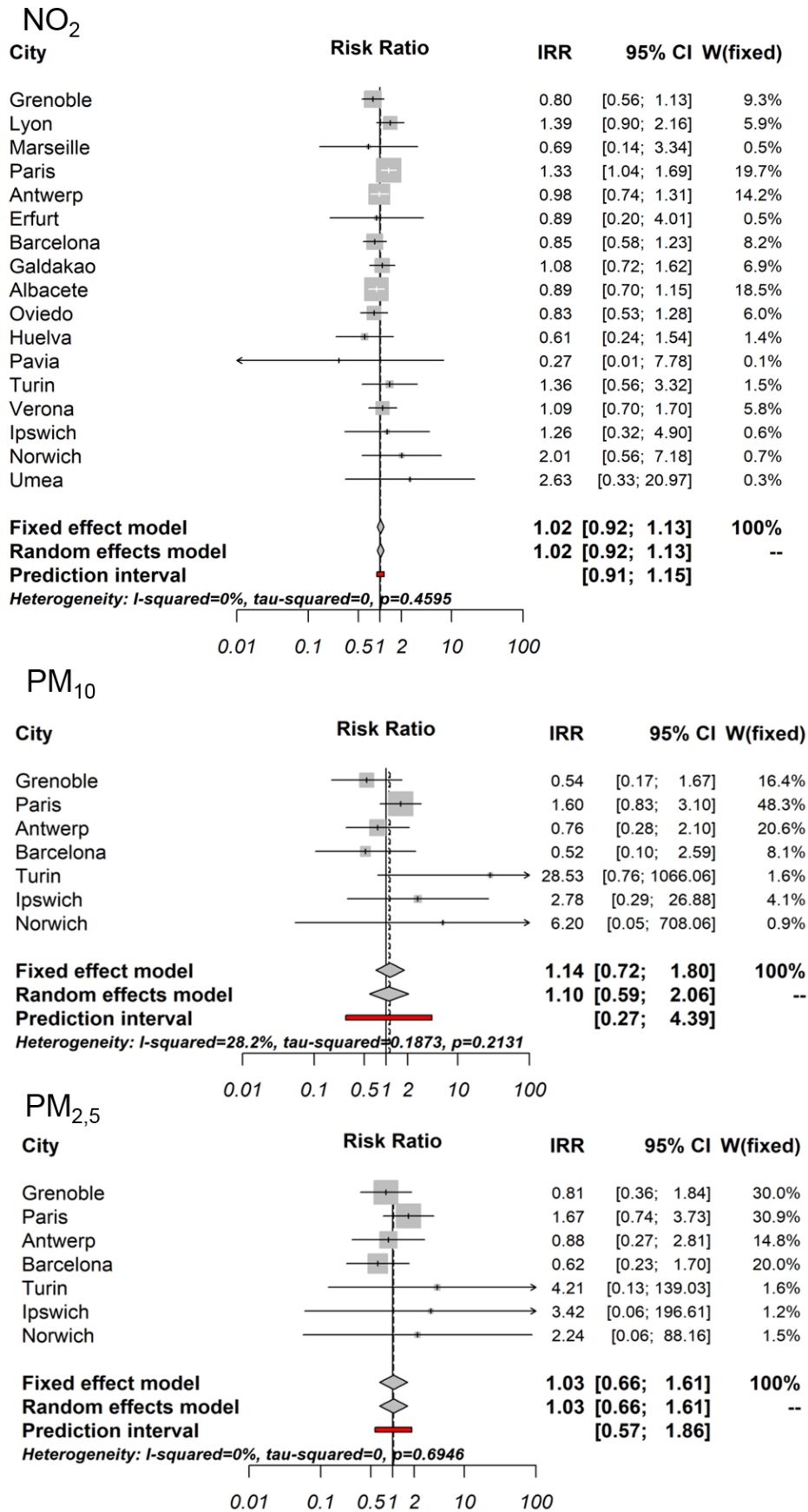


Figure 2 Association between NO<sub>2</sub>, PM<sub>10</sub> and PM<sub>2.5</sub> and incident rhinitis by city and meta-regression

## Discussion

In this longitudinal analysis of two multicentre cohorts' studies, we could not observe any clear or consistent association between modeled annual average residential exposure to air pollution and incident rhinitis. In stratified analyses, exposure to PM<sub>2.5</sub> was associated with smaller risk of rhinitis among participants with allergic sensitization and among males. Our results are difficult to compare with the literature as our study is the first to have investigated the association between long-term air pollution and incident rhinitis in adults. However, our reported overall null findings reported are in line with the literature in children where results are mixed according to the age, the window of exposure and the pollutant (Deng et al. 2016; Jang et al. 2016; Rancière et al. 2016). It is also worthy to note that our incident rate of rhinitis may seem high at first glance. However, there is little information on rhinitis incidence in adults in the literature, and the inclusion criteria of our analysis combined with a population enriched in asthmatics cases could explain this high rate. We showed that the strength and direction of the associations between air pollutants and incident rhinitis differed across the 17 European cities and also according to the study: an increase in NO<sub>2</sub> being associated with rhinitis incidence among participants in EGEA but not in ECRHS. This result could be due to the fact that there are more cities included in ECRHS and given that air pollution strongly differs according to the city, air pollution also varies a lot according to the study. However, when looking at Paris and Grenoble, included in both EGEA and ECRHS, results strongly differ according to the study in the same city. Thus, it seems that there is a study effect which could be explained by the higher prevalence of asthmatics in the EGEA study due to its recruitment specificity. Indeed, when adjusting for asthma status, no statistically significant results appear but the effect of air pollution exposure on rhinitis incidence was increased among participants with asthma compared to those without asthma.

In stratified analyses, we found that PM exposure was negatively associated with incidence of rhinitis in some groups, even if there were no significant interactions. Due to the lack of studies on air pollution and incident rhinitis in adults, we have compared our results with literature in children and with studies on the association between air pollution and prevalence of rhinitis. We found that exposure to PM<sub>2.5</sub> was negatively associated with incident rhinitis among males, and no effect was found among females. In a study on the association between proximity to traffic and prevalence of rhinitis in a Swedish population, no differences according to sex were found (Lindgren et al. 2009). Our results are also discordant with the paper by Deng who found a significant risk effect of early life exposure to traffic-related air pollutants and development of allergic rhinitis in males and with other studies in children discussed in the same paper (Deng et al. 2016). However, regarding rhinitis more broadly, a male predominance in childhood for allergic rhinitis has been shown in some studies (Alm et al. 2011) whereas there is no clear sex ratio among adults, although there might be a possible higher risk of non-allergic rhinitis among females (Cazzoletti et al. 2015). In our study, stratifying by smoking status gave discordant results according to air pollutant: a higher exposure to NO<sub>2</sub> was associated with a non-significant increase in incident rhinitis among non-smokers whereas a higher exposure to PM<sub>10</sub> was negatively and significantly associated with incident rhinitis among smokers. Among Italian adults, Cesaroni et al. (Cesaroni et al. 2008) showed a positive association between an index of traffic exposure related to air pollution - based on self-report of traffic intensity, distance to busy road, concentrations of PM and NO<sub>2</sub> - and prevalence of rhinitis among non-smokers only. Our results are thus not concordant for PM<sub>10</sub> but concordant for NO<sub>2</sub>, a good marker of traffic and therefore more comparable to the index of traffic exposure related to air pollution used by Cesaroni et al. Rhinitis is a complex phenotype, often associated with asthma and/or allergic sensitization. Based on this fact and on literature showing a possible effect of allergic sensitization in the

association between air pollution and rhinitis or asthma (Burte et al. 2016; Lindgren et al. 2009), we stratified our results by allergic sensitization to obtain results for allergic rhinitis and nonallergic rhinitis separately. We found that a higher exposure to air pollutants was negatively associated with incident rhinitis among sensitized participants (allergic rhinitis). This is discordant with the study by Lindgren et al. who found a positive association between air pollution and prevalence of allergic rhinitis, but not with rhinitis triggered by non-allergic factors. These discrepancies may be due to the fact that allergic sensitization was based on objective tests (SPT or specific IgE) in our analysis, whereas Lindgren et al. used self-reported triggers of rhinitis symptoms to distinguish between the two types of rhinitis. Our results also discord with several studies in children where exposure to air pollution has been associated to the development of allergic rhinitis (Brauer et al. 2007; Deng et al. 2016; Gehring et al. 2010). However, phenotypes of rhinitis are not the same in adults and in children (Izquierdo-Domínguez et al. 2013) and particularly regarding allergic rhinitis that is an integral part of the allergic march in children, but not in adults. The mechanisms explaining the differences in results according to allergic sensitization are unclear. However, the interaction between air pollution and allergens and particularly with pollen, further discussed below, is likely to play an important role.

There are complex interactions between climate change, air pollution and allergens (Carlsten and Rider 2017; D'Amato et al. 2018; Reinmuth-Selzle et al. 2017), and in particular pollen (Annesi-Maesano et al. 2012). A study in Italy has shown that NO<sub>2</sub> exposure was associated with an increase in allergic rhinitis prevalence, but only among participants living in the Mediterranean region, and not in the subcontinental one (de Marco et al. 2002). Data from our study came from 17 cities from all over Europe, reflecting different climates. However, we found no clear geographical pattern of the association between air pollution and rhinitis incidence when looking at each city separately. Climate is associated with air pollution levels

and may also act on the allergens by altering local and regional allergen production or by increasing the allergenicity of pollen (D'Amato et al. 2016; Sénéchal et al. 2015). Air pollution acts directly on pollen (D'Amato et al. 2007), and particles carrying pollen allergen molecules are likely to play a role in the association between air pollution and respiratory allergic diseases (Bono et al. 2016; Marchetti et al. 2017). Finally, the level of pollen exposure is associated to allergic rhinitis incidence and prevalence and has also been associated to severity of rhinitis (Annesi-Maesano et al. 2012). Unfortunately, data were not available on climate change or on allergen concentration. This would have helped to better understand our results, and particularly among those with allergic rhinitis for which allergen-pollution interaction may drive an important part of the association. In future studies, it will be important to consider these factors when studying air pollution exposure and allergic diseases, particularly hay fever.

Socio-economic status may play a role in the relation between air pollution and respiratory symptoms and particularly asthma (Burte et al. 2016). However, in our study, adjusting for educational level did not change the results. Furthermore, the association between socio economic status and air pollution is not clearly established in Europe and is very heterogeneous according to the city (Temam et al. 2017). Similarly, our study, which also used data from ESCAPE, found results that varied considerably according to the city with no clear pattern.

In our study, stratifying by allergic sensitization enabled us to distinguish results for allergic and nonallergic rhinitis but not for the other phenotypes of rhinitis, e.g mixed rhinitis (subjects having both allergic and nonallergic rhinitis). However, it is difficult to catch subjects with such phenotypes in epidemiological studies when allergy is based only on skin prick test or specific IgE. Another limitation of the present study is that despite the individual measure of air pollution, this measure was carried out using residential address and therefore

may not have taken into account the correct annual personal exposure of each participant. However, this is a limitation that often arises when dealing with long-term air pollution measurements. Another limitation is that analyses by city and meta-regression were adjusted only for age due to small sample size. Further adjustment would probably not have changed the results since in the general analysis adjusted results were similar to the crude analysis. However, results of the meta-regression have to be considered with caution because of the small sample size and the wide confidence intervals. For the same reason, results on the effect of PM exposure should also be considered with caution.

The major strength of this study is that the population comes from two multicentric cohorts, followed for more than 20 years and including 17 European cities. Furthermore, there is a detailed characterization on respiratory phenotypes at both first and second follow-up as well as an individual measure of exposure to air pollution, obtained within the ESCAPE project. We were therefore able to perform a longitudinal analysis studying the long-term air pollution effect on incidence of rhinitis. Rhinitis definition is often based on the report of nasal allergy, hay fever or allergic rhinitis (de Marco et al. 2012; Smit et al. 2014). However, in our study we aimed to study the incidence of all types of rhinitis and not only the allergic subtypes. We therefore based our definition of rhinitis on nasal symptoms (Cazzoletti et al. 2015; Rancière et al. 2016). This choice also enabled the stratification of results by allergic sensitization and the possibility to distinguish the two types of rhinitis. Nevertheless, the definition of rhinitis is questionnaire-based and thus may not be as reliable as a physician diagnosis as it is often the case in epidemiological studies.

The total air pollution exposure of an individual is not restricted to outdoor air pollution but is actually composed of a cocktail of pollutants, with both outdoor and indoor sources. The present study focused on the association between outdoor air pollution and rhinitis outcomes. We acknowledge that our study suffers from the lack of data on indoor air pollution exposures

that are very important as we spend most of the time indoor. Future studies should integrate both sources of pollution to give a more complete overview of the effects of air pollution on rhinitis.

The inconsistent results may also reflect the fact that single factors – such as air pollution – may play a relevant role in the etiology of very complex multifactorial and often allergic diseases, mostly under multi-factorial interrelationships of many co-factors, among which climate change and allergen concentrations. This is consistent with the findings of the long-term association between air pollution and onset of asthma: inconsistent findings (Guarnieri and Balmes 2014) have also been reported and a more specific definition of traffic-related exposures such as typically encountered in high concentrations among those living very close to busy roads resulted in more consistent results. It will be interesting to investigate the role of air pollution in the development of rhinitis or other atopic diseases in countries with very high levels of air pollution but with very different patterns of possibly relevant etiologic co-factors. For example in low income countries with so far rather low prevalence of asthma or atopic diseases.

Overall, no clear association was found between air pollution and incident rhinitis, whether in the main analysis, the bi-pollutant model or the stratified analysis.

**Conclusions:** In this longitudinal study, we have analysed the effect of long-term exposure to air pollution on the incidence of rhinitis among 1533 adults, including 394 incident cases, from 17 European cities. We have found no clear association between long-term air pollution exposure and incident rhinitis. However, it could be interesting to look further into the association between air pollution and rhinitis, concentrating on the effect of air pollution on rhinitis phenotypes or rhinitis characteristics such as type of symptoms or severity.



## References

- Alm B, Goksör E, Thengilsdottir H, Pettersson R, Möllborg P, Norvenius G, et al. 2011. Early protective and risk factors for allergic rhinitis at age 41/2 yr. *Pediatr. Allergy Immunol.* 22:398–404; doi:10.1111/j.1399-3038.2011.01153.x.
- Annesi-Maesano I, Rouve S, Desqueyroux H, Jankovski R, Klossek J-M, Thibaudon M, et al. 2012. Grass pollen counts, air pollution levels and allergic rhinitis severity. *Int. Arch. Allergy Immunol.* 158:397–404; doi:10.1159/000332964.
- Beelen R, Hoek G, Vienneau D, Eeftens M, Dimakopoulou K, Pedeli X, et al. 2013. Development of NO<sub>2</sub> and NO<sub>x</sub> land use regression models for estimating air pollution exposure in 36 study areas in Europe - The ESCAPE project. *Atmos. Environ.* 72:10–23; doi:10.1016/j.atmosenv.2013.02.037.
- Beelen R, Raaschou-Nielsen O, Stafoggia M, Andersen ZJ, Weinmayr G, Hoffmann B, et al. 2014. Effects of long-term exposure to air pollution on natural-cause mortality: An analysis of 22 European cohorts within the multicentre ESCAPE project. *Lancet* 383:785–795; doi:10.1016/S0140-6736(13)62158-3.
- Bono R, Romanazzi V, Bellisario V, Tassinari R, Trucco G, Urbino A, et al. 2016. Air pollution, aeroallergens and admissions to pediatric emergency room for respiratory reasons in Turin, northwestern Italy. *BMC Public Health* 16:722; doi:10.1186/s12889-016-3376-3.
- Bousquet J, Bewick M, Arnavielhe S, Mathieu-Dupas E, Murray R, Bedbrook A, et al. 2017. Work productivity in rhinitis using cell phones: The MASK pilot study. *Allergy* 38:42–49; doi:10.1111/all.13177.
- Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. 2008. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008\*. *Allergy* 63:8–160; doi:10.1111/j.1398-9995.2007.01620.x.
- Bouzigon E, Nadif R, Le Moual N, Dizier M-H, Aschard H, Boudier A, et al. 2015. Facteurs génétiques et environnementaux de l'asthme et de l'allergie : synthèse des résultats de l'étude EGEA. *Rev. Mal. Respir.* 32:822–840; doi:10.1016/j.rmr.2014.12.005.
- Brauer M, Hoek G, Smit H a., de Jongste JC, Gerritsen J, Postma DS, et al. 2007. Air pollution and development of asthma, allergy and infections in a birth cohort. *Eur. Respir. J.* 29:879–888; doi:10.1183/09031936.00083406.
- Brunekreef B, Sunyer J. 2003. Asthma, rhinitis and air pollution: Is traffic to blame? *European Respiratory Journal*.
- Burney PG, Luczynska C, Chinn S, Jarvis D. 1994. The European Community Respiratory Health Survey. *Eur. Respir. J.* 7:954–60; doi:10.1183/09031936.94.07050954.
- Burte E, Nadif R, Jacquemin B. 2016. Susceptibility Factors Relevant for the Association Between Long-Term Air Pollution Exposure and Incident Asthma. *Curr. Environ. Heal. Reports* 3:23–39; doi:10.1007/s40572-016-0084-1.
- Carlsten C, Rider CF. 2017. Traffic-related air pollution and allergic disease: an update in the context of global urbanization. *Curr. Opin. Allergy Clin. Immunol.* 17:85–89; doi:10.1097/ACI.0000000000000351.

- Cazzoletti L, Ferrari M, Olivieri M, Verlato G, Antonicelli L, Bono R, et al. 2015. The gender, age and risk factor distribution differs in self-reported allergic and non-allergic rhinitis: a cross-sectional population-based study. *Allergy, Asthma Clin. Immunol.* 11:36; doi:10.1186/s13223-015-0101-1.
- Cesaroni G, Badaloni C, Porta D, Forastiere F, Perucci C a. 2008. Comparison between various indices of exposure to traffic-related air pollution and their impact on respiratory health in adults. *Occup. Environ. Med.* 65:683–90; doi:10.1136/oem.2007.037846.
- D’Amato G, Cecchi L, Bonini S, Nunes C, Annesi-Maesano I, Behrendt H, et al. 2007. Allergenic pollen and pollen allergy in Europe. *Allergy* 62:976–90; doi:10.1111/j.1398-9995.2007.01393.x.
- D’Amato G, Pawankar R, Vitale C, Lanza M, Molino A, Stanziola A, et al. 2016. Climate Change and Air Pollution: Effects on Respiratory Allergy. *Allergy. Asthma Immunol. Res.* 8:391; doi:10.4168/air.2016.8.5.391.
- D’Amato M, Cecchi C, Annesi-Maesano I, D’Amato G. 2018. News on Climate change, air pollution and allergic trigger factors of asthma. *J. Investig. Allergol. Clin. Immunol.* 28; doi:10.18176/jiaci.0228.
- De Marco R, Accordini S, Marcon A, Cerveri I, Antó JM, Gislason T, et al. 2011. Risk factors for chronic obstructive pulmonary disease in a European cohort of young adults. *Am. J. Respir. Crit. Care Med.* 183:891–897; doi:10.1164/rccm.201007-1125OC.
- de Marco R, Cappa V, Accordini S, Rava M, Antonicelli L, Bortolami O, et al. 2012. Trends in the prevalence of asthma and allergic rhinitis in Italy between 1991 and 2010. *Eur. Respir. J.* 39:883–92; doi:10.1183/09031936.00061611.
- de Marco R, Poli A, Ferrari M, Accordini S, Giammanco G, Bugiani M, et al. 2002. The impact of climate and traffic-related NO<sub>2</sub> on the prevalence of asthma and allergic rhinitis in Italy. *Clin. Exp. Allergy* 32: 1405–12.
- Deng Q, Lu C, Yu Y, Li Y, Sundell J, Norb D. 2016. Early life exposure to traf fi c-related air pollution and allergic rhinitis in preschool children. 121; doi:10.1016/j.rmed.2016.10.016.
- Eeftens M, Beelen R, De Hoogh K, Bellander T, Cesaroni G, Cirach M, et al. 2012. Development of land use regression models for PM<sub>2.5</sub>, PM<sub>2.5</sub> absorbance, PM<sub>10</sub> and PM<sub>coarse</sub> in 20 European study areas; Results of the ESCAPE project. *Environ. Sci. Technol.* 46:11195–11205; doi:10.1021/es301948k.
- Gehring U, Wijga AH, Brauer M, Fischer P, De Jongste JC, Kerkhof M, et al. 2010. Traffic-related air pollution and the development of asthma and allergies during the first 8 years of life. *Am. J. Respir. Crit. Care Med.* 181:596–603; doi:10.1164/rccm.200906-0858OC.
- Guarnieri M, Balmes JR. 2014. Outdoor air pollution and asthma. *Lancet* 383:1581–92; doi:10.1016/S0140-6736(14)60617-6.
- Hajat S, Haines A, Atkinson RW, Bremner SA, Anderson HR, Emberlin J. 2001. Association between air pollution and daily consultations with general practitioners for allergic rhinitis in London, United Kingdom. *Am. J. Epidemiol.* 153: 704–14.
- HEI. 2010. Traffic-related air pollution: a critical review of the literature on emissions,

- exposure, and health effects. *Heal. Eff. Inst. Special Re*: 1–386.
- Heinrich J, Wichmann H. 2004. Traffic related pollutants in Europe and their effect on allergic disease. *Curr. Opin. Allergy Clin. Immunol.* 4: 341–8.
- Izquierdo-Domínguez A, Valero AL, Mullol J. 2013. Comparative analysis of allergic rhinitis in children and adults. *Curr. Allergy Asthma Rep.* 13:142–51; doi:10.1007/s11882-012-0331-y.
- Jang A, Jun YJ, Park MK. 2016. Effects of air pollutants on upper airway disease. *Curr. Opin. Allergy Clin. Immunol.* 16:13–17; doi:10.1097/ACI.0000000000000235.
- Jarvis D. 2002. The European Community Respiratory Health Survey II. *Eur. Respir. J.* 20:1071–1079; doi:10.1183/09031936.02.00046802.
- Kauffmann F. 1999. EGEA - descriptive characteristics. *Clin. Exp. Allergy* 29: 17–21.
- Kauffmann F, Dizier MH, Pin I, Paty E, Gormand F, Vervloet D, et al. 1997. Epidemiological study of the genetics and environment of asthma, bronchial hyperresponsiveness, and atopy: phenotype issues. *Am. J. Respir. Crit. Care Med.* 156:S123-9; doi:10.1164/ajrccm.156.4.12tac9.
- Kogevinas M, Zock JP, Jarvis D, Kromhout H, Lillienberg L, Plana E, et al. 2007. Exposure to substances in the workplace and new-onset asthma: an international prospective population-based study (ECRHS-II). *Lancet* 370:336–341; doi:10.1016/S0140-6736(07)61164-7.
- Leynaert B, Soussan D. 2003. Monitoring the quality-of-life in allergic disorders. *Curr. Opin. Allergy Clin. Immunol.* 3:177–83; doi:10.1097/01.all.0000072713.82112.d9.
- Lindgren A, Stroh E, Nihlén U, Montnémy P, Axmon A, Jakobsson K. 2009. Traffic exposure associated with allergic asthma and allergic rhinitis in adults. A cross-sectional study in southern Sweden. *Int. J. Health Geogr.* 8:25; doi:10.1186/1476-072X-8-25.
- Linneberg A, Dam Petersen K, Hahn-Pedersen J, Hammerby E, Serup-Hansen N, Boxall N. 2016. Burden of allergic respiratory disease: a systematic review. *Clin. Mol. Allergy* 14:12; doi:10.1186/s12948-016-0049-9.
- Marchetti P, Pesce G, Villani S, Antonicelli L, Ariano R, Attenu F, et al. 2017. Pollen concentrations and prevalence of asthma and allergic rhinitis in Italy: Evidence from the GEIRD study. *Sci. Total Environ.* 584–585:1093–1099; doi:10.1016/j.scitotenv.2017.01.168.
- Peden DB. 2001. Effect of pollutants in rhinitis. *Curr. Allergy Asthma Rep.* 1: 242–6.
- Rancière F, Bougas N, Viola M, Momas I. 2016. Early Exposure to Traffic-Related Air Pollution, Respiratory Symptoms at 4 Years of Age, and Potential Effect Modification by Parental Allergy, Stressful Family Events, and Sex: A Prospective Follow-up Study of the PARIS Birth Cohort. *Environ. Health Perspect.* 125:737–745; doi:10.1289/EHP239.
- Reinmuth-Selzle K, Kampf CJ, Lucas K, Lang-Yona N, Fröhlich-Nowoisky J, Shiraiwa M, et al. 2017. Air Pollution and Climate Change Effects on Allergies in the Anthropocene: Abundance, Interaction, and Modification of Allergens and Adjuvants. *Environ. Sci.*

- Technol. 51:4119–4141; doi:10.1021/acs.est.6b04908.
- Sénéchal H, Visez N, Charpin D, Shahali Y, Peltre G, Biolley JP, et al. 2015. A review of the effects of major atmospheric pollutants on pollen grains, pollen content, and allergenicity. *Sci. World J.* 2015; doi:10.1155/2015/940243.
- Shaaban R, Zureik M, Soussan D, Neukirch C, Heinrich J, Sunyer J, et al. 2008. Rhinitis and onset of asthma: a longitudinal population-based study. *Lancet* 372:1049–57; doi:10.1016/S0140-6736(08)61446-4.
- Siroux V, Basagaña X, Boudier A, Pin I, Garcia-Aymerich J, Vesin A, et al. 2011. Identifying adult asthma phenotypes using a clustering approach. *Eur. Respir. J.* 38:310–7; doi:10.1183/09031936.00120810.
- Smit L a. M, Hooiveld M, van der Sman-de Beer F, Opstal-van Winden a. WJ, Beekhuizen J, Wouters IM, et al. 2014. Air pollution from livestock farms, and asthma, allergic rhinitis and COPD among neighbouring residents. *Occup. Environ. Med.* 71:134–140; doi:10.1136/oemed-2013-101485.
- Temam S, Burte E, Adam M, Antó JM, Basagaña X, Bousquet J, et al. 2017. Socioeconomic position and outdoor nitrogen dioxide (NO<sub>2</sub>) exposure in Western Europe: A multi-city analysis. *Environ. Int.* 101:117–124; doi:10.1016/j.envint.2016.12.026.
- Wang J, Engvall K, Smedje G, Norbäck D. 2014. Rhinitis, asthma and respiratory infections among adults in relation to the home environment in multi-family buildings in Sweden. *PLoS One* 9:24–26; doi:10.1371/journal.pone.0105125.
- Zhang F, Wang W, Lv J, Krafft T, Xu J. 2011. Time-series studies on air pollution and daily outpatient visits for allergic rhinitis in Beijing, China. *Sci. Total Environ.* 409:2486–92; doi:10.1016/j.scitotenv.2011.04.007.
- Zhang Y, Zhang L. 2014. Prevalence of allergic rhinitis in China. *Allergy. Asthma Immunol. Res.* 6: 105–113.