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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_2, PM_{10} and $PM_{2.5}$ 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 $\mu g.m^{-3}$ of NO_2: 1.00[0.91-1.09], for an increase of 5$\mu g.m^{-3}$ of $PM_{2.5}$: 0.88[0.73-1.04]). Similar results were found in the two-pollutant model (aIRR for an increase of 10 $\mu g.m^{-3}$ of NO_2: 1.01[0.87-1.17], for an increase of 5$\mu g.m^{-3}$ of $PM_{2.5}$: 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).

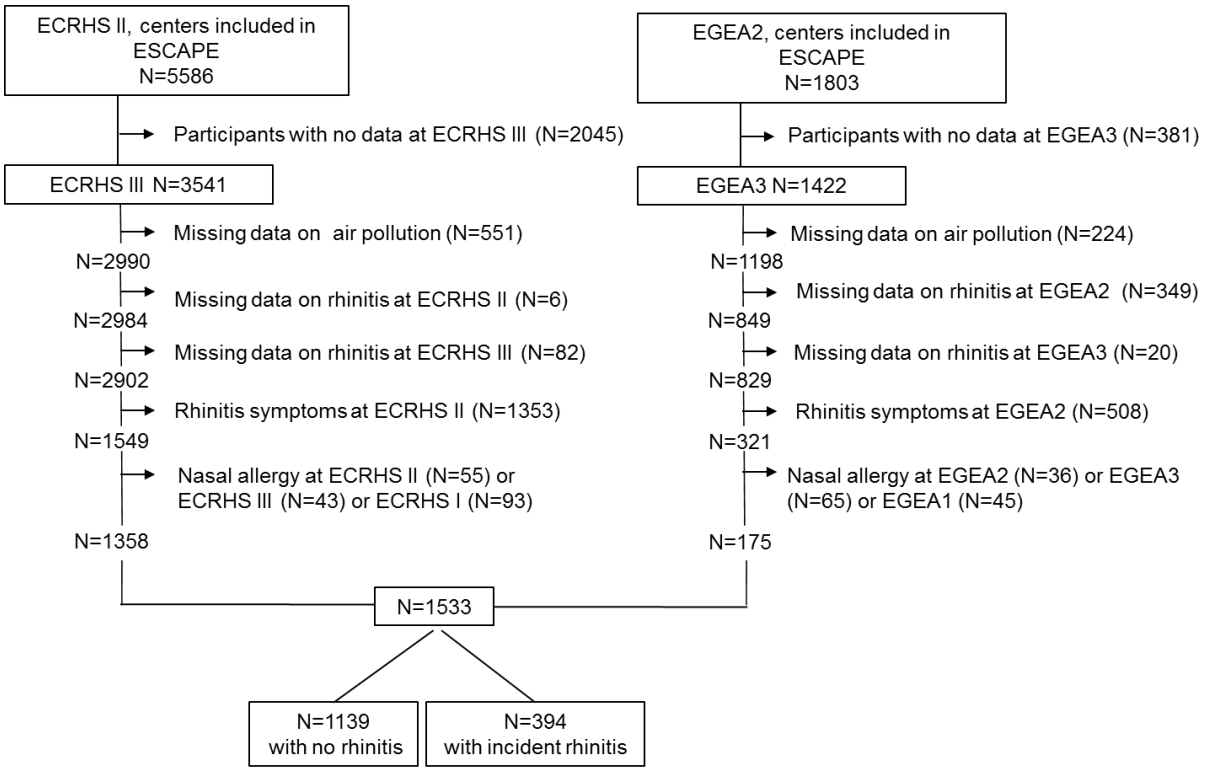

Figure 1 Flow-chart of the participants

Estimation of air pollution exposure

Within the frame of the European Study of Cohorts for Air Pollution Effects (ESCAPE www.escapeproject.eu (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_2 (nitrogen dioxide), PM_{10} (airborne particles with an aerodynamical diameter ≤10 μm) and $PM_{2.5}$ (airborne particles with an aerodynamical diameter ≤25 μm) model estimates developed between 2009 and 2010. Estimates of NO_2 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 of air pollutant concentrations were estimated at participants' residential addresses with land use regression models. Results are reported for an increase of 10 $\mu g.m^{-3}$ for PM_{10} and NO_2 and 5 $\mu g.m^{-3}$ for $PM_{2.5}$, 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 NOx (nitrogen oxides), $PM_{2.5}$absorbance, PMcoarse 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 ≥3 mm and superior to the negative control wheal to at least one of the allergen among: cat, *Dermatophagoides pteronyssinus*, *Blattela germanica*, olive, birch, *Parieteria 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≥35kU/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 $\mu g/m^3$ for NO_2 and PM_{10}, 5 $\mu g/m^3$ for $PM_{2.5}$ and PM_{coarse}, 10 $\mu g/m^3$ for NOX, 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 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 3rd 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).

Variables	All (N=1533)	No rhinitis (N=1139)	Incident rhinitis (N=394)	p crude overall
Age, mean±sd	43.4±8.9 (N=1533)	43.7±8.9	42.7±8.9	0.06
Study, % EGEA	11.4 (N=1533)	11.4	11.4	1
Sex=women	51.2 (N=1533)	50.1	54.3	0.17
BMI, %	(N=1374)			0.27
<18	1.8	2.0	1.4	
18-25	49.6	48.1	54.1	
25-30	34.2	35.2	31.4	
>=30	14.3	14.7	13.2	
Smoking status, %	(N=1520)			0.34
current	30.7	29.7	33.7	
ex-smoker	27.8	28.2	26.5	
never	41.5	42.1	39.8	
Educational level, %	(N=1529)			0.49
low	26.3	26.8	24.7	
medium	34.7	34.9	33.8	
high	39.0	38.2	41.5	
Asthma ever, %	5.1 (N=1533)	4.1	7.9	<0.01
Asthma age of onset, mean±sd	17.8±16.2 (N=75)	18.6±16.9	16.7±15.4	0.61
Report of hay fever or AR ever, %	5.6 (N=1522)	0	22.2	<0.01
Allergic sensitization, %	18.4 (N=1306)	17.6	22.2	0.25
NO_2, □ g.m^{-3}, mean±sd*	29.3±15.1 (N=1533)	28.9±15.4	30.3±14.2	0.11
PM_{10}, □ g.m^{-3}, mean±sd*	26.9±8.3 (N=738)	27.2±8.7	26.2±7.1	0.09
$PM_{2.5}$, □ g.m^{-3}, mean±sd*	16.4±4.9 (N=738)	16.6±5.2	15.9±4.4	0.08

*Annual averaged

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_2 and PM_{10}, 0.70 between NO_2 and $PM_{2.5}$ and 0.77 between PM_{10} and $PM_{2.5}$, Table 1 in Supplementary material).

Main analysis

Pooled analyses of the associations between NO_2, PM_{10} or $PM_{2.5}$ and incident rhinitis showed no statistically significant results (Table 2). In a two-pollutant model including NO_2 and $PM_{2.5}$, results were very similar to those of the single pollutant-model. No association was found when considering other pollutants or traffic measures (NOx, $PM_{2.5}$ 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_2 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_{10} and $PM_{2.5}$. Results were statistically significant only for $PM_{2.5}$ (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_{10} and $PM_{2.5}$ and statistically significant only for $PM_{2.5}$ (Table 2). No statistically significant association was found among females or with NO_2.

Stratifying by smoking status

Finally, when stratifying by smoking status, a borderline positive association of rhinitis with NO_2 was found among non-smokers, while an inverse significant relationship was found with PM_{10} 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_2 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_{10} and $PM_{2.5}$. However, no statistical heterogeneity between cities was found in the meta-regression, with I^2 values ranging from 0% for $PM_{2.5}$ to 36% for PM_{10}. No significant association was found in the meta-regressions (Figure 2).

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

	No of subjects (No of incident cases) in adjusted model		crude IRR (95%CI)			aIRR (95%CI)		
Analyses	NO_2	PM_{10} and $PM_{2.5}$	NO_2	PM_{10}	$PM_{2.5}$	NO_2	PM_{10}	$PM_{2.5}$
Main analyses	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_2, $PM_{2.5}$)			1.05[0.91-1.21]		0.84[0.66-1.05]	1.01[0.87-1.17]		0.87[0.68-1.08]
Stratified analyses								
By study						**		
EGEA	112(30)	80(21)	**1.42[1.12-1.82]**	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]	**0.66[0.35-0.95]**	0.95[0.77-1.14]	0.73[0.42-1.15]	**0.52[0.29-0.87]**
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]	**0.75[0.56-0.99]**	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]	**0.78[0.61-0.98]**	0.99[0.88-1.10]	0.83[0.61-1.08]	**0.76[0.57-0.98]**
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]
Secondary analysis								
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]

aIRRR : 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 $\mu g.m^{-3}$ for NO_2 and PM_{10} and for an increase of 5 $\mu g.m^{-3}$ for $PM_{2.5}$. **: p-interaction= 0.047, *: p-interaction=0.08, all other p-interaction>0.12.

304 *Table 2 IRR of the associations between pollutants (NO_2, PM_{10}, $PM_{2.5}$) and incident rhinitis, in all, and stratifying by study, asthma status, allergic sensitization and smoking*

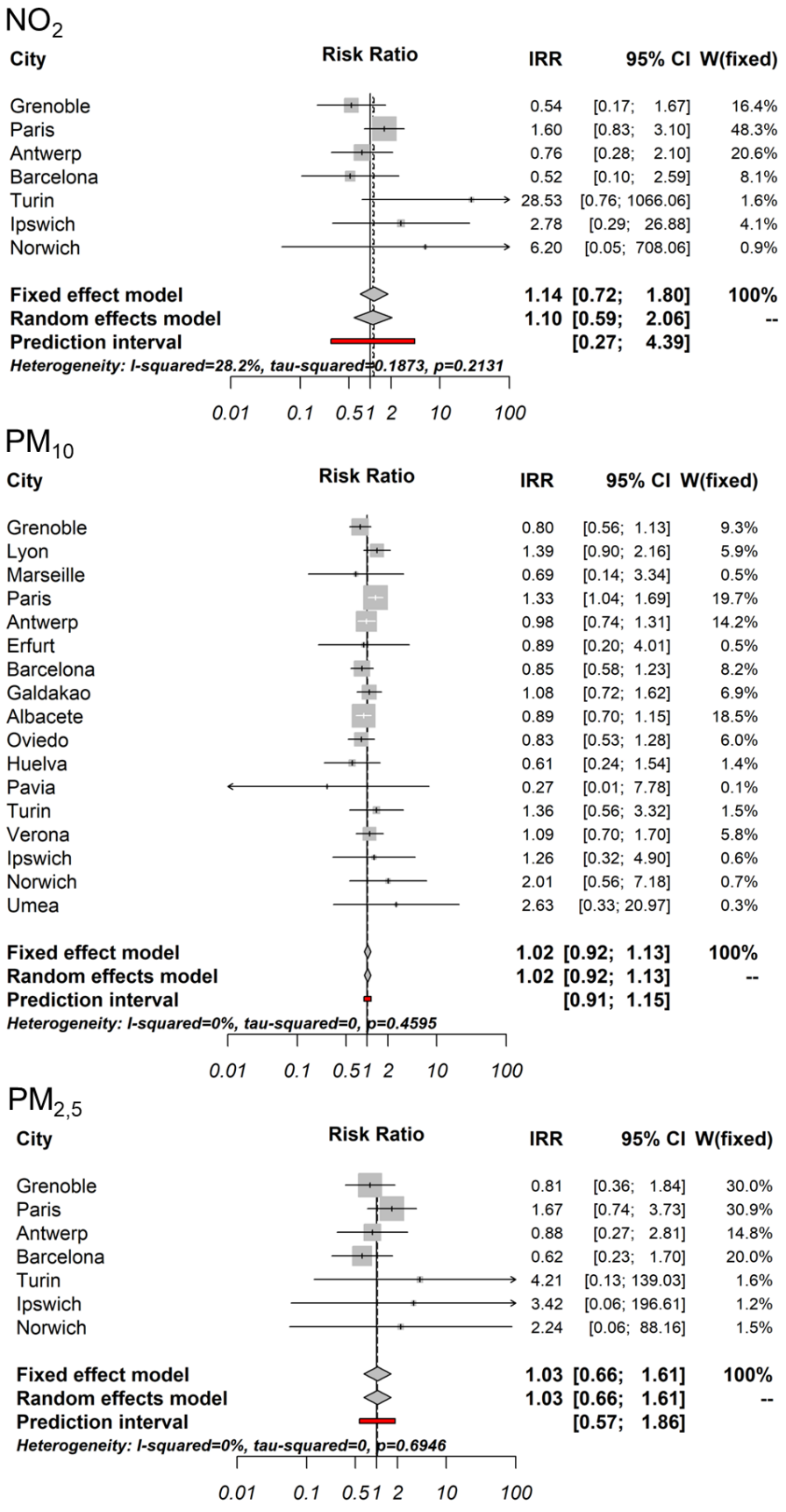

Figure 2 Association between NO_2, PM_{10} and $PM_{2.5}$ and incident rhinitis by city and meta-regression

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 $PM_{2.5}$ 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_2 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 $PM_{2.5}$ 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_2 was associated with a non-significant increase in incident rhinitis among non-smokers whereas a higher exposure to PM_{10} 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_2 - and prevalence of rhinitis among non-smokers only. Our results are thus not concordant for PM_{10} but concordant for $NO_{2,}$ 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_2 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. Data on indoor air pollution exposures –which can be as harmful as the outdoor ones- were

not considered. Future studies should integrate both sources of pollution to give a more complete overview of the effects of air pollution on health.

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.

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