Rhinite : caractérisation et association avec la pollution atmosphérique

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Rhinitis: characterisation and association with air pollution

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Thèse de doctorat

RHINITIS: CHARACTERISATION AND ASSOCIATION WITH AIR POLLUTION

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A mon papa

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ABSTRACT

Whereas rhinitis has an important public health impact, in adults there is no standardized definition of rhinitis in epidemiological studies. Furthermore, environmental factors of rhinitis are barely known, and in particular, there are very few studies on the effects of long-term exposure to air pollution on rhinitis in adults. To fill these gaps, we used data from two European multicentre epidemiological studies with extensive data on respiratory health and individual estimated exposures to long-term air pollution. Our findings showed that to better characterize rhinitis, one need to consider together all the characteristics of the nasal symptoms, the comorbidities and the allergic sensitization, and not to restrict the disease to one question or one allergic sensitization test. We found no association between long-term air pollution and incidence of rhinitis, but we showed that long-term exposure to air pollution is associated to an increased severity of rhinitis, emphasising that air pollution needs to be controlled.

RESUME

Alors que la rhinite a un fort impact sur la santé publique, chez l'adulte, il n'existe pas de définition standardisée de la rhinite dans les études épidémiologiques. De plus, les facteurs environnementaux de la rhinite sont mal connus et, en particulier, il existe très peu d'études sur les effets à long terme de la pollution atmosphérique sur la rhinite chez l'adulte. Pour combler ces lacunes, nous avons utilisé les données de deux études épidémiologiques multicentriques européennes ayant des données détaillées sur la santé respiratoire et d'exposition annuelle individuelle à la pollution atmosphérique. Nos résultats ont montré que pour mieux caractériser la rhinite, il faut considérer l'ensemble des caractéristiques des symptômes nasaux, les comorbidités et la sensibilisation allergique, et ne pas limiter la maladie à une question ou à un test de sensibilisation allergique. Nous n'avons trouvé aucune association entre la pollution atmosphérique à long terme et l'incidence de la rhinite, mais nous avons montré que l'exposition à long terme à la pollution était associée à une augmentation de la sévérité de la rhinite, soulignant le besoin de contrôler les niveaux de pollution atmosphérique.

RESUMEN

La rinitis tiene un impacto importante en la salud pública, sin embargo en los adultos no existe una estandarización de la definición en los estudios epidemiológicos. Además, apenas se conocen los factores ambientales de la rinitis y, en particular, existen muy pocos estudios sobre los efectos de la contaminación atmosférica a largo plazo sobre la rinitis en adultos. Para llenar estos vacíos, utilizamos datos de dos estudios epidemiológicos europeos multicéntricos con datos extensos sobre la salud respiratoria y con datos de exposición individual a la contaminación atmosférica a largo plazo. Nuestros resultados mostraron que para caracterizar mejor la rinitis, es necesario considerar conjuntamente todas las características de los síntomas nasales, las comorbilidades y la sensibilización alérgica, y no restringir la enfermedad a una pregunta o a una prueba de sensibilización alérgica. No encontramos asociación entre la contaminación atmosférica a largo plazo y la incidencia de rinitis, pero demostramos que la exposición a la contaminación del aire a largo plazo aumenta la severidad de la rinitis, enfatizando que es necesario controlar la contaminación atmosférica.

RESUM

La rinitis té un impacte important en la salut pública, però en els adults no hi ha una estandardització de la definició en els estudis epidemiològics. A més, gairebé no es coneixen els factors ambientals de la rinitis i, en particular, hi ha pocs estudis sobre els efectes de la contaminació atmosfèrica a llarg termini sobre la rinitis en adults. Per omplir aquests buits, utilitzem dades de dos estudis epidemiològics europeus multicèntrics amb dades extenses sobre la salut respiratòria i amb dades d'exposició individual a la contaminació atmosfèrica a llarg termini. Els nostres resultats van mostrar que per caracteritzar millor la rinitis, cal considerar conjuntament totes les característiques dels símptomes nasals, les comorbiditats i la sensibilització al·lèrgica, i no restringir la malaltia a una pregunta o a una prova de sensibilització al·lèrgica. No es va trobar associació entre la contaminació atmosfèrica a llarg termini i la incidència de rinitis, però va demostrar que l'exposició a la contaminació de l'aire a llarg termini augmenta la severitat de la rinitis, emfatitzant que cal controlar la contaminació atmosfèrica.

LIST OF ORIGINAL PUBLICATIONS

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Burte E, Bousquet J, Siroux V, Jacquemin B, Nadif R. Polysensitization and comorbidities of asthma and rhinitis in adults in the EGEA study . *European Respiratory Society (ERS) congress*, Amsterdam, 26-30 September 2015.

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Burte E, Leynaert B, Künzli N, Siroux V, Jarvis D, Nadif R, Jacquemin B. Association between air pollution and severity of rhinitis in two European cohorts. *ISEE (International Society for Environmental Epidemiology) Europe Young and Early Career Conference 2018*, Munich, 19-21 March 2018, accepted.

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LIST OF ABBREVIATIONS AND ACRONYMS

AIT	allergen-specific immunotherapy
AR	allergic rhinitis
ARIA	Allergic Rhinitis and its Impact on Asthma
BC	before Christ
CO	carbon monoxide
CO2	carbon dioxide
COPD	chronic obstructive pulmonary disease
DEP	diesel particles exhaust
ECRHS	European Community Respiratory Health Survey
EGEA	Epidemiological study on the Genetics and Environmental factors of Asthma
EU	European Union
GA2LEN	Global Allergy and Asthma European Network
GIS	geographic information system
GP	general practitioners
GWAS	genome-wide association studies
HDM	house dust mites
IARC	International Agency for Research on Cancer
IgE	immunoglobulin E
IL	interleukin
ISAAC	International Study of Asthma and Allergies in Childhood
LUR	land-use regression
MASK	MACVIA-ARIA Sentinel NetworK
MeDALL	Mechanisms of the Development of Allergy
NAR	non-allergic rhinitis
NARES	non-allergic rhinitis with eosinophilia syndrome
NO	nitrogen oxide
NO_2	nitrogen dioxide
Nox	nitrogen oxides
O_3	Ozone
PM	particulate matter
RNSA	Réseau National de Surveillance Aérobiologique

SES	socioeconomic status
SFAR	score for allergic rhinitis
SO2	sulphur dioxide
SPT	skin prick test
Th	T helper cell
UFP	ultrafine particles
US	United States
USD	United states dollar
VOC	volatile organic compounds
WHO	World Health Organization

1 INTRODUCTION

Rhinitis is a global health problem that causes major illness and disability worldwide, often associated with asthma. Individuals from all countries, all ethnic groups and of all ages suffer from rhinitis. It affects social life, sleep, school and work and induces substantial cost for the society.

Prevalence of rhinitis has increased during the last decades and continues increasing. Similarly to other respiratory or allergic diseases, this increase is probably due to complex interactions between genetic predispositions and environmental factors, possibly including outdoor air pollution.

1.1 Rhinitis

Rhinitis, from Greek *rhino* -nose- and itis -suffix denoting diseases characterized by inflammation- is defined as an inflammation of the lining of the nose and is characterized by nasal symptoms including anterior or posterior rhinorrhoea, sneezing, nasal blockage and/or itching of the nose. Rhinitis often starts early in life and persists through the life.

The first patient reported in the literature is probably Hippias, former tyrant of Athens who guided Persian forces in the bay of Marathon in 490 BC (1). Hay fever was actually first documented as "*rose fever*" during the fifteenth and sixteenth centuries (2), and the first detailed description of hay fever occurred in the early 19th century, at that time it was regarded as most unusual. By the end of the 19th century, it had become commonplace in both Europe and North America (3). However, the prevalence of allergic rhinitis was still low and estimated at 1.5% in America in 1923 (4), but probably partly underdiagnosed. It is during the past last 60 years that prevalence of rhinitis has considerably increased reaching between 20 and 50% of the population worldwide (5,6). The management of rhinitis was then subject of several working groups, among which The Allergic Rhinitis and its Impact on Asthma (ARIA) group: a world health initiative on allergic rhinitis who provided the first set and the most widely used guidelines (7). ARIA aims to "*educate and implement evidence-based management of allergic rhinitis in conjunction with asthma worldwide*" (5,8,9) (http://www.euforea.eu/about-us/aria.html).

1.1.1 Phenotypes of rhinitis

There are several phenotypes of rhinitis, generally categorized in two major categories: allergic and non-allergic rhinitis. Allergic rhinitis is associated with an allergic reaction whereas non-allergic rhinitis is actually an umbrella term including a wide range of phenotypes (Table I). A particular phenotype is the infectious rhinitis -also called rhinosinusitis- that is typically regarded as a separate clinical entity as it is generally an acute condition due to a virus of bacterial infection. Therefore, we will not talk further on this specific type of rhinitis.

Table I Classification of rhinitis

- Infectious
- Allergic
- Non-allergic rhinitis
  - Drug-induced
    - Aspirin
    - Medication
  - Hormonal
  - Other causes
    - NARES
    - Irritants
    - Food
    - Emotional
    - Atrophic
    - Gastroesophageal reflux
  - Idiopathic
- Occupational (allergic and non-allergic)

Adapted from ARIA (5)

1.1.1.1 Allergic rhinitis

1.1.1.1.1 Definition and characteristics

Allergic rhinitis (AR) is the most common form of non-infectious rhinitis. It is induced after allergen exposure by an immunoglobulin E (IgE)-mediated inflammation.

Several aero-allergens are frequently implicated in allergic-rhinitis:

- Mites

House dust mites (HDM) represent the larger part of house dust allergens. The most common are: *Dermatophagoides pteronyssinus* (European house dust mite), *Dermatophagoides farinae* (American house dust mite), *Dermatophagoides microceras* and *Euroglyphus maynei* (Mayne's house dust mite). They feed on skin flakes and

therefore, are often present in mattresses, bed, pillows, carpets or stuffed animals (10). HDM are present all over the year but there is a peak of HDM in humid periods.

- Animal danders

The most common animals whose danders cause allergic reaction are cat and dog. However, rodents' or horses' danders may also be responsible for allergic symptoms.

- Molds

There are four principal molds responsible of allergic rhinitis symptoms (11). *Cladosporium* and *Alternaria* are probably among the most commons mold *genua*, both have an increased concentration in summer or early fall. *Cladosporium* is present in both outdoor (e.g. plants or organic matter) and indoor environments (e.g. carpet or wallpapers), whereas *Alternaria* is more commonly found in soil, plants or other vegetation but can also be present in indoor environment. *Aspergillus*, the major organism found in spoiling food and *Penicillium,* often found in damp basement and spoiled food, predominates in indoor environment and do not have particularly seasonal variation.

- Pollens

Nasal symptoms induced after pollen exposure is commonly known as "hay fever" and often refer to the period of the year of a high rate of pollination.

The pollens causing the most common allergies are grasses, weeds such as Ragweed or Parietaria and trees such as Birch, Olive tree, Cypress tree, Oak or Cedar (12). The pollen grains are usually carried on by the wind or insects and can travel up to kilometres from the original source. Levels of pollen vary a lot according to vegetation, geography, temperature and climate (see Figure 1).

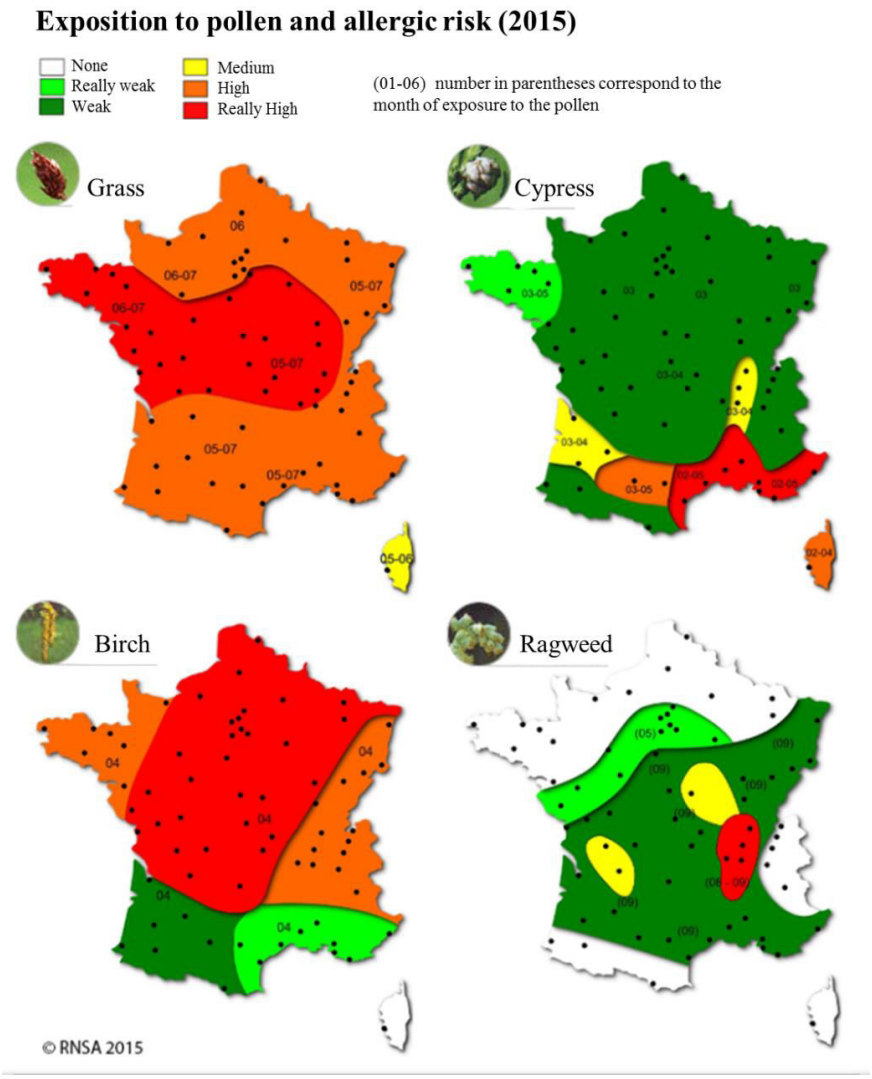


Figure 1 Exposition to pollen and allergic risk among French regions (adapted from Réseau National de Surveillance Aérobiologique (RNSA http://www.pollens.fr/en/) 2015)

Other factors that may trigger allergic rhinitis are occupational allergens (e.g. flours, laboratory animals, wood dusts, enzymes (13)), insects or spores. Food allergens are not discussed here as food allergy is associated with allergic rhinitis only throughout cross-reactivity between food and inhalant allergens (14).

1.1.1.1.2 Allergic sensitization

The World Allergy Organization states about allergy and allergic sensitization as follows: "*Allergy is a hypersensitivity reaction initiated by specific immunologic mechanisms*". Allergic reactions may occur after exposure to an allergen, by ingestion (food allergy),

inhalation (aero-allergen), injection or skin contact. In respiratory allergic diseases, symptoms are triggered by aeroallergens.

To test the allergic sensitization of a patient, two methods are commonly used (15):

- Skin Prick Test (SPT) (16):

Skin prick test relies on the cutaneous reactivity as a surrogate marker for allergic sensitization. A drop of a possible allergen is pricked into the skin. When allergen contact skin, a wheal and flare response appear and is quantitated. The wheal is compared with positive (Histamine dihydrochloride (10 mg/ml or 0.1%)) and negative (diluent) controls (Figure 2).

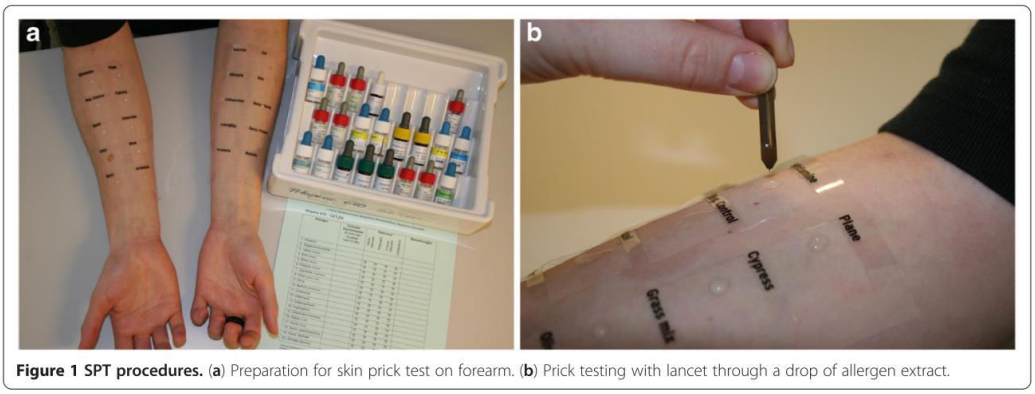


Figure 1 SPT procedures. (**a**) Preparation for skin prick test on forearm. (**b**) Prick testing with lancet through a drop of allergen extract.

Figure 2 SPT procedures (from Heinzerling *et al.* (16))

In clinical practice and in academic research, positive allergic sensitization is usually defined as an average wheal diameter ≥3 mm compared to the positive control. However, considering the average diameter may not be optimal and few alternatives methods has been proposed such as using the largest diameter of the wheal (16) or using a scanning device to calculate the wheal area (17).

The standard prick test panel for Europe for inhalants developed by the Global Allergy and Asthma European Network (GA2LEN) includes hazel (*Corylus avellana*), alder (*Alnus incana*), birch (*Betula alba*), plane (*Platanus vulgaris*), cypress (*Cupressus sempervirens*), grass mix (*Poa pratensis, Dactilis glomerata, Lolium perenne, Phleum pratense, Festuca pratensis, Helictotrichon pretense*), Olive (*Olea europaea*), mugwort (*Artemisia vulgaris*), ragweed (*Ambrosia artemisiifolia*), *Alternaria alternata* (tenuis), *Cladosporium herbarum, Aspergillus fumigatus, Parietaria*, cat, dog, *Dermatophagoides pteronyssinus, Dermatophagoides farinae,* and cockroach (*Blatella germanica*).

Several allergens can be tested simultaneously and the test can be interpreted within 15 to 20 minutes after the application on the skin.

- Specific IgE

A blood test enables to evaluate the quantity of IgE antibody for a specific allergenic component. Generally, a positive allergic sensitization is defined as a concentration of specific IgE higher than 0.35 kUA/l . Many allergens can be tested simultaneously using a single blood sample. In Europe, the Mechanisms of the Development of Allergy (MeDALL) allergen-chip has been developed to study IgE reactivity to a more than 170 food and pneumo-allergens including pollen (birch, alder, olive, cedar, Cypress, Plane tree, Timothy grass, Bermuda Grass, Ragweed, Mugwort, Goosefoot, Annual mercury, Plantain, Wall pellitory, Saltwort, Latex), indoor allergens (*Alternaria, Cladosporium*, House dust mites, *blomia tropicalis*, cockroach) and animals (cat, dog, horse, mouse) (18). In everyday practice, the use of such chips is complicated because of its high price.

Specific IgE determination is necessary in individuals with extensive eczema or urticaria or in those taking medications that make SPT impossible to perform. Conversely, in individuals with very high total serum IgE antibodies, low levels of specific IgE antibodies of doubtful clinical relevance are often detected and then SPT would be preferred. There is substantial discordance between SPT and specific-IgE levels and this whatever the study populations or of the allergens considered (19–21). On average, using only one testing method may misdiagnose a quarter of allergically sensitized patients as non-sensitized (19), suggesting that the two methods are complementary and cannot be used interchangeably (5). For both methods, comparability between studies depends on the use of the same allergen extracts -or batch of allergen extract- but also on the same analytical tools, which is not always the case in practice. SPTs is generally preferred for the diagnosis of IgE-mediated sensitivity in rhinitis (15,22) but both methods can confirm sensitization to a specific allergen.

For rhinitis, allergy is not systematically tested and general recommendations for allergy testing vary. The decision of testing relies on the clinical judgment (16) and depends on the severity of the disease, the usefulness of the test for treatment plans or when the diagnosis is not clear.

Caution has to be taken when dealing with "allergic sensitization" term as "allergy' or "atopy" may have been used instead. The European Academy of Allergology and Clinical Immunology proposed a revised Nomenclature for Allergy (23) where it stated that "*Allergy is a hypersensitivity reaction initiated by specific immunologic mechanisms*" and "*Atopy is a personal and/or familial tendency, usually in childhood or adolescence, to become sensitized and produce IgE antibodies in response to ordinary exposures to allergens, usually proteins. As a consequence, these persons can develop typical symptoms of asthma, rhinoconjunctivitis, or eczema. We propose that the terms atopy and atopic be reserved to describe this clinical trait and predisposition, and not be used to describe diseases*". Furthermore, "allergy" actually needs two components to be confirmed: a positive allergic sensitization and associated symptoms. Indeed, a patient with allergic sensitization will probably have symptoms related to this allergic sensitization, but this is not necessarily the case: some individuals are actually asymptomatic despite allergic sensitization (24). However, as the number of allergens tested is limited, a patient with allergic sensitization to a non-tested allergen may be considered wrongly as "non-allergic". This is particularly the case in epidemiological studies, and less likely to occur in clinical practice as medical history generally precedes testing. Allergic sensitization may also be looked as a quantitative trait depending on the number of positive sensitization, referring to monosensitization when a patient has a positive allergic sensitization to one allergen only and polysensitization for more than one sensitization.

1.1.1.2 Non-allergic rhinitis

Non-allergic rhinitis (NAR) is the term regrouping all the non-IgE mediated nasal symptoms of rhinitis. Therefore, there are many types of rhinitis considered as non-allergic, and there is currently no standard definition for NAR (25). NAR consists of a variety of heterogeneous conditions (26) whose underlying mechanisms are often unknown:

- Vasomotor rhinitis that is triggered by irritants in the environments such as perfumes, smog, second-hand smoke, changes in the weather, …
- Rhinitis triggered by food or alcohol ingestion (gustatory rhinitis: ingestion of spicy food)

- Rhinitis triggered by exercise (e.g. running)
- Drug-induced rhinitis: a number of medications including aspirin, oral contraceptives, nonsteroidal anti-inflammatory drugs

  A particular condition is rhinitis medicamentosa that is a rebound nasal congestion due to a repetitive use (for 4 to 7 consecutive days) of vasoconstrictive medications.

- Non-Allergic Rhinitis with Eosinophilia Syndrome (NARES): NAR with profound eosinophilia (abnormally increased number of eosinophils) in nasal secretions
- Rhinitis in the elderly (classical drop on the tip of the nose)
- Hormonal rhinitis: hormonal changes associated with pregnancy or menstruation
- Rhinitis due to emotional stress

NAR is sometimes known as idiopathic rhinitis, reflecting the frequent difficulty to detect the origin of the condition. The definition of NAR is largely based on exclusion criteria: absence of infectious rhinitis and absence of allergic sensitization.

1.1.1.3 Other types of rhinitis

Some individuals suffering from rhinitis may actually suffer from mixed rhinitis, *i.e.* allergic rhinitis and non-allergic rhinitis (27). This phenotype is not easy to diagnose for several reasons: mechanisms of non-allergic rhinitis are not well known and understood, and clinical symptoms often overlap between NAR and AR. Furthermore, when a patient has a positive allergic sensitization, he will be generally considered as having only allergic rhinitis (22). Another phenotype that has been recently described is local rhinitis involving nasal production of specific IgE antibodies, in the absence of atopy (28). The term entopy has been proposed to describe this concept (29). This new rhinitis entity is considered in patients with symptoms suggestive of allergic rhinitis but with negative SPT or specific IgE results.

1.1.1.4 Differences in characteristics according to rhinitis phenotypes (allergic and non-allergic rhinitis)

General characteristics of an individual with allergic or non-allergic rhinitis often strongly differ: allergic rhinitis is more often associated to an early age of onset and seasonality whereas non-allergic rhinitis more often occurs later in life and is generally present all-over the year. Table II summarizes the major differences in characteristics of these two phenotypes.

Table II Characteristics of AR and NAR

	Allergic rhinitis	**Non-allergic rhinitis (or alternative diagnoses)**
Age of onset	early age of onset	late age of onset (after 20 years of age)
Symptoms		
blocked nose	common	common
watery nose	common	usually not common
Sneezing	prominent	usually not prominent
Itchy nose	common	rare
Postnasal drip	usually not prominent	Prominent
Other related symptoms	other allergic symptoms, eyes associated symptoms	symptoms on only one side of the nose; thick, green or yellow discharge from the nose; facial pain, recurrent nosebleeds; loss of smell (30)
Family history of allergy	Usually present	Usually not present
Seasonality	Often present (depending on the allergen)	Usually no seasonality
Specific characteristics		Predominant among women (31)

Adapted from Quillen and Feller, 2006 (32)

This is a general frame of the differences between AR and NAR but some individual may have unusual characteristics and only a detailed interview with the clinician will disentangle the phenotype. Furthermore, although rhinitis is generally a chronic disease, it may evolve and some non-allergic patients may be later re-evaluated and present allergic –or mixed– rhinitis symptoms (33).

To distinguish between AR and NAR, SPT or specific IgE levels have been widely used although both AR and NAR are capable of demonstrating test positivity as schematized in Figure 3 (34). SPT or specific IgE remain an important complementary diagnosis tool but its use alone is probably not enough. A detailed patient history including type of symptoms, age of onset, duration, severity and frequency of symptoms; seasonality of the

symptoms, type of trigger (indoor, outdoor, allergic, non-allergic); previous response to treatments; comorbidity; and family history of allergies will help to make an accurate diagnosis for rhinitis subtypes (22,32,35,36): "*The greater the detail obtained in the history, the easier will be to accurately assess the type of rhinitis*" (37).

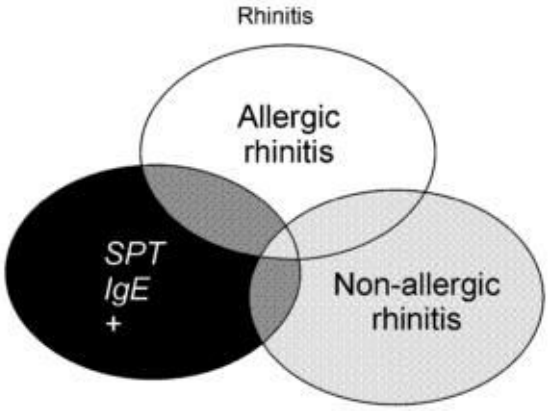


Figure 3 Schematic representation of allergic and non-allergic patients demonstrating skin test positivity from Bachert *et al.* (34) **)**

The correct diagnosis of the phenotypes and sub-phenotypes of rhinitis is crucial to correctly adjust the treatment and make appropriate recommendations (e.g. allergen avoidance).

Beyond the difficulty of the correct diagnosis of rhinitis, that concerns patients already managed by a clinician, the major difficulty in the care of rhinitis is that most of the individuals suffering from rhinitis do not seek for medical help and thus are often badly auto-diagnosed and auto-medicated.

1.1.2 Definition of rhinitis in epidemiological studies

A detailed patient's history is a major challenge to face in epidemiological settings of large populations as it is not always possible to have a medical interview for all participants as in the clinical practice. Rhinitis is generally assessed by questionnaire, and up to now there is no consensus on which question(s) have to be used to correctly classify participants.

Over the years, several questionnaires have been proposed using different terms to define rhinitis: the first questionnaire assessing rhinitis was proposed in 1960 by the British

Medical Research Council and included a question on "*usual stuffy nose or catarrh in the summer*" (Table III).

Table III Standardized questionnaires for the assessment of Upper and Lower airway Diseases in Epidemiological studies

	Outcome investigated	
Questionnaire[a]	Upper airways	Lower airways
BMRC 1960	Usual stuffy nose or catarrh in the summer	COPD
ESCC-MRC 1962 (4)	Runny nose in spring	COPD
ESCC-MRC 1967	Hay fever	COPD
ATS (1978) (5)	Hay fever confirmed by a doctor	COPD
South London Community Survey (7)	Rhinitis in the absence of cold or flu	Asthma
ECRHS (6)	Nasal allergies including hay fever in adults	Asthma in adults
ISAAC (59)	Allergic as well nonallergic rhinitis in the absence of cold or flu in children	Asthma in children
Jessen (14)	Nonallergic rhinitis	-
Annesi (9)	Allergic as well nonallergic rhinitis	COPD (as in the BMRC-ESCC) and asthma
Score for Allergic Rhinitis (10)	Allergic as well as nonallergic rhinitis	Asthma and familial resemblance of asthma

[a] BMRC, British Medical Research Council; COPD, chronic obstructive pulmonary disease; ESCC-MRC, European Steel and Coal Community–Medical Research Council; ECRHS, European Community Respiratory Health Study; ISAAC, International Study of Asthma and Allergies in Childhood; ATS, American Thoracic Society.

(from Annesi-Maesano et al. (38)

The European Steel and Coal Community has further questions on "*runny nose in spring*" or "*hay fever*". Some studies used questions for each symptom of rhinitis "*rhinohorrea – without a cold or the flu*", "*sneezing –without cold or the flu*", (such as in the questionnaire of inclusion of the Epidemiological study on the Genetics and Environmental factors of Asthma (EGEA)). Several questionnaires had only questions related to allergic rhinitis and/or hay fever (such as the questionnaire at inclusion of the European Community Respiratory Health Survey (ECRHS) "*Do you have any nasal allergies, including hay fever?*").

Other questions introducing the term of seasonal allergic rhinitis were successively used: "*Have you ever had seasonal allergic rhinitis?*" or "*Has a doctor ever told you that you suffer from seasonal allergic rhinitis?*" (5). Finally, many questionnaires have included the general question on nasal symptoms: "*Has your child/Have you ever had a problem with sneezing or a runny or blocked nose when he/she/you DID NOT have a cold of flu?*"

(such as International Study of Asthma and Allergies in Childhood (ISAAC), 1st and 2d follow-ups of ECRHS, 1st and 2d follow-ups of the EGEA study). This kind of question addressing the principal symptoms of rhinitis may be preferable as it does not include medical terminology (39). With the latter, questions on allergic rhinitis and or hay/fever were commonly asked jointly: "*Have you ever had allergic rhinitis?*" and/or "*Have you ever had hay fever?*". Indeed, the question on nasal symptoms gives information on the presence of rhinitis, but does not give any information on the allergic status of the rhinitis. Furthermore, the understanding of the question by each participant is strongly dependent of the wording: the change of word in the question on general rhinitis (from "*Do you have any nasal allergies including hay fever?*" to "*Have you now or have you ever had allergic rhinitis (hay fever) or allergic eye catarrh?*") do not change much the prevalence, but the change in wording on rhinorrhoea (from "*Have you had discoloured nasal discharges (snot) or discoloured mucus in the throat for more than 12 weeks during the last 12 months?*" to "*Do you have a runny nose more or less permanently?*") gave prevalence from single to double among Swedish adults (40). A study in 1991 has shown that more than a quarter of the participants defined by a questionnaire as having hay fever had not been diagnosed as such by a doctor (41). Despite the continuous improvement in questionnaires on rhinitis, some problems remain: "*Many patients poorly perceive nasal symptoms of allergic rhinitis: some exaggerate symptoms, whereas many others tend to dismiss the disease. Moreover, a large proportion of rhinitis symptoms are not of allergic origin*" (5).

Beyond classical questionnaires, several scores have been proposed and/or tested to study rhinitis (42,43), and some of them have focused on rhinitis control assessment that is useful in clinical practice but not reproducible in epidemiological studies (44). The only score that has been validated and used in several epidemiological studies was the Score for allergic rhinitis called SFAR (45). SFAR is based on 8 items: nasal symptoms, months of the year where these symptoms are present, associated itchy eyes, triggers of nasal symptoms, perceived allergic status, previous positive allergic tests, previous medical history of allergy and familial history of allergy. A SFAR value ≥7 (max value = 16) is associated with AR. This score has been shown to be very discriminant for AR, however it does not enable to distinguish other types of rhinitis.

Some studies had used only the question related to allergic rhinitis and/or hay fever to define rhinitis, and results must then be interpreted with caution as participants with non-allergic rhinitis are probably not included. However, it is noteworthy that even in general practice, physicians tend to diagnose all rhinitis patients as having allergic rhinitis because they usually have more knowledge about allergic rhinitis than other types of rhinitis (46).

To distinguish allergic from non-allergic rhinitis in epidemiological studies, several methods have been used in the literature, mostly:

- Based on medical diagnosis (general practitioners (GP) or specialist) –when available-
- Using allergic sensitization assessed by skin-prick test or specific IgE: a positive SPT or positive IgE test was associated with allergic rhinitis
- Using the answer to one of the following questions: *"Have you ever had allergic rhinitis"* or "*Have you ever had hay fever*" or "*Have you ever had nasal allergy*"
- Based on the declared triggers of the symptoms: hay, flowers, pets, dusts and molds being associated with allergic rhinitis whereas triggers such as cold air, perfume, air pollution were associated with non-allergic rhinitis.

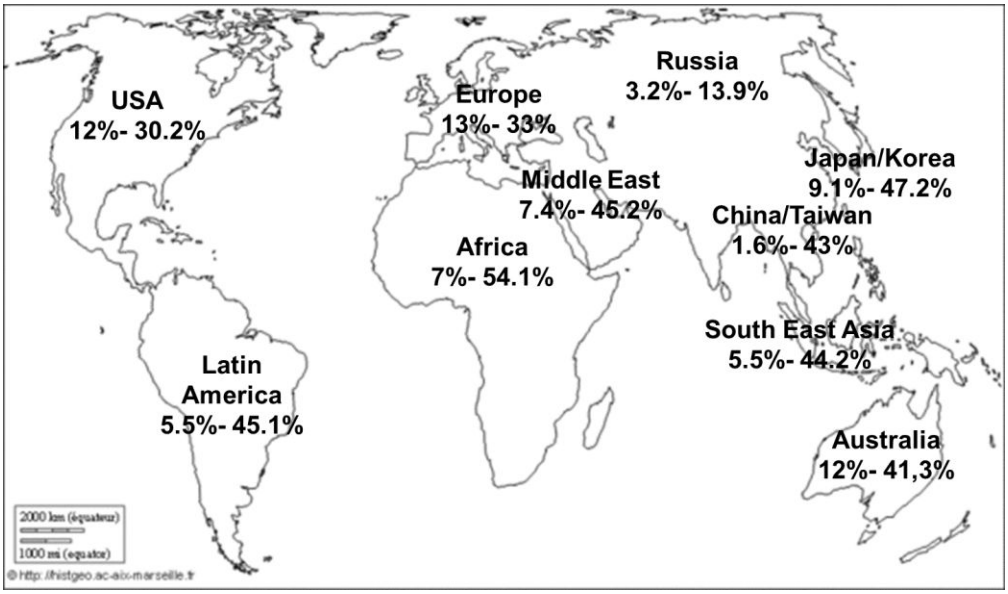
A detailed questionnaire (by physician, by examiner or self-reported) on symptom's triggers may be a good option to differentiate allergic from non-allergic rhinitis (47). In absence of medical diagnosis, it seems very difficult to identify other type of rhinitis than the allergic and non-allergic ones.

As a matter of fact, there is a wide range of definition of rhinitis and of phenotypes of rhinitis in the literature but up to now there is no consensus or standardization of the definitions.

1.1.3 Prevalence of rhinitis

There is no clear data on prevalence of rhinitis that varies from around 10 to 50 % according to the country and the rhinitis definition (30,48) (Figure 4). The important differences in the definitions of rhinitis in epidemiological studies are largely responsible from the wide range of its prevalence. In "westernized" countries, rhinitis affects approximately 15-30% of the population (49).

Many studies assessing prevalence of rhinitis have focused on allergic rhinitis, and thus general prevalence is certainly underestimated as other phenotypes of rhinitis are not taken into account. However, several studies have reported prevalence of nasal symptoms of rhinitis, and prevalence also varies a lot according to the country and the rural/urban area. In fact, rhinitis prevalence is strongly country and even region and city-dependent.



Adapted from Katelaris et.al 2012 (49)

Figure 4 Prevalence of rhinitis in different regions of the World (49–58)

Regarding the repartition in prevalence of the different types of rhinitis, there is no clear value either, for the same reasons as those discussed above: most of the studies on rhinitis have focused on allergic rhinitis. In the literature, prevalence of allergic rhinitis ranges between 43 and 87%, whereas prevalence of non-allergic rhinitis ranges between 17 and 52% (59). Regarding mixed rhinitis, the National Rhinitis Classification Task Force has estimated that 43% of individuals with chronic rhinitis have allergic rhinitis, 23% non-allergic rhinitis, and 34% mixed rhinitis (60).

Although the exact prevalence of rhinitis remains difficult to obtain, several studies used longitudinal analyses to assess the change in prevalence and showed that prevalence strongly increased during the last decades in European countries (61,62) as well as in Asia, Africa and Middle East countries (49,54).

1.1.4 Frequency and Severity

The ARIA group has proposed a classification of AR frequency and severity in 2001 (63).

1.1.4.1 Frequency

Previously, AR was subdivided according to the season of the symptoms (perennial, only during spring or summer ...) and to the type of allergen involved (indoor, outdoor). Then, one talked about seasonal AR for rhinitis related to outdoor allergens such as pollens or molds, and perennial AR for rhinitis related to indoor allergens such as mites, or animal danders. However, this classification was not satisfactory as symptoms related to indoor allergens are not necessarily present all over the year and some pollens are present all over the year. Furthermore, an important part of the individuals with AR has symptoms related to both indoor and outdoor allergens. Therefore, the ARIA group has proposed a new subdivision of AR based on the number of consecutive days with rhinitis symptoms as follows:

- Intermittent: symptoms are present less than 4 days a week or for less than 4 consecutive weeks
- Persistent: symptoms are present more than 4 days a week and more than 4 consecutive weeks.

This classification, although initially proposed for AR, may also be used for other types of rhinitis and particularly for NAR (34) as it does not rely on allergen trigger or seasonality but on the frequency of the symptoms itself.

1.1.4.2 Severity

The ARIA group has also proposed a subdivision of AR severity, based on the severity of the symptoms and their impact on social life, school and work, as follows:

- Mild: symptoms present but not troublesome, no sleep disturbance, no impairment of daily activities, leisure or sport, no impairment of school or work.
- Moderate/Severe: troublesome symptoms or sleep disturbance, or impairment of daily activities, leisure or sport, or impairment of school or work.

As for frequency of the symptoms, this classification was initially proposed for AR but may be extended to all types of rhinitis.

Severity of rhinitis may also be assessed by several objective measures of severity such as symptom scores, visual analogue scale –the patient may visually specify the impairment due to rhinitis by indicating a position along a continuous line between two end-points-, or clinical measurements (nasal obstruction, inflammation, the sense of smell, …).

1.1.5 Impact on quality of life/impairment

Despite an important burden, rhinitis is often trivialized and considered as mild disorder. Therefore, adverse effects of rhinitis on quality of life are often underestimated. Rhinitis impairs quality of life, has a strong impact on work productivity and school performance (64,65) and its impact on presenteeism and abstenteeism is sometimes greater than that of other chronic diseases such as diabetes, hypertension or asthma (66).
Rhinitis is also responsible of sleep disturbance, a reduced ability to concentrate, reduced cognitive capacities, and anxiety disorders (67–69). Rhinitis may also be responsible of emotional stress and alters social life (5,70). Impairment due to rhinitis appears to depend more on the severity of rhinitis than on duration of the symptoms (71).

1.1.6 Physiopathology and treatment

1.1.6.1 Physiopathology

Nasal symptoms are caused by an inflammation of the nasal mucosa. Several defensive reactions of nasal membranes of the lining of the nose may occur: swelling causing nasal congestion or excessive production of mucus causing rhinorrhoea. Sensory nerves transmitting a signal from the mucosa generate sensations such as pruritus (itchy nose) and motor reflexes such as sneezing. This inflammation of the nasal mucosa may result from allergic or non-allergic mechanisms.

Non-allergic rhinitis actually encompasses number of subtypes of rhinitis (See Paragraph 1.1.1.2), including the lack of allergic sensitization as common characteristic. Because of such definition, these conditions are heterogeneous and of widely diverse pathophysiologies (26).

Allergic rhinitis is the most common manifestation of IgE-mediated disease. Upon first exposure to allergen, antigen-presenting cells process antigen and present it to CD4 T lymphocytes that react and release Type 2 helper cell (Th2) pro-inflammatory cytokines

including interleukin (IL)-4 or IL-13 that will activate the production of antigen-specific (IgE antibody). IgE antibody binds to mast cells, leading to their sensitization. In non-atopic individuals, allergen exposure leads to a low-grade immunologic response and subsequent release of cytokines produced mainly by Th1 cells, rather than the overproduction of Th2 cytokines.

Once an individual is sensitized, subsequent exposure will cause an allergic reaction that can be divided in two phases: the early-phase reaction -also known as type I immediate hypersensitivity reaction- and a late-phase reaction. The early-phase reaction occurs within few minutes after the exposure and is the response of mast cells to allergen exposure. Mast cells degranulate and release inflammatory mediators, mostly histamines that will cause immediate symptoms such as rhinorrhoea, nasal congestion or itching. Mast cells also release basophils, eosinophils, neutrophils, T lymphocytes and newly synthesized mast cells that are activated few hours later and induce the late-phase reaction. This late-phase reaction will cause similar symptoms to those from the early-phase, with prominent nasal congestion. Overall, these late symptoms occur in approximately 50% of individuals. The “priming” effects refer to an increase in allergen reactivity after repeated allergen exposure (72) and can be considered as a form of nasal hyperresponsiveness. The priming effect is probably due to several factors: the additional inflammatory cells released during the late phase, an increased permeability of the epithelium and easier penetration to IgE-bearing cells and exaggeration of the responses of the nasal end-organs (26).

1.1.6.2 Treatment

There are three types of treatments to reduce rhinitis symptoms: allergen (e.g. pollen) or irritant (e.g. tobacco) avoidance, pharmacotherapy and allergen-specific immunotherapy.

The first strategy is to reduce the exposure to the associated trigger. For allergic rhinitis, reducing pollen exposure in case of hay fever, or avoiding contact with pets (cat, dog, horse …) in case of allergy to pet is usually efficient. In the case of allergic sensitization and symptoms associated to House Dust Mites, the situation is more complicated as allergen avoidance is impossible, and even reduction of exposure is difficult (73). For non-allergic rhinitis, avoidance of the irritant –spicy food, tobacco, medication- is also the first recommendation.

When avoidance of the allergen or of the irritant is not enough or is not possible or too complicated to set up, patients have to use medications to reduce their symptoms. Principal medications are intranasal or oral decongestants, corticosteroids which help to reduce swelling and inflammation, and antihistamines a group of medicines which reduces or blocks the action of the histamine that are mostly used for allergic rhinitis but has also an effect on non-allergic rhinitis. According to the type of rhinitis and the severity of the disease, a stepwise pharmacotherapeutic approach should also be undertaken (74), with possible step-up or step-down from intranasal or oral antihistamine use to a combination use of intranasal corticosteroids and intranasal antihistamine, and further add-on therapy options in severe case.

In patients with severe allergic rhinitis, allergen-specific immunotherapy (AIT) is often considered. AIT consists in administrate increasing doses of an allergen extract to an allergic patient in order to increase the tolerance and decrease the symptoms and medications needed. AIT must be done under controlled setting as there is a risk of anaphylaxis for the patients.

1.1.7 Costs of rhinitis

Rhinitis represents an important economic burden, either in term of direct (health-care visits, use of medication and hospitalization) or indirect (absenteeism and presenteeism) costs (65). Similarly to prevalence, estimation of burden of rhinitis seems to vary according to the country, the study and the definition of the disease that is used. In 2003, annual costs of AR in the Unites States (US) were estimated at $2–$5 billion USD (75). In Europe, the mean annual cost per person due to AR may vary between 961€ in Sweden in 2013 to 1543€ in Germany in 2003, with 50-80% coming from indirect costs (76,77). The costs vary according to the frequency and severity of the disease: in Sweden, the cost of an individual with moderate to severe persistent AR was 4 times higher than for an individual with mild persistent AR (76). Most of the studies have focused on AR, but a study in Sweden has calculated as 2.7€ billion a year the cost of rhinitis (infectious, AR and NAR) in term of loss productivity (78).

Individuals with rhinitis often perceive it as trivial: over half of individuals with AR do not seek for medical advice and most of them use over-the-counter medication (79,80).

Important economic loss could be avoided with a regular follow-up with a physician and an adapted treatment.

1.1.8 Comorbidities

Rhinitis has much comorbidity that are anatomically related to the nose (asthma, conjunctivitis, and sinusitis) or related to allergy (asthma, allergic conjunctivitis, atopic dermatitis, food allergy).

The major comorbidity of rhinitis is asthma. Asthma is a chronic inflammatory disorder of the airways, characterized by recurrent symptoms such as wheezing, breathlessness, chest tightness or coughing, a variable airflow obstruction that is often reversible spontaneously or with treatment, and by airway hyperresponsiveness. Asthma is a complex heterogeneous disease caused by multiple factors such as aeroallergens, respiratory infections, physical activity or air pollutant. Asthma can be allergic (IgE-mediated), non-allergic or intrinsic. Asthma affects the lower respiratory tract whereas rhinitis affects the upper respiratory tract, but both are characterized by inflammation of the respiratory mucosa and involve same inflammatory cells and mediators.The concept that rhinitis and asthma are part of one disease entity affecting one airway: "*One Airway, one disease*" has been suggested and has led to more use of a common approach of the two diseases rather than considering each disease individually (81). Indeed, 6% to 85% of individuals with asthma have rhinitis and 15-38% of participants with rhinitis have asthma (9,63,82). For a long time, the association between both diseases has been attributed to the common allergic sensitization, and the co-occurrence of the two diseases is indeed, particularly true for allergic rhinitis, but has also been shown in absence of allergic sensitization (82). Both diseases are risk factor for each other, but rhinitis often precedes asthma and is a good predictor for asthma (83). The prevalence of rhinitis is increasing during the last decades, whereas asthma prevalence is still increasing in low or middle-income countries with a low prevalence rate, but is stabilized in high income countries with an already high prevalence rate. During the last years, increasing attention has been given to multimorbidity: the *"coexistence of two or more chronic conditions in the same individual*" as defined by the World Health Organization (WHO). Regarding rhinitis and asthma, the primary disease is poorly known and the term multimorbidity should actually be preferred to comorbidity (84).

Another allergic condition that often coexists with rhinitis is allergic conjunctivitis that commonly manifests as itchy, watery or itchy eyes, after a contact with an allergen. The coexistence of the two diseases occurs in 50-70% of individuals with rhinitis and is referred as rhinoconjunctivitis (85,86). Rhinoconjunctivitis is more common in AR than in NAR and particularly when related to outdoor allergens and pollen (5). Allergic eczema or atopic dermatitis, whose symptoms are itchy skin with lichenified plaques affecting the flexures, head, and neck, also coexists with rhinitis. This is mostly the case in children in whom atopic dermatitis is the first step of the "*atopic march*" where allergic diseases progress from eczema or atopic dermatitis in infancy to asthma and rhinitis later in life. Food allergy is also associated to allergic rhinitis, mainly through the "oral allergy syndrome" that occurs after a cross-reactivity between an aeroallergen and a food allergen, mostly pollen and raw fruits, vegetables or nuts.

Sinusitis is also a frequent extension of rhinitis: it is an inflammation of the nose and paranasal sinuses, attributed to many potential factors. Principal symptoms of sinusitis are nasal obstruction or blockage, facial pain/pressure, recurring headaches or loss of smell. Sinusitis and rhinitis often coexist; the condition is then referred to "rhinosinusitis". The extend of rhinosinusitis is still in debate and it may be different according to the chronic or acute characteristic of the disease. Other disorders may commonly be associated with rhinitis but in a less extend such as middle ear problems or throat and laryngeal effects.

1.1.9 Risk factors

Allergen exposure is the primary environmental risk factor for AR as it is directly responsible for the symptoms (already discussed in section 1.1.1.1.1). Besides, there are several risk factors for rhinitis, ranging from general characteristics to environmental or genetic factors.

<u>General characteristics</u>

Age

The clinical characteristics of rhinitis are similar in children and in adults in term of symptoms, severity of the disease, impairment, and comorbidity with asthma, but there are differences in other comorbidities (87,88). Natural course of rhinitis in children

includes ever-changing status of rhinitis (remission or not) and of the phenotype of rhinitis (with allergic sensitization or not) (89). In adults, changes are also possible, but less frequently. Furthermore, phenotypes of rhinitis do not represent the same disease in adults and in children. In children, rhinitis is an integral part of the allergic march and is associated with atopic dermatitis/eczema and food allergy, which is not the case in adults. Therefore, it is important to distinguish between children and adults onset in the study of rhinitis but it is also important to take age *per se* into account in adults as rhinitis symptoms tend to become milder with age (5).

Gender

Regarding other general characteristics, female gender seems to be at higher risk for non-allergic rhinitis but there is no sex difference in allergic rhinitis (60,90).

Early life factors

Prevalence in allergy strongly increased during the last decades and one of the explanations for it has long been the "Hygiene hypothesis" whereby a decrease in infection in early childhood, a decline in family size and improved in hygiene and house cleaning were associated with a higher risk of allergy later in life. This hypothesis was first formulated by Strachan in 1989 who found that the number of siblings was inversely associated with hay fever (91). The underlying biological mechanism rested on the balance of the two types of Helper T immune cell: Helper T cell 1(Th1) type that is mostly associated with autoimmune diseases or infection and Th2 type that is rather associated to allergic disease. Th1 and Th2 must be in balance for proper immune system function, and a lack in exposure to microorganisms may inhibited Th1 and thus increases Th2 response which leads to more allergic diseases. However, Th2 also has elevated level in some infections and the Th1/Th2 balance has been reconsidered since the discovery of another Helper T cell (Th17). Indeed, hygiene hypothesis has been much discussed and today it seems that it was probably a too simplistic hypothesis (92). In 2003, a less well-known hypothesis emerged suggesting that early and regular exposure to a diverse range of harmless microorganisms ("*old friends*") is necessary to train the human immune system to react appropriately to stimuli. This "*old friends*" hypothesis is also known as "*theory of biome depletion*" as this lack of exposure to friendly microorganisms reduces the number of species found in the human microbiome. The rise in allergy is still not

completely understood, but its explanation is definitely multifactorial. Besides the hygiene hypothesis, the general changes in lifestyle such as diet or use of antibiotics and medication probably also play an important role.

For rhinitis, besides the number of siblings, other early life factors are known to be associated with rhinitis: childhood living in a farm has been associated to a lower risk of AR, partly explained by contact with farm animals (93,94) and more generally, prevalence of allergic rhinitis was found to increase with degree of urbanization (93).

There is considerable controversy as to pet ownership -and particularly cat and dog- may be a risk or a protective factor for allergic symptoms or allergic sensitization (95).

Genetic factors

Genetic is probably the strongest risk factor for rhinitis, with heritability of allergic rhinitis estimated between 0.66 and 0.78 (96). Parental history of allergic rhinitis or of allergy is associated with both allergic and non-allergic rhinitis, although in an less extend for non-allergic rhinitis (5,97). There are many Genome-Wide Association Studies (GWAS) on allergic diseases or allergic sensitization (98), but only one has focused on allergic rhinitis specifically (99). The single nucleotide polymorphisms (SNPs) associated with AR were further analysed in a candidate-gene study (96) and some regions seem to be of interest in the study of AR including TSLP- SLC25A46 genes. However, repeated replications in different populations covering various phenotypes of AR are still needed to identify regions of the genome susceptible to influence disease onset. No study has assessed genetic factors of phenotypes of rhinitis more broadly than AR. GWAS have focused on the particular combined phenotype of "hay fever plus asthma" and several loci have emerged, mostly belonging to those associated with allergic diseases (100). Besides a power concern, the major difficulty, either in the set up or in the replication of genetic studies is the important heterogeneity of the outcome definition, and this is particularly true for rhinitis.

Environmental factors

Smoking

There are inconsistent results on smoking as a risk factor for rhinitis and findings seem to depend on the definition of rhinitis subtypes and particularly on allergic status. Some

studies have shown an association between smoking and a higher risk of chronic rhinitis or rhinitis symptoms (101,102) while others found no association between smoking and allergic rhinitis (101,103). Regarding prenatal and postnatal second-hand smoking, results are also not clear but they seem to be associated to a higher risk of allergic rhinitis (104,105).

Socioeconomic status (SES)

One could think that SES plays a role in rhinitis development as it is strongly related to housing conditions, lifestyle and environmental exposures but literature is discordant (106), similarly as for allergic diseases where some studies suggested that allergic diseases are more prevalent in lower SES (107) while others have shown that low SES can be a protective factor for atopic diseases as suggested by the hygiene hypothesis (108).

Indoor and outdoor risk factors

Besides the outdoor and indoor allergens that are unquestionable risk factors for allergic rhinitis, indoor and outdoor air pollutions are suspected to be risk factors for rhinitis. The literature of the effect of outdoor air pollution on rhinitis will be detailed in section 1.3. Regarding indoor air pollution, there are only few studies on the association between indoor air pollution and rhinitis. Volatile organic compounds (VOC) emitted by various sources have been associated to an increase risk of rhinitis (109) but results about the effect of use of woodstoves, candles or gas kitchen cookers on rhinitis are discordant (110). Besides the indoor and outdoor pollution, climate and meteorological factors may also impact rhinitis symptoms as they can increase or change allergen exposure.

Rhinitis is thus a multifactorial disease and its rapid prevalence increase is unlikely to be due to genetic changes, but rather changes in environmental factors and complex interactions between genetic susceptibility and environmental factors influencing the disease development.

This thesis will focus on the effect of outdoor air pollution on rhinitis, and particularly on traffic-related air pollution.

1.2 Traffic-related air pollution

According to the WHO definition, air pollution is "*the contamination of the indoor or outdoor environment by any chemical, physical or biological agent that modifies the natural characteristics of the atmosphere. Household combustion devices, motor vehicles, industrial facilities and forest fires are common sources of air pollution. Pollutants of major public health concern include particulate matter, carbon monoxide, ozone, nitrogen dioxide and sulphur dioxide. Outdoor and indoor air pollution cause respiratory and other diseases, which can be fatal*".

Air pollution represents the biggest environmental risk to health, with around 4.5 million death worldwide per year attributable solely to ambient (outdoor) air pollution and is responsible for 7.2% of the global deaths (111). Exposure to air pollutants can affect human health in various ways, leading to increase mortality and morbidity (112). Ninety-four per cent of air pollution-related deaths are due to non-communicable diseases – notably cardiovascular diseases, stroke, chronic obstructive pulmonary disease and lung cancer. Air pollution also increases the risk of acute respiratory infections.

Air pollution affects all regions, settings, socioeconomic groups, and age groups and is a non-avoidable risk as breathing is vital. However, there are important geographical differences in exposure to air pollution, with particularly high level in Africa, Asia or in the Middle East as compared to other parts of the world. The new WHO air quality model shows that 92% of the world's population lives in places where air quality levels exceed WHO limits. In Europe, even if the level of the main air pollutants declined in the last decade (113), air pollution still poses a threat to human health as it has not been possible to bring out a minimum threshold of harmfulness. Air pollution related to industry has been controlled and major acute episodes have vanished and nowadays, the main source of air pollution, and probably the most harmful, is traffic. In this thesis, I will focus on the effect of long-term exposure to air pollutants more related to traffic.

1.2.1 Description of the pollutants

Air pollution has many sources and can be either natural such as dust storm or volcanic eruptions or anthropogenic such as fuel combustion. The latter can further be divided into mobile (e.g. cars, boats, aircrafts …) or stationary (e.g. factories, homes ...).

Sources of pollutants are usually divided into three major categories: primary, secondary and re-emission source (114). A primary pollutant is directly emitted into the air from the source of pollution (e.g. Carbon Monoxide). Secondary source results from the formation of a pollutant in the atmosphere due to the chemical reaction of two pollutants such as ozone (O_3), formed when nitrogen oxides (NOx) and VOCs react in sunlight and stagnant air. Finally, a re-emission source results from primary or secondary pollutants deposited on the Earth's terrestrial or aquatic surfaces, followed by a re-emission to the atmosphere.

Traffic-related air pollution is a complex mixture of pollutants derived from exhaust emissions from fuel combustions such as carbon dioxide (CO_2), carbon monoxide (CO), NOx, sulphur dioxide (SO_2) and particulate matter (PM), and non-exhaust emissions generated from brakes, tyres and road wears who contribute to the formation of PM. Because of the complexity of measuring all components of this mixture, exposure to traffic-related air pollution is commonly measured through surrogates of the traffic emissions. Common surrogates are nitrogen dioxide (NO_2), NOx and PM concentrations, but also proximity to traffic itself (e.g. distance of the residence to the nearest road). In Europe, although the transport sector has reduced significantly emissions of certain air pollutants in the last 20 years, transports contribute to around 25% of PM and about 55% of emissions of NOx (European Environment Agency, https://www.eea.europa.eu/).

1.2.1.1 Nitrogen dioxide

NOx include nitrogen oxide (NO) which is not harmful to health at the concentrations typically found in the atmosphere and NO_2. NO_2 is soluble in water, reddish-brown in colour and is a strong oxidant. It can be either a primary or a secondary pollutant due to the reaction of NO with air. Actually, in most ambient situation, NO_2 is emitted as NO and almost immediately transformed to NO_2. NO_2 can contribute to impair atmospheric visibility by absorbing solar radiation and NO_2 also regulates the oxidizing capacity of the troposphere and therefore, determines the O_3 concentration in the troposphere.

NO_2 has both natural and anthropogenic sources. The most common natural sources are intrusion of stratospheric NOx, bacterial and volcanic action, and lightning. The major anthropogenic source of NO_2 emissions is the combustion of fossil fuels in stationary sources (heating, power plants, and industrial point sources) and in motor vehicles (internal combustion engines). Indoor sources are also important and include tobacco

smoking, use of gas-fired appliances and oil stoves. Differences in NOx emissions of various countries are due mainly to differences in the consumption of fossil fuels.

NO_2 is also directly responsible for an increase in O_3 concentration as O_3 is formed in the atmosphere by photo-chemical reactions in the presence of sunlight and precursor pollutants, such as NOx and VOCs. In epidemiological studies, NO_2 has widely been used as a marker of traffic because traffic is probably its main outdoor source in urban settings and because of the low cost and practicality of available measurement techniques for this pollutant (115). However, in the last decade it has been also used as a marker of exposure for itself, as it is responsible of health effects *per se*.

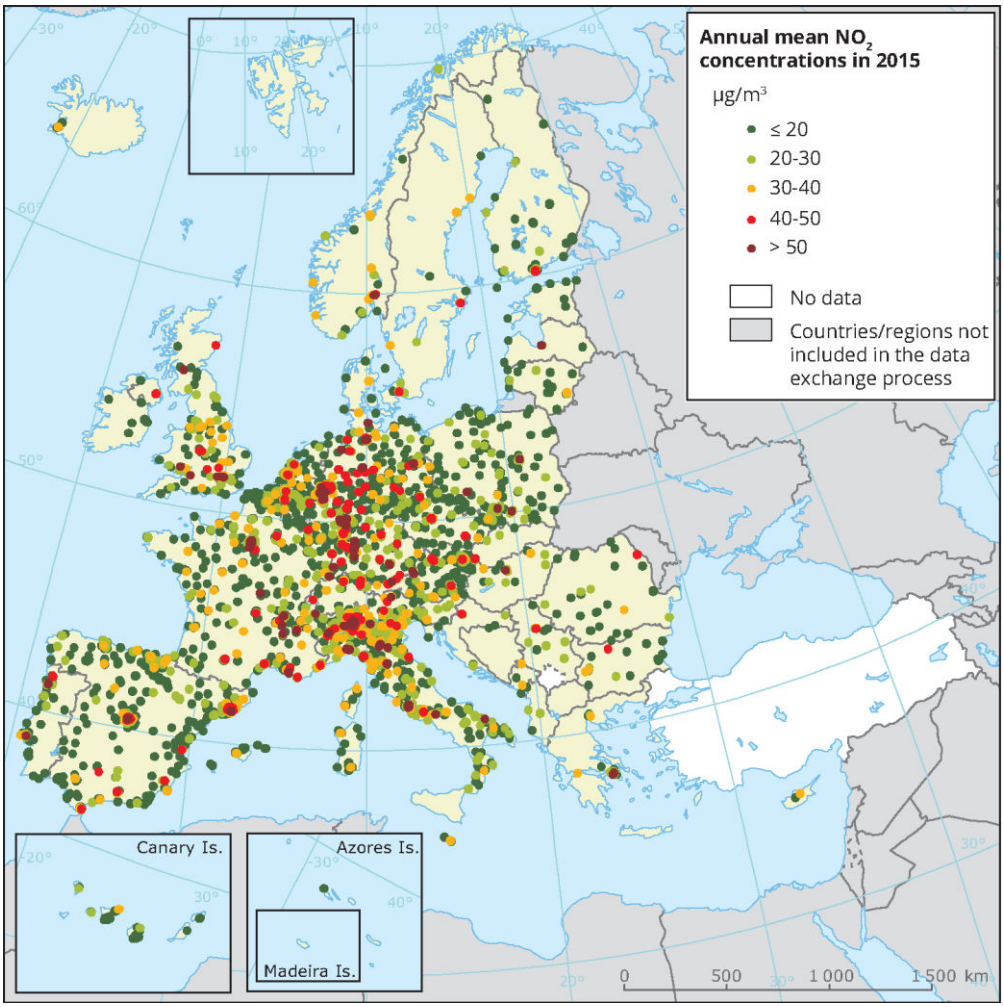


Figure 5 Concentration of NO_2 in 2015 in Europe (Based on Air Quality e-reporting database https://www.eea.europa.eu (116))

The Ambient Air Quality Directive of the European Union sets limit values for long-term (annual) NO_2 concentration. The annual limit value set by both European Environmental

Agency and WHO for NO_2 is at 40µg/m^3. An exceedance of the annual limit value was observed in most European Union (EU) Member States at one or more stations in 2015 (Figure 5).

1.2.1.2 Particulate matter

PM is a widespread air pollutant, consisting of a mixture of solid and liquid particles suspended in the air. PM is actually a complex mixture of diverse components with physical and chemical characteristics varying spatially and temporally. However, some results suggest a higher toxicity from traffic-related PM (117).

PM can either be a primary or a secondary pollutant coming from gaseous precursors. PM is further classified by size, from few nanometres to tens of micrometres in diameter. PM has been traditionally classified using the aerodynamical diameters because they determine their transport in the atmosphere as well as their likelihood and sites of deposition into the respiratory tract. PM is usually divided into PM_{10} (aerodynamical diameter ≤10µm), $PM_{2.5}$ (aerodynamical diameter ≤2.5µm), often called fine PM, and $PM_{0.1}$ (aerodynamical diameter ≤0.1µm), also called ultrafine particles (UFP). In addition, coarse PM is the mass concentration of the coarse fraction of particles between 2.5 µm and 10 µm. Another measurement of air pollution is PM absorbance which measures the blackness of PM filters; this is a proxy for elemental carbon, which is the dominant light absorbing substance. The absorbance is traditionally measured in the $PM_{2.5}$ filters as most of the elemental carbon is found in the fine fraction (118).

PM can have both natural (sea salt, naturally suspended dust, pollen, volcanic ash) and anthropogenic sources (fuel combustion in vehicles, thermal power generation, incineration, domestic heating ...). It has been suggested that in urban sites in developed countries, more than two thirds of the $PM_{2.5}$ and UPF are anthropogenic. The most common sources of $PM_{2.5}$ in urban sites are traffic, long-range transport and crustal. Globally 25% of urban ambient air pollution from $PM_{2.5}$ and PM_{10} is contributed by traffic, around 16% by industrial activities, 18% by domestic fuel burning, 21% from unspecified sources of human origin, and 20% from natural dust and salt (119). In European cities, the principal source of airborne PM_{10} and $PM_{2.5}$ is road traffic emissions and domestic heating. In most locations in Europe, $PM_{2.5}$ constitute 50-70% of PM_{10}, but it is strongly dependent on the location, of the characteristics of the region (coast, desert,

winds) and of the land-use (population density, industry, level of urbanization ...) As for UPF, it contributes up to 90% of total particle number concentration at busy roadsides (120).

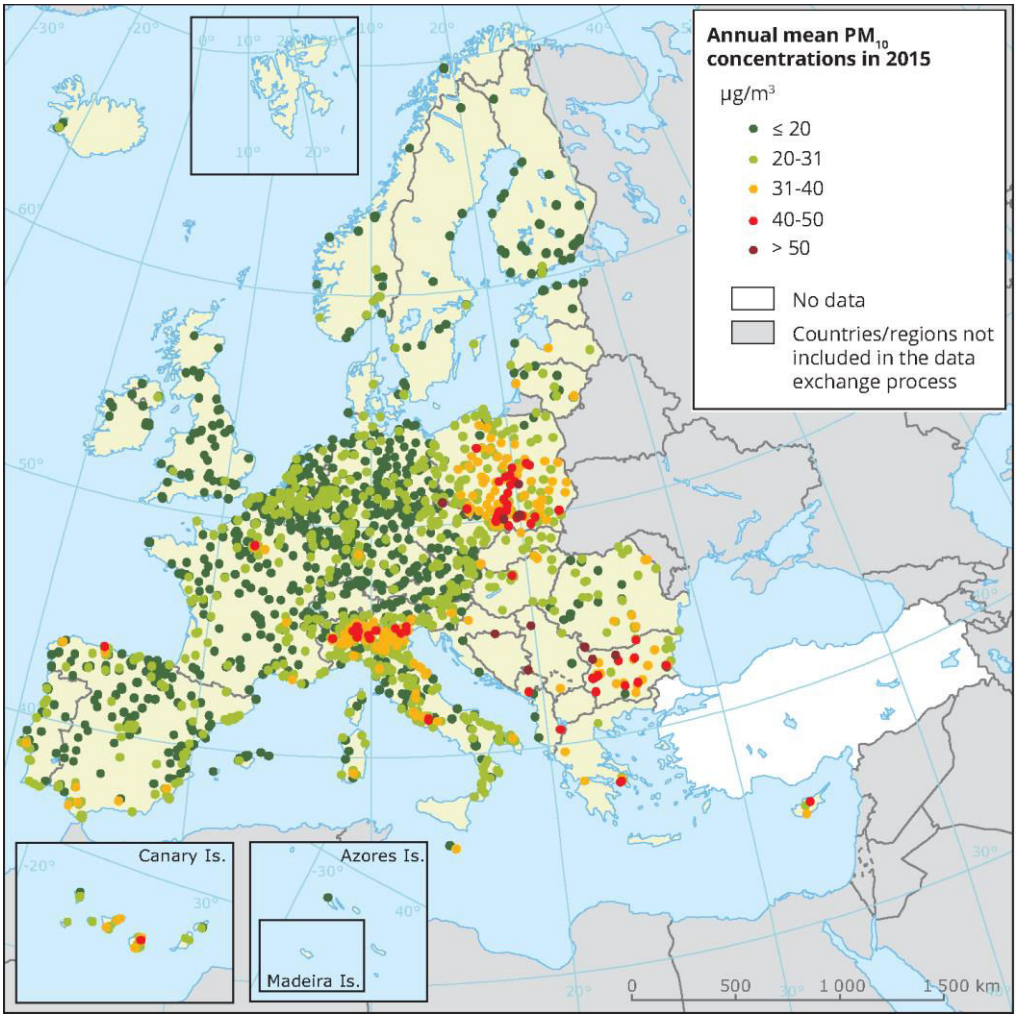


Figure 6 Concentration of PM_{10} in 2015 in Europe (Based on Air Quality e-reporting database https://www.eea.europa.eu/ (104))

The Ambient Air Quality Directive of the European Union sets limit values for long-term (annual) PM_{10} and $PM_{2.5}$ concentrations. The annual limit value is set at 40µg/m^3 for PM_{10} and at 25µg/m^3 for $PM_{2.5}$. The EU limit value for PM_{10} (not revised since 2005) continues to be exceeded in large parts of Europe in 2015 according to the data of the European air quality database (Figure 6).

The Air Quality Guidelines set by WHO are stricter than the EU air quality standards for PM with an annual limit value set at 20µg/m^3 for PM_{10} and at 10µg/m^3 for $PM_{2.5}$. The $PM_{2.5}$ annual mean guideline corresponds to the lowest levels beyond which total,

cardiopulmonary and lung cancer mortalities have been shown to increase (with > 95% confidence) (121). Considering the WHO threshold stricter than the one from EU, even more Europeans are exposed to levels of PM_{10} and $PM_{2.5}$ exceeding the limit value.

1.2.2 Exposure assessment

Exposure assessment of traffic-related air pollution can be done at regional, local or individual scale according to the underlying research question.

1.2.2.1 Area-level

At a regional, city or neighbourhood level monitoring, central fixed monitors are generally used. These large-scale monitoring are generally used for the record and surveillance of air quality but also in epidemiological studies, mainly in the study of short-term effect of air pollution.

Generally, concentrations in pollutants are reported in annual, daily or hourly averages, depending on the characteristics of the pollutant and on the device with which it is measured. In epidemiological studies assessing the effect of short-term air pollution, daily –or even hourly- concentration in a pollutant within a neighbourhood or a city may be used. However, these measures are not useful to assess the effect of long-term exposure to air pollutant, as there is a high spatial variability of exposure within small urban areas (Figure 7).

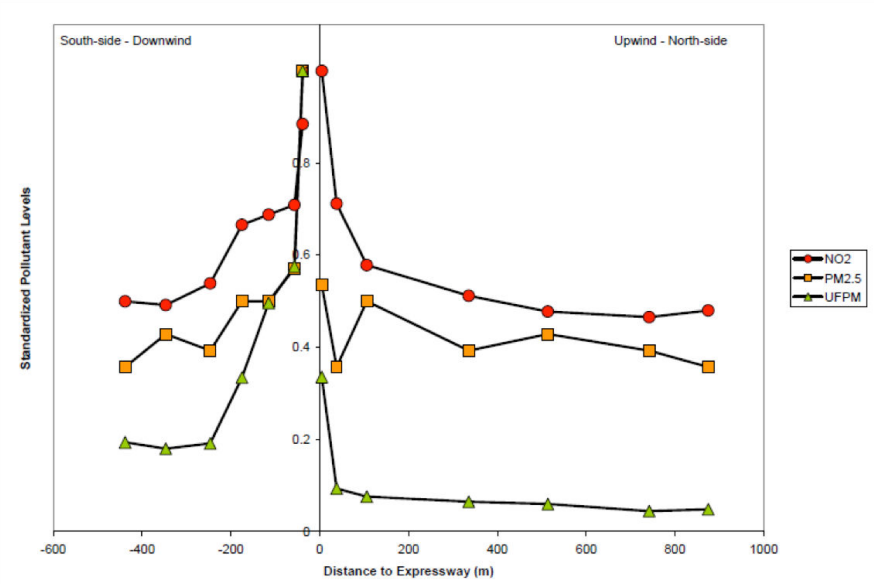


Figure 7 Concentration of pollutants according to the distance to expressway, from Beckerman et al. (122)

1.2.2.2 Individual Exposure assessment

Individual exposure may be assessed using different approaches: by using questionnaires, by using personal monitoring (direct method), or by using indirect methods such as environmental monitoring based on central fixed monitors or environmental modelling (123).

The use of self-reported exposure to air pollution using questionnaires has the advantage to be easy to set up and to be probably the cheapest way. Estimates of the exposure usually rely on self-reported type of street of the leaving place or proximity to a major road. However, collecting air pollution through questionnaire may be misleading because of reporting bias (124); indeed, the agreement rate between self-reported and modelled exposure is often low (125–128).

Generally, directly measuring personal exposure which consists in a device with pollutant monitor permanently carried by each participant is probably the more accurate way to obtain personal air pollutant concentration. Nevertheless, it is not feasible in studies analysing long-term exposure and/or in large population as it has many constraints such as costs, weight or battery charging. Another option to personal monitoring is to place a fixed monitor at the participant's home (or more rarely at his work/school place). This method is less accurate than the personal monitor as it does not include exposure data at work/ school or during commuting. In any case, personal monitoring is very expensive to set up and thus rarely available in large population, especially in studies analysing effect of long-term exposure where annual average concentrations are needed, implying multiple daily or weekly samples (129).

One of the simplest and cheapest way to approximate personal exposure is by linking directly the participant's address to traffic data in the corresponding area (e.g. distance from a high traffic road or traffic volume at different distances or buffers from participant's home address) or with pollutant concentrations from the nearest monitor. However, this method assumes that exposure is homogeneous and that individuals living in the same area have the same exposure level. To obtain a more accurate assessment of exposure at home address, environmental modelling are commonly used as estimates of personal exposure (130). Several environmental modelling approaches are available, including interpolation models, land-use regression (LUR), dispersion, integrated

meteorological emission, remote sensing and hybrid approach involving both personal sampling and one of the above methods (131). Complexity and precision differ according to the approaches (Table IV):

-Interpolation models rely on geostatistical techniques: measurement of a pollutant is obtained using monitoring data from several fixed monitors in the area. The aim is to estimate the concentration of the pollutant at sites other than the location of monitoring stations. There are several geostatistical techniques used such as spatial averaging, nearest monitor, inverse distance weighting and kriging.

-LUR models (initially termed regression mapping (129)) consider the pollutant of interest as the dependent variable and proximate land-use, traffic and physical environment as independent predictors. LUR models combine measured data with geographic information system (GIS)-based predictor data reflecting pollutant sources to predict pollutant concentrations at a specific location with no measurement (Figure 8).

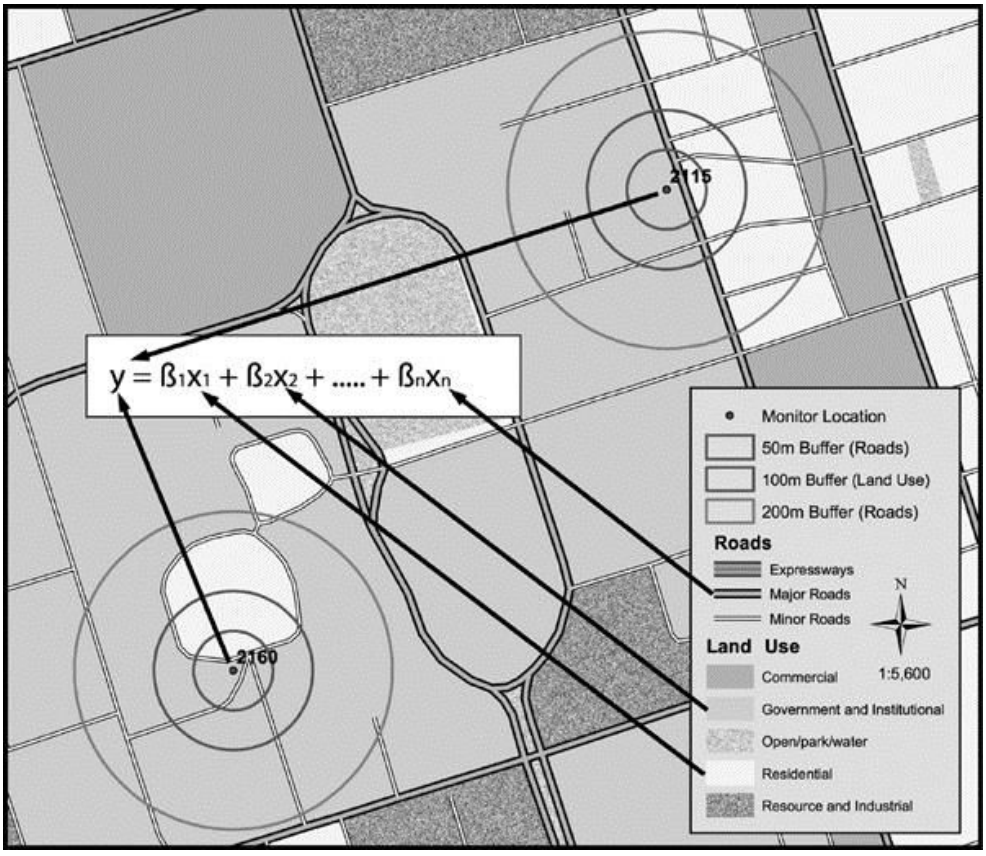


Figure 8 Illustration of elements of a LUR model from Jerret *et al.* 2005 (131)

-Dispersion models use mathematical formulations to predict how air pollutants disperse from their sources in the atmosphere. Dispersion model is generally based on Gaussian model. Similarly to LUR model, dispersion model requires data on meteorological conditions and geophysical locations but also data on emissions (stationary and mobile sources).

-Integrated Meteorological-Emission Models use emission data coupled with meteorological and chemical models to simulate dynamics of atmospheric pollutants (132). Integrated Meteorological-Emission Models are associated with high implementation costs and data requirements and are starting to be used in epidemiological studies.

-Remote sensing collects data about area characteristics directly from satellite and few resources are needed. However, these methods are relatively new and still need to be refined.

In epidemiological studies, LUR and dispersion model are the most adequate exposure assessment for traffic-related air pollution (133), as they provide a better spatial resolution than models using only monitoring stations which are less costly to set up. It is difficult to determine which of the LUR or dispersion model is the best method because it depends on "*available resources, the quality of the input data, expertise, place of study and transferability considerations*" (134).

A general limitation of all these methods is that estimations are generally based on participant's home address (or more rarely on work/school address). People are considered to spend most of the time at home (135,136) and assigning outdoor pollutant concentration at homes' address of each participant capture a relevant part of the individual's total exposure. New hybrids methods are being developed to better take into account the time-activity pattern, commuting habits, following individual's movement and location with GPS and combining both environmental and personal data. The use of hybrid models incorporating remote sensing or GIS data together with estimation of concentration in pollutants obtained with LUR, dispersion model or even surrogate of individual exposure models seems to significantly improve estimates of air pollution exposure (137,138).

Table IV Advantages and disadvantages of individual exposure models in epidemiological studies

Exposure model	Advantages	Disadvantages
Personal monitoring	precise, individualized and actual data (not predictions), take into account exposure variability of participants including commuting	high cost, resource intensive, feasible for short-term estimation, need to carefully define settings, agreement of participants (heavy or cumbersome)
Fixed monitor (at home/school): surrogate of personal exposure	precise, actual measurements (not prediction)	high cost, resource intensive, no variability in exposure (no data on commuting or school/home), not available or cost-prohibitive for all pollutants
Questionnaire	Simple, cost effective, easy to set up in large population, no need for measurement	Self-reported, declaration bias, low precision
Environmental monitoring (proximity to fixed monitor or road)	simple, cost effective, easy to set up in large population, actual measurement on site (not prediction)	assume all pollutants disperse similarly, concentrations assigned to the area and not specifically to the address, no variability in exposure (no data on commuting or school/home), not present at all locations
Interpolation	simple, cost effective, relatively easy to set up in large population	no variability in exposure, dependent on number and quality of closest monitors, geostatistical prediction (not actual)
LUR (Land Use Regression)	practical, relatively low cost, modelling based on measurement and information around measurements points, relatively easy to set up in large population	no variability in exposure, only reflects the predictors used in the model, truth contribution of traffic to the regression not always known, model's output sensitive to the location and density of the sampling sites
Dispersion models	traffic-specific metric, covers relatively large areas, take into account meteorological data,	no variability in exposure, severe data demands, high cost, resource intensive, possible overestimation during period of calm wind
Integrated Meteorological-Emission Models	coupled meteorological and chemical models,	no variability in exposure, high implementation costs, not usually used in epidemiological studies
Remote sensing	estimates for large areas, can provide estimates for areas where measurements are not available	no variability in exposure, availability depends on satellite presence, only available for selected pollutants,

Adapted from Khreis and Nieuwenhuijsen2017 (134)

1.3 Effect of air pollution on rhinitis

1.3.1 Effect of air pollution on health

Outdoor air pollution is now largely recognised as a major environmental health problem affecting everyone in the world (139).

It is now more than 60 years ago that the "*London smog*" killed thousands of people and prompted to look into the effect of air pollution on health. Studies have first focused on the effect of pollution peaks as only high level of exposure was thought to be harmful. Air pollution was first associated with an increase in mortality (140) and then quickly with cardiovascular and respiratory diseases (141). After many years of research narrowed to short-term air pollution effect (few minutes to few weeks), deleterious effect of long-term exposure (few years) has also been shown and beyond respiratory or cardiovascular track, effect of air pollution expanded to a wide range of health outcomes, such as neurodevelopment and cognition, reproductive and perinatal outcomes or even endocrine outcomes such as type 2 diabetes (142–144). Outdoor air pollution has also been classified as carcinogenic to humans (Group 1) by the International Agency for Research on Cancer (IARC) in 2013, mostly because of its effect on lung cancer, but there are also some evidences of effect of outdoor air pollution on kidney and bladder cancer (144). Overall adverse health effects of pollution depend on both exposure concentrations and length of exposure, and long-term exposures have been suggested to be larger, with more persistent cumulative effects than short-term exposures (145).

Regarding specifically respiratory health, short-term increase in air pollution is strongly associated to lung function decline and to aggravation and exacerbation of symptoms of asthma or chronic obstructive pulmonary disease (COPD) (146,147). In addition, long-term air pollution is also associated with a lower lung function and is suspected to increase asthma and COPD incidence (134,148–153). Long-term outdoor air pollution exposure is not only a risk factor for the incidence of respiratory diseases but it also increases the control and severity of these diseases (154). Whereas the increase in allergy is still not fully understood, environmental changes have been suspected to be a major driver of this rise, and during these last years the link between outdoor air pollution and allergy continue to strengthen both in children and in adults (152).

1.3.2 Effect of air pollution on rhinitis

In this section we will first discuss the potential mechanisms underlying the association between exposure to air pollution and rhinitis, and then will review the epidemiological literature on the effect of air pollution on rhinitis.

1.3.2.1 Potential underlying mechanisms

Several experimental studies have focused on the effect of air pollutants on upper airway diseases, mostly focusing on diesel particles exhaust (DEP) and some on O_3 and NO_2. Biological effect of PM specifically is complicated to estimate as PM is composed of a variety of different entities: any chemical or biological component of PM account for the effect on nasal airway.

There are three major mechanisms that may explain how air pollution affects rhinitis: the first mechanism is an inflammatory effect on respiratory airways that can be neutrophilic or eosinophilic (often a Th2 inflammation) (155). This inflammation can lead to an increased permeability of the epithelium barrier and possibly to an easier access of allergens to the immune system. Furthermore, UFP, PM and O_3 may induce production of reactive oxygen species within the airway epithelium and macrophages resulting in an oxidative stress that increases -or causes- the inflammatory effect (156,157). The two other mechanisms are specific to allergic rhinitis: DEP can act on mast cells and enhances the immunological response to allergens (158,159) but also increases the severity of clinical symptoms to allergens (160). Finally, air pollution has been shown to modify allergen release, morphology and allergenicity and by acting and interacting with allergens, indirectly act on allergic rhinitis (161). Furthermore, duration of exposures may be an important factor in the impact of air pollution on rhinitis and on the different rhinitis phenotypes: a study in mice showed that O_3-induced nasal inflammation where predominantly neutrophilic after acute exposure (one or two days) but turned to be eosinophilic after repeated daily exposures (162).

As a matter of fact, the mechanisms underlying the association between exposure to air pollution and rhinitis are mostly related to allergic rhinitis and are still relatively unknown and not well understood.

1.3.2.2 Association between air pollution and rhinitis in epidemiological studies

Most of the epidemiological studies on the effects of either short-term or long-term outdoor air pollution on rhinitis have focused on children, and mostly reported positive associations although not all were significant (163). In adults, short-term exposures to NO_2, $PM_{2.5}$, PM_{10} and O_3 have been associated with an increase in daily visit to practitioners for allergic rhinitis in two Chinese cities and in London (164–166), whereas no associations were found among elderly in Canada (167).

Studies focusing on the association between long-term air pollution and rhinitis in adults are rare and most of them have considered allergic rhinitis or hay fever as outcome. Actually, the role of air pollution in the rising prevalence of allergy was initially suggested by Ishizaki in 1987 who reported a higher prevalence of cedar pollinosis –allergic reactions provoked by pollen- in people living along inner road with heavy vehicular traffic compared to those living in rural area with less intense traffic (168). Thereafter, many studies have focused on the effect of proximity to traffic or of distinguishing rural/urban area on allergic sensitization, suggesting an interaction between pollen and air pollutants (158), but studies considering rhinitis itself as outcome are rare.

Only few studies have assessed the effect of long-term exposure to air pollution on prevalence of rhinitis in general, mostly in Europe or Mediterranean countries.

Some studies have assessed the effect of proximity to traffic: proximity to traffic road or to major road was associated with a higher prevalence of AR in two studies, one in Sweden and one in Germany, but results were not statistically significant in Germany (169,170). A third study in Switzerland found no association between proximity to busy road and AR (171). In the Swedish study, NAR was not associated with distance to traffic. Another study in Rome found an association between distance to traffic and prevalence of rhinitis (subtypes not specified) (172).

Others studies have focused on the effect of modelled air pollutants exposure, namely NO_2, PM_{10}, $PM_{2.5}$, and O_3 and air pollution was generally associated with prevalence of AR. In a multicentre study in Italy, an increase in NO_2 level was associated with an increased prevalence of AR in Mediterranean region, but not in the subcontinental one (173). Another study in Rome found an association between PM, NO_2 and prevalence of rhinitis (subtypes not specified). When further considering a score of traffic-related air

pollutant including both modelled pollutants and distance to traffic, an association was found only among non-smokers (172). In Sweden, both NAR and AR were associated with NOx level (169). Finally, a study among postal workers in Athens found a positive association between PM_{10}, NO_2 and O_3 levels –however, not statistically significant for NO_2- and symptoms of rhinitis with or without eyes-associated symptoms (174).

No clear conclusion can be reached as each of these studies used a different question to define rhinitis, and most of them considered allergic rhinitis or hay fever only. A correlation between air pollution level and prevalence of allergic rhinitis seems to exist (175,176) and further studies using similar definition of rhinitis and comparable exposure model are needed to better understand and confirm the hypothesis that outdoor air pollution is associated with rhinitis prevalence.

Air pollution is suspected to play a role in the development of asthma and allergic diseases, and there is growing literature on the subject, but up to now, no epidemiological study has assessed the effect of exposure to air pollution on rhinitis incidence in adults.

Similarly, no study has assessed the effect of long-term exposure to air pollution on different phenotypes of rhinitis, either by considering different subtypes of rhinitis, the type of symptoms, the duration or the severity of the disease. One study has focused on the association between grass pollen counts, air pollution levels and severity of seasonal allergic rhinitis and found a positive but not statistically significant association between air pollution levels and the score of severity of allergic rhinitis (177).

2 RATIONALE

Whereas rhinitis has an important public health impact, there is no standardization of its definition in epidemiological studies in adults. This lack has led to a range of literature on rhinitis not easy to compare and analyse. Furthermore, environmental factors of rhinitis are barely known, and in particular, there are very few studies on the effects of long-term exposure to air pollution on rhinitis, and its different phenotypes, in adults.

3 OBJECTIVE

3.1 General

The general aim of this thesis is to identify different phenotypes of rhinitis in adults and to better understand the associations between long-term exposure to air pollution and the development and severity of rhinitis.

3.2 Specific

This general aim is divided into two specific aims:

1) To identify different phenotypes of rhinitis in adults using an unsupervised approach and to further disentangle the links between rhinitis, allergic sensitization, and asthma.

2) To study the association between long-term air pollution and incidence of rhinitis and to study the association between long-term air pollution and severity of symptoms of rhinitis.

4 METHODS

4.1 Studies involved in the thesis

This thesis is based on data from two European multicentre studies on respiratory heath.

4.1.1 EGEA

The French cooperative Epidemiological study on the Genetics and Environmental factors of Asthma, bronchial hyperresponsiveness and atopy (http://egeanet.vjf.inserm.fr) is a family and a case control study. The overall objectives of the EGEA study were to study the genetic and environmental factors and their interactions in asthma and asthma-related phenotypes (bronchial hyperresponsiveness, atopy), and to clarify the heterogeneity of the disease.

A first survey took place between 1991 and 1995 (EGEA 1, (178,179)) and consisted in 2047 participants from five French cities (Paris, Lyon, Marseille, Montpellier and Grenoble). The participants included 348 cases with current asthma recruited in chest clinics, their 1244 first-degree relatives and 415 population-based controls. The protocol included standardized questionnaires on health and environment, clinical examination with lung function tests, allergen skin prick tests according to international protocols to 11 allergens (cat, *Dermatophagoides pteronyssinus*, *Blattela germanica*, olive, birch, *Parieteria judaica*, timothy grass, ragweed pollen, *Aspergillus*, *Cladosporium herbarum*, *Alternaria tenuis*), biological data including total serum IgE level, specific IgE to 160 allergen measurements and genetic data.

A first follow-up of the initial cohort was conducted between 2003 and 2007 (EGEA 2, (180)). Alive participants from EGEA1 and 58 relatives that had not been examined at EGEA1 were included in this second survey (n =2,002), and 92% (n = 1,845) completed a short self-administered questionnaire; among them 1,601 had a complete examination (1570 adults). The protocol of EGEA2 included standardized questionnaires on health and environment, clinical examination with lung function tests, allergen skin prick tests

according to international protocols to 12 allergens (cat, *Dermatophagoides pteronyssinus*, *Blattela germanica*, olive, birch, *Parieteria judaica*, timothy grass, ragweed pollen, *Aspergillus*, *Cladosporium herbarum*, *Alternaria tenuis*, cypress), total IgE level, white blood cell counts and several cytokines measurements, and genetic data. EGEA collection is certified ISO 9001 and referenced in the Biobank network (181).

A second follow-up was conducted in the whole study population (participants to EGEA1 or EGEA2) between 2011 and 2013 (EGEA 3, (182)). The protocol of EGEA3 included a standardized self-completed questionnaire on health and environment, and 1558 participants filled in their questionnaires (response rate=79.2%).

4.1.2 ECRHS

The European Community Respiratory Health Survey (http://www.ecrhs.org/) is a European project whose objective was to estimate the variation in the prevalence, exposure, risk factors and treatment of respiratory diseases, and especially asthma, in young to middle age adults living in Europe. The ECRHS was carried out in twenty-eight urban centres, in eleven European countries (Figure 9).

A first survey (ECRHS I (183), N=17880) took place between 1990 and 1992. Within each centre, a random sample of 1,500 males and 1,500 females aged between 20–44 years was selected from appropriate local sampling frames. Each participant was sent a brief questionnaire on respiratory symptoms, and among participants who responded, a random sample of 300 males and 300 females was selected. In addition to these 600 participants, an asthma "symptomatic" sample – chosen among those that had not been selected from the random sample- has also been added. The protocol included a detailed clinical examination with an extended interviewer-administered questionnaire, blood tests for total immunoglobulin (Ig)E and specific IgE levels to house dust mite, grass, cat and *Cladosporium*, and lung function tests.

Figure 9 Centres involved in ECRHS III

A first follow-up of the initial cohort (ECRHS II (184), N=10933) was conducted between 1999 and 2002. ECRHS II included a questionnaire on health and environment, lung function tests, blood samples including total serum IgE level, specific IgE level to 4 house dust mite, grass, cat and *Cladosporium* and genetic data.

A second follow-up was conducted between 2011-2013 (ECRHS III) and included 7040 participants. ECRHS III included a questionnaire on health and environment, lung function tests and blood samples.

4.2 Air pollution estimation

The European Study of Cohorts for Air Pollution Effects (ESCAPE, www.escapeproject.eu) is a European project who aimed to investigate the effect of long-term exposure to air pollution effects on human health in Europe. ESCAPE was based on the collaboration between more than 30 existing European population studies including EGEA and ECRHS. The objectives of ESCAPE were to develop a flexible methodology for assessment of long-term population exposure to air pollution focused primarily on fine particles, particle composition, and NOx, and to apply the exposure assessment methodology on existing cohort studies. Investigations focused on several health outcomes such as mortality, cardiovascular diseases, cancer, adverse perinatal outcomes and respiratory diseases.

Ambient concentrations of $PM_{2.5}$, PM_{10}, particle composition, NO_2 and NOx were measured in 36 study areas across Europe, selected because of the availability of informative cohort studies in these areas. NO_2 and NOx were measured in all 36 areas; PM was measured in 20 out of 36 areas. For each area, a mean of 40 measurement sites for NO_2 and NOx and a mean of 20 sites for PM were classified as regional background, urban background and street site (185,186). The objective was to capture the large diversity of potential sources of air pollution variability (e.g. population density, traffic intensity, industry, proximity to harbours …). Measurements were done between October 2008 and April 2011 in a 14-day period of each of three seasons (cold, warm and intermediate). Annual average concentrations for each monitoring site were calculated after adjustment for temporal variation using routine monitor background data.

For each cohort participants, home address has been geocoded and linked with individual annual exposure estimates based on predictions of LUR models, corresponding to the year of the questionnaire (129). LUR models were based on air pollution measurements at monitoring site and geographic predictors including digital road network (traffic intensity data), land use, population density, altitude and study local area specific data (e.g. distance to the sea or wood smoke) (187). Additionally, each participant also had

indicators of traffic corresponding to home address from digital road networks: traffic intensity on the nearest road (traffic intensity, vehicles/day) and total traffic load on major roads in a 100 m buffer (traffic load, vehicles*m/day).

Within the ESCAPE project, more than 25 published articles on the effect of long-term air pollution on several health outcomes and particularly cardiovascular and respiratory diseases have been published.

4.3 Statistical analyses

Two major strategies of statistical analyses have been used in this thesis, depending on the underlying research question: supervised and unsupervised learning. Here I present the general frame or the statistical analyses and specific methods are detailed in each article.

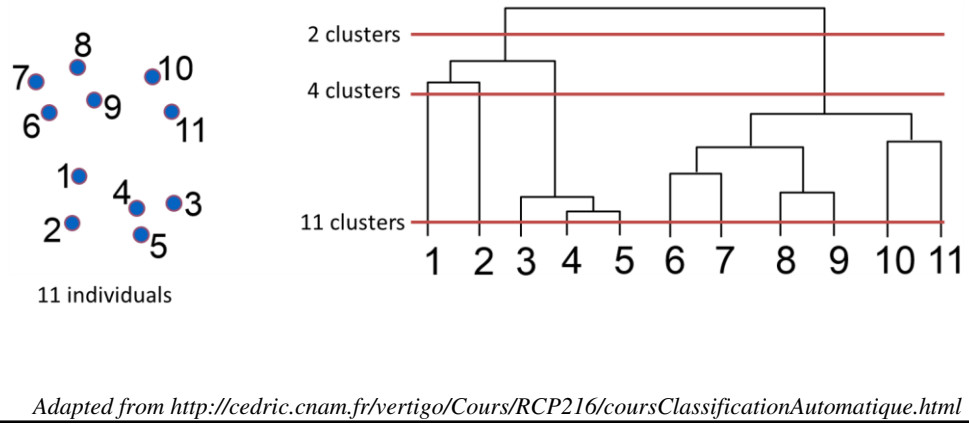
In supervised learning, the outcome disease is initially defined and the goal is to obtain a set of variables that can predict the outcome or to study the association between a set of variables and the specific disease. Supervised learning encompasses several methods used daily in epidemiology such as regression analyses, support vector machine, or regression tree. These methods are used to study the links between rhinitis, allergic sensitization, and asthma, and the association between air pollution and rhinitis.

In unsupervised learning, the objective is precisely to discover structures and patterns in individual's characteristics and one of the objectives is to group individuals with similar patterns together, through clustering. In high-dimensional data, clustering reduces the complexity and facilitates the interpretation and for unexplored or complex diseases, this method can help to discover different phenotypes (188). These approaches are increasingly used in epidemiology as in other fields where the amount of data is constantly increasing. To explore phenotypes of rhinitis with no *a priori* assumptions about the characteristics of the disease and its phenotypes, we used clustering approach on rhinitis data.

There are several clustering approaches:

- Hierarchical clustering which aims to provide multiple levels of clustering solutions either starting from the number of clusters equal to the number of

samples (agglomerative) or starting with the whole data set considered as a one single cluster (divisive). An illustrative example of hierarchical clustering is available in Figure 10. The obtained hierarchy allows choosing the partition that satisfies the aimed criterion, but the number of clusters has to be set beforehand and for high-dimensional data it is computationally demanding.



Adapted from http://cedric.cnam.fr/vertigo/Cours/RCP216/coursClassificationAutomatique.html

Figure 10 Illustrative example of a dendrogram obtained with a hierarchical clustering

- Distance-based clustering (k-means, partition around medoid …) tries to find centroids of data and to group individuals based on their proximity to them. This approach is easy to implement and simple; however, it presents several problems of optimization and cannot take both qualitative and quantitative data in output.
- Model-based clustering is based on the mixture models and belong to a vast family of probabilistic approaches assuming that each cluster is represented by a parametric distribution. The clustering consists in estimating the parameters associated with these distributions and in determining the probability of each object belonging to a certain cluster. This method has the advantage that input data can be either qualitative or quantitative and that contrariwise to algorithms such as k–means, it does not assume clusters to be of any geometrical shape.

Clustering has been widely used in epidemiology, generally using hierarchical or distance-based approaches. More recently study used increasingly latent class analysis, a subgroup of mixture models in the specific case where all observed variables are qualitative. In respiratory diseases, clustering has been used to highlight phenotypes of

asthma and COPD in adults (189–192); in children cluster analyses has also been used to identify phenotypes of allergic-related phenotypes and not one specific disease (193–195). In rhinitis, despite the lack in characterisation of rhinitis, there are only two studies that used cluster analyses to assess rhinitis phenotypes in adults. The first one was conducted in young adults with rhinitis from the Isle of Wight birth cohort (196). In clustering analyses, output is strongly dependent on the input data and this study included only three variables directly related to rhinitis: age of onset, seasonality and SPT; the other variables were related to pulmonary function tests or comorbidity. The phenotypes derived from the clusters were characterized by different age of onset, lung function and asthma levels. The other study using clustering with rhinitis data tried to improve clinical decision of treatment among French adults consulting general practitioners for AR (197). No study has explored rhinitis subtypes using a detailed history of the disease. In this study, we used mixture model to cluster participants into rhinitis subtypes.

5 RESULTS

5.1 Characterization of Rhinitis According to the Asthma Status in Adults Using an Unsupervised Approach in the EGEA Study.

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RESEARCH ARTICLE

Characterization of Rhinitis According to the Asthma Status in Adults Using an Unsupervised Approach in the EGEA Study

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Abstract

Background

The classification of rhinitis in adults is missing in epidemiological studies.

Objective

To identify phenotypes of adult rhinitis using an unsupervised approach (*data-driven*) compared with a classical *hypothesis-driven* approach.

Methods

983 adults of the French Epidemiological Study on the Genetics and Environment of Asthma (EGEA) were studied. Self-reported symptoms related to rhinitis such as nasal symptoms, hay fever, sinusitis, conjunctivitis, and sensitivities to different triggers (dust, animals, hay/flowers, cold air. . .) were used. Allergic sensitization was defined by at least one positive skin prick test to 12 aeroallergens. Mixture model was used to cluster participants, independently in those without (Asthma-, n = 582) and with asthma (Asthma+, n = 401).

Results

Three clusters were identified in both groups: 1) Cluster A (55% in Asthma-, and 22% in Asthma+) mainly characterized by the absence of nasal symptoms, 2) Cluster B (23% in Asthma-, 36% in Asthma+) mainly characterized by nasal symptoms all over the year,

sinusitis and a low prevalence of positive skin prick tests, and 3) Cluster C (22% in Asthma-, 42% in Asthma+) mainly characterized by a peak of nasal symptoms during spring, a high prevalence of positive skin prick tests and a high report of hay fever, allergic rhinitis and conjunctivitis. The highest rate of polysensitization (80%) was found in participants with comorbid asthma and allergic rhinitis.

Conclusion

This cluster analysis highlighted three clusters of rhinitis with similar characteristics than those known by clinicians but differing according to allergic sensitization, and this whatever the asthma status. These clusters could be easily rebuilt using a small number of variables.

Introduction

Rhinitis is a common respiratory disease worldwide and affects between 20 and 50% of the population depending on the country and on the definition [1–3]. Rhinitis is characterized by nasal congestion, rhinorrhea, itching and/or sneezing [1]. Classically, rhinitis can be divided into two major categories: allergic rhinitis (AR) and non-allergic rhinitis (NAR), with the need of allergic sensitization tests to distinguish between them [1]. Rhinitis is a complex disease, frequently associated with asthma, whatever the allergic sensitization [1] and phenotypes of rhinitis need to be explored.

In a systems biology study (the MeDALL approach, http://medall-fp7.eu/ [4]), classical and novel phenotypes of allergic rhinitis in children ascribed to *hypothesis-driven* and *data-driven* phenotypes were defined using epidemiologic questionnaires [5]. Even if symptoms of rhinitis are similar for children and adults, the disease may differ for comorbidities [6], and till now phenotypes of rhinitis are unexplored in adults.

Unsupervised learning methods (*data driven*) are useful as they allow studying a large data set without historical knowledge, and identifying distinct phenotypes not always detectable by classical approach. On the other hand, these methods can reinforce *hypothesis-driven* approaches and can thus confirm their validity. These methods have already been used with success to identify phenotypes of asthma [7], [8], chronic obstructive pulmonary diseases (COPD) [9], and other respiratory diseases [10]. To our knowledge, only one study has performed cluster analysis in 18 years old participants, all having current rhinitis [11].

The French Epidemiological study of Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy (EGEA)) is a case-control cohort on asthma. Participants of this study had a very good phenotypic characterization of respiratory health, including allergic sensitization and several specific questions related to rhinitis. The EGEA study offers the unique opportunity to study rhinitis separately in participants with (AS+) and without (AS-) asthma. The objective of this study was to identify distinct types of rhinitis using unsupervised learning methods in adults from the EGEA study.

Methods

Study design

EGEA is a French case-control and family study based on an initial group of asthma cases and their first-degree relatives, and a group of controls (EGEA1 [12,13], n = 2047; https://egeanet.vjf.inserm.fr). A first follow-up was conducted between 2003 and 2007.

Setting

Protocol and descriptive characteristics of the EGEA study have been previously published [12]. Briefly, 2047 children (<16 years) and adult participants were enrolled at baseline, including 348 participants with current asthma from chest clinics, their 1244 first-degree relatives, and 415 population-based controls. Approximately 12 years later, this population was contacted (EGEA2 [14]). Among the alive cohort (n = 2002), 92% (n = 1845) completed a short self-administered questionnaire and among them 1601 had a complete examination. All participants responded to questionnaires based on international standardized tools to diagnose asthma and to determine respiratory and allergic symptoms, treatments, and environmental exposures.

Participants

The present cross-sectional analysis includes adults at EGEA2 (n = 1571 adults, ≥16 years) without missing data on rhinitis, allergic sensitization and asthma (n = 983, 41% with asthma Fig 1).

Ethics

Ethical approval was obtained from the relevant institutional review board committees (Cochin Port-Royal Hospital and Necker-Enfants Malades Hospital, Paris). Written informed consent was signed by all participants.

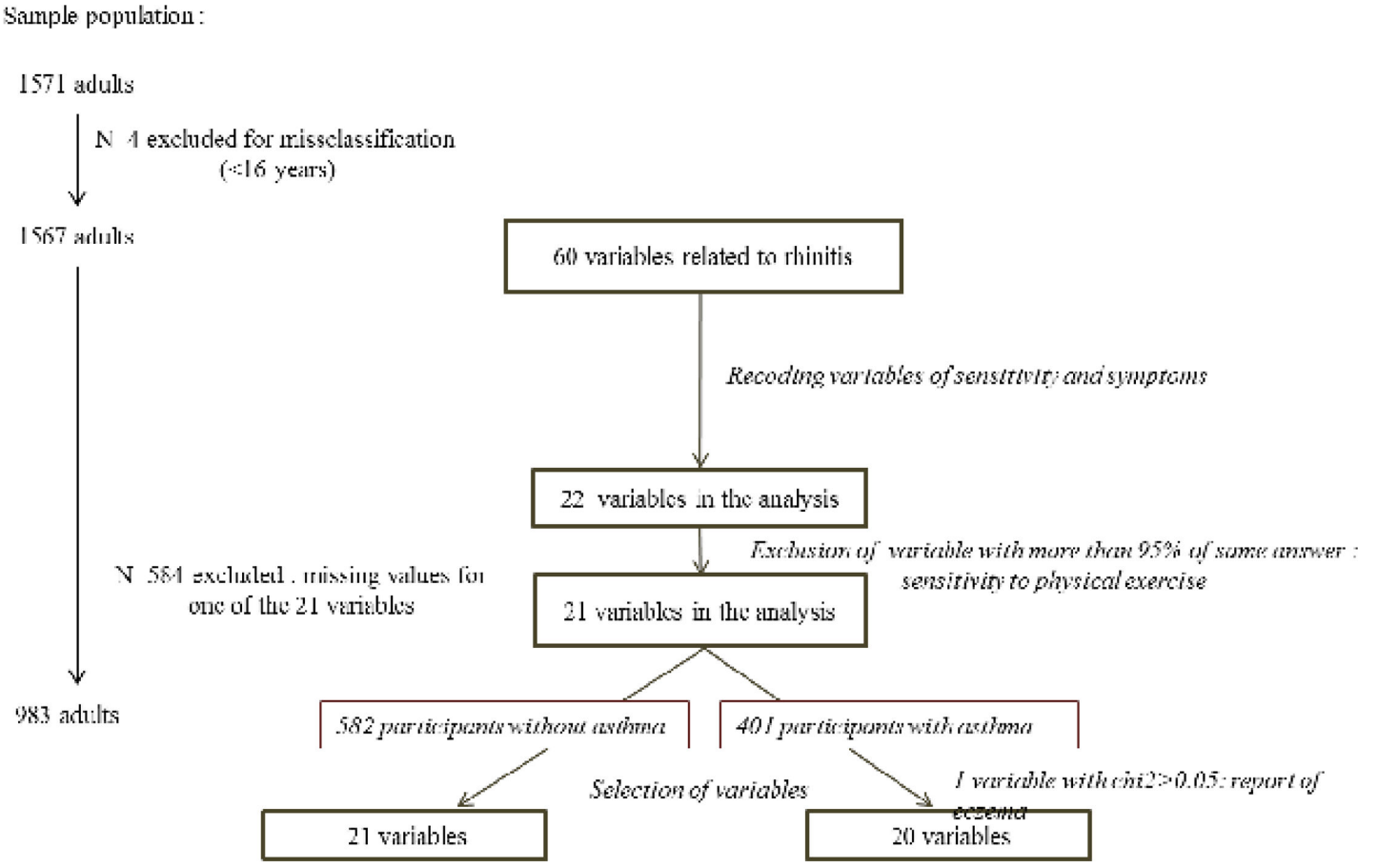

Fig 1. Flow-chart of the variables and of the participants included in the analysis.

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Variables

Rhinitis symptoms. Report of nasal symptoms were defined as a positive answer 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?"*. Eyes-associated symptoms were defined as a positive answer to *"Have you ever had itchy or watering eye when you have these nose problems?"*. Current nasal symptoms were defined as a positive answer to the question over the last 12 months. Nasal symptoms were considered as persistent if they occur more than a month per year. They were considered as persistent$_{low}$ if they occur less than 4 days per week and persistent$_{high}$ if they occur more than 4 days per week. Moreover, if the symptoms occurred less than a month per year, persistence of nasal symptoms was considered as intermittent. This classification was built as close as possible to the ARIA guidelines [1], but with some modifications. Answers to the question "*Have these nose problems disturbed you daily activities?*" enabled a score of disturbance from 0 to 3 (0: no, 1: a little bit, 2: moderately, 3: a lot). Participants reported the months in which they had nasal symptoms, and a seasonal pattern was created according to the answer: 0 if no symptom, 1 if symptoms in spring (hay fever), 2 if symptoms in spring/summer, 3 if symptoms in fall/winter, 4 if symptoms all over the year and 5 for the others. Sensitivity to trigger was defined as a positive answer to *"Trigger x usually provoking rhinorrhea"* and *"Trigger x usually provoking sneezing"*. The sensitivity for different triggers was available for animals, weed/flower, dust, cold air, physical exercise, weather, and tobacco smoke exposure (see questionnaires on https://egeanet.vjf.inserm.fr). This sensitivity was coded for the analysis 0: no sensitivity, 1: rhinorrhea or sneezing and 2: rhinorrhea and sneezing. Reports of allergic rhinitis by participants were defined as a positive answer to *"Have you ever had allergic rhinitis?"*, and in the same way for hay fever: *"Have you ever had hay fever?"*. The diagnostic of allergy by a physician was defined as a positive answer to *"Has a doctor ever told you that you are allergic?"*. Positive answers to conjunctivitis, sinusitis and eczema were also considered.

Use of medication for rhinitis. Report of use of medication relative to rhinitis were obtained by a positive answer to either: "*Have you took nasal sprays to treat disorders of the nose in the last 12 months?*" or to "*Have you took pills, capsules, tablets or drugs (other than nasal spray) to treat disorders of the nose in the last 12 months?*".

Asthma. Participants with asthma were defined by a positive answer to either: "*Have you ever had attacks of breathlessness at rest with wheezing?*", or "*Have you ever had asthma attacks?*", or if they were recruited as asthmatic cases at the first survey [12].

Allergic sensitization. Allergic sensitization was defined by a positive skin prick test (SPT +) with a mean wheal diameter $\geq$3mm than the negative control for at least one of 12 aeroallergens (indoor: cat, *Dermatophagoides pteronyssinus*, *Blattela germanica*, outdoor: olive, birch, *Parieteria judaica*, timothy grass, *Cupressus and* ragweed pollen, and molds: *Aspergillus*, *Cladosporium herbarum*, *Alternaria tenuis*). Report of allergic immunotherapy since the first survey (EGEA1) was also available.

Statistical methods

To take into account the specific design of the EGEA study, we conducted the analyses separately in participants without and with asthma.

***Hypothesis-driven*: classical phenotypes.** The analysis based only on the report of nasal symptoms (yes/no) and allergic sensitization (yes (SPT+)/no) enabled to define four profiles separately for participants with and without asthma: phenotype 1: no nasal symptoms and no allergic sensitization, phenotype 2: allergic sensitization only, phenotype 3: nasal symptoms without allergic sensitization and phenotype 4: nasal symptoms and allergic sensitization.

These profiles have already been used to study rhinitis and its relationship with other respiratory diseases [15].

***Data-driven*: novel phenotypes.** *Data and variable selection*. Sixty variables were first considered, known to be commonly associated with rhinitis or allergic sensitization. After recoding and grouping the variables of the sensibility to different triggers, skin prick test (SPT) and symptoms, 22 variables were available. Sensitivity to "physical exercise" having more than 95% of the same answer was excluded. Twenty-one variables were selected for the analysis: report of nasal symptoms, current/ever symptoms, persistence and disturbance of these symptoms, seasonal pattern, sensitivity to seven triggers, report of allergic rhinitis, hay fever, conjunctivitis, sinusitis and eczema, report of diagnostic of allergy by a physician, SPT, report of spray, report of drug except spray, and allergic immunotherapy since the last survey. A variable selection step (chi2 p-value lower than 0.05) led to select 21 variables for As- and 20 for As+ (Fig 1) and finally the analysis included 983 participants (582 As- and 401 As+) with no missing data (Fig 1 and Table B in S1 Supporting Information).

Missing Data. Participants included in the analysis had no missing values, as the data set was built according to that criterion.

Statistical analysis. To describe the phenotypes of disease without the need for historical or a priori assumptions, cluster analysis–or clustering- was used [16]. Cluster analysis is a data mining tool for dividing subjects into several groups so that subjects in the same group are more similar (or related) to each other than to those from others groups. This technique defines the distance of each subject from each other based on the combined values-the multidimensional vector- of their measured characteristics.

Mixture model. The mixture model is a flexible and powerful parametric algorithm of clustering.where each cluster is mathematically represented by a parametric distribution. The entire data set is then modeled by a mixture of these distributions [17]. The number of clusters associated with the lowest Bayesian Information Criterion (BIC) was chosen. As the solution may depend on the initialization, the algorithm was repeated 100 times and the model with the highest likelihood for mixture model was selected. The χ^2 test was used to analyze differences between groups for all qualitative variables. ANOVA was used to compare continuous variable according to the group. To display the subjects in two-dimensional space, multiple correspondence analysis was generated from the dataset; each subject was plotted along the two firsts components.

Tree analysis. To assess which of the 21 or 20 variables were most predictive of the finale cluster, recursive partitioning based on Classification and Regression Tree (CART) was used. The Gini index was used as the splitting index. The dataset was divided into a training set (70% of the original sample) and a validation set (30% of the original sample) to avoid overfitting. Accuracy was used to select the optimal model using the largest value. The validation of the model on the validation set was assessed using the error-rate value of prediction. Results were expressed as percentage of participants assigned to the right cluster (100%-error rate).

Bias. Participants included in the analyses (983) were not significantly different of those not included in the analyses (n = 588, see Table A in S1 Supporting Information) neither for age, sex, body mass index (BMI), nor for nasal symptoms, allergic sensitization, lung function and asthma status.

Due to the familial design of the study, a sensitivity analysis was conducted in a sub-sample of the population with one randomly selected member per family (n = 684 participants, 420 without asthma and 264 with asthma).

All the analyses were performed using the R statistical software. The Rmixmod package (http://cran.r-project.org/web/packages/Rmixmod/index.html) was used to run the algorithm of mixture models, and the rpart package was used to perform the tree analysis.

Table 1. Characteristics of adult participants.

		All (n = 983)	Participants without asthma (n = 582)	Participants with asthma (n = 401)	P value*
Age, mean ± sd		42.6 ± 16.5	45.9 ± 15.9	37.7 ± 16.1	<0.001
Sex, women %		49.5	51.6	46.6	0.13
Tobacco status, %	**Non-smoker**	49.6	48.0	51.9	0.052
	Ex-smoker	26.3	29.1	22.2	
	Smoker	24.1	22.9	25.9	
BMI(kg/m2), %	**<20**	10.7	9.6	12.2	0.09
	[20–25]	49.6	48.5	51.4	
	[25–30]	29.4	32.3	25.2	
	> = 30	10.3	9.6	11.2	
Educational level, %	**Low**	24.5	28.7	18.5	<0.001
	Med	27.7	25.1	31.5	
	high	47.8	46.2	50.0	
Allergic sensitization, %		65.2	46.8	82.0	<0.001
Ever asthma, %		40.8	-	-	
BHR#, n		663	396	n = 267	
%		44.3	27.0	70.0	<0.001
FEV_1% predicted, mean±sd		102 ± 18	106 ± 16	97 ± 18	<0.001
Nasal symptoms, %		58.9	45.5	78.3	<0.001
Reports of AR, %		36.2	21.8	57.1	<0.001
Reports of Hay fever, %		38.8	24.7	59.1	<0.001

BMI = Body Mass Index, FEV1 = Forced Expiratory Volume, AR: allergic rhinitis

#: BHR: Bronchial Hyper Responsiveness (Methacholine test, PD20≤4 mg, Methacholine challenge test was not performed if baseline FEV1 <80% predicted, PD20 = Provocative Dose). BHR was then available for 663 participants (396 without asthma and 267 with asthma).

SPT+: a mean wheal diameter ≥3mm than the negative control for at least one of 12 aeroallergens.

* comparing participants without and with asthma (χ_2 test)

doi:10.1371/journal.pone.0136191.t001

Results

The characteristics of the 983 adults according to their asthma status are summarized in Table 1. Participants with asthma had significantly lower Forced Expiratory Volume in one second (FEV_1) level, more often bronchial hyper-responsiveness (BHR), allergic sensitization (SPT+), and reported more often nasal symptoms, AR and hay fever than participants without asthma.

Hypothesis-driven (classical phenotypes) (Table C and D in S1 Supporting Information)

Varied prevalence of the four phenotypes were observed according to the asthma status: Phenotype 1: no symptoms, no allergic sensitization (39% for As- and 4% for As+), phenotype 2: allergic sensitization only (15 for As-and 17% for As+), phenotype 3: nasal symptoms without allergic sensitization (24 for As- and 14% for As+), and phenotype 4: nasal symptoms and allergic sensitization (22 for As- and 65% for As+). Whatever the asthma status, participants of phenotype 4 had the highest rates of hay fever report, allergic conjunctivitis report and sensitivity to hay/flower and animals. Participants of phenotype 3 had the highest rates of sinusitis report and of sensitivity to cold air.

Data-driven (novel phenotypes obtained by cluster analysis)

A three-cluster model was selected as the best model for both As- and As+ participants using the BIC criterion (S1 Fig) and the three clusters were well separated (Fig 2) whatever the asthma status. In participants without asthma: 55% of the participants were in cluster A, 23% in cluster B (23%) and 22% in cluster C. In participants with asthma: 22% of the participants were in the cluster A', 36% in the cluster B' and 42% in cluster C'.

Whatever the asthma status, cluster A and A' were characterized by the absence of nasal symptoms, low reports of AR, hay fever and sensitivity to all triggers (Tables 2 and 3).

In participants without asthma (Table 2). **Cluster B** was characterized by the highest rate of nasal symptoms without eyes-symptoms associated, a high report of sinusitis and eczema, and a low report of AR, hay fever and conjunctivitis as compared to cluster A. The rate of allergic sensitization was lower than for cluster A. Sensitivities to different triggers were lower for hay/flower and animals but higher for cold air, compared to cluster A (Table 2). **Cluster C** was characterized by the highest rate of nasal symptom mostly associated with eyes-symptoms, the highest rate of SPT, the highest rate of sinusitis, eczema and conjunctivitis reports and the highest rates of sensitivity to hay/flower, animals, dust and weather.

The allergic sensitization was mostly monosensitization for clusters A and B while it was mostly polysensitization for cluster C (Table 2). Among participants with allergic sensitization (SPT+), 61% of cluster A, 54% of cluster B, and 30% of cluster C were monosensitized, mostly for *Dermatophagoides pteronyssinus*.

Regarding seasonality of symptoms, cluster B reported symptoms all over the year whereas cluster C reported symptoms mainly during spring (hay/flower season). The score of disturbance was higher for cluster C than for cluster B. No significant difference between clusters was observed in term of persistent or intermittent symptoms.

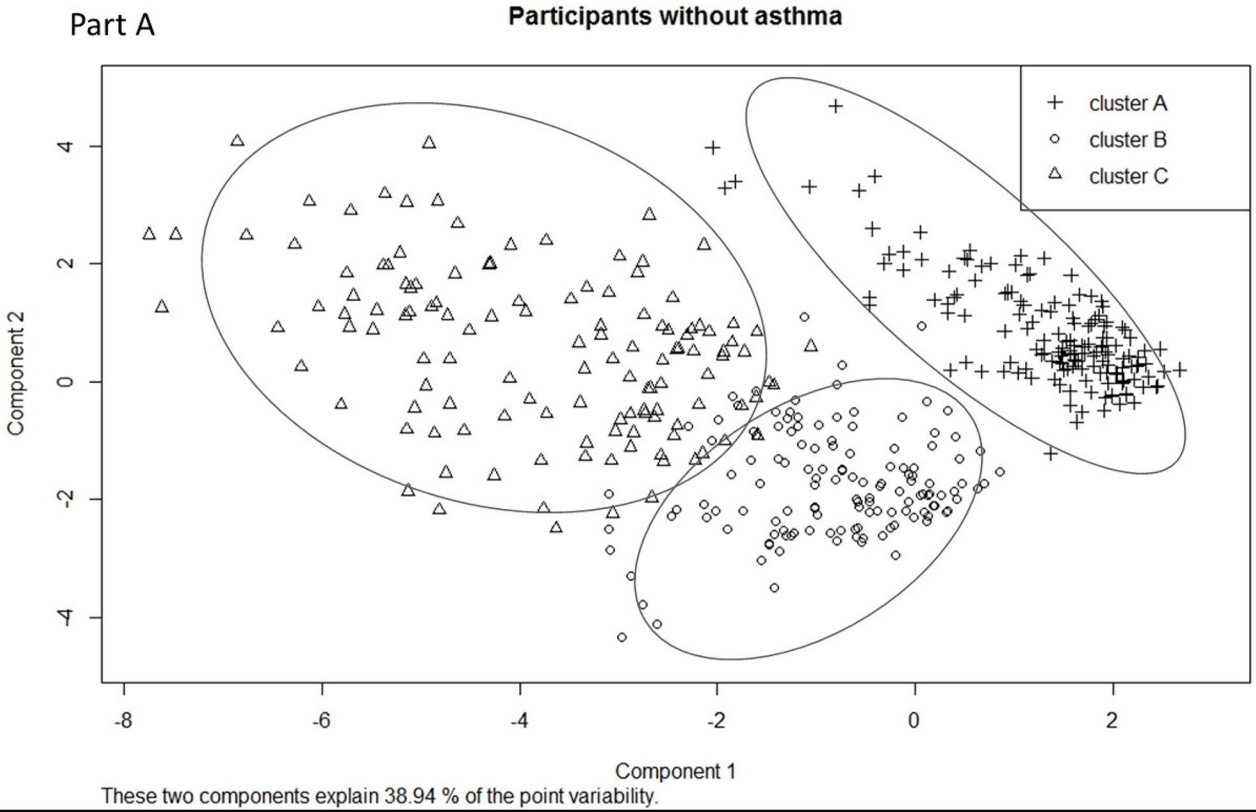
In participants with asthma (Table 3). **Cluster B'** was characterized by a high rate of nasal symptoms, a low report of AR, hay fever and conjunctivitis and the lowest rate of SPT. Sensitivities to different triggers were low for hay/flower and animals but high for cold air, tobacco and weather. **Cluster C'** was characterized by the highest rate of nasal symptoms with eyes-symptoms, the highest rate of allergic sensitization, the highest rates of report of AR, hay fever, sinusitis and conjunctivitis and the highest rates of sensitivity to hay/flower, animals, dust and weather.

The allergic sensitization rate was high whatever the cluster (Table 3), and mostly characterized by a polysensitization. Similarly to participants without asthma, monosensitization was higher for clusters A' and B'. Among participants with allergic sensitization (SPT+), 34% of cluster A', 29% of cluster B', and 16% of cluster C' were monosensitized mostly for *Dermatophagoides pteronyssinus*. The polysensitization rate was particularly high in cluster C' (80%).

Cluster B' and cluster C' reported symptoms all over the year but cluster C' had a very high peak during spring. The score of disturbance due to nasal symptoms was higher for cluster C' than for cluster B'. Cluster C' declared more $persistent_{high}$ than $persistent_{low}$ symptoms while cluster B' declared more intermittent or $persistent_{low}$ symptoms. The age of onset of asthma was lower for participants of cluster C' than for cluster A' and B'. BHR was higher in participants of cluster B' than in participants of clusters A' or C', but the difference was not significant.

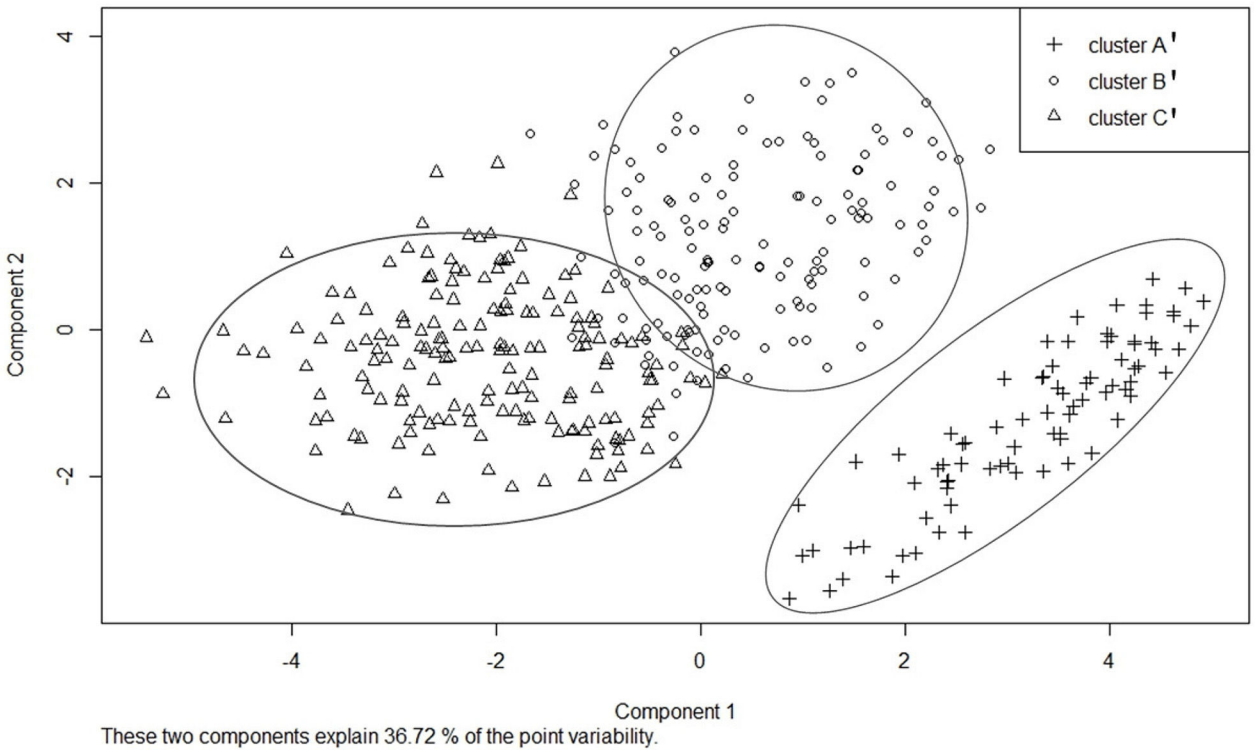
Whatever the asthma status, the report of spray or pills/tablet use to nasal problem was higher for cluster C (respectively C') than for cluster B (resp. B'). Participants of cluster B (resp. B') reported more use of spray than pills/tablet whereas participants of cluster C (resp. C') reported more use of pills/tablet than spray. Age of onset of nasal symptoms was lower in participants with asthma than in those without asthma, and whatever the asthma status,

Part A



These two components explain 38.94 % of the point variability.

Part B



These two components explain 36.72 % of the point variability.

Fig 2. Visualization of the clusters for participants without asthma (Part A) and participants with asthma (Part B) on the first factorial map.

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participants of cluster C (resp. C') had an age of onset of nasal symptoms significantly lower than participants of cluster B (resp. B').

Comparison between *data-driven* clusters and *hypothesis-driven* phenotypes (Tables 4 and 5)

Clusters obtained by *data-driven* approach may be easily assimilated to no rhinitis (NoR: cluster A and A'), non-allergic rhinitis (NAR: cluster B and B') and allergic rhinitis (AR: cluster C and C') based on their characteristics. These clusters are similar to the phenotypes 1, 3 and 4 from the classical *hypothesis-driven* phenotypes a *prima facie* but differ in their internal characteristics and particularly regarding the allergic sensitization. When comparing *data-driven* and *hypothesis-driven* approach, 10% of participants without asthma were not classified in the same category by the two approaches and 26% of participants with asthma. Considering only participants having nasal symptoms, 21% of participants without asthma were not classified in the same category by the two approaches and 30% of participants with asthma.

Decision tree

For participants without asthma, a classification tree on the 21 variables enabled to highlight 4 variables as being the most important to discriminate the cluster and particularly to distinguish cluster B from cluster C: report of nasal symptoms, report of AR, sensitivity to hay/flowers stimuli and type of nasal symptoms-with or without eyes symptoms- (Fig 3, Part A). Using only these 4 variables, 96% of the participants were assigned to the correct cluster.

For participants with asthma, a classification tree on the 20 variables enabled to highlight 4 variables as being the most important to discriminate the cluster and particularly to distinguish cluster B' from cluster C': report of nasal symptoms, sensitivity to "hay/flower" stimuli, diagnosis of allergy by a MD and report of hay fever (Fig 3, Part B). Using only these 4 variables, 87% of the participants were assigned to the correct cluster.

Sensitivity analysis

The cluster analysis on the sub-sample of the population including only one member per family has shown very similar results than the study on the 983 participants (same number of cluster, same characteristics–data not shown-).

Discussion

This study using a clustering approach identified three rhinitis phenotypes in adults with almost no overlap between them. They are similar to the *hypothesis-driven* phenotypes of no rhinitis (NoR: cluster A and A'), non-allergic rhinitis (NAR: cluster B and B') and allergic rhinitis (AR: cluster C and C'). However, hypothesis and data-driven phenotypes differ in terms of allergic sensitization. Near of a quarter of participants without asthma would have been considered as having allergic rhinitis considering the *hypothesis-driven* phenotypes whereas they have a non-allergic rhinitis pattern. Our study was able to highlight the importance of the NAR phenotypes, less understood and which need to be studied [18] and enhanced the importance of the non-allergic component in rhinitis. In participants with asthma, the AR cluster was associated with the highest rate of allergic sensitization and number of allergens, suggesting a comorbid effect of asthma and allergic rhinitis on the polysensitization.

Table 2. Characteristics of participants without asthma according to each cluster.

		Cluster A-no rhinitis- (n = 317)	Cluster B-non-allergic rhinitis- (n = 136)	Cluster C-allergic rhinitis- (n = 129)	p-value*
Age, mean ± sd		46.7 ± 16.2	48.9 ± 15.5	40.9 ± 14.5	<0.001
Sex, women %		46.7	58.1	56.6	0.036
Tobacco, %	**Non-smoker**	47.2	47.0	51.2	0.90
	Ex-smoker	30.0	30.2	25.6	
	Smoker	22.8	22.88	23.3	
BMI (kg/m2), %	**<20**	10.1	8.8	9.3	0.53
	[20–25]	47.0	47.8	52.7	
	[25–30]	33.4	36.0	25.6	
	> = 30	9.5	7.4	12.4	
Educational level, %	**Low**	31.2	34.6	16.3	0.007
	Medium	25.2	23.5	26.4	
	High	43.5	41.9	57.4	
Nasal symptoms, %	**No symptoms**	100.0	0.0	0.0	<0.001
	Symptoms without eyes symptoms	0.0	71.3	17.1	
	Symptoms with eyes symptoms	0.0	28.7	82.9	
Type of nasal symptoms, %	**No symptoms**	100	0.0	0.0	-
	Symptoms: ever but not current	0.0	4.4	0.0	
	Ever and current symptoms	0.0	95.6	100	
Persistence of nasal symptoms, %	**Intermittent**	-	50.0	40.3	0.22
	$Persistent_{low}$	-	18.4	25.6	
	$Persistent_{high}$	-	31.6	34.1	
Disturbance due to nasal	**No**	-	77.2	42.6	<0.001
symptoms, %	**Low**	-	17.7	39.5	
	Medium	-	4.4	14	
	High	-	0.7	3.90	
Allergic sensitization,%	SPT = 0	71.9	80.9	23.3	<0.001
	SPT = 1	17	10.3	23.3	
	SPT = 2	7.6	4.4	19.4	
	SPT>2	3.5	4.4	34.1	
Report of diagnosis of allergy by a physician, %		15.5	18.4	72.1	<0.001
Immunotherapy since first survey (EGEA1)		1.60	0.0	13.2	<0.001
Age of onset of nasal symptoms, mean ± sd	**(n = 224)**	-	33.7 ± 18.2	22.1 ± 14.1	<0.001
Report of allergic rhinitis, %		5.70	6.6	77.5	<0.001
Report of hay fever, %		10.7	10.3	74.4	<0.001
Report of conjunctivitis, %		13.4	22.1	49.6	<0.001
Report of sinusitis, %		34.7	55.1	56.6	<0.001
Report of eczema, %		22.1	30.9	36.4	0.005
Sensitivity to hay/flowers, %	**No sensitivity**	89.3	82.4	29.5	<0.0001
	Rhinorrhea or sneezing	8.2	16.9	30.2	

(*Continued*)

Table 2. (*Continued*)

		Cluster A-no rhinitis- (n = 317)	Cluster B-non-allergic rhinitis- (n = 136)	Cluster C-allergic rhinitis- (n = 129)	p-value*
	Rhinorrhea and sneezing	2.5	0.7	40.3	
Sensitivity to animals, %	**No sensitivity**	98.1	100	78.3	<0.0001
	Rhinorrhea or sneezing	1.60	0.0	13.2	
	Rhinorrhea and sneezing	0.30	0.0	8.50	
Sensitivity to dust, %	**No sensitivity**	74.1	58.1	27.1	<0.0001
	Rhinorrhea or sneezing	24.3	39.7	46.5	
	Rhinorrhea and sneezing	1.60	2.20	26.4	
Sensitivity to tobacco smoke, %	**No sensitivity**	98.1	90.4	87.5	<0.0001
	Rhinorrhea or sneezing	1.60	7.40	11.7	
	Rhinorrhea and sneezing	0.30	2.20	0.80	
Sensitivity to cold air, %	**No sensitivity**	84.2	66.9	67.4	<0.0001
	Rhinorrhea or sneezing	15.1	30.2	27.9	
	Rhinorrhea and sneezing	0.60	2.90	4.70	
Sensitivity to weather, %	**No sensitivity**	97.5	88.2	83.0	<0.0001
	Rhinorrhea or sneezing	1.60	11.8	10.8	
	Rhinorrhea and sneezing	0.90	0.00	6.20	
Use of nasal spray in the last 12 months, %		23.0	39.7	54.3	<0.0001
Use of other drug in the last 12 months, %		17.7	27.9	62.0	<0.0001

BMI = Body Mass Index

*p-value overall

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Participants of the study had a very good phenotypic characterization of respiratory health and allergic sensitization that gave us the opportunity to consider several questions related to rhinitis. The design of the study allowed us to compare the characteristics of rhinitis phenotypes according to the asthma status. One of the limitations is that the sample is not big enough to study finest clusters and particularly mixed rhinitis (participants having non allergic and allergic rhinitis). Our analysis did not identify some very specific adult rhinitis phenotypes such as hormonal rhinitis [19] probably because of their low prevalence. Overall, to our knowledge, our study is the first with such detailed questionnaires and allergic sensitization available. As the analyses were performed separately for participants without and with asthma, our results cannot be transposed to population-based studies.

Cluster of rhinitis have consistent characteristics with previous literature and clinician's knowledge. We reported that AR cluster was more related to conjunctivitis and eyes-associated symptoms whereas NAR cluster was more related to sinusitis. NAR cluster was more associated with sensitivity to trigger as cold air whereas AR cluster was more associated with sensitivity to multiple allergens as pet, hay, and flower. Age at onset of nasal symptoms was lower for AR cluster than for NAR cluster. These results are concordant with several papers comparing

Table 3. Characteristics of participants with asthma according to each cluster.

		Cluster A'-no rhinitis- (n = 87)	Cluster B'-non-allergic rhinitis- (n = 144)	Cluster C'-allergic rhinitis-(n = 170)	p-value*
Age, mean ± sd		39.9 ± 16.8	38.5 ± 17.6	35.9 ± 14.3	<0.001
Sex, women %		44.8	44.4	49.4	0.63
Tobacco, %	**Non smoker**	51.7	45.1	57.7	0.054
	Ex-smoker	28.7	25.0	16.5	
	Smoker	19.5	29.9	25.9	
BMI (kg/m2), %	**<20**	8.1	11.1	15.3	0.32
	[20–25]	52.9	47.2	54.1	
	[25–30]	25.3	28.5	22.4	
	> = 30	13.8	13.2	8.2	
Educational level, %	**Low**	25.3	20.8	13.0	0.12
	Medium	31.0	31.9	32.4	
	High	43.7	47.2	55.6	
Nasal symptoms,	**No symptoms**	100	0.0	0.0	<0.001
%	**Symptoms without eyes symptoms**	0.0	43.8	7.6	
	Symptoms with eyes symptoms	0.0	56.2	92.4	
Type of nasal symptoms	**No symptoms**	100	0.0	0.0	<0.001
%	**Symptoms: ever but not current**	0.0	1.4	0.0	
	Ever and current symptoms	0.0	98.6	100	
Persistence of nasal symptoms, %	**Intermittent**	-	50.0	20.6	<0.001
	Persistent$_{low}$	-	29.2	31.2	
	Persistent$_{high}$	-	20.8	48.2	
Allergic sensitization,%	**SPT = 0**	19.5	33.3	4.1	<0.001
	SPT = 1	27.6	19.4	15.3	
	SPT = 2	20.7	14.6	19.4	
	SPT>2	32.2	32.6	61.2	
Report of diagnosis of allergy by a physician, %		58.6	60.4	96.5	<0.001
Immunotherapy since first survey (EGEA1)		8.0	8.3	22.9	<0.001
Age of onset of nasal symptoms, mean ± sd	**(n = 290)**	-	19.3 ± 86.9	11.5 ± 10.0	<0.001
Report of allergic rhinitis, %		26.4	41.7	85.9	<0.001
Report of hay fever, %		35.6	34.0	92.4	<0.001
Report of conjunctivitis, %		26.4	30.6	69.4	<0.001
Report of sinusitis, %		46.0	49.3	60.0	0.053
Report of eczema, %		42.5	47.2	53.5	0.22
Sensitivity to hay/flowers, %	**No sensitivity**	77.0	76.4	10.0	<0.0001
	Rhinorrhea or sneezing	12.6	20.1	30.0	
	Rhinorrhea and sneezing	10.3	3.5	60.0	
Sensitivity to animals, %	**No sensitivity**	88.5	81.3	52.9	<0.0001
	Rhinorrhea or sneezing	6.9	12.5	18.8	

(*Continued*)

Table 3. (*Continued*)

		Cluster A'-no rhinitis- (n = 87)	Cluster B'-non-allergic rhinitis- (n = 144)	Cluster C'-allergic rhinitis-(n = 170)	p-value*
	Rhinorrhea and sneezing	4.6	6.3	28.2	
Sensitivity to dust, %	**No sensitivity**	64.4	50.7	16.5	<0.0001
	Rhinorrhea or sneezing	25.3	37.5	42.9	
	Rhinorrhea and sneezing	10.3	11.8	40.6	
Sensitivity to tobacco smoke, %	**No sensitivity**	95.4	90.2	78.2	0.0002
	Rhinorrhea or sneezing	1.0	9.1	14.1	
	Rhinorrhea and sneezing	0.0	0.7	4.7	
Sensitivity to cold air, %	**No sensitivity**	86.2	71.5	63.5	0.001
	Rhinorrhea or sneezing	13.8	26.4	30	
	Rhinorrhea and sneezing	0.0	2.1	6.5	
Sensitivity to weather, %	**No sensitivity**	94.3	86.8	70.6	<0.0001
	Rhinorrhea or sneezing	5.8	9.7	14.7	
	Rhinorrhea and sneezing	0.0	3.5	14.7	
Disturbance due to nasal symptoms, %	**No**	-	65.3	29.4	<0.001
	Low	-	20.1	34.1	
	Medium	-	11.1	23.5	
	High	-	3.5	12.9	
Use of nasal spray in the last 12 months, %		44.8	47.2	64.1	0.0018
Use of other drug in the last 12 months, %		42.5	42.4	80.6	<0,0001
Age of onset of asthma, mean ± sd		16,8±16,2	15,6±15,7	12,2±13,2	0.6 (A vs B) and 0.02 (A vs C)
BHR, %	**(n = 267)**	64.4	75.0	69.0	0.36
FEV_1% predicted, mean±sd		96 ± 0.18	98 ± 0.16	96 ± 0.22	0.42

BMI = Body Mass Index, FEV1 = Forced Expiratory Volume, #: BHR: Bronchial Hyper Responsiveness (Methacholine test, PD20≤4 mg, Methacholine challenge test was not performed if baseline FEV1 <80% predicted, PD20 = Provocative Dose). BHR was then available for 663 participants (396 without asthma and 267 with asthma).

*p-value overall

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allergic rhinitis to non-allergic rhinitis [20], [21], [22]. Overall, it is reassuring that *prima facie*, unsupervised approaches find similar phenotypes than the ones used in the clinical setting.

Interestingly, we observed that AR cluster was associated with more severe symptoms (greater disturbance) than NAR cluster. This result is consistent with the studies by Bachert [23] and Di Lorenzo [21] but discordant with the study by Molgaard [24]. This discordance between studies seems not to be due to the design of the studies, but to the difference in the definitions of the types of rhinitis and particularly in the way that allergic and non-allergic rhinitis were differentiated. Overall, the definitions and particularly the way to define the allergic part of rhinitis seem to be crucial to establish the characteristics of the phenotypes. Furthermore,

Table 4. Comparison of the repartition of the participants without asthma into the different *hypothesis-driven*'s phenotypes and *data-driven*'s cluster.

		Data-driven clusters			
	n (%)	A (No rhinitis)	B (NAR)	C (AR)	
Hypothesis-driven Phenotypes	1 (no symptoms, no SPT)	228 (39)	0	0	228
	2 (no symptoms, SPT+)	89 (15)	0	0	89
	3 (symptoms, no SPT ~ NAR)	0	110 (19)	**30 (5)**	140
	4 (symptoms, SPT+ ~AR)	0	**26 (5)**	99 (17)	125
		317	136	129	**582**

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whatever the cluster of rhinitis (NAR or AR), we found that almost all of the participants who reported ever rhinitis also reported current nasal symptoms which suggest that considering rhinitis ever or current rhinitis would give the same result.

Prevalence and repartition of non-allergic and allergic rhinitis are very different according to the study: between 63% and 77% of rhinitis would be of allergic type [22,24], but some other studies argue that over 75% of rhinitis is non-allergic rhinitis or mixed rhinitis [20]. In our study, we found a higher prevalence of rhinitis in participants with asthma. However, within each asthma status, the prevalence of NAR cluster was similar to that of AR cluster.

Whereas rhinitis is classically divided in allergic and non-allergic rhinitis based on the allergic sensitization, our results suggest that allergic sensitization may be insufficient to differentiate correctly AR and NAR and to make the diagnosis of AR. This result is concordant with a paper studying predictor factors to differentiate between allergic and non-allergic rhinitis in children [25], which found out that features of rhinitis as seasonality, moderate/severe symptoms help in the differentiation of rhinitis. Di Lorenzo [21] has showed that several clinical and laboratory parameters may help to reinforce or exclude the diagnosis of AR obtained with SPT, and Quillen said that: "allergy testing is not necessary in all patients but may be useful in ambiguous or complicated cases"[26]. Finally, Berstein [27] said that "taking into account age of symptom onset, family history, quantification of inciting allergic and/or non-allergic triggers, and seasonality followed by aeroallergen skin testing to assess atopic status has been shown to be the most useful approach for clearly differentiate rhinitis subtypes". Overall, these results are concordant with known complexity to define phenotypes of rhinitis.

This study enabled to validate and confirm phenotypes of rhinitis often described in the literature, but for the first time highlighted in a statistical way. Thanks to a classification tree, our results showed the clinical interest of using only a few numbers of questions to classify the participants in the 3 clusters and particularly to distinguish between non-allergic and allergic rhinitis. These questions are often available in respiratory epidemiological study making easier the reconstruction and the use by general physician and pharmacist.

Table 5. Comparison of the repartition of the participants with asthma into the different *hypothesis-driven*'s phenotypes and *data-driven*'s cluster.

		Data-driven clusters			
	n (%)	A' (No rhinitis)	B' (NAR)	C' (AR)	
Hypothesis-driven Phenotypes	1 (no symptoms, no SPT)	17 (4)	0	0	17
	2 (no symptoms, SPT+)	70 (17)	0	0	70
	3 (symptoms, no SPT ~ NAR)	0	48 (12)	**7 (2)**	55
	4 (symptoms, SPT+ ~AR)	0	**96 (24)**	163 (41)	259
		87	144	170	**401**

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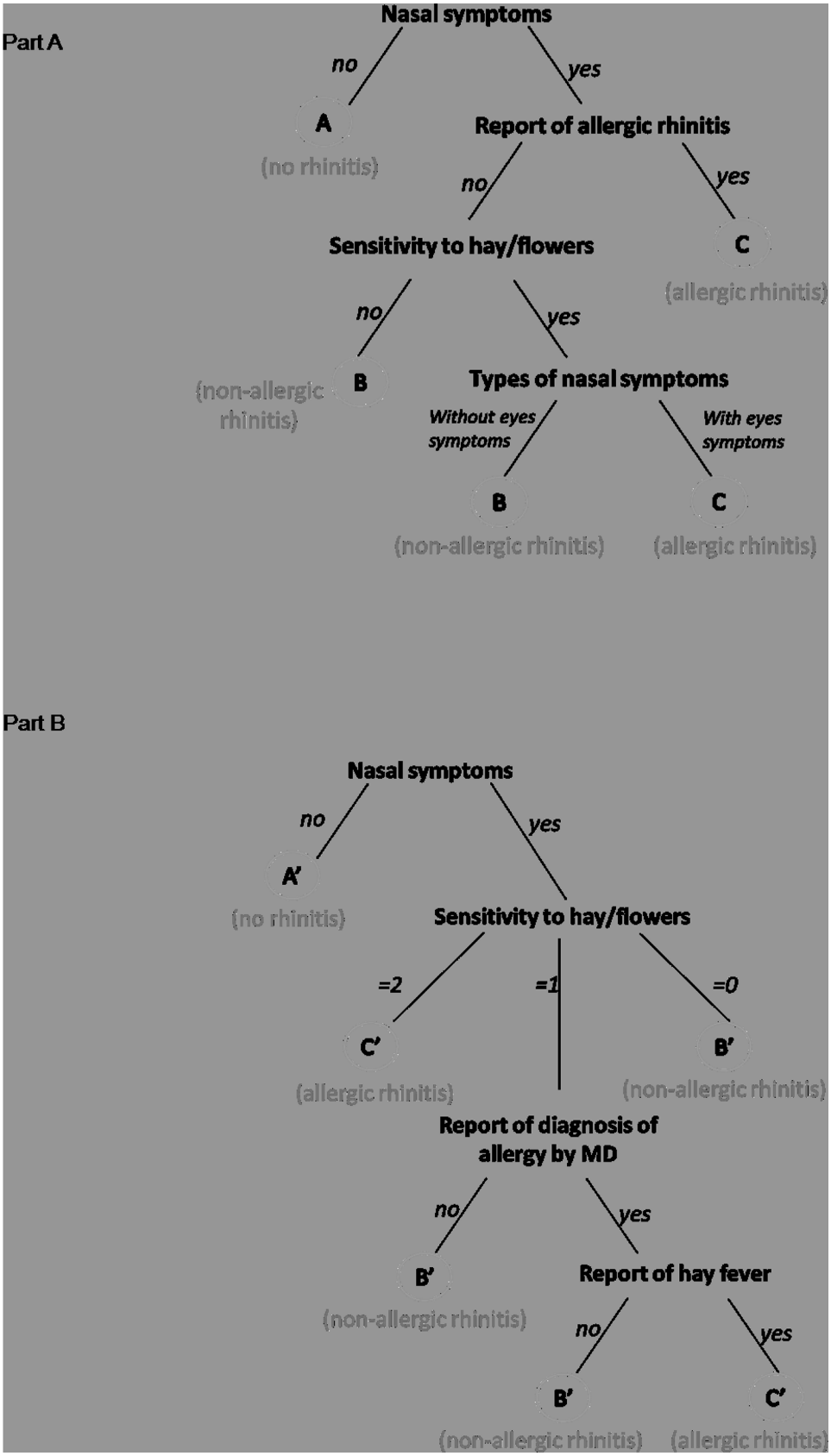
Part A
Nasal symptoms
no
yes
A
(no rhinitis)
Report of allergic rhinitis
no
yes
Sensitivity to hay/flowers
C
(allergic rhinitis)
no
yes
B
(non-allergic rhinitis)
Types of nasal symptoms
Without eyes symptoms
With eyes symptoms
B
(non-allergic rhinitis)
C
(allergic rhinitis)
Part B
Nasal symptoms
no
yes
A'
(no rhinitis)
Sensitivity to hay/flowers
=2
=1
=0
C'
(allergic rhinitis)
B'
(non-allergic rhinitis)
Report of diagnosis of allergy by MD
no
yes
B'
(non-allergic rhinitis)
Report of hay fever
no
yes
B'
(non-allergic rhinitis)
C'
(allergic rhinitis)

Fig 3. Classification tree obtained with the most predictive variables in participants without (Part A) and with asthma (Part B).

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In conclusion, taking into account all available specific questions related to rhinitis, a cluster analysis enabled to highlight three clusters of rhinitis with similar characteristics than those known by clinicians but differing according to allergic sensitization, and this whatever the asthma status. The clusters obtained by *data-driven* approach may be considered as "smoothed" phenotypes compared to the ones obtained only using nasal symptoms and allergic sensitization. These clusters could now be used to study the association with biological and environmental factors. Overall, although cluster analysis is thought to be hypothesis generating, studies in asthma, COPD and now rhinitis show that is may also be useful in hypothesis confirmation.

Supporting Information

S1 Fig. BIC criterion according to the number of cluster for participants without (Part A) and with (Part B) asthma.
(EPS)

S1 Supporting Information. Comparison of the characteristics of the participants included and non-included in the analysis (Table A). Missing values for each variables (Table B). Description of the participants without asthma according to the four classical phenotypes (hypothesis driven) (Table C). Description of the participants with asthma according to the four classical phenotypes (hypothesis driven) (Table D).
(DOC)

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Conceived and designed the experiments: FG BJ JJ RM RN IP VS RV. Performed the experiments: FG JJ RM RN IP. Analyzed the data: EB. Contributed reagents/materials/analysis tools: EB JB BJ RN. Wrote the paper: EB JB BJ RN. Commented on the manuscript, read and approved the final version: EB JB RV FG JJ RM IP VS BJ RN.

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Supplementary Material: Characterization of rhinitis according to the asthma status in adults using an unsupervised approach in the EGEA study

5.2 The sensitization pattern differs according to rhinitis and asthma multimorbidity in adults: the EGEA study.

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ORIGINAL ARTICLE **Epidemiology of Allergic Disease**

The sensitization pattern differs according to rhinitis and asthma multimorbidity in adults: the EGEA study

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Clinical & Experimental Allergy

Summary

Background Mono- and polysensitization are different IgE-mediated allergic phenotypes in children. Allergic sensitization is associated with both allergic asthma and allergic rhinitis, however, associations between the sensitization pattern and particularly polysensitization with asthma and rhinitis remains poorly studied in adults.

Aim The aim of this study was to assess how the allergic sensitization pattern associates with asthma, rhinitis and their multimorbidity.

Methods 1199 adults from the EGEA study, with extensive phenotypic characterization and all data available on skin prick tests to 10 allergens, total IgE and blood eosinophils were included. Using questionnaires only, participants were classified into 6 groups: asymptomatic (no asthma, no rhinitis), non-allergic rhinitis alone, allergic rhinitis alone, asthma alone, asthma+non-allergic rhinitis and asthma+allergic rhinitis. Mono- and polysensitization were defined by a positive skin prick test to one or more than one allergen respectively.

Results Asymptomatic participants and those with non-allergic rhinitis alone were mostly non-sensitized (around 72%) while around 12% were polysensitized. Between 32% and 43% of participants with allergic rhinitis alone, asthma alone and asthma+non-allergic rhinitis were non-sensitized and between 37% and 46% of them were polysensitized. 65% of the participants with asthma+allergic rhinitis were polysensitized. The level of total IgE followed a similar trend to that of allergic sensitization. Eosinophils were increased in asthma, especially when associated with rhinitis. Nasal symptoms were more severe and eczema more common in participants with both asthma and allergic rhinitis than in the other groups.

Conclusions Allergic sensitization and particularly polysensitization rates widely differ according to asthma and rhinitis status. This study emphasized the importance of taking into account multimorbidity between asthma and rhinitis and showed that allergic sensitization is not a dichotomic variable.

Keywords allergic sensitization, asthma, rhinitis, multimorbidity, monosensitization, polysensitization

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Introduction

According to the World Allergy Organization [1], IgE-mediated allergic diseases, including allergic respiratory diseases such as rhinitis [2] and asthma are complex [3]. These diseases are associated with both allergen-specific IgE and non-allergic mechanisms that may coexist in the same patient. In addition, they tend to cluster and patients may present concomitant or consecutive diseases (allergic multimorbidity) [4] as shown in children within the European MeDALL project [5].

*Contributed equally to the work.

Most epidemiological studies define allergic status as being sensitized or not (thus as having at least one positive skin prick test or at least one specific IgE > 0.35 kU/L). Nevertheless, sensitization to an allergen does not necessary imply nasal symptoms [6] and, conversely, nasal symptoms may possibly be due to a non-allergic rhinitis despite an allergic sensitization. Over 70% of symptomatic patients are sensitized to more than one allergen i.e. polysensitized as found in both children and adults [7–9]. Important clinical and immunological differences exist between mono and polysensitized patients suggesting that polysensitization is the expression of a distinct disease both in children and adults [5, 10, 11]. Moreover, persistence of allergic diseases over time is associated with multimorbidity and/or allergic polysensitization [2]. A recent study in Finnish adults showed that polysensitization -but not monosensitization- was associated with asthma [12]. All of these studies emphasize phenotypic differences between mono and poly sensitized subjects, as recently summarized in a review [6]. However, to our knowledge, no study has ever specifically assessed the sensitization pattern (mono- vs. polysensitization, total IgE rate, eosinophil counts, severity of the symptoms) according to asthma and rhinitis status in adults.

In adults, using an unsupervised approach, we have previously identified three clusters of rhinitis with similar characteristics similar to those known by clinicians but differing in term of allergic sensitization, and this whatever the asthma status [13]. Furthermore, in the cluster combining asthma and allergic rhinitis, participants showed a particularly high rate of polysensitization compared to the other clusters. This finding prompted us to perform a study assessing allergic sensitization in relation to asthma and rhinitis. Our hypothesis is that allergic sensitization, and particularly polysensitization, differ according to asthma and rhinitis status comorbidity and, in adults, this confirms the MeDALL concept that has previously been shown in children [5].

The aim of this study was to assess how the allergic sensitization pattern, assessed by mono- vs. polysensitization, total IgE, eosinophil counts and severity of the symptoms, associates with asthma, rhinitis and their multimorbidity in 1199 adults of the EGEA (Epidemiological study of the Genetics and Environment of Asthma) study.

Methods

Study design

The EGEA study is a French case-control and family study based on an initial group of asthma cases and their first-degree relatives, as well as a group of controls (EGEA1, n = 2047; https://egeanet.vjf.inserm.fr).

Setting and participants

The protocol and descriptive characteristics of the EGEA study have been previously published [14]. Briefly, EGEA is a 20-year follow-up study combining a case-control study with a family study of asthma cases (children or adults). 2047 children (< 16 years) and adults from five French cities were enrolled between 1991 and 1995. The participants included 348 cases with current asthma recruited in chest clinics, their 1244 first-degree relatives, and 415 population-based controls. A follow-up of the initial cohort was conducted between 2003 and 2007 (EGEA2) [15]. Among the alive cohort (n = 2002), 92% (n = 1845) completed a short self-administered questionnaire and among them 1601 had a complete examination (1570 adults). All participants responded to questionnaires based on international standardized tools to characterize asthma, respiratory and allergic symptoms and treatments, and environmental exposures.

Ethical approval was obtained from the relevant institutional review board committees (Cochin Port-Royal Hospital and Necker-Enfants Malades Hospital, Paris). Written informed consent was signed by all participants.

Variables

Allergic sensitization. Skin-prick tests (SPTs) to 10 of the most commons aero-allergens (cat, *Dermatophagoides pteronyssinus*, olive, birch, *Parieteria judaica*, timothy grass, *Cupressus*, ragweed pollen, *Cladosporium herbarum*, *Alternaria tenuis*, Stallergènes, Antony, France) were selected for the analysis [16, 17]. Negative (uncoated) and positive (histamine) SPT controls were assessed. SPT with a mean wheal diameter 3 mm ≥ than the negative control was considered as positive [16]. SPTs assessment was performed by trained professionals and in the same way for all adult participants, whatever the center. SPTs to *Blattela germanica* and *Aspergillus* were also available but not included in the analysis as the quality of the reagents was insufficient.

Asthma and allergic rhinitis definitions. Asthma status was based on a positive answer to either *'Have you ever had attacks of breathlessness at rest with wheezing?'* or *'Have you ever had asthma attacks?'* or as being recruited as an asthma case. Allergic Rhinitis (AR) ever was defined by a positive answer to nasal symptoms: '*Have you had a problem with sneezing or runny or blocked nose when you did not have a cold or the flu?*' and a positive answer to '*Have you ever had allergic rhinitis?*' or '*Have you ever had hay fever?*'. Non-allergic Rhinitis (NAR) ever was defined by a positive answer to nasal symptoms and a negative answer to

'*Have you ever had allergic rhinitis?*' and '*Have you ever had hay fever?*'.

The quantitative asthma symptom score, as defined by Pekkannen et al. was used to describe the phenotype of asthma and as a proxy of severity of asthma [18].

Participants were classified into 6 groups, based only on their responses to the questionnaire: no asthma and no rhinitis (Reference group), non-allergic rhinitis (NAR) only, allergic rhinitis (AR) only, asthma only (As+), asthma + NAR (As + NAR), and asthma + AR (As + AR). These groups are similar to those highlighted by a clustering approach, but using only two questions on rhinitis and not using allergic sensitization [13].

Nasal symptoms were considered, similarly to the ARIA guidelines [2], as intermittent if they occur more than one month per year but less than 4 days per week or as persistent if they occur more than a month per year and more than 4 days per week. Moreover, if the symptoms occurred less than one month per year, persistence of nasal symptoms was considered as rare. Severity of nasal symptoms was assessed using the answers to the question '*Have these nose problems disturbed you daily activities?*'. This enabled a score of disturbance to be obtained from 0 to 3 (0: no, 1: a little bit, 2: moderately, 3: a lot).

Other phenotypes – definition. Eczema, conjunctivitis or sinusitis were defined as a positive answer to '*Have you ever had eczema?*' (respectively conjunctivitis or sinusitis).

Biological phenotypes. Total IgE were assessed by the UniCAP system (Pharmacia®) from blood samples in a centralized laboratory, and expressed in international units (IU) per milliliter.

Eosinophil cell counts were obtained from white blood cell counts.

Study size. The present analysis was conducted in 1199 adult participants of EGEA2 who had available data on asthma status, rhinitis status, SPT, total Immunoglobulin E (IgE), and blood eosinophils. Since this is an exploratory study, no power calculation was needed.

Bias. Analyses were also performed using the 12 allergens including *Aspergillus* and *Blatta Germanica*, and results were very similar, with similar percentages of mono- and polysensitization according to the groups (data not shown).

Due to the familial design of the study, a sensitivity analysis was conducted in a sub-sample of the population with one randomly-selected member per family. These analyses with 566 participants have shown very similar results to those of the study on the 1199 participants (data not shown).

Statistical analysis

To test whether general, phenotypic and allergic characteristics differ among the groups and differs from the reference group (no asthma no rhinitis), the Chi2 test and univariate polytomic logistic regression with no further adjustment were performed. For variables available only in subjects with rhinitis (such as age of onset, persistence or severity) or asthma (such as age of onset), these tests were performed only among the adequate population (i.e. subjects with rhinitis or asthma).

To test whether some groups tend to be more non-sensitized (no positive SPT) or monosensitized (1 positive SPT) than poly-sensitized ($\geq$ 2 SPTs), a polytomic logistic regression was used, adjusting results on several variables: age, sex, smoking status and educational level, chosen as they differed significantly according to the six groups. The reference class was the group with neither asthma nor rhinitis. This same methodology was used to compare sensitization to each of the 10 allergens among the groups. Severity and persistence of nasal symptoms, total IgE level and eosinophil count were compared group by group using logistic regression adjusted for age, sex, smoking status and educational level.

As a sensitivity analysis, we also adjusted the results using occupation instead of educational level, adjusting on parental asthma and childhood spent on a farm.

All the analyses were performed using the R statistical software [19].

Results

Characteristics of the participants

Participants were classified into 6 groups: no asthma no rhinitis (Reference group, $N = 362$), NAR alone (NAR, $N = 169$), AR alone (AR, $N = 167$), asthma alone (As+, $N = 65$), asthma + NAR (As + NAR, $N = 78$) and asthma + AR (As + AR, $N = 358$). The characteristics are presented in Table 1. The participants of the groups with asthma were younger (P-value As vs. non-As: < 0.001), and more likely to be male (P-value As vs. non-As: 0.015). The participants who had asthma and rhinitis – allergic or non-allergic – declared a younger age of onset than those without asthma (P-value rhinitis vs. rhinitis + As: < 0.001). The participants with As + AR had a higher prevalence of eczema to those in the other groups (P-value < 0.05 whatever the group).

Allergic sensitization evaluated by SPT

Participants without symptoms of rhinitis or asthma and those with NAR had no allergic sensitization in

over 71%, and less than 14% were sensitized to over 2 allergens (Fig. 1). Participants with AR alone or As+ alone had no allergic sensitization in about 33% of cases whereas about 42% of them were sensitized to over 2 allergens. Participants with As + NAR had no positive SPT in 43.6% of cases and 37.0% of them were sensitized to over 2 allergens. Participants with As + AR had no positive SPT in 14.8% of cases and 65% of them were sensitized to over 2 allergens.

Compared to the participants without asthma and rhinitis, polysensitization (vs. non or mono-sensitized) was highly associated with AR alone and even more so with As + AR (crude and adjusted odds-ratios in Table 2). Lower aORs were observed for As+ and As + NAR and no significant association was found for NAR alone. Using different levels of adjustment did not modify the results (see Table S1 in the Online Repository).

Sensitization according to different allergens

The repartition of the allergic sensitization according to the group and to the 10 allergens is given in Fig. 2. *Dermatophagoides pteronyssinus*, cat, and allergens related to hay/pollen were the most common allergens. The sensitization rate to *D. pteronyssinus* was higher in all groups of symptomatic participants i.e. AR alone, As+ alone, As + NAR and As + AR groups as compared to the reference group (no asthma no rhinitis). The sensitization rate to cat was higher in all groups of symptomatic participants except for the NAR alone group. For hay/pollen allergens, the sensitization rate was particularly high for participants with AR alone and As + AR, whatever the allergen. Sensitization to timothy grass was the most common allergen for hay/pollen, followed by Olive tree. Sensitization rates to *Parietaria* and Cypress were low in all groups. Sensitization to *Cladosporium* and *Alternaria* was over 10% only in the As+ alone and As + AR groups.

Persistence and severity of nasal symptoms

Nasal symptoms were more persistent in As + AR participants compared to As + NAR (P-value adjusted < 0.001) or NAR alone (adjusted P-value $= 0.018$) and slightly more persistent compared to AR alone (adjusted P-value $= 0.14$). There was no difference between NAR alone and As+NAR (adjusted P-value $= 0.81$). Nasal symptoms were more severe in participants with As + AR compared to As + NAR (P-adjusted < 0.001), NAR alone (P-value < 0.001) or AR alone (adjusted P-value $= 0.010$). Nasal symptoms were also more severe in participants with As + NAR than in those with NAR alone (adjusted P-value $= 0.036$) (Table 1).

Blood eosinophils and total IgE

Blood eosinophil counts were higher in all symptomatic groups compared to the reference group (no asthma, no rhinitis). AR alone and As+ alone had a similar level whereas eosinophils were even higher when asthma was associated with rhinitis, allergic or non-allergic. Total IgE levels followed a similar trend to allergic sensitization, with a higher value in participants with As + AR, compared to participants without asthma and rhinitis or NAR alone, whereas participants with As+ alone, As + NAR and As + AR had intermediate levels (Table 1).

Discussion

In the present study, using new analyses, we showed that polysensitization was the highest among participants with asthma and allergic rhinitis multimorbidity by comparison to asthma or rhinitis alone. Asymptomatic participants or those with non-allergic rhinitis are in the vast majority, non-sensitized or sensitized to one allergen. Levels of total IgE followed a similar trend to allergic sensitization. Eosinophil counts were increased in asthma alone, and the greatest number was found when asthma was associated with rhinitis. Nasal symptoms were more severe in participants with As+AR than in participants from other groups.

This study presents several strengths and limitations. It was performed among over 1000 adults from the EGEA study that is not representative of the French population, but enriched in participants with asthma, allowing a good statistical power to address allergic multimorbidities. This particular design (case control and family study) and the age differences at inclusion between cases, relatives and controls explains in part that participants with asthma were younger than participants without asthma [20]. The age of onset of nasal symptoms differs according to the group, and is significantly lower in participants with allergic rhinitis. This result is not surprising because allergic rhinitis often appears at a younger age than non-allergic rhinitis whereas non-allergic rhinitis is often characterized by onset after the age of 20 years [21]. The age of onset of nasal symptoms is also lower in participants with asthma, and this can be explained by the concomitance of two facts: (i) rhinitis and asthma are strongly related, often coexist, and one often leads to the other; (ii) the mean age of onset of asthma is generally lower than 20 years and, even more, often occurs during childhood. Thereupon, the age of onset of nasal symptoms was the lowest in participants with asthma+AR. The extensive phenotypic characterization regarding respiratory health, and particularly rhinitis and asthma, is clearly a strength. Rhinitis was not diagnosed by a

Table 1. Characteristics of the participants

	No asthma, no rhinitis	NAR alone	AR alone	Asthma alone (As+)	Asthma +NAR	Asthma + AR	*P* crude, overall
N	362	169	167	65	78	358	
Age, mean ± SD	46.8 ± 16.3	47.2 ± 16.3	45.2 ± 14.8	40.8 ± 17.1	40.2 ± 17.9	38.4 ± 16.0	< 0.0001
Sex, % women	50.0	60.9	57.5	47.7	43.6	48.0	0.02
Tobacco status, %							
Non-smoker	49.7	50.3	52.7	41.5	50.0	51.1	0.51
Ex-smoker	29.2	26.0	26.9	35.4	23.1	22.9	
Smoker	21.1	23.7	20.4	23.1	26.9	26.0	
BMI, mean ± SD	24.6 ± 3.8	23.9 ± 3.8	24.1 ± 3.5	24.8 ± 3.7	25.0 ± 4.4	23.7 ± 3.9	
Educational level, %							
Low	30.9	27.8	21.0	21.5	29.5	16.3	0.0008
Medium	23.8	25.4	22.8	24.6	21.8	32.6	
High	45.3	46.7	56.3	53.8	48.7	51.1	
Current nasal symptoms, %		84.4	87.3		85.5	90.7	0.17
Eyes symptoms associated, %		32.1	76.6		47.4	80.4	< 0.0001
Persistence of nasal symptoms %							
Rare		50.7	42.5		53.6	30.4	< 0.0001
Intermittent		17.8	26.7		17.4	31.0	
Persistent		31.5	30.8		29.0	38.7	
Severity of nasal symptoms (disturbance), %							
No		76.7	50.7		64.7	40.4	< 0.0001
Low		17.1	33.6		22.1	32.4	
Medium		4.8	13.0		5.9	18.3	
High		1.4	2.7		7.4	9.0	
Age of onset of nasal symptoms, mean ± SD		32.7 ± 18.8	25.1 ± 15.0		23.2 ± 17.7	14.2 ± 12.2	< 0.0001
Eczema, %	22.7	25.6	35.3	38.5	38.5	52.7	< 0.0001
Conjunctivitis, %	13.8	22.3	46.7	26.6	25.7	55.5	< 0.0001
Sinusitis, %	34.9	47.6	59.3	47.7	50.0	58.0	< 0.0001
Allergic rhinitis, %	5.5	0	73.7	0	0	81.3	< 0.0001
Hay fever, %	10.8	0	77.8	0	0	78.2	< 0.0001
Current asthma, %	0	0	0	91.5	96.6	97.1	0.17
Asthma Symptom score, %							
0	77.6	66.2	62.5	27.7	22.4	17.6	< 0.0001
1	19.9	25.4	31.2	36.2	36.2	27.6	
2	2	7	3.8	25.5	13.8	22.8	
3	0.5	1.4	2.5	6.4	19	20.2	
4	0	0	0	4.3	6.9	9.9	
5	0	0	0	0	1.7	1.8	
BHR, % of yes	23.7	28.4	29.8	55.8	69.8	67.8	< 0.0001
FEV1, % predicted ±SD	107	106	109	94.9	95.5	98.2	0.0006
Age of onset of asthma, mean ± SD				15.8 ± 15.5	19.9 ± 16.3	13.9 ± 14.3	0.0015
Eosinophils, *, mean ± SD	149 ± 106	178 ± 145	191 ± 123	196 ± 129	249 ± 198	253 ± 192	< 0.0001
Total IgE, *, IU/mL, geometric mean ± SD	33.9 ± 3.7	47.9 ± 4.6	79.4 ± 3.6	72.4 ± 5.1	100.0 ± 5.6	166.0 ± 3.6	< 0.0001
Number of positive SPT, mean ± SD	1.4 ± 0.9	1.5 ± 1.1	2.7 ± 1.7	2.6 ± 1.6	2.3 ± 1.5	3.5 ± 1.8	< 0.0001

NAR, Non-allergic rhinitis; AR, Allergic rhinitis, SD, standard deviation; FEV1, Forced Expiratory Volume in one-second; BHR, Bronchial Hyper Responsiveness (Methacholine test, PD20 ≤ 4 mg, Methacholine challenge test was not performed if baseline FEV1 < 80% predicted, PD, Provocative Dose); IgE, Immunoglobulin E; SPT, skin prick test.

physician but was defined by self-reported symptoms, as is mostly the case in epidemiological studies. Thereby, using self-reported questionnaires leads to a possible misclassification of the subjects due to a poor knowledge of the disease. However, to classify our participants we used their answers to questions from an interviewer-based, standardized and validated questionnaire from the European Community Respiratory Health Study (ECRHS). Several epidemiological studies have already used these self-reported symptoms to define rhinitis [22–24]. Using self-reported questionnaires also leads to another possible misclassification due to recall

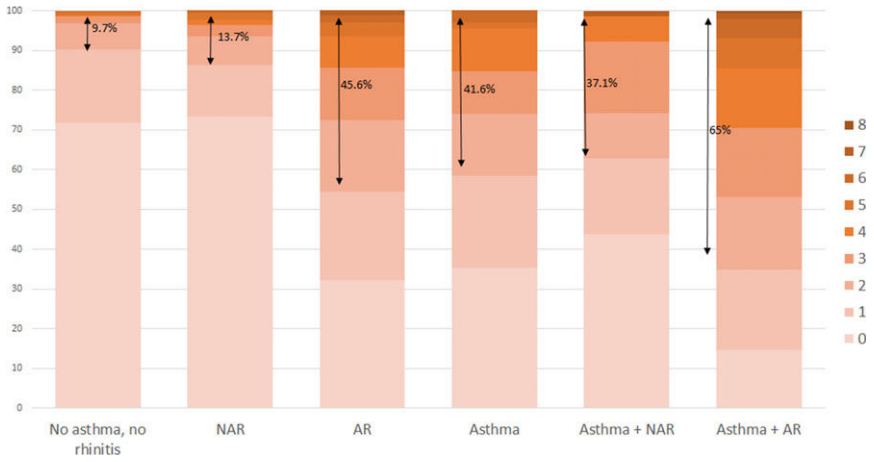

Fig. 1. Number of allergic sensitization – Number of positive SPT- according to the group and percentage of polysensitization.

Table 2. Odds Ratio of the association between polysensitization (vs. no or monosensitized) and the 6 groups

OR [95% CI]	No asthma, no rhinitis	NAR alone	AR alone	Asthma alone (As+)	Asthma +NAR	Asthma + AR
Crude OR	1 (ref)	1.47 [0.84–2.58]	7.8 [4.91–12.40]	6.64 [3.63–12.14]	5.53 [3.11–9.84]	17.34 [11.50–26.15]
aOR (on age, sex and education)	1 (ref)	1.59 [0.89–2.84]	8.62 [5.30–14.02]	6.01 [3.20–11.31]	4.79 [2.62–8.75]	15.24 [9.95–23.34]

aOR, adjusted Odd Ratio; NAR, Non-allergic rhinitis; AR, Allergic rhinitis.

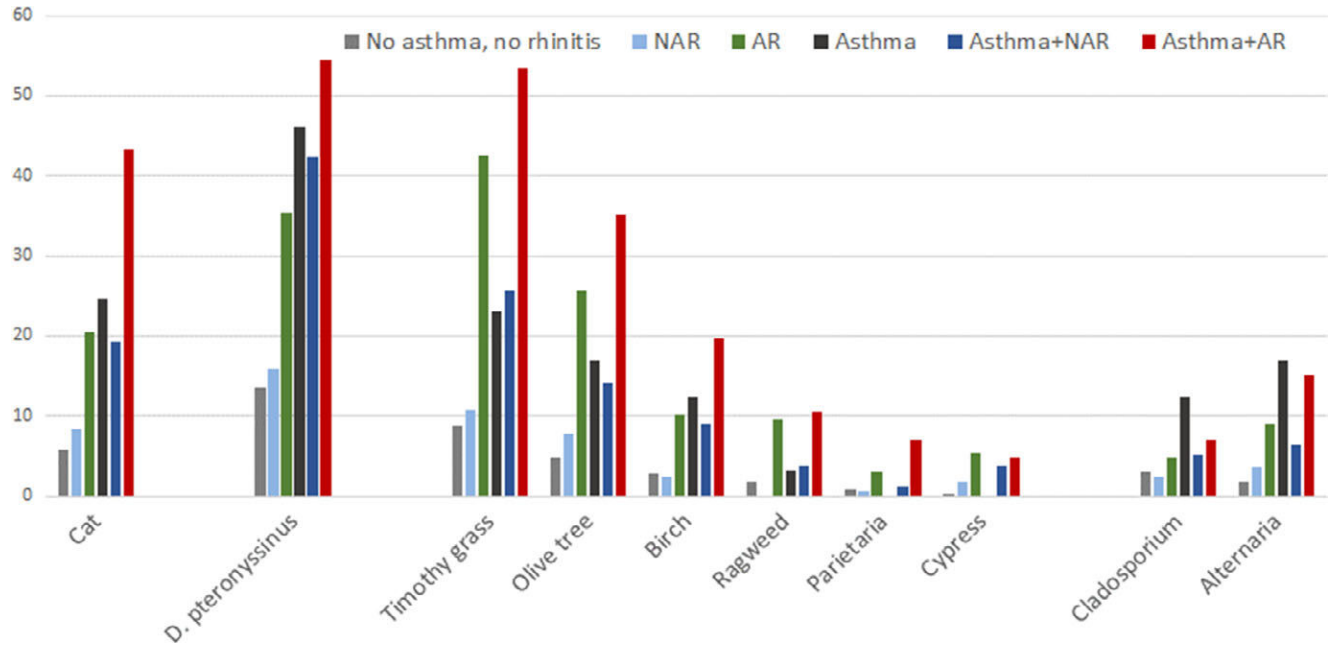

Fig. 2. Rate of allergic sensitization to the 10 allergens according to the group.

bias, as is often the case in epidemiology. The differentiation between allergic and non-allergic rhinitis was also based on self-reported symptoms and did not take allergic sensitization into account. This classification could be surprising at first glance, as some participants have unusual characteristics such as in the NAR or no rhinitis groups where some reported hay fever or allergic rhinitis or in the AR group where some were not sensitized to any of the 10 allergens. This definition, although unusual, enabled us to refine questionnaire-based

phenotypes and our results support that choice. In our previous unsupervised study, we found 3 clusters of rhinitis [13] whatever the asthma status. Whereas characteristics of the participants were similar to the phenotypes of rhinitis known by clinicians, the allergic sensitization differed strongly among the three phenotypes. In this study, we have put forward 3 groups based only on two frequent rhinitis questions. The level of allergic sensitization was similar to the one found in the cluster analysis as opposed to the classical phenotypes, and this confirms the interest of taking this particular definition of rhinitis. Another limitation of our study is the difficulty to distinguish allergic asthma from non-allergic asthma phenotypes. First, because we stratified asthma sub-groups according to rhinitis, and secondly because of the inherent difficulty to differentiate between both types of asthma in epidemiological settings. However, participants with co-occurrence of allergic asthma and non-allergic rhinitis should exist and this may be one explanation as to why participants with asthma + NAR were sensitized.

In this study, we decided to define allergic sensitization using SPTs rather than specific-IgE – because the SPTs have a better predictive value for rhinitis [25]. Thus, some differences may be found with other studies, since the two methods are not exactly comparable [2]. Furthermore, SPTs were defined at the extract level (i.e. IgE reactivity to several non-related – or not obviously related – allergenic source materials) and not at the molecular level (i.e. IgE reactivity to several nonrelated – or non-obviously related – allergenic molecules) [5]. This could have changed the way of defining polysensitization and may have increased the number of allergenic molecules detected. As allergic sensitization is a transient phenotype and as asthma is a complex disease that changes over time, it would have been interesting to perform a longitudinal analysis. However, EGEA1 questionnaires regarding rhinitis were slightly different to those in EGEA2 and 30% of the participants were children, and no SPT were available at the second-follow-up of EGEA. This disabled the opportunity to perform the longitudinal analysis in EGEA, but the question remains of interest.

Among the 10 studied allergens, the most frequently involved were *D. pteronyssinus*, cat, Timothy grass and Olive tree, and this whatever the group. Participants with As + AR had the highest rate of sensitization to cat and *D. pteronyssinus*, but also to all the allergens related to hay/pollen and *Alternaria*. Participants with AR alone and As + AR were particularly sensitized to allergens related to hay/pollen which bring out the "hay fever" part of allergic rhinitis. Participants with asthma seem to be particularly sensitized to *Alternaria* and *Cladosporium*, which is concordant with the literature [26, 27]. The 10 allergens tested were chosen for being the most common, but it is possible that participants are sensitized to other allergens such as dog or *Dermatophagoides farinae* [28], and then, considering these other allergens may increase the number of positive SPT. However, it is unlikely that adding more allergens would increase the number of sensitized participants as it has been shown that using from eight to ten allergens allowed the identification of the majority of sensitized subjects [29]. Overall, participants of the As+ alone and As+NAR groups had significantly higher rates for *D. pteronyssinus*, cat, Timothy grass and Olive tree than the reference group. This suggests that these allergens are not only related to nasal symptoms or allergic rhinitis, but also to asthma itself.

In the present study, we showed that mono- and polysensitized individuals represent different phenotypes of allergic diseases. This was found for children in the EU-FP7 MeDALL project [5, 30] and now also extends to adults. More specifically, we confirmed that asymptomatic subjects are often monosensitized as shown in Russian and Finnish children for House Dust Mite monosensitization [31]. Furthermore, allergic sensitization was lower in asymptomatic subjects than in symptomatic ones as found in a Finnish adult case-control on asthma study [12]. We have also found that the polysensitization rate is the highest among participants with both allergic rhinitis and asthma, which is concordant with previous studies among European adults [32, 33]. Recent studies in genetics, including one using the EGEA study data [34, 35], have also shown that genetic variants associated with asthma plus hay fever or asthma plus allergic rhinitis were different from those associated with only asthma or hay fever. This again suggests that asthma plus allergic rhinitis is a very specific phenotype. The As + AR group seems to have a specific phenotype – characterized by a high level of polysensitization, total IgE and eosinophil counts, and severe symptoms. This group is also the one with the youngest age of onset of asthma and rhinitis.

Interestingly, one could note a trend in the number of positive SPTs: being the lowest in asymptomatic and NAR alone participants, the highest in multimorbid diseases (participants with As + AR), and with intermediate levels in participants with AR alone, As+ alone or As + NAR. This trend was also found when looking at each allergen separately. Moreover, nasal symptoms were more severe among participants with As + AR, compared to the other groups with rhinitis. We showed that the As + AR group is the most polysensitized group. This result is concordant with the following studies where polysensitization was associated with more severe symptoms: (i) 9044 children aged 0–18 years in the Netherlands [10], (ii) 2415 young Italian adults with allergic rhinitis [8], (iii) 3225 Spanish and

Portuguese patients with allergic rhinitis aged 10–50 years [33], (iv) 130 Korean patients with childhood asthma [36]. On the contrary, other studies have shown no change in severity according to polysensitization, neither in the 784 children aged 6–18 years in primary care diagnosed with allergic rhinitis [9], nor in the 523 Finnish adults with asthma from a population-based case-control [12]. These discordant results do not seem to be due to the differences in the age of the participants, to the size of the samples, or to geography, as the studies were conducted in both children and adults in America, Europa or Asia. However, the different protocols used to define asthma or rhinitis (by questionnaire, by relevant medication use, by history of symptoms, by lung function test, by a physician or GP, by GINA or by ARIA classification), and allergic sensitization (by SPT or by specific-IgE) may partly explain the between-study discrepancies. Furthermore, we also found that participants with As + NAR had more severe nasal symptoms compared to those with NAR only, meaning that severity is not related only to sensitization, but also to multimorbidity diseases. These results suggest that multimorbidity and polysensitization are two different aspects of allergic disease, probably interacting together.

The MeDALL study in birth cohorts showed that multimorbid-polysensitized participants have a more persistent disease, and the authors suggested that a recurrence of a Th2 pathway may partly explain the results [5]. The current study confirms the findings of the MeDALL study in adults, with a multimorbid-polysensitized phenotype associated with an earlier onset and a greater severity compared to other phenotypes. Therefore, the same hypothesis may be proposed to explain, at least in part, our results. Our results suggest that this multimorbid-polysensitized phenotype could constitute a specific phenotype. A key unanswered question is the extent to which a particular phenotype (pattern) profile may identify "treatable" traits. Further researches is required to explore this possibility. Overall, this study emphasized the importance of taking into account multimorbidity between asthma and rhinitis and showed that allergic sensitization should not be used as a dichotomic variable. This result may lead to a different classification of allergic phenotypes in future epidemiological studies.

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Conflict of interest

The authors declare no conflict of interest.

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Supplementary Material: The sensitization pattern differs according to rhinitis and asthma multimorbidity in adults: the EGEA study

5.3 Association between air pollution and rhinitis incidence in two European cohorts.

In revision at Environment International.

Association between air pollution and rhinitis incidence in two European cohorts

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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 multicenter 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 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 done.

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 by city, but no regional pattern emerged for any of the pollutant.

Conclusions: This study did not find 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

Data came from two multicenter 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 multicenter cohort of young adults, aged 20 to 44 years old 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 two times: 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 on air pollution exposure at the 2nd follow up (EGEA3, ECRHS III, Figure 1) .

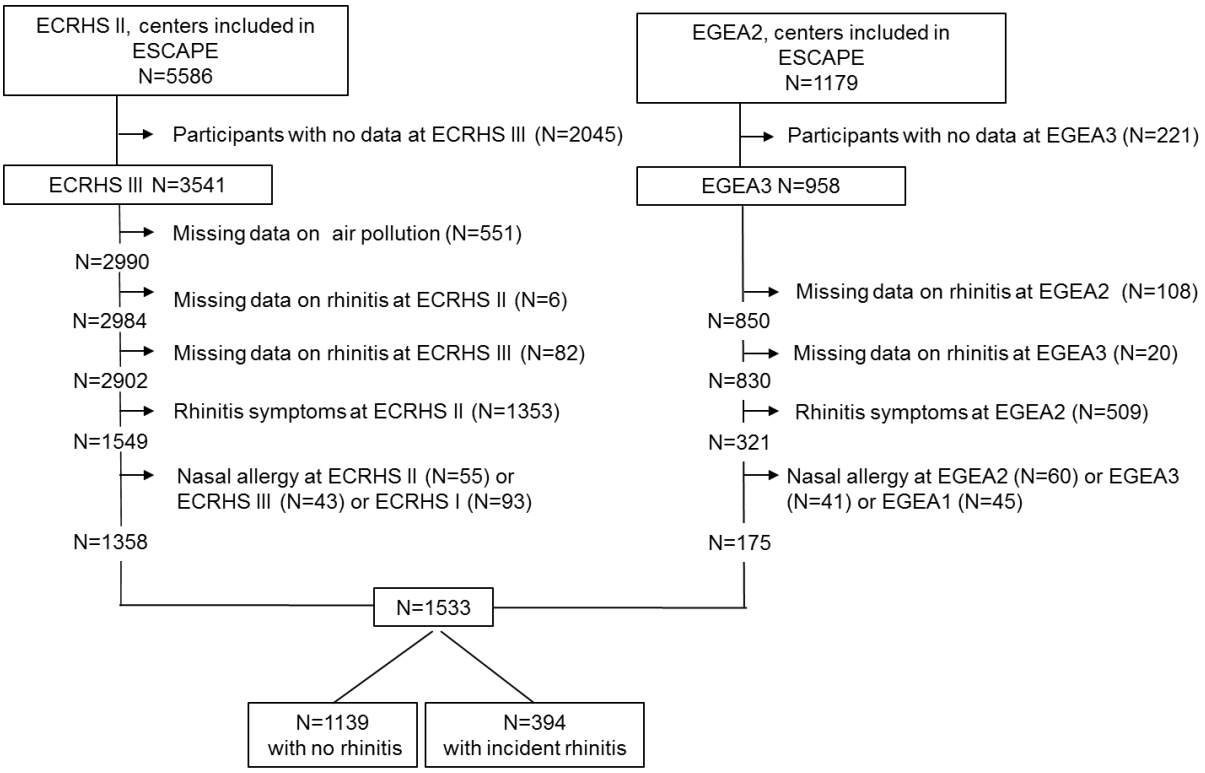

Figure 1 Flow-chart of the participants

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) and as 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.

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 supplemental 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 participants with nonallergic rhinitis to 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 caution has to be 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 asthmatic cases in EGEA.

Allergic sensitization was defined using 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 of general characteristics between the two studies were evaluated using Student test for quantitative variables and 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 Spearman coefficient.

Associations between air pollutants and incident rhinitis were evaluated using incidence rate ratio (IRR) in a pooled dataset. The IRR 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/ EGEA 2- 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 between studies 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).

<u>Results:</u>

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-

165 years (95% CI: [21.2-25.8]) with 394 participants reporting incident rhinitis and a median
166 length of the follow-up of 11 years. Participants with incident rhinitis were younger and
167 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, μ g.m^{-3}, mean±sd*	29.3±15.1 (N=1533)	28.9±15.4	30.3±14.2	0.11
PM_{10}, μ g.m^{-3}, mean±sd*	26.9±8.3 (N=738)	27.2±8.7	26.2±7.1	0.09
$PM_{2.5}$, μ g.m^{-3}, mean±sd*	16.4±4.9 (N=738)	16.6±5.2	15.9±4.4	0.08

*Annual averaged

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

169 Correlations between the three pollutants were high (0.71 between NO_2 and PM_{10}, 0.70 between
170 NO_2 and $PM_{2.5}$ and 0.77 between PM_{10} and $PM_{2.5}$, Table 1 in Supplemental Material).

171 *Main analysis*

172 Pooled analyses of the associations between NO_2, PM_{10} or $PM_{2.5}$ and incident rhinitis showed
173 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). 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 but none of the result was statistically significant (Table 2).

Stratifying by allergic sensitization status

Among 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 none 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.

196 *Stratifying by smoking status*

197 Finally, when stratifying by smoking status, a borderline positive association of rhinitis with
198 NO_2 was found among non-smokers, while an inverse significant relationship was found with
199 PM_{10} among smokers (Table 2).

200 Additionally adjusting results for study did not change any results (data not shown).

201 *Analysis by city and meta-regression*

202 Estimates for NO_2 were positive in 8 out of 17 cities but reached statistical significances only
203 in Paris. Estimates were negative in 9 cities but not statistically significant (Figure 2). Similarly,
204 positive and negative estimates were found according to the city for PM_{10} and $PM_{2.5.}$ However,
205 no statistical heterogeneity between cities was found in the meta-regression, with I^2 values
206 ranging from 0% for $PM_{2.5}$ to 36% for PM_{10}. No significant association was found in the meta-
207 regressions (Figure 2).

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

Analyses	No of subjects (No of incident cases) in adjusted model		crude IRR (95%CI)			aIRR (95%CI)		
	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.

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

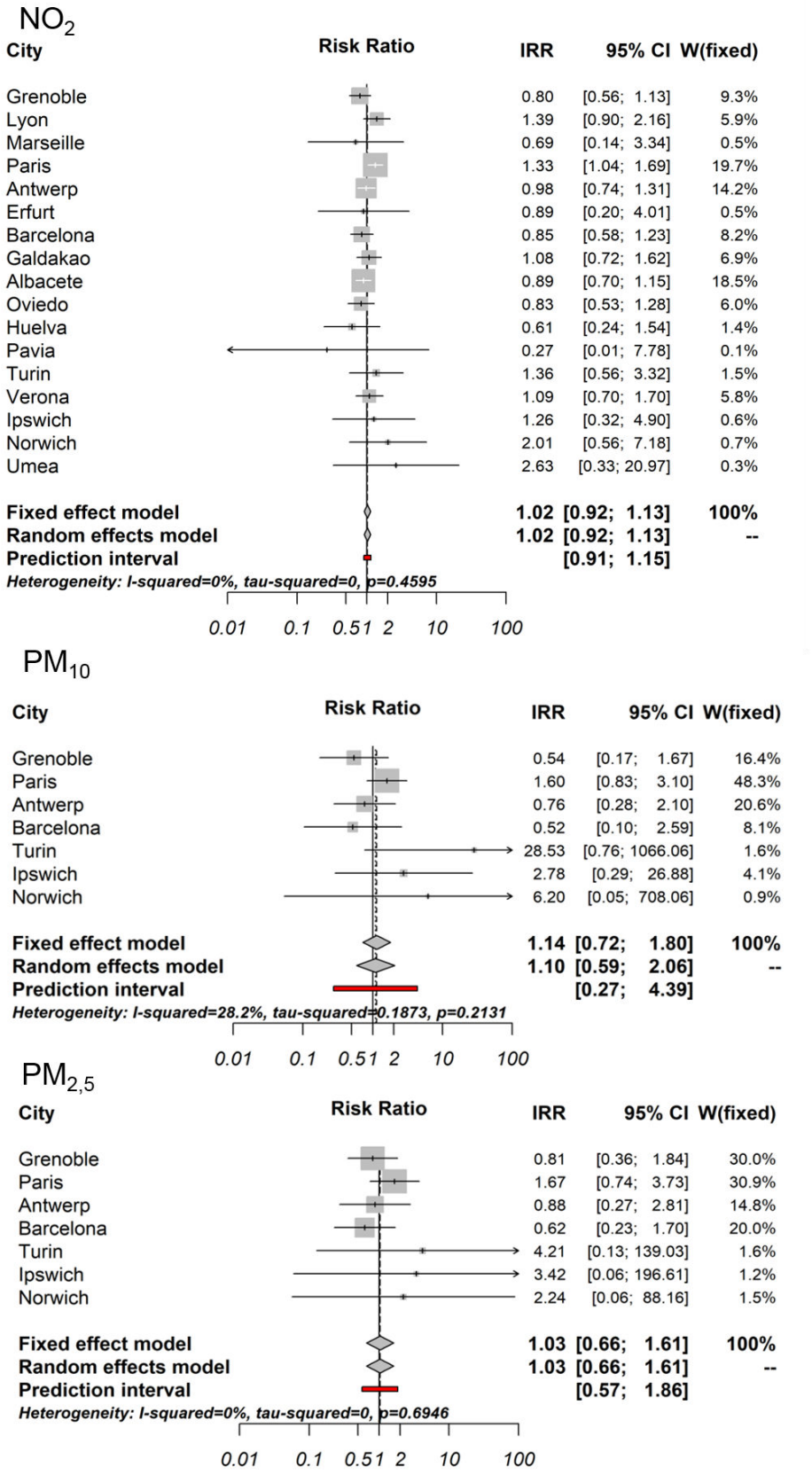

Figure 2 Association between NO_2, PM_{10} and $PM_{2.5}$ and incident rhinitis by city and meta-regression

Discussion

In this longitudinal analysis of two multicenter 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 literature as it is the first to have investigated the association between long-term air pollution and incident rhinitis in adults. However, our overall null findings reported are in line with those 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 also 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 a high incident 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 as 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 have 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 to 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 showed 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 female (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 that 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) which 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 but the interaction between air pollution

and allergens and particularly with pollen, further discussed below, also likely plays 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 climate but we found no clear geographical pattern of the association between air pollution and rhinitis incidence when looking at each city separately. Climate is associated to air pollution levels and may also acts 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, no data were available on climate change or on allergen concentration that 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 –and 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 any results. Furthermore, 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). Alike, our study which also used data from ESCAPE found results varying a lot according to the city and no clear pattern stood out.

In our study, stratifying by allergic sensitization enable 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 to air pollution, this measure was done at residential address and then may not take into account the correct annual personal exposure of each participant. However, this is a limitation that often comes up 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 taken 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 taken with caution.

The major strength of this study is the population coming from two multicentric cohorts, followed during more than 20 years, including 17 European cities with a detailed

characterization on respiratory phenotypes at both first and second follow-up and individual measure of exposure to air pollution, obtained within the ESCAPE project. This enabled us 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 and thus we based our definition of rhinitis on nasal symptoms (Cazzoletti et al. 2015; Rancière et al. 2016). This choice also enabled to stratify the results by allergic sensitization and then 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 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 where inconsistent findings (Guarnieri and Balmes 2014) have been reported

as well and where 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 very different patterns of possibly relevant etiologic co-factors 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 main analysis, bi-pollutant model or stratified analysis.

Conclusions: In this longitudinal study, we have studied 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 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 looking more deeply at the effect of air pollution on rhinitis phenotypes or rhinitis characteristics such as type of symptoms or severity.

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Supplementary material: Association between air pollution and rhinitis incidence in two European cohorts

5.4 Air Pollution increases the severity of rhinitis in two European cohorts

In preparation.

Air Pollution increases the severity of rhinitis in two European cohorts

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Abstract:

Introduction: Little is known about the effects of outdoor air pollution on severity of rhinitis. The objective is to assess the association between individual exposure to long-term air pollution and severity of rhinitis in two multicenter European cohorts on respiratory health (EGEA and ECRHS).

Methods: 1550 adults with rhinitis and available data on air pollution were included. Annual exposure to pollutants (NO_2, PM_{10}, $PM_{2.5}$ and PMcoarse) was estimated at participants' residential address using land use regression models derived from the ESCAPE project. Severity of rhinitis was defined in two ways: 1) according to the importance of the disturbance due to each of the four symptoms of rhinitis (runny nose, blocked nose, sneezing and itchy nose) categorized in 3 groups: no (reference), mild or moderate/severe rhinitis, 2) using an overall score of severity including disturbances to all symptoms, varying from 0 to 12, and categorized in quartile (reference: quartile 1). Adjusted polytomous logistic regressions with city as a random intercept were used.

Results: The 1550 adults with rhinitis (mean age=52.4yrs, 45% men, 75% from ECRHS) from 17 cities had a median[Q1-Q3] score of severity of 4[2-6]. Exposure to NO_2 was associated to an increased severity of runny and blocked nose, and exposure to PM_{10} was associated to an increased severity of the four symptoms, and particularly for moderate/severe rhinitis. Exposure to $PM_{2.5}$ was associated to an increased severity of blocked nose and sneezing, particularly for moderate/severe rhinitis and exposure to PMcoarse was associated to moderate/severe rhinitis for runny and blocked nose. Exposure to PM_{10}, $PM_{2.5}$ and PMcoarse were associated with an increased score of severity of rhinitis with an effect more evident for PM_{10} (aOR[95% CI], for quartile 2(qu2): 1.49 [1.05-2.12], for quartile 3(qu3): 1.35[2.07-3.19], for quartile 4(qu4): 1.41[2.37-3.97]).

Conclusions: Air pollution exposure is associated to an increased severity of rhinitis and particularly of blocked nose symptoms. Results differed according to the pollutants and to the symptoms of rhinitis.

Introduction

Rhinitis is a very frequent disease affecting between 20% and 50% of the population according to countries and definitions (1–3). Principal symptoms of rhinitis are sneezing and a runny, blocked or itchy nose, in absence of a cold or the flu (4). It is often considered as a trivial disease though it has an important impact on quality of life (5,6). Rhinitis is frequently associated with asthma for which air pollution has been shown to strongly aggravate symptoms (7,8). There are very few studies focusing on the effect of air pollution on rhinitis in adults.

Short-term exposure to air pollution has been associated to exacerbation of rhinitis leading to more daily visit to a clinician (9,10), but effect of long-term air pollution on rhinitis has been scarcely studied. In a previous study, we found no consistent evidence for an association between long-term exposure to air pollution and incidence of rhinitis (Burte et al., submitted). However, rhinitis is a complex disease with several phenotypes that often differ in term of symptoms, duration, treatment and/or severity (11,12) and the effect of air pollution on rhinitis may possibly differ according to the studied phenotypes. No study has assessed the effect of exposure to long-term air pollution according to the phenotypes of rhinitis, and particularly severity. Severity of rhinitis actually reflects the intensity of each symptom of rhinitis throughout its impairment of daily life (2). One 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 score of severity of allergic rhinitis and air pollutant level (13). Furthermore, the authors only considered seasonal allergic rhinitis and no other type of rhinitis.

In the present study, we aimed for the first time to study the association between long term exposure to air pollution and severity of the four principal symptoms of rhinitis in two European studies.

Methods:

Study design and participants

Participants included in the analysis were part of two large multicentre epidemiological European studies.

The Epidemiological Study on the Genetics and Environment on Asthma (EGEA (14,15), 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 1991–1995 from five French cities. A first follow-up has been conducted between 2003 and 2007 (EGEA2, N=2121, (14,16)) and a second follow-up between 2011 and 2013 (EGEA 3, N=1558 (17)).

The European Community Respiratory Health Survey (ECRHS, (18)) 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 two times: between 2000 and 2002 (ECRHS II, n=10933 (19,20)) and between 2011 and 2013 (ECRHS III, N=7040).

Participants of both studies have been 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 (Hôpital Necker–Enfants Malades, Paris, France, for EGEA; Comité de Protection des Personnes Participant à la Recherche Biomédicale de Bichat-Claude-Bernard, Paris, France, for ECRHS France), and written informed consent was obtained from each participant.

Population

This study included 1550 participants from EGEA3 and ECRHS III with rhinitis, having available data on rhinitis severity (for at least one of the four symptoms) and individual air pollution estimates (Flow-chart available in Figure 1).

Definition of rhinitis, severity of symptoms of rhinitis and asthma

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.

Report of allergic rhinitis or hay fever was defined as a positive answer to "*Do you have any nasal allergies, including hay fever?*" in ECRHS III and as a positive answer to "*Have you ever had allergic rhinitis?"* and/or "*Have you ever had hay fever?"* in EGEA3.

Severity of rhinitis for the following symptoms was assessed at EGEA3 and ECRHS III: 1) watery runny nose, 2) blocked nose, 3) itchy nose, 4) sneezing, especially violent and in bouts. For each of these four symptoms, participants had indicated how important it was 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

We used the classification similar to the ARIA guidelines (2) as follows: The category 0 was considered as the reference compared to mild rhinitis (1), and moderate/severe rhinitis (2/3). A numeric score, adapted from the Symptomatic Global Score for seasonal allergic rhinitis (SGS, (21)) was calculated according to the answer to the severity of the four symptoms, described above, summing the answers. Each symptom scoring from 0 (no problem) to 3 (problem that hampers certain activities or sleep), the overall score could vary between 0 and 12. This score was further considered in quartiles, with the lowest quartile as the reference.

Ever asthma was defined (22) 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 asthmatic cases in EGEA.

Estimation of air Pollution exposure

As part of the ESCAPE (European Study of Cohorts for Air Pollution Effects www.escapeproject.eu (23,24)) project, home address of each participant at the first follow-up of both studies (EGEA2 and ECRHS II) was geocoded and linked with ambient concentrations of NO_2 (nitrogen dioxide), PM_{10} (airborne particles with an aerodynamic diameter $\leq$10 µm), $PM_{2.5}$ (airborne particles with an aerodynamic diameter $\leq$25 µm), PMcoarse and $PM_{2.5}$ absorbance, developed between 2009 and 2010 using land-use regression (LUR) models. 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) 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. Estimates were calculated for an increase of 10 µg/m^3 for NO_2 and PM_{10}, 5 µg/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.

Statistical analysis

Association between air pollutants and the variables of severity of rhinitis were analysed using polytomous logistic regression. The estimates were adjusted for pre-selected variables based on

previous literature: age, sex, number of siblings, family history of allergy, smoking status, asthma status and report of allergic rhinitis or hay fever. To account for between-city heterogeneity, a random effects model with a random intercept for city was used. Analyses with traffic density or traffic load were further adjusted for NO_2 background level. Analyses were done using the gsem procedure from STATA (Stata 14) and R statistical software (R version 3.0.3).

This article is still in preparation. Principal results are reported below, however, several sensitivity analyses will be realised such as taking study into account, stratifying the results on sex, adjusting the results for allergic sensitization instead of report of allergic rhinitis, test for p-trend, etc.

Results:

Participants were on average 52.4 years old, 54.5% were women, 29.2% had asthma and 75% came from ECRHS study. The mean score of severity of rhinitis was 4.3 (median[Q1-Q3]=4[2-6]). A detailed description of the characteristics of the participants is available in Table 1 (the detailed description according to the study is available in Table 1 in the Supplementary Material)

The effects of air pollutants exposure on the symptoms are shown in figures 2 and 3 and exacts odds ratios are available in Table 2 in the Supplementary material.

Severity of blocked nose

Severity of blocked nose increased with air pollution exposure when compared to the reference (no symptom). A similar effect size was found for mild and moderate/severe rhinitis for NO_2, whereas there was a higher effect of PM_{10}, $PM_{2.5}$ and PMcoarse on moderate/severe than on mild rhinitis. Estimate of the association between PMcoarse and blocked nose was borderline significant for the mild category (See Figure 2). Traffic intensity increased the severity of runny nose only for mild rhinitis, but not significantly for moderate/severe rhinitis. No association was found between traffic load and severity of blocked nose (Figure 3).

Severity of runny nose

Severity of runny nose increased with air pollution exposure when compared to the reference. A similar effect size was found for mild and moderate/severe rhinitis for NO_2, even if the estimate for moderate/severe rhinitis was not statistically significant. There was a higher effect of PM_{10}, and PMcoarse on moderate/severe than on mild rhinitis and estimates for mild rhinitis

were not statistically significant. For $PM_{2.5}$, estimates were positive but not statistically significant for either mild or moderate/severe rhinitis (Figure 2). Severity of runny nose increased with traffic intensity, slightly more for mild than for moderate/severe rhinitis where results were borderline significant. No association was found between traffic load and severity of runny nose (Figure 3).

Severity of itchy nose

Severity of itchy nose increased with air pollution exposure when compared to the reference for all pollutants, except for NO_2. For PM_{10} and $PM_{2.5}$, results were similar to those for runny nose, and for PMcoarse, estimates were positive but not statistically significant for both severity, although higher for moderate/severe rhinitis. For NO_2, estimate was null for mild and negative for moderate/severe rhinitis (Figure 2). No association was found between traffic load or traffic intensity and severity of itchy nose (Figure 3).

Severity of sneezing

Severity of sneezing increased with air pollution exposure when compared to the reference (Figure 2). A similar effect size was found for mild and moderate/severe rhinitis for NO_2 and PMcoarse, but estimates were not statistically significant. For PM_{10} and $PM_{2.5}$, results were similar to those for runny nose. No association was found between traffic load or traffic intensity and severity of sneezing (Figure 3).

Score of severity

Increase in air pollution exposure was associated with an increased score of severity of rhinitis (Figure 4). For NO_2, a similar effect size was found for the three quartiles, with ORs around 1.13, borderline significant for quartiles 3 and 4. For PM_{10}, $PM_{2.5}$ and PMcoarse, estimates increased with the quartiles and were all statistically significant, except for the estimate of quartile 2 of PMcoarse. No association was found between traffic load or traffic intensity and score of severity.

Discussion

In 1550 participants from two European studies with detailed characterization of rhinitis, we have investigated for the first time 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, with a higher effect on moderate/severe than on mild rhinitis. To a lesser extent, an increase in PMcoarse or NO_2 also increased the severity of rhinitis, but

only for some symptoms of rhinitis. No association was found between traffic load or traffic intensity and severity of rhinitis.

To our knowledge, our study is the first one to assess effect of air pollution on severity of different symptoms of rhinitis, and not specifically on allergic rhinitis. Our results are consistent with a previous French study that has assessed the association between seasonal allergic rhinitis (SAR), grass pollen counts and air pollution. This study found a positive association between air pollution level and SAR severity, but not statistically significant (13). However, results are not exactly comparable as they considered a particular phenotype of allergic rhinitis and as their results were adjusted on grass pollen counts. We had no data on pollen concentration to compare with. However, as air pollution and pollen interact with each other (25), it may indeed be very interesting to consider both factors together in the study of allergic rhinitis.

An asset of our study is that we considered patients with both allergic and non-allergic rhinitis and even if the ARIA classification on severity has been initially build for allergic rhinitis, this classification may be extended to other types of rhinitis. Indeed, questions used to define severity are not particularly related to the allergic facet of the disease. The cut-off of the categories and the questions used by ARIA in the definition of severity have been discussed in the literature, one study has suggested to consider “high” severity apart (26), but another study have shown that this distinction would not add much clinically (27). Anyway, in our study we would not have enough power to distinguish the moderate from the severe rhinitis.

Rhinitis is usually defined not by one symptom only, but by the combination of several symptoms of rhinitis, characterizing the disease as a whole (2). That is why we have considered the score of severity: to appraise the general effect of long-term air pollution on rhinitis severity. On the other side, mechanisms of the effect of air pollution exposure may differ according to the type of symptoms. Particularly, some symptoms are generally more related to allergic rhinitis than non-allergic or vice versa (12), and separating the symptoms may give a different vision of the effect of air pollutant on rhinitis severity, according to the allergic type of rhinitis. In our study, results differed according to the symptom, however higher estimates were found for the “blocked nose” that is common in both allergic and non-allergic rhinitis. We did not highlight differences according to any of the other symptoms.

Generally, we have found a higher effect of exposure to PM on moderate/severe rhinitis and it may suggest that individuals with a more severe phenotype of rhinitis are more susceptible to

the effect of exposure to air pollution. This different effect size was not found for NO_2 for which the estimates were much smaller than for PM.

Using data from 1550 adults with rhinitis from two European studies on respiratory health, we showed that long-term air pollution exposure was associated with an increased severity of rhinitis and particularly with blocked nose symptom. Results were particularly high for PM for which a trend association was found with severity of rhinitis. These results are of particular importance as rhinitis is a hidden major public health challenge and or results contribute to a better understanding of the environmental factors od the diseases.

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Table 1 Characteristics of the participants

Variable	ALL N=1550	Score of Severity				
		Quartile 1 N= 431	*Quartile 2 N=426*	*Quartile 3 N=257*	*Quartile 4 N=322*	*p-value*
Age, mean±sd	52.4±10.9	54.1±9.7	52.6±10.4	50.4±11.1	50.5±10.5	<0.001
Study, % EGEA	24.9	13.9	20.0	24.9	25.5	<0.001
Sex=women, %	54.5	51.0	52.3	59.1	57.5	0.1
Smoking status, %						0.005
current	18.1	19.8	17.7	23.6	13.0	
ex-smoker	37.8	39.5	40.8	29.9	37.8	
never	44.1	40.7	41.5	46.5	49.2	
Educational level, %						0.356
low	21.6	21.5	17.7	22.4	25.2	
medium	29.8	29.7	30.8	28.0	29.0	
high	48.5	48.8	51.6	49.6	45.9	
Asthma ever, %	29.2	18.1	28.5	32.2	38.9	<0.001
Asthma age of onset, mean±sd	16.4±14.0	16.8±13.8	18.2±14.6	16.1±13.9	15.6±13.3	0.53
Report of AR or hay fever, %	58.8	35.0	58.8	70.1	81.6	<0.001
Allergic sensitization, %	48.1	36.2	46.2	48.1	64.3	<0.001
NO_2, m g.m^{-3}, mean±sd	28.9±14.4	28.2±14.1	30.5±14.8	30.4±15.0	30.8±14.2	0.047
PM_{10}, m g.m^{-3}, mean±sd	25.2±6.7	24.1±6.3	24.9±7.0	25.9±7.0	26.7±7.2	0.0007
$PM_{2.5}$, m g.m^{-3}, mean±sd	15.3±3.7	14.5±3.4	15.3±4.1	15.6±3.7	15.9±3.8	0.0012
Pmcoarse, m g.m$^{-3,}$ mean±sd	10.0±3.8	9.7±3.8	9.8±3.6	10.3±3.9	10.8±4.3	0.015
Traffic load, mean	1573040	1429407	1495923	1752656	1751743	0.49
Traffic intensity, mean±sd	5721±9994	4339±7165	5576±9197	7132±13235	6439±11877	0.0124
Severity of runny nose						
no	26.3	57.77	23.0	11.3	2.8	<0.001
mild	36.8	37.82	59.4	34.6	9.0	
moderate/severe	36.9	4.41	17.6	54.1	88.2	
Severity of blocked nose						<0.001
no	31.9	72.16	26.5	14.0	2.2	
mild	25.2	22.51	44.6	20.2	9.0	
moderate/severe	43	5.34	28.9	65.8	88.8	
Severity of itchy nose						<0.001
no	44.1	82.6	47.0	28.4	6.2	
mild	31.6	16.47	49.1	44.4	17.7	
moderate/severe	24.2	0.93	4.0	27.2	76.1	
Severity of sneezing						<0.001
no	30.4	61.48	29.3	16.7	3.7	
mild	37.3	35.73	56.3	39.7	37.7	
moderate/severe	32.3	2.78	14.3	43.6	31.3	

Figure 1: Flow-chart of the participants

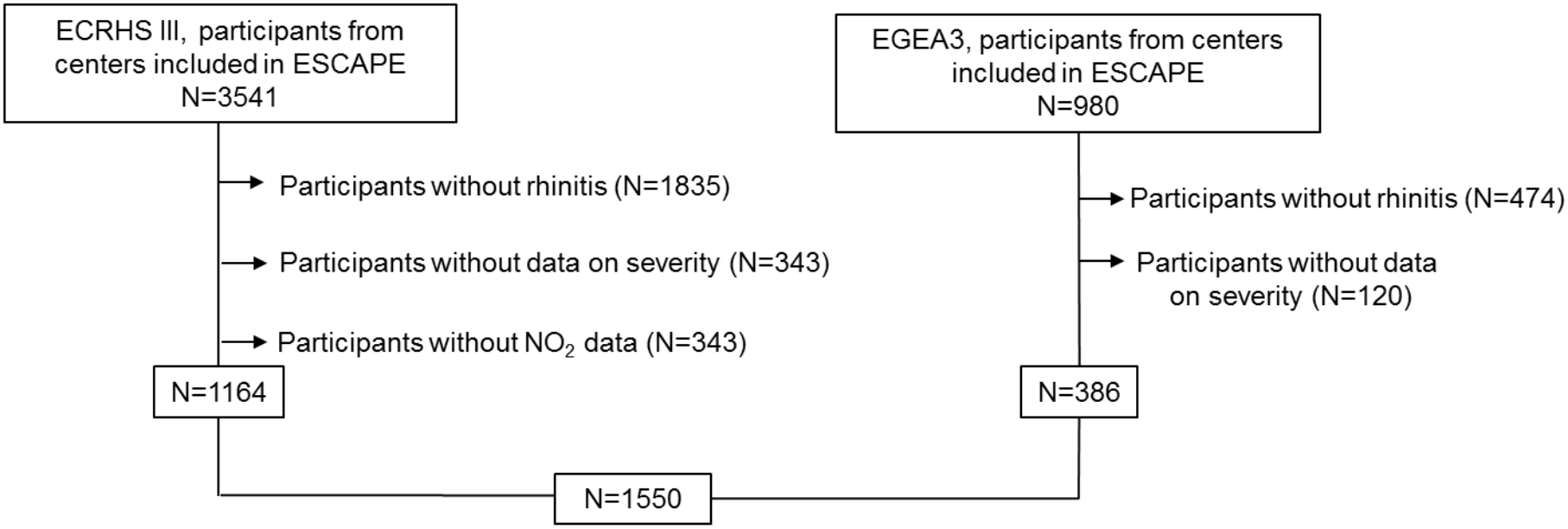
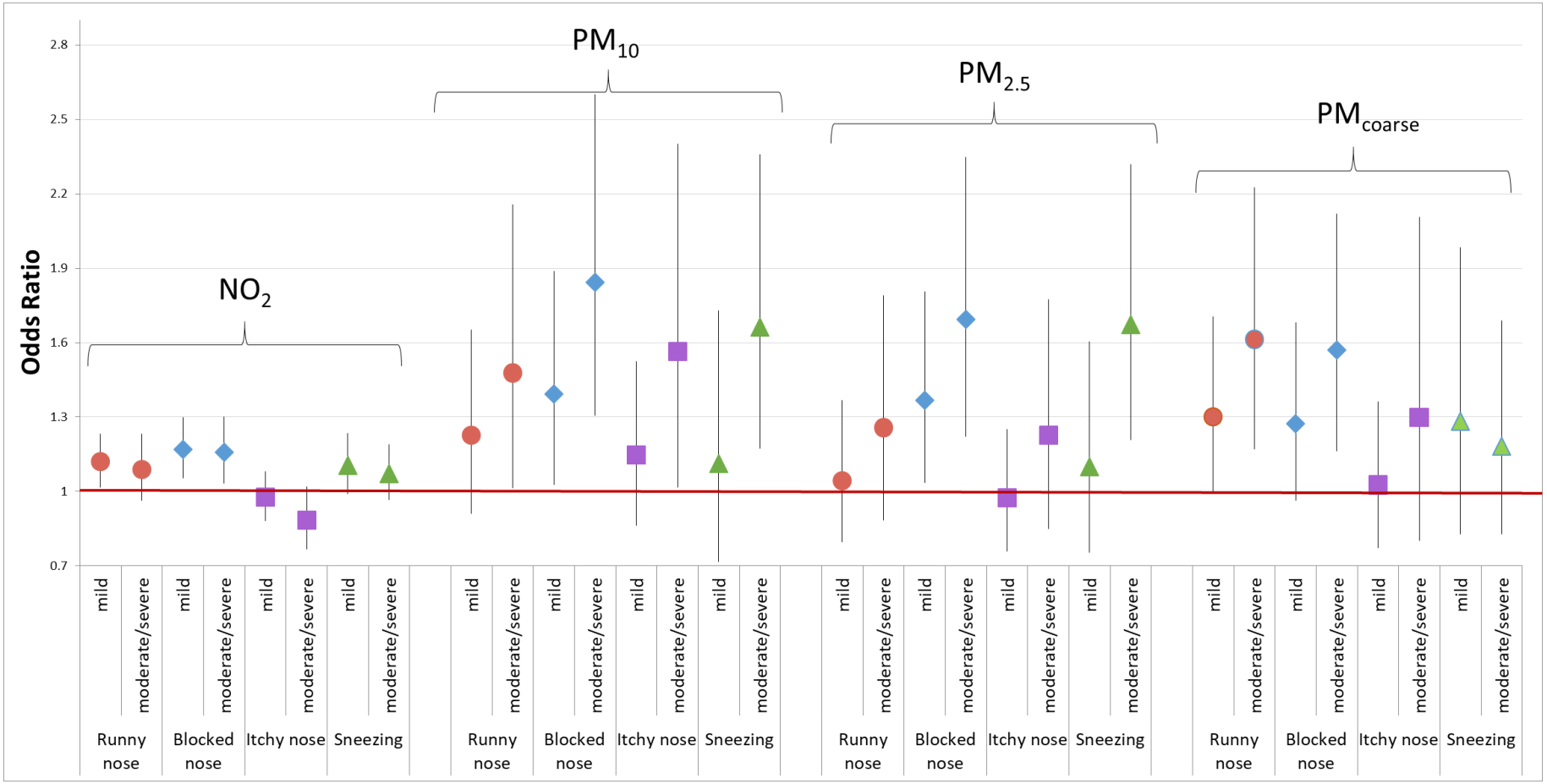
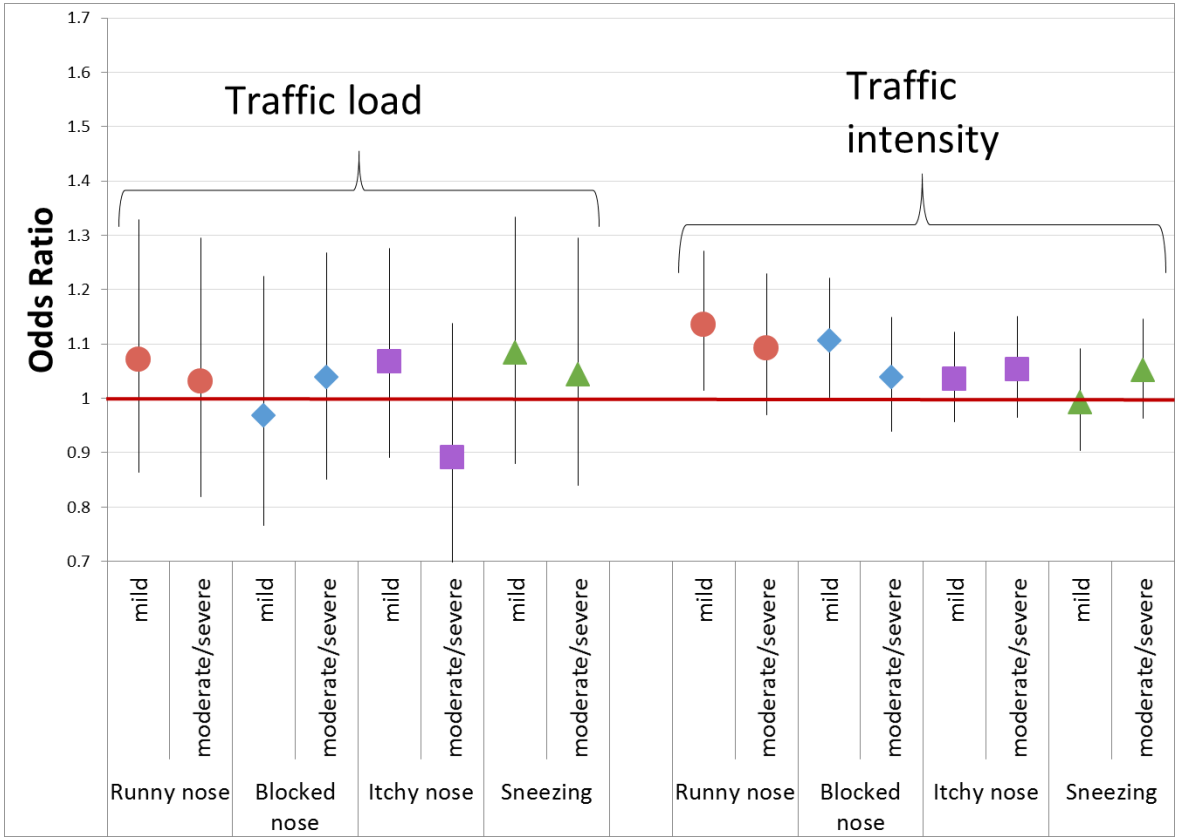


Figure 2: Association between exposure to NO_2, PM_{10}, $PM_{2.5}$ and PM coarse and the severity of the four main symptoms of rhinitis



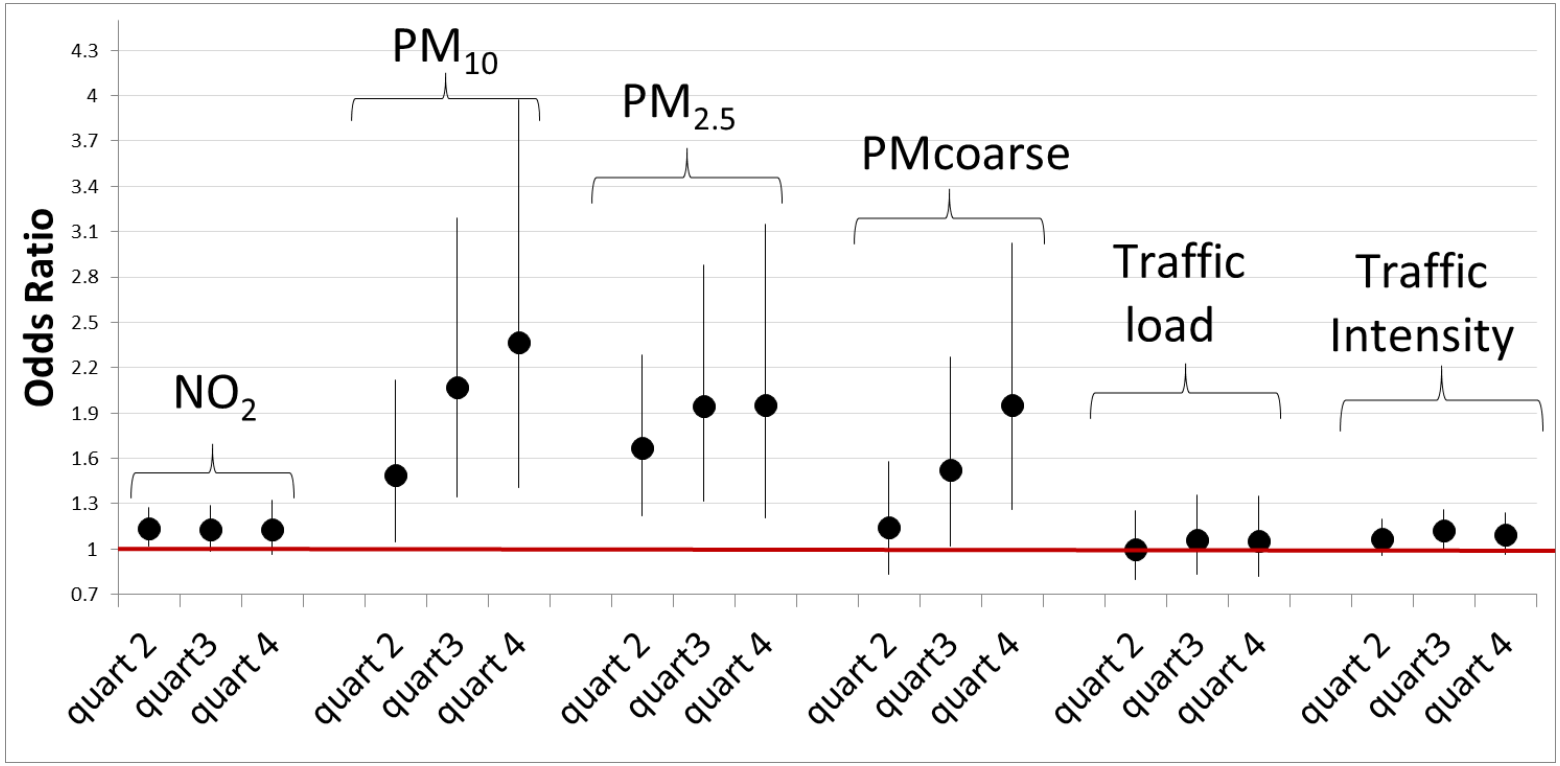
Reference : no problem (symptom not present), Odds Ratio adjusted for age, sex, smoking status, number of siblings, family history of allergies, asthma, and report of nasal allergies or hay fever, with city as a random intercept. Estimates are presented for an increase of 10 µg/m3 for NO_2 and PM_{10} and 5 µg/m3 for $PM_{2.5}$ and PMcoarse.

Figure 3: Association between traffic load and traffic intensity and the severity of four symptoms of rhinitis



Reference : no problem (symptom not present), Odds Ratio adjusted for age, sex, smoking status, number of siblings, family history of allergies, asthma, report of nasal allergies or hay fever and NO_2 background, with city as a random intercept. Estimates are presented for an increase 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.

Figure 4: Association between all air pollutants metrics and score of severity of rhinitis expressed as quartiles



Reference : quartile 1, Odds Ratio adjusted for age, sex, smoking status, number of siblings, family history of allergies, asthma, report of nasal allergies or hay fever (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/m3 for NO_2 and PM_{10} and 5 µg/m3 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.

Supplementary Material: Air Pollution increases the severity of rhinitis in two European cohorts

6 DISCUSSION & PERSPECTIVES

This thesis is based on data from two epidemiological European studies with participants having a detailed questionnaire on rhinitis and individual annual air pollution estimates. This gave us the opportunity to better understand rhinitis phenotypes and to study the association between exposure to outdoor air pollution and rhinitis.
Our results have been discussed in the published or ongoing articles (see section 5), and we will provide here an overview of the main findings and a general discussion. We will also discuss some perspectives and the public health impact of our findings.

6.1 Characterization of rhinitis

There are many epidemiological studies on rhinitis, most of them focusing on allergic rhinitis. The clinical diagnosis is rarely available in epidemiological studies where rhinitis is mostly defined using questionnaires, and whatever the considered phenotypes of rhinitis, there is no consensus on rhinitis definition or characterisation. In this thesis, we aimed to better understand phenotypes of rhinitis assessed by questionnaire.

We have first used an unsupervised approach to obtain phenotypes of rhinitis without any *a priori* knowledge of the disease, separately in asthmatics and non-asthmatics to take into account the comorbidity between the two diseases. Whatever the asthma status, we have identified 3 clusters of rhinitis that could easily be assimilated to no rhinitis, non-allergic rhinitis and allergic rhinitis. We validated and confirmed phenotypes of rhinitis often described in the literature, but for the first time highlighted in a statistical way. These clusters may be considered as "smoothed" phenotypes compared to the traditional phenotypes defined using only nasal symptoms and allergic sensitization. This work also showed that the pattern of allergic sensitization was strongly different according to combined phenotypes of asthma and rhinitis. We have then decided to further explore the link between asthma, rhinitis and allergic sensitization. We have found that allergic sensitization and particularly polysensitization strongly differed according to asthma and

rhinitis phenotypes, and that sensitization must probably not be used as a dichotomic variable. We have also emphasized the combined phenotype of asthma+AR as particularly severe and polysensitized.

All these results were found using data from a case-control and familial study on asthma, and thus cannot be generalized to the whole population. Indeed, the prevalence and incidence rates of rhinitis we observed in our population is somehow higher than we could have expected, even if there is no real literature in general population to compare with. The analyses were done according to the asthma status to disentangle what may come from the association between rhinitis and asthma and what is a more general result on rhinitis, and took into account the familial design of the study. Although not generalizable, the phenotypes we found are similar in participants with and without asthma and concordant with the ones that clinicians usually see in their practice. Our results are based on rhinitis assessed only by a questionnaire and no clinician has validated the diagnosis of rhinitis. This is a common limitation in epidemiological study. However, rhinitis is often considered as a trivial disease and individuals with rhinitis often do not seek for medical advices: questionnaire-based study may be a unique way to catch these individuals and to take them into account in the study of rhinitis.

In epidemiology, there is no "gold standard" for the definition of rhinitis phenotypes leading to a wide range of prevalence, estimation of costs and characteristics of the disease. Our cluster-based phenotypes emphasized the fact that patient's history is primordial to the diagnosis of rhinitis, and that allergic sensitization may not be enough to correctly distinguish between allergic and non-allergic rhinitis. This is a strong assumption as distinction between AR and NAR is often made using SPT or specific IgE only. However, this assumption seems plausible as it is concordant with several previous studies (5,19,34). It is worthy to keep in mind these results for future epidemiological studies on rhinitis. In clinical practice, allergy testing is recommended for patients who already have clinician diagnosis of AR, "*who do not respond to empiric treatment, or when the diagnosis is uncertain, or when knowledge of the specific causative allergen is needed to target therapy*" (198). In epidemiological studies, clinician diagnosis is not available, but considering only allergic sensitization at a first rank may be misleading.

Our second study emphasizes that allergic sensitization is of first importance in the care of rhinitis and asthma, and beyond the dichotomic response, the level of allergic sensitization also provides a wealth of information on the disease. When available, we strongly recommend to use the level of allergic sensitization instead of considering only the presence of allergic sensitization, and particularly when studying rhinitis or asthma.

A recent report in the Lancet raised the need to redefine airways diseases and particularly to rethink asthma, by deconstructing the disease into identifiable and treatable traits and "*less emphasis on arbitrary diseases labels*" (199). For rhinitis, it may also be necessary to rethink the disease and particularly in epidemiological studies. Over the years, questions used to define rhinitis have evolved: initially, questions were often related to hay fever or to seasonality and little by little the use of one simple question on the four symptoms of rhinitis is becoming more common. The diagnosis of rhinitis probably needs to be based on this simple question on symptoms, and to further distinguish treatable traits for rhinitis, one need to consider 1) what triggers the symptoms and 2) the co-occurrence of other respiratory or allergic diseases. In our first work, we have shown that self-report of both sensitivity to hay/flowers and of allergic rhinitis -or hay fever- helped to differentiate the type of rhinitis and several studies have also enhanced the importance of the initial trigger. Thus, finding out if the initial cause of the disease is from allergic or non-allergic source (or both) is crucial. Diagnosis and treatment are strongly dependent on the initial cause of the disease, and focusing on the trigger will probably enable to adapt treatments and recommendations. The second point refers to comorbidity or multimorbidy. Asthma and rhinitis are so entangled that considering both diseases separately may lead to a loss of knowledge. In the past years, several studies including ours have brought forward the combined phenotype of asthma and allergic rhinitis as having specific characteristics, and associated with specific genetic variants (84,100,200–202). Besides asthma, considering the combined phenotype of two or more diseases may lead to a more specific and adapted treatment.

Since ARIA has published guidelines on the definition of severity and frequency of rhinitis, the literature is much more comparable regarding these two characteristics. We think that similar guidelines for the definition of rhinitis in epidemiological study, indicating which principal question(s) should be used, is a real need to improve research area in rhinitis. Similarly, specific guidelines on "*how to distinguish between AR and*

NAR" or even more "*how to distinguish between rhinitis phenotypes*" in epidemiological studies would enable to consider not only AR but also other phenotypes in most of the literature. However, the question may not be how to distinguish allergic and non-allergic rhinitis, but rather how to distinguish different "traits" of rhinitis, and within these traits, what is from allergic or non-allergic origin. Phenotypes can be described on the basis of several characteristics such as allergic sensitization, predominant symptom, severity or duration of the disease or response to specific treatment (203); whatever the approached angle, there is a need to standardise rhinitis definition and characterization. Such recommendations would improve not only knowledge on rhinitis, but also knowledge on asthma and on other comorbid diseases.

From a public health perspective, rhinitis care is complicated as most of the individuals suffering from rhinitis consider the condition as trivial and rarely seek for medical care. Those suffering from both asthma and rhinitis are probably better managed as the physician treating asthma will also consider symptoms of rhinitis. Despite its high prevalence, rhinitis is poorly known and the first primary prevention step will be improving the information on the disease. Rhinitis is too often resumed to allergic rhinitis and it is time to look beyond and consider the other phenotypes that are often associated with specific treatment or recommendation. This awareness is important including for general practitioners as they are the first step in rhinitis care. However, it is important to acknowledge that among individuals suffering from rhinitis, only a small part is managed by a physician, including general practitioners: most patients ignore their conditions and have no treatment -what is *per se* not a problem if symptoms are mild-, and others make a large use of over-the-counter medications, that is nowadays not always associated with pharmacist advices. Management of rhinitis is really heterogeneous (specialist, general practitioner, pharmacist or no professional) and a multilevel prevention plan is necessary. The MACVIA-ARIA Sentinel NetworK (MASK) for allergic rhinitis aimed to fill several unmet, among which the set-up of a multidisciplinary team for integrated care pathways "*structured multidisciplinary care plans which detail essential steps in the care of patients with a specific clinical problem*". It would be interesting to further integrate all the phenotypes of rhinitis in the MASK project.

6.2 Effect of outdoor air pollution on rhinitis

The continuous increase in prevalence of rhinitis these last decades is probably multifactorial, but changes in environmental factors, including air pollution have for sure an important role in the disease development. However, there are almost no study on the effect of outdoor air pollution on rhinitis and no study on incidence of rhinitis. We aimed to assess the association between exposure to air pollution and incidence of rhinitis, and phenotypes of rhinitis, namely severity. We have first studied the association between individual exposure to traffic-related air pollution and incidence of rhinitis in two large European cohorts. We found no consistent evidence of an association between long-term exposure to air pollution and incidence of rhinitis, whether in single pollutant or two-pollutant model. We found a negative association between air pollution on rhinitis among male participants and among those with allergic sensitization. The strength and direction of the associations between air pollutants and incident rhinitis differed across the 17 European cities but no statistically significant heterogeneity was found and no regional pattern stood out. We have further studied the association between exposure to traffic-related air pollution and severity of rhinitis, as a particular phenotype of rhinitis. We found that a higher annual exposure to traffic-related air pollution was associated with an increased severity of rhinitis, particularly for the "blocked nose" symptom. The association was stronger for all PM metrics than for NO_2 and remained when the city was considered as a random effect.

Our results used annual individual exposure to several air pollutants estimated at the home's addresses, and thus other exposures such as the ones at work or during commuting are unknown. This is a usual limitation of air pollution assessment in environmental epidemiology, and continuous researches are ongoing to offset this problem. Since the ESCAPE project, technological advances in several exposure assessment methods such as Integrated Meteorological-Emission Models or the use of satellite observations (204) have occurred. These improvements will definitely help in the precision of pollutant exposure assessment at home, work and/or school addresses, but the difficulty in assessing exposure during commuting, considered as a high-exposure period, still remains (205,206). There have also been improvements in personal devices related to the weight and constraints of carrying permanently the device. However, such a personal exposure is for now not feasible in large epidemiological studies because of elevated costs and at

this time, the best method seems to be combining different exposure assessments. Similarly to various studies assessing the effect of air pollution on health outcomes, some of our results changed according to the pollutant, making the interpretation of the results more complex. Whereas NO_2 is often considered as a marker of traffic, PM is directly associated to traffic, but it is actually a mixture of several components (117). For now, recommendations are going in the directions of new exposure metrics such as the composition of PM, its oxidative potential and ultra-fine particles that are probably the more harmful type of PM. The difficulty in air pollution exposure assessment remains that an individual is exposed not to one or few pollutants, but actually exposed to a cocktail of pollutants.

Our work is based on data from two longitudinal epidemiological studies using questionnaires and in that respect, one of the limitation of this kind of studies is the loss to follow-up and missing data. We acknowledge that we did not have dealed with this complicated problem in our analyses -as most of the studies in this field-. It would have been a real asset to consider this issue by using adapted methodologies such as ponderation, multiple imputation or Bayesian approach (207,208). However, we do not think that these methods would have change the conclusion of our analyses. Another important point is that we had no data on climate that is known to be directly associated to air pollution level (209). Short-term changes in climate are directly linked to short-term air pollution level and from a long-term point of view, climate change may also affect air pollution levels (210). On the other hand, climate change is directly associated to rhinitis as climate may act on the allergens by altering local and regional allergen production or by increasing the allergenicity of pollen (210,211). Furthermore, prevalence and specificity of rhinitis seem to be strongly region or country dependent (49) and pollution also varies a lot according to the region: climate plays a role in this heterogeneity, together with other social or economic factors (*i.e.* percentage of diesel cars). The association between air pollution and asthma was found to differ according to the regional climate in Italy (212) and this is in line with our study where the association strongly differed by city.

Pollen exposure is directly associated to allergic rhinitis incidence and prevalence and it has also been associated to severity of allergic rhinitis (177). More generally, allergen exposure is associated to both air pollution and allergic rhinitis and thus is a possible

confounding factor in the association between air pollution and allergic rhinitis. Unfortunately, we had no data on level of pollen or allergen exposure and could not take into account this factor. As air pollution, climate and allergen –and particularly pollen-concentration seem to be strongly interrelated,there is clearly a need to further study the role of the interactions between these three environmental factors and respiratory diseases and in particular rhinitis (213,214).

We did not find any association between exposure to air pollution and incident rhinitis, however, it does not mean that air pollution does not contribute to the development of the disease, but probably that air pollution is only one component of complex interplay between many environmental and genetic factors. In this thesis we have focused on outdoor air pollution and specifically to traffic-related air pollution, but the indoor pollution may be as harmful as the outdoor one. Furthermore, some genetic susceptibilities have already been suggested for the effect of air pollution on allergy or asthma (215) and it could be interesting to study gene-environment interactions in rhinitis as well.

We found no effect of air pollution on the development on rhinitis in adults, but we must stress that rhinitis generally occurs early in life and even if we considered a large number of incident cases, we may possibly think that individuals with late age of onset belong to a specific phenotype of rhinitis and thus are not well adapted to study the general effect of pollution on incidence of rhinitis.

Lastly, there are several types and phenotypes of rhinitis and the underlying biological mechanisms of the effect of air pollution on rhinitis may differ according to these phenotypes and particularly according to the allergic or non-allergic types of rhinitis. Our results were along these lines as they differed according to allergic sensitization status. There are currently many studies considering allergic outcomes but very few on non-allergic ones (216), and as there are no clear definition for AR or NAR, results are and will be difficult to compare and interpret. In the future, once the definition of rhinitis phenotypes will be validated and/or standardized, it will be interesting to further assess the association between exposure to air pollution and the different phenotypes of rhinitis. In addition, in a large study with enough power, studying the effect of air pollution on combined phenotypes of asthma and rhinitis may be relevant for both the study of the diseases and the study of air pollution effect. To go above and beyond, integrating

biological markers in the study of the association between air pollution and rhinitis may help to better understand the underlying mechanisms of the association. Particularly, markers related to inflammation and to oxidative stress could be of high interest as they are involved in rhinitis physiopathology but also in the mechanisms of damages due to air pollution.

Several health outcomes have been already associated to air pollution, and the harmfulness of air pollution is now established. We have found that long-term exposure to air pollution increases rhinitis severity and even though it is a lesser evil compared to effect on mortality or life-threatening diseases, it is associated to a strong daily impairment and high cost to society. Anyway, to encourage stakeholders to take steps to improve air pollution worldwide, one needs to continue focusing the effect of air pollution on human health to increase scientific proofs. Most of the studies on the effect of air pollution on health have been conducted in industrialized countries where air pollution levels, although high, are paltry as compared to the levels in some newly industrialized countries such as India or China where the situation is worrying. Scientific proofs will probably be even more striking in such countries and may help moving faster in a worldwide action.

7 CONCLUSION

The objective of this thesis was firstly to improve the characterization of rhinitis in epidemiological study and secondly to study the association between long-term exposure to air pollution and rhinitis. When considering rhinitis, we have shown that allergic sensitization should be considered together with the clinical characteristics of the patients and not only on its own. One also needs to take advantage of the information that allergic sensitization test provide: when several tests are performed, the number of positive tests may help to appraise the severity of the disease, and to point the adequate treatment. Finally, when asthma and rhinitis co-occur, a common approach of the two diseases rather than considering each one individually may help to take into account the multimorbidity between the two diseases; this also extends to other comorbities. Specific guidelines clarifying the relevant questions to define rhinitis in epidemiological studies are further needed. This will be useful for the study of rhinitis and also for studying environmental factors of rhinitis, including air pollution. For the first time we have studied the association between individual exposure to long-term air pollution and rhinitis. We found no association between long-term air pollution and incident rhinitis, but we showed that air pollution increases the severity of rhinitis. In the future, it could be interesting to consider both genetic susceptibility and biological markers underlying the association between air pollution and rhinitis.

Our results shown that rhinitis need to be better characterized in epidemiological studies, and this recommendation can also be extended to clinical practice. A better characterization will help in the management and the treatment of the disease. We found an association between long-term exposure to air pollution and severity of rhinitis and this is enough to re-emphasise that air pollution needs to be controlled.

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9 APPENDICES

Appendix 1 Susceptibility factors Relevant for the Association Between Long-Term Air Pollution Exposure and Incident Asthma.

Appendix 2 Socioeconomic position and outdoor nitrogen dioxide (NO2) exposure in Western Europe: A multi-city analysis.

Appendix 3 Supplementary Material: Characterization of rhinitis according to the asthma status in adults using an unsupervised approach in the EGEA study

Appendix 4 Supplementary material: The sensitization pattern differs according to rhinitis and asthma multimorbidity in adults: the EGEA study

Appendix 5 Supplementary material: Association between air pollution and rhinitis incidence in two European cohorts

Appendix 6 Supplementary Material: Air Pollution increases the severity of rhinitis in two European cohorts

Appendix 7 Substantial abstract in French

9.1 Appendix 1 Susceptibility factors Relevant for the Association Between Long-Term Air Pollution Exposure and Incident Asthma.

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Susceptibility Factors Relevant for the Association Between Long-Term Air Pollution Exposure and Incident Asthma

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Abstract In this review, we identified 15 studies in children and 10 studies in adults that assessed the association between long-term exposure to air pollution and incident asthma and that conducted stratified analyses to explore potential susceptibility factors. Overall, adult never-/former smokers seem to be at higher risk of incident asthma due to air pollution. Children without atopy and children from low socioeconomic status families also seem to be at higher risk of incident asthma due to air pollution. While interaction between air pollution and genes involved in the response to oxidative stress pathways have been explored, results are somewhat inconsistent and in need of replication. To evaluate interactions, large sample sizes are necessary, and much more research, including data pooling from existing studies, is needed to further explore susceptibility factors for asthma incidence due to long-term air pollution exposure.

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Keywords Air pollution · Incident asthma · Susceptibility factors · Long-term exposure

Introduction

Ambient air pollution has been associated with several health outcomes such as cardiovascular and respiratory diseases [1], lung cancer [2] or low birth weight [3]. Some specific population groups seem to be more sensitive to air pollution effects such as children, elderly people, overweight or obese individuals [4], and subjects with chronic respiratory disease such as asthma [5] or chronic obstructive pulmonary disease [6]. Sex differences have also been found [7]. Regarding air pollution, there is no consensus on specific susceptibility factors that would be common across all health outcomes. The association between air pollution and asthma has been widely studied. Some studies evaluated acute exposure to air pollution and its relation with asthma exacerbation or hospitalization [8]; others have evaluated long-term air pollution and its relation with prevalence and incidence of asthma [9]. To our knowledge no (systematic) review has evaluated potential susceptibility factors in relation to the effects of air pollution on incident asthma. Thus, the aim of this review is to fill in this gap by summarizing results from studies that reported on air pollution and incident asthma while stratifying according to possible susceptibility factors.

Methods

This review focuses on studies that assessed the effect of long-term air pollution on asthma incidence and reported stratified analysis on possible susceptibility factors. Through PubMed research, we selected articles in peer-reviewed journals. The

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search terms included "air pollution" and "asthma or wheeze"—in the title or abstract—and "inciden*" or "onset." The search resulted in 272 papers, for which we screened the title, abstract and full article when necessary to identify studies according to the criteria that will be described here. We also compared the list with recent reviews based on the effect of air pollution on asthma [8–10], confirming that our search did not miss any eligible papers. We included only articles in English, in adults or children (not animals), that studied long-term pollution effects on incidence asthma and that stratified according to possible susceptibility factors (a flow chart of the article selection is available in Fig. 1).

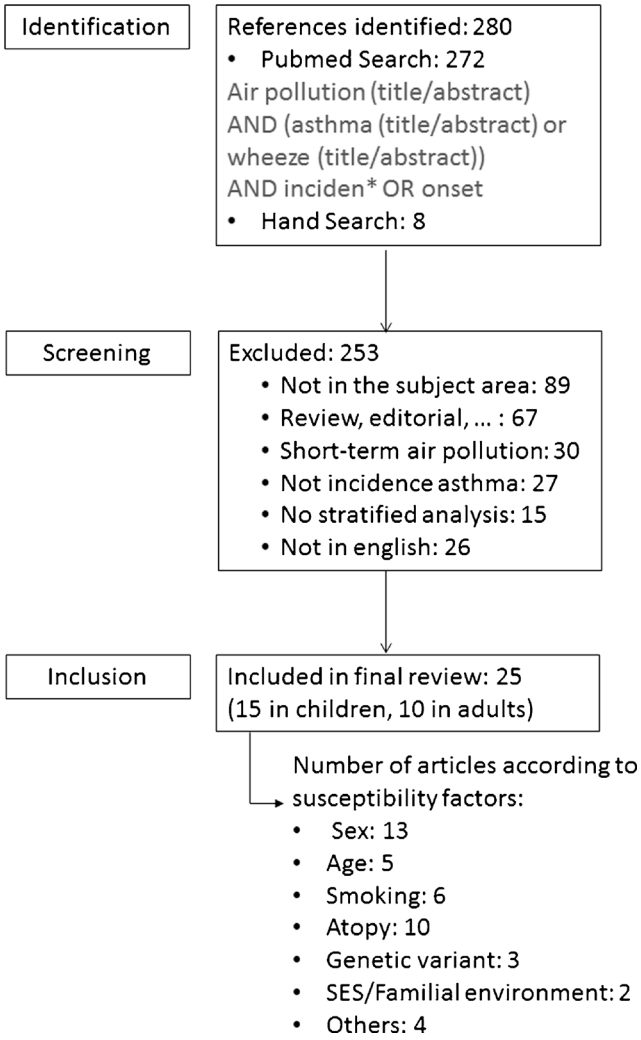

Fig. 1 Flow chart of the article selection

Pollution Exposure

Pollutants studied in the articles were: nitrogen oxides (NOx), nitrogen dioxide (NO_2), particulate matter up to 10 μm (PM_{10}), particulate matter up to 2.5 μm ($PM_{2.5}$), ozone (O_3), sulfur dioxide (SO_2) and soot. Most of the papers included in this review used modeled [land-use regression (LUR) or dispersion models] exposure at individuals' residential addresses [11–18, 19•, 20–25, 26•]; one study used modeled individual exposures at both home and school addresses [27]. Three articles used proximity to traffic/major roads as a proxy of air pollution exposure; one relied on the residential address [28], one on school and home addresses [29], and one only on the school address [30]. Two studies used community exposure to air pollution as proxies of individual exposure [31, 32], and three studies used zip code level exposures corresponding to home and work/school [33–35].

Asthma Incidence

In adults, incident asthma was the variable of interest, whereas in children incident asthma or incident wheeze was considered. Incident asthma or wheeze was assessed mostly using questionnaires, and questions used across studies vary from report of asthma symptoms to report of diagnosed asthma (parental report for children). Five studies used a physician diagnosis of incident asthma (personal visit to the physician) [17, 18, 20, 29, 35]. One study used the asthma symptom score as a proxy to identify asthma incidence [23].

Susceptibility Factors

The susceptibility factors of a priori interest were:

Age: the effect of air pollution exposure could differ according to each stage of life [4] (in particular in the prenatal period [36], early childhood and the elderly [37]). Actually, regarding age, two concepts appear: on the one hand the age of exposure and on the other the age at diagnosis. Regarding the first, it is possible that there are different windows of susceptibility. Regarding the latter, it is well known that childhood asthma is different from adulthood asthma, and, within adulthood asthma, teenage or elderly asthma can be also different phenotypes; thus, air pollution could have a different effect on these different phenotypes. Most of the studies stratified their analyses on age using age at inclusion or follow-up (possibly trying to integrate both concepts). However, some birth cohorts have air pollution exposure during pregnancy or early in life and therefore stratified by age of exposure.

Sex/gender: exposure to air pollution could be different according to gender (for example, women spending more time at home), or the effect of air pollution could be biologically different according to sex. Throughout the manuscript we will use the term "sex" as it is very difficult to disentangle what is related to sex—biological differences—and what is related to gender—life habit differences—regarding air pollution effects [38].

Tobacco and secondhand smoke for children: air pollution effects could be masked among smokers (or passive smokers) as smoking and air pollution share several mechanisms [24]; furthermore, recently it has been suggested that there could be an interaction between smoking and air pollution [39].

Atopy: atopic and non-atopic asthma are possibly two different diseases with different mechanisms, and air pollution may have a different effect according to atopic status [40].

Body mass index (BMI): subjects with obesity have been found to be more susceptible to air pollution in terms of lung function (and as lung function is an asthma-related phenotype, it seems plausible that susceptibility factors related to lung function may also be interesting to study regarding asthma incidence) and asthma [41–43].

Genetic variants [4]: mainly the ones associated with oxidative stress or inflammation have been investigated so far.

During the review we also identified a posteriori socioeconomic status (SES, individual SES for adults, family SES for children) or family environment (such as parental stress or exposure to violence), race, wheeze or bronchial hyperresponsiveness at baseline and parental history as being other potentials susceptibility factors that we will examine in the manuscript.

Results and Discussion

Twenty-five articles fulfilled the inclusion criteria (17 from the PubMed research and 8 from the hand research) (Fig. 1) and are presented separately for adults and children. Study characteristics and main results for each study are summarized in Table 1 for children and in Table 2 for adults.

Sex

Seven studies stratified the effects of air pollution on asthma by sex [13, 14, 17, 18, 19•, 30, 35] in children. In Canadian children at high risk for asthma [17], the association between exposure, measured at year of birth, and incident asthma at 7 years old was reported as higher among boys, but no further details were given. In a pregnancy cohort in the US [19•], the association between in-utero exposure to $PM_{2.5}$ and asthma onset at age 6 showed a sensitive exposure window between 12-26 weeks of gestation for boys but not for girls, and the authors reported a significant interaction term for sex [*p*-interaction = 0.01, OR ($PM_{2.5}$*boys): 1.33 (1.05-1.69)]. In the five other studies, associations were similar in boys and girls: in children aged 6-9 years from the Chiba prefecture in Japan [30], the association between air pollution, measured as school proximity to traffic and asthma incidence, was similar in boys and girls [OR (95 % CI): 3.75 (1.00-14.06) for boys and 4.06 (0.91-18.10) for girls]. The same result was found among more than 4000 children aged 8-21 years from the US and Puerto Rico [18], for NO_2 and PM ($PM_{2.5}$ and PM_{10}), considering air pollution exposures during the first year of life or first 3 years of life [first year of life: NO_2: OR (95 % CI): 1.26 (1.05-1.52) in boys, 1.11 (0.96-1.29) in girls; PM_{10}: 1.10 (0.89-1.36) in boys, 1.15 (0.97-1.37) in girls; the *p*-interaction was not significant; the first 3 years of life: PM_{10}: 1.08 (0.86-1.35) in boys, 1.19 (1.00-1.41) in girls, *p*-interaction NS]. In a Swedish birth cohort [13], an association between traffic NOx and persistent wheezing was also similar whatever the sex [OR (95 % CI) = 1.94 (1.07-3.50) in girls, OR: 1.55 (0.92-2.63) in boys, *p*-interaction = 0.43]. In another birth cohort conducted in Oslo, NO_2 was not associated with asthma incidence among girls [RR (95 % CI): 1.05 (0.74-1.49)], while the effect estimate was negative among boys [RR: 0.73 (0.56-0.95), *p*-interaction = 0.10]. Finally, in Canadian children aged between 36 and 59 months [35], associations were similar in boys and girls for both NO and NO_2 [OR (95 % CI) for NO_2: 1.17 (1.09-1.26) for girls and 1.09 (1.03-1.16) for boys, OR for NO: 1.13 (1.06-1.20) for girls and 1.05 (1.00-1.10) for boys].

In adults, six studies stratified by sex when they assessed the associations between air pollution and asthma [22–24, 28, 33, 34]. In American non-smokers [34], for an IQR increase in the 20-year average of O_3-8 h concentration, the association was positive in men, while there was no association in women [RR (95 % CI): 2.09 (1.03-4.16) in men, 0.86 (0.58-1.26) in women]; in the same study population, another paper [33] reached a similar conclusion when considering the 1-year O_3-8 h average as exposure. In a European study conducted in seven countries [23], the association between NO_2 concentration and incident asthma was similar but slightly stronger among men [OR (95 % CI): 1.32 (1.12-1.56)] than among women [1.14 (0.97-1.34; *p*-interaction = 0.13]. Among Swiss never-smokers [24], the OR per 1 $\mu g.m^{-3}$ increase in traffic-related PM_{10} (TPM_{10}) was also slightly higher in men, but no precise ORs were available as the results were only presented in a figure. Other studies found no significant difference between men and women in the association between air pollution and asthma [22, 26•, 28]: no difference according to sex was found in a European study conducted in seven countries [OR for NO_2: 1.31 (0.76-2.27) in men and 1.53 (0.99-2.38) in women (*p*-interact = 0.69)] [22] or in a Swedish cohort (OR for NO_2: 1.32 (0.64-2.74) in men, 1.67 (0.98-2.74) in women (*p*-interact = 0.63)] [28]. Similarly, in a European study regrouping six cohorts, no difference was found according to the sex, and no association between air pollution and incident asthma was found [OR for NO_2: 1.06 (0.92-1.24) in men, 1.07 (0.97-1.19) in women, *p*-interact = 0.66, PM_{10}: 1.00 (0.63-1.59) in men, 1.07 (0.91-1.26) in women, *p*-interact = 0.80] [26•].

In both adults and children, sex was the most studied susceptibility factor. Among children, the effect of air pollution on incident asthma was similar in boys and girls. Among adults, results are discordant, with some studies showing a higher effect of air pollution exposure on incident asthma in men, whereas others reported no difference according to sex. This contradicts what Clougherty [38] pointed out in her review where she found a higher effect of air pollution among women. Overall, in both adults and children, evidence mostly supports no effect modification between air pollution measures and sex on incident asthma.

Table 1 Description of studies assessing the association between air pollution exposure and incident asthma in adults (by year of publication) and that had stratified their analyses by possible susceptibility factors

First author, year, journal, reference	Design, study, outcome	Population; age	Exposure assessment	Main association	Susceptibility factors	Modifying effect
Shima, 2003, J Epidemiology [30]	Prospective cohort study. Recruitment in 1992, follow-up yearly until 1995. Outcome: incident asthma	1858 children from 8 communities in Chiba prefecture, Japan. (6-9 years at baseline)	School proximity to roadside: rural area, non-roadside area: ≥50 m from the roads, roadside area: <50 m from the roads	Symptoms of asthma tended to increase in the order of roadside > non-roadside > rural areas	Sex	Sex: Ref: rural area. OR (95 % CI) for non-roadside area: 1.99 (0.79-4.99) among boys, 1.74 (0.63-4.81) among girls. OR (95 % CI) for roadside area: 3.75 (1.00-14.06) among boys, 4.06 (0.91-18.10) among girls. Significant trend among boys ($p = 0.013$), not among girls
Zmirou, 2004, JECH [29]	Case control study, conducted in 5 French metropolitan areas: VESTA, between 1998 and 2000. Outcome: incident asthma	195 pairs of matched cases and controls investigated. Aged 4-14 years	Traffic density: time-weighted average of the traffic density to road distance ratio; index of lifetime exposure to traffic exhaust. Exposure index considered in tertile. Home and school addresses	Traffic density associated with asthma when considering 3 first years of life, but not when averaging on life. OR (95 % CI) for traffic density as a quantitative predictor: 1.30 (1.04-1.62). Results in tertiles: ref = tertile 1; tertile 2: 1.48 (0.73-3.02), tertile 3: 2.28 (1.14-4.56)	Atopy (at least one positive SPT to one of nine tested allergens)	Atopy (positive SPT). Tertile 1 as reference. Atopic: tertile 2: 0.61 (0.1-3.6), tertile 3: 11.03 (1.3-100.9). Non-atopic: tertile 2: 1.23 (0.29-5.31), tertile 3: 1.47 (0.32-6.97) (p interaction = 0.20)
Pierse, 2006, Thorax [11]	Cohort study. Recruitment in 1998, follow-up in 2001. Outcome: incident wheeze, asthma symptoms	4400 children recruited in Lanceister. 1-5 years at baseline	Annual exposure to PM_{10} (dispersion mode). Year of exposure assessment: 1998 and 2001 (mean of both years). Home addresses	Exposure to PM_{10} and incidence of asthma symptoms: 1.42 (1.02-1.97) for wheeze (adjusted results)	Age, secondhand smoke	- Age: 1.43 (0.91-2.26) in children aged 1-2.99 years and 1.39 (0.86-2.25) in children aged 3-4.99 years - Secondhand smoke: (p-interact > 0.1)
Clougherty, 2007, EHP, [12]	Birth cohort, recruitment: between 1987 and 1993, follow-up in 1997. Outcome: incident asthma	413 children from Boston, recruiting pregnant women	Measured NO_2, weekly collected. Monthly averaged, corresponding to address of participants. Year of exposure assessment: monthly from January 1987 through December 2004	Univariate OR: 1-SD increase in year of diagnosis of NO_2 showed near-significant associations with asthma: 1.17 (0.94-1.46)	Exposure to violence (ETV)	ETV: exposed above the median: 1.65 (1.16-2.34), lower than median: 0.94 (0.70-1.26). (Year of diagnosis NO_2). Multivariate: increased risk among children with above median ETV 1.63 (1.14-2.33). Above median: 2.40 (1.48-3.88)
Islam et al., 2008, AJRCCM, [31]	Prospective cohort (CHS). Recruitment between 1993 and 2004, follow-up yearly during 2-8 years. Outcome: incident asthma	1125 non-Hispanic white and 576 Hispanic white from 12 southern California communities. Age: >7 years	Average hourly levels of O_3, NO_2 and PM (PM_{10} and $PM_{2.5}$). For ozone: annual average of 8 h daytime average computed. Communities were classified as higher ozone communities or lower ozone communities. (1994-2003)	No general effect assessed	Genetic variants *MNSOD* Ala-9Val (rs4880), *CAT-262C* > T (rs1001179), and *CAT-844C* < T (rs769214) *HMOX-1* (GT)n repeats. Short allele (S): <23 repeats), race	Genetic: (GT)n repeat polymorphism of *HMOX-1*: low-ozone communities: HR (95 % CI): 0.44 (0.23–0.83; high ozone communities HR = 0.88 (0.33–2.34). *P* for interaction = 0.003.

Table 1 (continued)

First author, year, journal, reference	Design, study, outcome	Population; age	Exposure assessment	Main association	Susceptibility factors	Modifying effect
						Low PM_{10} communities: HR: 0.94 (0.54–1.62); high PM_{10} communities HR = 0.62 (0.20-1.87). *P* for interaction = 0.18
Nordling, 2008, Epidemiology, [13]	Birth cohort, recruitment between 1994 and 1996, follow-up at 1, 2 and 4 years of age. Outcome: persistent wheezing and late-onset asthma	4089 infants from 4 Swedish municipalities. Age different according to the follow-up (1, 2 and 4 years old)	Dispersion model. NOx, PM_{10}, SO2. Home addresses. 1990: traffic NOx and heating SO2. 2000: traffic NOx, heating SO2 and traffic PM_{10}. Outdoor levels of air pollution for the children's first year of life (1994-1997): interpolation from the data of 1999 and 2000	Persistent wheezing: Association with traffic NOx (for a difference between the 5th and 95th percentile range in the cohort): OR: 1.60 (1.09-2.36). Similar but ns results for PM_{10}. No association between pollutant and late-onset asthma	Sex, atopy [atopic wheeze: allergic sensitization to pollen (specific-IgE)]	- Sex: persistent wheezing: girls: OR: 1.94 (1.07-3.50), boys: OR: 1.55 (0.92-2.63) - Atopy: persistent wheezing and late onset: non-atopic wheeze: NOx: 1.46 (1.00-2.13), atopic wheeze: NOx: 1.11 (0.55-2.22). (*p*-interaction = 0.43)
Islam, 2009, Thorax, [32]	Prospective cohort (CHS). Recruitment between 1993 and 2004, follow-up yearly during 2-8 years. Outcome: incident asthma	1064 non-Hispanic white and 576 Hispanic white from 12 southern California communities. Age: >7 years	Average hourly levels of zone (O_3), nitrogen dioxide (NO_2) and particulate matter (PM_{10} and $PM_{2.5}$). For ozone: annual average of 8 h daytime average computed Communities were classified as higher ozone communities or lower ozone communities. Years of exposure assessment: 1994-2003	None	Genetic variants *GSTP1* haplotype tagging SNPs: rs6591255, rs4147581 and Ile105Val and rs749174 *GSTM1* null genotype *CAT-262C* > T (rs1001179) and *HMOX-1* (GT)n repeats. Short allele (S): <23 repeats, sport played	Genetic: risk of new onset asthma among Ile105 homozygotes in high ozone community: HR (6.15; 2.2-7.4, *P* for interaction = 0.10, limited sample size) Ile105 homozygotes in low ozone community: 1.06 (0.3-4.0) [among those who played >2 team sports, no difference among those playing less than 2 sports]
Oftedal, 2009, EHP, [14]	Oslo Birth Cohort. Recruitment in 1992-1993, follow-up: 2001-2002 (and cross-sectional study). Outcome: incident asthma	2871 children born in Oslo	NO_2 dispersion model. Home addresses	No positive associations between any long-term TRAP and onset of doctor-diagnosed asthma (but a negative association). Association for late asthma onset (>4 years of age) was positive but NS	Sex	Sex: RR of 0.73 (0.56-0.95) in boys and 1.05 (0.74-1.49) in girls (*p*-interaction = 0.10)
Shankardass, 2009, PNAS, [15]	Prospective cohort study (CHS). Recruitment: 2002-2003 and follow-up during 3 years. Outcome: incident asthma	2497 children from 13 southern California communities, aged 5-9 years at baseline	NOx dispersion model. Annual concentrations. Home address. Year of exposure assessment: 1997	Risk of asthma increased with exposure to traffic-related pollution: HR (95 % CI) 1.31 (1.07-1.61), for an IQR of 21 ppb of NOx	Parental stress, SES	- Parental stress (*p* interaction 0.05): high parental stress: HR: 1.51 (1.16-1.96). Low parental stress: 1.05 (0.74-1.49). *p*-interact for 3-way "gender--parental stress-air pollution" = 0.10): high parental stress: males: 1.60 (1.16-2.22), females: 1.36(0.87-2.11). Low parental stress: males: 0.98 (0.61-1.59), females: 1.14 (0.68-1.90)

Table 1 (continued)

First author, year, journal, reference	Design, study, outcome	Population; age	Exposure assessment	Main association	Susceptibility factors	Modifying effect
						-SES: (p interaction 0.25): high SES: 1.20 (0.93-1.55). Low SES: 1.55 (1.09-2.19)
Clark, 2010, EHP, [35]	Nested case control in a cohort study, all 1999 and 2000 births in British Columbia (Canada). Outcome: incident asthma	3482 cases and 17,410 controls, among 37,401 children. 36-59 months at the end of the follow-up	LUR modeling/IDW. High resolution (10 m) TRAP: NO, NO_2, $PM_{2.5}$ and black carbon. Exposure levels assigned at the zip code level. Average exposure calculated for duration of pregnancy and first year of life	Increased risk of asthma diagnosis with increased early life exposure (in utero and 1st year of life; greater results for 1st year of life). OR for 1st year of life: 1.08 (1.04-1.12) for a 10 $mg.m^{-3}$ increase of NO, 1.12 (1.07-1.17) for a 10 $mg.m^{-3}$ increase of NO_2, 1.10 (1.06-1.13) for a 100 $mg.m^{-3}$ increase of CO, 1.07 (1.03-1.12) for an increase of 1 $mg.m^{-3}$ in PM_{10}	Sex	Sex: NO: 1.13 (1.06-1.20) for girls and 1.05 (1.00-1.10) for boys. NO_2: 1.17 (1.09-1.26) for girls and 1.09 (1.03-1.16) for boys
Gehring, 2010, AJRCCM, [16]	Prospective birth cohort (PIAMA). Recruitment in 1996-1997 of pregnant women, follow-up yearly during 8 years. Outcome: incident asthma	3863 Netherlands children	LUR. NO_2, $PM_{2.5}$, soot: four times 2-week measurement in a year and then adjustment on temporal trend to calculate long-term average concentrations. Birth address	Association between $PM_{2.5}$ concentration and incidence of asthma: 1.28 (1.10-1.49) (same results for NO_2 and soot)	Atopy (specific IgE to 6 allergens), age	Non-adjusted models (due to small sample size) - Atopy: Non-atopic: NO_2, $PM_{2.5}$ and soot: 1.85 (0.92-3.73), 2.98 (1.21-7.37) and 2.06 (0.99-4.3). Atopic: NO_2, $PM_{2.5}$ and soot: 0.95 (0.64-1.40), 1.00 (0.63-1.58) and 0.97 (0.641.46). - Age: effect of air pollution on incidence of asthma was stronger at ages 6-8 years (OR ≈ 1.6, significant at 8, NS at 7 and borderline at 6 compared to OR ≈ 1.2 NS for younger age. Results available in a figure)
Carlsten, 2011, OEM, [17]	Intervention prenatal study. Recruitment during pregnancy in 1995, follow-up until 7 years of age. Outcome: incident asthma	184 children from Vancouver, at high risk for asthma	LUR. NO, NO_2, black carbon and $PM_{2.5}$. Year of exposure assessment: 2003, exposure of birth year estimated. Residential address	Elevation in exposure to some traffic-related air pollution during the year of birth is associated with new-onset asthma at 7. Results by quartile. Significant for last quartile only for $PM_{2.5}$. No significant results for the others pollutants, despite the increase	Sex, race	Suggestion of increase in males (data not shown) Suggestion of increase in Caucasians (data not shown)
Gruzieva, 2013,	Swedish birth cohort BAMSE. Recruitment	4089 children	Gaussian dispersion model and wind model used to assess the concentration of PM_{10} and	Incidence of wheeze symptoms seems to be highest during the first 2 years of life.	Sex, allergic/non-allergic asthma (atopy assessed by specific IgE to 8 allergens), age	- Sex: no significant interaction p =0.21 - Allergic/non-allergic asthma

Table 1 (continued)

First author, year, journal, reference	Design, study, outcome	Population; age	Exposure assessment	Main association	Susceptibility factors	Modifying effect
Epidemiology, [27]	between 1994 and 1996, follow-up during 12 years. Outcome: incident wheeze, incident asthma		NOx. Years of exposure assessment: 1994 to 1998. Interpolation of concentrations for some years for NOx. Residential, daycare and school addresses	Associations between exposure to NOx or PM_{10} and incident asthma over the first 12 years of life: OR: 1.21 (0.79–1.84) for NOx, OR: 1.34 (0.80–2.23) for $PM_{10.}$ Results significant only at age 12		4 years: non-allergic asthma: OR (95 % CI) 1.6 (0.5-5.3) for PM_{10} and 2.4 (1.0-5.6) for NOx. Allergic asthma: 1.4 (0.3-6.8) for PM_{10} and 1.5 (0.4-5.1) for NOx 8 years: non-allergic asthma: 3.8 (0.9-16.2) for PM_{10} and 2.6 (0.9-8.1) for NOx. Allergic asthma: 1.1 (0.3-3.8) for PM_{10} and 0.8 (0.2-2.4) for NOx. (ref of OR: no asthma/no sensitization) - Age: in children aged 8 to 12 years: 2.0 (1.1-3.5) Incident asthma ORs: 1 years: 0.85 (0.44-1.62) for NOx and 0.79 (0.39-1.62) for PM_{10} 2 years: 0.96 (0.51-1.80) for NOx and 1.14 (0.57-2.25) for PM_{10} 4 years: 1.48 (0.85-2.57) for NOx and 1.59 (0.83-3.05) for PM_{10} 8 years: 1.07 (0.53-2.14) for NOx and 1.30 (0.61-2.74) for PM_{10} 12 years: 1.87 (1.01-3.44) for NOx and 2.39 (1.18-4.86) for PM_{10}
Nishimura, 2013, AJRCCM, [18]	GALA II (case control) and SAGE II. Recruitment between 2006 and 2011. Outcome: incident asthma	Latinos from urban regions in the USA and Puerto Rico and African Americans from SF bay, 3343 Latinos and 977 African Americans, with no history of other lung or chronic illness. 8-21 years	O_3, NO_2, SO_2, PM_{10}, $PM_{2.5}$. Inverse distance-squared weighted average. Residence address. Exposure over the first 3 years of life.	A 5-ppb increase in NO_2 during the first year of life associated with incident asthma: OR (95 % CI) for the first year of life: OR_1: 1.17 (1.04-1.31). OR (95 % CI) for first 3 years of life: OR_3: 1.26 (1.07-1.48). NS for PM and O_3	Sex, Total-IgE	-Sex: NO_2: OR_1: 1.26 (1.05-1.52) in boys, 1.11 (0.96-1.29) in girls; OR_3: 1.47 (1.05-1.52) in boys, 1.24 (1.02-1.50) in girls. PM_{10}: OR_1: 1.10 (0.89-1.36) in boys, 1.15 (0.97-1.37) in girls; OR_3: 1.08 (0.86-1.35) in boys, 1.19 (1.00-1.41) in girls. $PM_{2.5}$: OR_1: 0.92 (0.73-1.16) in boys, 1.13 (0.98-1.30) in girls; OR_3: 0.91 (0.77-1.06) in boys, 1.15 (1.02-1.30) in girls All *p* for interaction NS - Total IgE

Table 1 (continued)

First author, year, journal, reference	Design, study, outcome	Population; age	Exposure assessment	Main association	Susceptibility factors	Modifying effect
						NO_2: OR_1: 1.12 (0.93-1.36) in IgE <200, 1.20 (0.91-1.58) in IgE ≥200; OR_3: 1.19 (0.97-1.46) in IgE <200, 1.38 (0.90-2.12) in IgE ≥200 PM_{10}: OR_1: 1.12 (1.00-1.25) in IgE <200, 1.22 (0.97-1.55) in IgE ≥200; OR_3: 1.04 (0.83-1.29) in IgE <200, 1.35 (0.98-1.85) in IgE ≥200. $PM_{2.5}$: OR_1: 1.06 (0.93-1.21) in IgE <200, 1.00(0.85-1.17) in IgE ≥200; OR_3: 0.93 (0.72-1.21) in IgE <200, 1.10 (0.96-1.25) in IgE ≥200. All *p* for interaction NS
Hsu, 2015, AJRCCM, [19•]	Pregnancy cohort. Recruitment between 2002 and 2009, follow-up to age 6 years. Outcome: incident asthma	736 full-term birth children, from Brigham and Boston	$PM_{2.5}$. Novel spatio-temporal model incorporating moderate resolution imaging spectroradiometer (MODIS) satellite-derived aerosol optical depth (AOD) measurements at a 10*10 km spatial resolution. Residence over pregnancy	Significant sensitive window of $PM_{2.5}$ exposure around mid-pregnancy on asthma onset by age 6, specifically during 16-25-week gestation. OR: 1.09 (0.98-1.21)	Sex	Sex: Sensitive exposure window between 12-26-week gestations: boys: OR ≈ 1.2, significant, girls: OR ≈ 1.03, NS. Difference in log odds between boys and girls: significant in 14-20. Significant interaction between $PM_{2.5}$ and sex ($p = 0.01$). OR ($PM_{2.5}$*boy) : 1.33 (1.05-1.69)

Abbreviations: OR: odds ratio, RR: risk ratio, HR: hazard ratio, CI: confidence interval, PM: particulate matter, NO_2: nitrogen dioxide, NOx: nitrogen oxide, O_3: ozone, IgE: immunoglobulin E, SPT: skin prick test, BHR: bronchial hyperreactivity, NS: not significant, TRAP: traffic-related air pollution

Table 2 Description of studies assessing the association between air pollution exposure and incident asthma or wheeze in children (by year of publication) and that had stratified their analyses by possible susceptibility factors

First author, year, journal, reference	Design, study, follow-up	Population; age	Exposure assessment	Main association	Susceptibility factors	Modifying effects
Greer, 1993, JOM, [33]	Prospective cohort (California), AHSMOG. Recruitment in 1977, follow-up in 1987	3577 non-smokers Seventh-day Adventist. Mean age: 27-87 years	Monthly interpolations of O_3 from fixed-site monitoring stations applied to residential addresses and work site. Year of exposure assessment: 1987	Borderline association of increased risk of asthma associated with increased ambient concentrations of ozone exposure (RR = 1.31, CI: 0.96-1.78)	Sex	Sex: increase in ambient concentrations of ozone exposure (mean ozone concentration exposure through 1987). RR: 3.12, CI: 1.61-5.85 in males, RR: 0.94 "not significant at 0.05 level" in females)
McDonnell, 1999, Environmental Research, [34]	Prospective cohort (California), AHSMOG. Recruitment in 1977, follow-up in 1987	3091 non-smokers Seventh-day Adventist (101 cases). Mean age: 27-87 years	O_3, PM_{10}, SO_4, NO_2, SO_2. Exposure concentrations interpolated to zip code according to home and work location, cumulated and averaged over time. For ozone and PM_{10}: alternative indices: 8-h average ozone concentration (work hours) Years of exposure assessment: 1973-1992	20 years O_3-8-h average associated with report of doctor diagnosis of asthma: RR 2.09 (1.03-4.16)	Sex, smoking status	- Sex: Males: RR: 2.09 (1.03-4.16), females: 0.86 (0.58-1.26) -Smoking: similar association for ex-smoking and never-smoking
Modig, 2006, ERJ, [20]	Case-control study. Recruitment between 1995 and 1999	203 cases/203 sex and age-matched controls from Lulea, Sweden. 20-60 years	Home outdoor NO_2 measurements for 1 week, standardized and adjusted to represent annual average (for the year of recruitment). Traffic intensity at home address. Years of exposure assessment: 1999-2000	No association between NO_2 level and asthma incidence [OR: 1.1(0.9-1.2)]. Living close to high traffic was non-significantly associated with asthma incidence	Atopy (defined as positive SPT : no more details)	Atopy: [Among those who live >2 years in the present home]: OR for an increase of 1 $mg.m^{-3}$ of NO_2: >0 SPT: 1.2 (1.0-1.3); <0 SPT: 1.0 (0.9-1.1)
Castro-Giner, 2009, EHP, [21]	Prospective cohort, in 13 cities from 6 European countries (ECRHS). Recruitment in 1990-1994, follow-up: 1999-2001	2250 subjects. 20-44 years	NO_2 dispersion model (1 × 1 km) for 2001 (APMoSPHERE model). Extrapolated to place of residence	Significant association between NO_2 levels and new-onset asthma for the 120 subjects who developed asthma during the follow-up period (OR = 1.52; 95 % CI, 1.09–2.16)	Genetic variants *GSTM1* and *GSTT1* deletion *GSTP1* Ile105Val, *NQO1* (rs1800566, rs2917666) *TLR4* (5 SNPs) *TNFA* (3 SNPs) *ADRB2* (4 SNPs)	Genetic: homozygous for the *NQO1* rs291766 C allele: OR = 2.02 (1.16–3.73); subjects with CG/GG genotypes: OR = 1.26 (0.83–1.99). (*p*-value for interaction = 0.04)
Jacquemin, 2009, ERJ, [23]	Prospective cohort, in 17 cities from 7 European countries (ECRHS). Recruitment in 1990-1994, follow-up: 1999-2001	4185 subjects. Analysis on 387 participants: having no asthma and no symptoms at baseline; 20-44 years	NO_2 dispersion model (1 × 1 km) for 2001 (APMoSPHERE model). Extrapolated to place of residence	Outcome: score of symptoms of asthma, used as a tool to identify incidence of asthma. Ratio of the RMS after excluding participants with asthma and symptoms at baseline: 1.25 (1.05-1.51) for an increase of 10 $mg.m^{-3}$	Sex, smoking status, atopy (specific IgE to 4 allergens)	- Sex: males: 1.32 (1.12-1.56), females: 1.14 (0.97-1.34) (*p*-interact: 0.13) - Smoking status: never/ex-smokers: 1.30 (1.11-1.52). Current smokers: 1.07 (0.92-1.26) (*p*-interact = 0.005)

Table 2 (continued)

First author, year, journal, reference	Design, study, follow-up	Population; age	Exposure assessment	Main association	Susceptibility factors	Modifying effects
						- Atopy: without atopy: 1.20 (1.02-1.41). With atopy: 1.37 (1.14-1.65) (p-interact = 0.63)
Jacquemin, 2009, Epidemiology, [22]	Prospective cohort, in 17 cities from 7 European countries (ECRHS). Recruitment in 1990-1994, follow-up: 1999-2001	4185 subjects. 20-44 years	NO_2 dispersion model (1 × 1 km) for 2001 (APMoSPHERE model). Extrapolated to place of residence	Positive association between NO2 and asthma incidence [1.43 (1.02-2.01) per 10 $mg.m^{-3}$]. When known age of asthma onset between the 2 surveys: 1.72 (0.99-3.00)	Sex, atopy (specific IgE to 4 allergens)	- Sex: OR per 10 $mg.m^{-3}$ increase of NO_2: Males: 1.31 (0.76-2.27). Females: 1.53 (0.99-2.38) (p-interact = 0.69) - Atopy: OR: 1.31 (0.84-2.04) per 10 $mg.m^{-3}$ increase of NO_2 . No atopy: 1.57 (0.92-2.67) (p-interact = 0.77)
Künzli, 2009, Thorax, [24]	Prospective cohort in 8 Swiss areas (SAPALDIA). Recruitment in 1990-91 and follow-up in 2002	2725 never-smokers, without asthma or COPD. 18-60 years	Traffic-related PM_{10} (particulate matter up to 10 $mg.m^{-3}$, TPM_{10}) change, from 1990 and 2000 using the dispersion model. Exposure interpolated at participants' place	Incidence of asthma was associated with a change in PM_{10} in never-smokers. HR: 1.30 (1.05-1.61) per 1 $mg.m^{-3}$ change in PM_{10}	Sex, atopy (SPT to 8 allergens), age, parental asthma, parental allergy, BHR, smoking status	Results in a figure (HR) - Sex: males OR ≈ 1.4, borderline, females: OR ≈ 1.25 NS (p interaction > 0.1) - Atopy: atopic: OR ≈ 1.35, significant, non-atopic: OR ≈ 1.2 NS (p interaction > 0.1). - Age: >40: OR ≈ 1.65, significant, ≤40 years: OR ≈ 1.3 NS. (p interaction > 0.1) - Parental allergy: OR ≈ 1.7 significant, no parental allergy: OR ≈ 1.3 NS (p-interact = 0.088) - Smoking status: ever-smoker: HR: 0.99 (0.64-1.53)
Modig, 2009, ERJ, [28]	Prospective cohort, 3 Swedish cities (RHINE). Recruitment in 1990, follow-up in 1999	3609 participants. 18-45 years	NO_2 dispersion models (50 × 50 m), distance to major road <50 m. Both estimates at home address. Year of exposure assessment: 1990	Association between per 10 $mg.m^{-3}$ increase in NO_2 and incident asthma [1.54(1.00-2.36)] Risk of developing asthma related to living close to a major road: 3.88 (1.93-7.82)	Sex, atopy (hay fever as proxy)	- Sex: OR for NO_2 per 10 $mg.m^{-3}$: Females: 1.67 (0.98-2.74), males: 1.32 (0.64-2.74) (p-interact = 0.63) - Hay fever status: OR for NO_2 per 10 $mg.m^{-3}$: subject with hay fever: 1.15 (0.59-2.24) Subject without hay fever: 1.79 (1.04-3.05) a (p-interact = 0.30)
Young, 2014, AJRCCM, [25]	Sister study, cohort. Recruitment: 2003-2009, follow-up 2008-2012	50884 US sisters of women with breast cancer, mean age: 55	$PM_{2.5}$ and NO_2. National landuse/ Kriging model incorporating roadway information. Addresses of the participants geocoded.	OR of incident asthma for an IQR increase of $PM_{2.5}$: 1.20 (0.99-1.46) and NO_2: OR: 1.12 (0.96-1.30). OR of incident wheeze for an IQR increase of $PM_{2.5}$: 1.14	Smoking status	Smoking status: Never/ex-smoker: 1.14 (1.04-1.24). Current smoker: 0.89 (0.74-1.06) (p interaction = 0.012)

Table 2 (continued)

First author, year, journal, reference	Design, study, follow-up	Population; age	Exposure assessment	Main association	Susceptibility factors	Modifying effects
			Year of exposure assessment: 2006	(1.04-1.26) and NO_2: 1.08 (1.00-1.17)		
Jacquemin, 2015, EHP, [26•]	6 prospective cohorts (ECRHS, EGEA, SAPALDIA, E3N, NHSD, SALIA).	23704 adults. Mean age: 60 years	ESCAPE project. NO_2, NOx, PM_{10}, $PM_{2.5}$, $PM_{2.5absorbance}$, Pm_{coarse}. LUR model. Exposure estimated at participant's addresses. Back-extrapolated concentrations of NO_2 and PM_{10} when necessary according to the year of the follow-up. Years of exposure assessment: 2010 or 2011	Asthma incidence positively, but NS, associated with all exposure metrics, except for PM_{coarse}. OR: NO_2: 1.10 (0.99-1.21) per 10 $mg.m^{-3}$, NOx: 1.04 (0.99-1.08 per 20 $mg.m^{-3}$, PM_{10}: 1.04 (0.88-1.23) per 10 $mg.m^{-3}$, $PM_{2.5}$: 1.04 (0.88-1.23) per 5 $mg.m^{-3}$, $PM_{2.5absorbance}$: 1.06 (0.95-1.19) per 10-5/m. Traffic load: 1.10 (0.93-1.30). Traffic intensity: 1.10 (0.93-1.30). PM_{coarse}: 0.98 (0.87-1.14)	Sex, smoking status, age	- Sex: NO_2. Males: 1.06 (0.92-1.24). Females: 1.07 (0.97-1.19) (p-interact = 0.66). PM_{10}: Males: 1.00 (0.63-1.59) Females: 1.07 (0.91-1.26) (p-interact = 0.80) - Smoking status: NO_2: Ever-smokers: 1.13 (0.99-1.29). Never-smokers: 1.01 (0.88-1.16). (P-interaction = 0.35) . PM_{10}: Ever - smokers: 1.17 (0.79-1.74). Never-smokers: 1.10 (0.87-1.39), p-interact = 0.69 - Age: NO_2: <50: 1.08 (0.96-1.21), >50: 1.02 (0.94-1.12). (p-interact = 0.88). PM_{10}: <50: 1.07 (0.86-1.32) and >50: 1.05 (0.78-1.42) (p-interact = 0.99)

Abbreviations: OR: odds ratio, RR: risk ratio, HR: hazard ratio, CI: confidence interval, PM: particulate matter, NO_2: nitrogen dioxide, NOx: nitrogen oxide, O_3: ozone, IgE: immunoglobulin E, SPT: skin prick test, BHR: bronchial hyperreactivity, NS: not significant, TRAP: traffic-related air pollution

Age

In children, three studies stratified their analysis according to age, [11, 16, 27]. In children from Lanceister aged 1-5 years at baseline [11], no evidence for a modifier effect of age (1-2.9 years vs. 3-4.9 years) was found. In a Netherlands birth cohort [16], a slightly higher association of air pollution and onset asthma at 6-8 years vs. younger (age at follow-up, no exact OR available, only OR showed in a figure) was found. Among children followed-up at 1, 2, 4 and 12 years of age in a Swedish birth cohort [27], an association between air pollution during the first year of life and asthma risk increased with age [OR (95 % CI) = 1.48 (0.85-2.57) for NOx and 1.59 (0.83-3.05) for PM_{10} at 4 years of age at follow-up and 1.87 (1.01-3.44) for NOx and 2.39 (1.18-4.86) for PM_{10} at 12 years at follow-up].

In adults, we found only two studies stratifying the analysis of the association between air pollution and incident asthma according to age at baseline [24, 26•]. Among Swiss non-smokers [24], the association between traffic-related PM_{10} and incident asthma was slightly higher among participants aged >40 years at baseline (OR ≈ 1.65 significant in >40 years, OR ≈ 1.3 NS in ≤40 years, no exact OR available, *p*-interact > 0.1). In a meta-analysis of six European studies [26•], no difference was found in the association between NO_2 and incident asthma in participants with more or less than 50 years old at baseline.

In children as in adults, only few studies stratified according to age—whatever age at baseline or at follow-up—and no particular patterns were found, except perhaps stronger estimated effects among children between 6 to 12 years at diagnosis. As epidemiological studies are either conducted among adults or among children, and often focus on a specific age range, few studies stratify the results according to age. However it is of special interest that one study reported a higher incidence of asthma in children (even if only boys) who were more exposed in utero during 12-26 weeks of gestation, pointing out to a possible prenatal susceptibility window [19•]. This result is concordant with a study that found that prenatal exposure to air pollution was associated with long-term lung function deficits at preschool age [44].

Smoking

In children, we found no study that stratified according to passive smoking or maternal smoking. A study in children from Lanceister, however, stated that the "effect of PM_{10} on health outcomes did not depend on whether children were exposed to secondhand tobacco smoke (*p*-interaction > 0.1)" [11]. Generally, this factor was taken into account in the adjusted models.

In adults, five studies stratified their analysis on smoking status, but classification of smoking was not homogeneous across studies. An American study of women and a European study grouped never- and ex-smokers together. In both studies, they found a higher association between NO_2 and asthma or wheeze incidence among ex-/never-smokers: American study: OR (95 % CI) = 1.14 (1.04-1.24) in never-/ex-smokers and 0.89 (0.74-1.06) in current smokers, *p*-interaction = 0.01 [25]; European study: 1.30 (1.11-1.52) in never-/ex-smokers and 1.07 (0.92-1.26) in current smokers, *p*-interaction = 0.005 [23]. The interactions were significant in both studies, but the first one only stratified according to smoking status for incident wheeze because of a lack of power for incident asthma, and this population was restricted to women. Another study conducted in seven European countries [26•] considered ex-smokers and current smokers together, and associations were slightly stronger for NO_2 among ever-smokers [OR (95 % CI): 1.13 (0.99-1.29)] than never-smokers [OR = 1.01 (0.88-1.16; *p*-interact = 0.35)], and no difference was found for PM_{10} in ever-smokers [1.17 (0.79-1.74)] versus never-smokers [OR = 1.10 (0.87-1.39)]. Among American non-smokers [34], the association between ozone and incident asthma was similar among ex-smokers and never-smokers, but stratification was only done for men. In another study, for non-smokers only [24], there was an association between traffic-related PM_{10} and incident asthma among never-smokers [HR (95 % CI) =1.30 (1.05-1.61)] but no association among ex-smokers [HR = 0.99 (0.64-1.53)]. They also reported no association between air pollution and asthma in smokers.

Overall, the association between air pollution and incident asthma according to smoking status was studied only in adults, and while the results were not always consistent, the effects of air pollutants on incident asthma seemed to be stronger among never-/ex-smokers. This susceptibility might be explained by the fact that any air pollution effect may be masked among smokers, who may already have a higher risk of asthma [45].

Atopic Status

Five studies stratified their analyses according to atopy status in children. Atopy status was defined according to the level of specific immunoglobulin E (IgE >35 kU/l) [13, 16, 27], positive skin-prick test (SPT) [29] or levels of total IgE (total IgE ≥200) [18]. Two birth cohorts [13, 16, 27] reported a stronger association between air pollution and incident asthma in non-atopic children: a Swedish birth cohort [13] reported an association between NOx exposure and incident asthma in non-atopic children and no association in atopic children at age 4 [OR (95 % CI): 1.46 (1.00-2.13) in non-atopic, 1.11 (0.55-2.22) in atopic, *p*-interaction NS]. Another study conducted in the same birth cohort [27] reached similar results for exposure to PM_{10} and NOx and incident asthma at age 8 [OR (95 % CI) for NOx: 2.6 (0.9-8.1) in non-atopic, 0.8 (0.2-2.4 in atopic)].

In a Dutch birth cohort [16], the association between NO_2, $PM_{2.5}$ and soot and incident asthma was higher among non-atopic children at age 8, but in this study it was not possible to adjust for any type of confounding because of the small sample size [OR (95 % CI) for NO_2: 1.85 (0.92-3.73) in non-atopic, 0.95 (0.64-1.40) in atopic]. Contrary to all of these results, a French case-control study examined traffic density—expressed in tertiles—before age 3 [29], and associations between traffic density and incident asthma were stronger among atopic children, but with wide confidence intervals, and the results were probably mainly driven by the way they categorized exposure [tertile 1 as reference, OR (95 % CI): tertile 2: 0.61 (0.1-3.6) and tertile 3: 11.03 (1.3-100.9) and in non-atopic tertile 2: 1.23 (0.29-5.31) and tertile 3: 1.47 (0.32-6.97), *p*-interact = 0.20]. Finally, in a study in children from the US and Puerto Rico [18], there was no differences in estimated effects according to low or high total IgE levels.

In adults, five studies stratified the analyses according to allergic sensitization. Atopy status was defined by a positive SPT [20, 24], high levels of specific IgE [22, 23] or using the report of hay fever as a proxy of allergic sensitization [28]. No difference according to atopic status was found in a European study, regardless of how asthma incident cases were defined: OR for NO_2: (95 % CI): 1.20 (1.02-1.41) in non-atopic, 1.37 (1.14-1.65) in atopic, *p*-interaction = 0.63], using asthma symptom reports [23], and 1.31 (0.84-2.04) in atopic, 1.57 (0.92-2.67) in non-atopic, *p*-interaction = 0.77, using asthma symptom scores [22]. On the one hand, a study in Swiss non-smokers [24] reported an association between TPM_{10} concentration and asthma incidence among atopic but no association among non-atopic participants (OR ≈ 1.35 in atopic, CI higher than 1, OR ≈ 1.2, CI including 1 in non-atopic; OR available in a figure). In a Swedish case-control study [20], association only reached significance in atopic subjects [OR for NO_2 (95 % CI: 1.2 (1.0-1.3) in those with ≥1 SPT, 1.0 (0.9-1.1) in those with no SPT]; however, no significant associations were found for the whole population. On the other hand, in a prospective Swedish cohort [28], the association between NO_2 and asthma incidence was higher in participants without hay fever [OR (95 % CI): 1.15 (0.59-2.24) in those with hay fever, 1.79 (1.04-3.05) in those without, *p*-interaction = 0.30].

Stratification according to atopy status was one of the most commonly assessed susceptibility factors, particularly in children. Estimated effects of air pollution on incident asthma seem to be stronger in non-atopic children' possibly because air pollution effects may be masked among atopic participants, a sensitive population who already is at higher risk of asthma. In adults, the results were too discordant to come to a conclusion. Allergic and non-allergic asthma could be two distinct diseases, and it can be hypothesized that the biological response to air pollution differs according to allergic sensitization. Furthermore, studying the effect or air pollution with and without atopy may help to better understand the mechanism that air pollution exhibits on asthma.

Genetic Factors

Only two papers—both conducted in the same study—investigated interactions between genetic variants and air pollution on asthma incidence during childhood and adolescence [31, 32]. Among children from 12 Southern Californian communities, non-Hispanic white children carrying at least one "short" allele (<23 repeats) in the HMOX-1 gene and residing in low ozone communities had a twofold lower risk of new-onset asthma than those residing in high ozone communities: HR (95 % CI): 0.44 (0.23–0.83) for low-ozone communities, 0.88 (0.33–2.34) for high ozone communities, *p*-interaction = 0.003 [31]. Associations did not vary according to children's participation in sports or time spent outside [31]. No interaction was found with PM_{10} [31]. Among children from the same cohort, those homozygous for Ile105 in the *GSTP1* gene and playing more than two team sports had an increased risk of asthma, and the risk was highest in those living in high ozone communities: HR (95 % CI): 1.06 (0.3-4.0) in low-ozone communities, 6.15 (2.2-7.4) in high-ozone communities, *p*-interaction = 0.10 [32].

In adults, only one study investigated interactions between genetic variants and NO_2 concentration on asthma incidence [21]: in a European prospective cohort, subjects homozygous for the *NQO1* rs291766 C allele were at greater risk for developing asthma due to air pollution compared with those with CG/GG genotypes [OR (95 % CI): 2.02 (1.16–3.73)] in those homozygous for the NQO1 rs291766 C allele compared with those with CG/GG genotypes: OR (95 % CI): 1.26 (0.83–1.99), *p*-interaction = 0.04.

Polymorphisms in few genes involved in xenobiotic metabolism or in the NRF2-mediated oxidative stress response modified associations between ozone and asthma incidence in children and adolescents and between NO_2 and adult onset-asthma. No association was observed with PM, suggesting a different chemical mechanism of action between pollutants. Overall, results confirm the complex interplay among pollutants, ethnicity, exercise and antioxidant defenses on the development of asthma.

Familial Environment and SES

Among Californian children age 5-9 years at baseline [15], those exposed to a higher level of parental stress were more susceptible to the association between NOx and incident asthma [HR (95 % CI): 1.51 (1.16-1.96) in high parental stress, 1.05 (0.74-1.49) in low parental stress, *p*-interaction = 0.05], and this association was greater in boys. A stronger association was also found among children with low SES: 1.20 (0.93-1.55) in high SES, 1.55 (1.09-2.19) in low SES, *p*-

interaction = 0.25. In a US birth cohort [12], susceptibility due to exposure to violence was reported: associations between NO_2 concentration and incident asthma were stronger among children most exposed to violence [OR (95 % CI): 1.63 (1.14-2.33) lower than median exposure, 2.40 (1.48-3.88) above median].

In adults, we found no study that stratified according to SES.

Two studies included in our review reported that children with low SES or exposed to a harmful familial environment were at a higher risk of asthma due to air pollution, concordant with results related to short-term air pollution [46] or mortality [47] and with the fact that low SES has been traditionally associated with higher air pollution exposure even if recent studies found that this is not always the case [48]. The association between air pollution and SES still needs to be better understood to explore more effectively whether SES could be a susceptibility factor in the association between asthma and air pollution.

Some studies assessed others potential susceptibility factors. In Canadian children at high risk for asthma [17], the association between air pollution and incident asthma seemed stronger among Caucasian participants. In adults, two studies had looked at the association between air pollution and incident asthma according to baseline characteristic associated with asthma: wheeze [28] and BHR [23]. In a Swedish cohort, the association was positive among those with wheezing at baseline, but not in those without wheeze at baseline [28]. In the same way, in a European study, the association was positive and significant among those with BHR at baseline, whereas those without BHR at baseline had a nonsignificant association [23]. In a Swiss non-smokers population, the association between incident asthma and PM_{10} level was higher among those with a parental history of allergy [24]. These results may suggest that participants who are already predisposed to develop asthma or at higher risk of developing asthma may be more susceptible to air pollution.

Overall Discussion and Conclusion

In this review, we identified 15 studies in children and 10 in adults with stratified analyses on potential susceptibility factors assessing associations between long-term exposure to air pollution and incident asthma. Overall, never-/former smoker adults seem to be more susceptible to air pollution in relation to incident asthma. Children without atopy seem to have a higher risk of incident asthma due to air pollution, as well as children with low SES. Some early studies also suggest a role for gene involvement in the response to oxidative stress.

We focused on incident asthma, but incident asthma is strongly associated with prevalent asthma, and as they share commons features, we could expect to find similar susceptibility factors for both outcomes. Papers that had specifically studied susceptibility factors of the association between air pollution and prevalence of asthma found discordant results about sex [49, 50], parental asthma or allergic symptoms [50, 51]. As for incident asthma, it seems difficult to draw a firm conclusion on who could be more susceptible to the effects of air pollution. It also seems plausible that susceptibility factors involved in the association between air pollution and lung function have a role in the association between air pollution and asthma onset as lung function is an asthma-related phenotype. More previous studies investigated possible susceptibility factors in regard to air pollution and lung function. Downs et al. [52] showed that lung function in adults declined less in areas where air pollution improved more, but they did not find any interaction with sex, atopy or smoking status. Another study [53] reported that the association between NO_2 concentration and lung function decline was stronger among girls and older children, and stronger but not significantly so among children of high SES and in those exposed to parental smoking. However, the association was not modified by asthma status.

Surprisingly, very few studies have assessed the potential role of SES as a susceptibility factor in the association between air pollution and asthma incident, although asthma is known to be socially patterned [54] and SES is very probably associated with air pollution exposure [55]. We found no study with stratified analysis on BMI or dietary factors despite of the known association between BMI and asthma [43]. Several papers suggested that obesity can play a role in susceptibility to pollutants effects [41, 42] in lung function, and in a randomized trial [56] antioxidant intake was associated with a moderate impact of ozone exposure on lung function in children with moderate to severe asthma. Whereas susceptibility of older adults to the health effects of air pollution is well recognized, and particularly concerning lung function [57] where frailty was associated with a higher decline of forced vital capacity due to air pollution, we did not find a study stratifying according to these factors. Other potential susceptibility factors such as low birth weight, second-hand tobacco smoke or ethnicity have also been proposed in a recent review as risk modifiers of the association between air pollution and asthma in general [58•], but none of these were taken into account in the articles included in this review.

One of the limitations of this review is that most of the studies used different methodologies to assess air pollution exposure and also different definitions for some susceptibility factors. Some studies assessed the association between several pollutants and incident asthma, and correlations between pollutants were not always taken into account or reported. Some studies did not report the year of exposure assessment and did not clearly define the window of exposure. Whether in children or adults, half of the studies had considered the problem of participants having moved during the window of exposure

to air pollutants. Among those assessing this problem, several had conducted sensitivity analyses, and basically the results among non-movers were only either stronger or similar to those among all participants. Another limitation of this review is that several studies did not assess the interaction term related to the susceptibility factor, and for those who presented it, only a few reported a significant *p*-value. Among the 25 articles identified, a majority assessed air pollution exposure to NO_2 and few assessed PM or other pollutants, making it difficult to identify which pollutants could be more important for which susceptibility factor and not allowing the conducting of any meta-analyses. The definition of the susceptibility factors also differed according to the study; for example, for atopy some studies used IgEs, others SPT and others total IgE or concomitant allergic disease. In children, all studies that found stronger associations among non-atopic participants used specific IgEs to define atopy, while studies using other definitions did not find interactions between atopy and air pollution. Therefore, the question arises whether the results depend on the way atopy is defined. Differences in exposure or phenotypic characterization may explain, at least in part, the heterogeneity of results across studies.

Regarding genetic factors, it is now well established that asthma is due to a complex interplay of environmental and genetic factors. There have been considerable efforts to characterize the genetic determinants of asthma; however, the identified genetic factors explain only a small part of its genetic component. One of the reasons is that many genetic factors are likely to be involved in the development of asthma through complex mechanisms that involve interactions with environmental factors and with other genes through pathways or networks. Furthermore, the effect of such genetic factors may be missed if genes are considered alone, regardless of the biological functions they share or the pathways they are involved in [59]. Studies of candidate genes and long-term air pollution in relation to incident asthma are scarce, have only been conducted on genes involved in the response to oxidative/nitrosative stress and have explored a limited number of genes. Future studies should investigate a greater number of candidates genes selected from a pathway-based approach [60]. The gene selection process may need to integrate information on the biological processes shared by genes, the pathways to which genes belong and the biological knowledge related to the environmental exposure under study.

Overall, so far no clear susceptibility factors concerning the relation between outdoor air pollution and incident asthma have been established. Discordant results could be due to misclassification of exposure, such as not taking into account time-activity patterns, as is usually the case in epidemiological air pollution studies. Among the papers included, no study was explicitly designed to assess susceptibility factors concerning the association between air pollution and incident asthma. Few studies had enough power to stratify or find significant interaction terms. A major challenge in the future would be to have studies specifically designed, or pooling data from existing studies, to address the role of susceptibility factors in the association between air pollution and asthma and also to explore which pollutant is the most relevant for which susceptibility factors. For this purpose, we would need both a detailed characterization of the disease together with a precise modeled individual exposure to air pollution and a better definition of some susceptibility factors such as atopy or smoking.

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Compliance with Ethical Standards

Conflict of Interest Emilie Burte, Rachel Nadif and Bénédicte Jacquemin declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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9.2 Appendix 2 Socioeconomic position and outdoor nitrogen dioxide (NO_2) exposure in Western Europe: A multi-city analysis.

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Socioeconomic position and outdoor nitrogen dioxide (NO_2) exposure in Western Europe: A multi-city analysis

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ABSTRACT

Background: Inconsistent associations between socioeconomic position (SEP) and outdoor air pollution have been reported in Europe, but methodological differences prevent any direct between-study comparison.
Objectives: Assess and compare the association between SEP and outdoor nitrogen dioxide (NO_2) exposure as a marker of traffic exhaust, in 16 cities from eight Western European countries.
Methods: Three SEP indicators, two defined at individual-level (education and occupation) and one at neighborhood-level (unemployment rate) were assessed in three European multicenter cohorts. NO_2 annual concentration exposure was estimated at participants' addresses with land use regression models developed within the European Study of Cohorts for Air Pollution Effects (ESCAPE; http://www.escapeproject.eu/). Pooled and city-specific linear regressions were used to analyze associations between each SEP indicator and NO_2. Heterogeneity across cities was assessed using the Higgins' I-squared test (I^2).

Abbreviations: ECRHS, European Community Respiratory Health Survey; EGEA, French Epidemiological family-based study of the Genetics and Environment of Asthma; ESCAPE, European Study of Cohorts for Air Pollution Effects; LUR, land use regression; MAUP, modifiable area unit problem; NO_2, nitrogen dioxide; OC, occupational class; PM, particulate matter; SAPALDIA, Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults; SEP, socioeconomic position.

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Results: The study population included 5692 participants. Pooled analysis showed that participants with lower individual-SEP were less exposed to NO_2. Conversely, participants living in neighborhoods with higher unemployment rate were more exposed. City-specific results exhibited strong heterogeneity ($I^2 > 76\%$ for the three SEP indicators) resulting in variation of the individual- and neighborhood-SEP patterns of NO_2 exposure across cities. The coefficients from a model that included both individual- and neighborhood-SEP indicators were similar to the unadjusted coefficients, suggesting independent associations.
Conclusions: Our study showed for the first time using homogenized measures of outcome and exposure across 16 cities the important heterogeneity regarding the association between SEP and NO_2 in Western Europe. Importantly, our results showed that individual- and neighborhood-SEP indicators capture different aspects of the association between SEP and exposure to air pollution, stressing the importance of considering both in air pollution health effects studies.

1. Introduction

Environmental inequality refers to a differential distribution of environmental hazards across socioeconomic or socio-demographic groups (Bolte et al., 2012). Historically, research on environmental inequality has emerged in the United States (US) following the Environmental Justice Movement (O'Neill et al., 2003; Morello-Frosch et al., 2011; Evans & Kantrowitz, 2002; Bowen, 2002). Repeatedly, US studies reported that lower socioeconomic or minority groups were more likely to be exposed to higher traffic-related air pollution exposure such as nitrogen dioxide (NO_2) or particulate matter (PM) (Hajat et al., 2015). However, results from US studies cannot be extended to European countries because of very different socio-spatial characteristics, specifically in urban areas (Musterd, 2005). For example, one of the main differences is that in general in most US cities, lower socioeconomic groups tend to live downtown when upper socioeconomic groups reside in the suburbs. In European cities, compared to US, social segregation is lower and lower socioeconomic groups rather live on the outskirts of the city (Musterd, 2005).

In Europe, a rather limited number of studies compared to US had investigated the association between socioeconomic position (SEP) and air pollution, mainly in the UK first and then in other European countries (Hajat et al., 2015; Pye et al., 2008). Inconsistent results have been reported in the European literature (Deguen & Zmirou-Navier, 2010). Some studies reported that populations with low SEP are more exposed to outdoor air pollution (Chaix et al., 2006a; Rotko et al., 2001; Schikowski et al., 2008; Wheeler & Ben-Shlomo, 2005; Brainard et al., 2002) while other studies reported an inverse association (Forastiere et al., 2007; Nafstad et al., 2004; Fernandez-Somoano & Tardon, 2014; Wheeler, 2004). Nonlinear association (higher exposure in middle class) (Havard et al., 2009) and no association (Vrijheid et al., 2012) were also reported. Inconsistent results were also reported within the same country, for instance in France or Spain (Vrijheid et al., 2012; Padilla et al., 2014; Fernández-Somoano et al., 2013; Morelli et al., 2016). However, these studies were difficult to compare with each other because they used different methodologies to assess air pollution exposure or to define SEP (Hajat et al., 2015; Miao et al., 2015). Moreover, most studies relied on ecological data that can raise methodological issues such as ecological fallacy, modifiable area unit problem (MAUP) or spatial autocorrelation (Havard et al., 2009; Jerrett & Finkelstein, 2005). Few studies used individual-level data (i.e. air pollution exposure at residential address and individual-level SEP) or multilevel data (i.e. SEP estimated at individual- and area-level) (Forastiere et al., 2007; Fernandez-Somoano & Tardon, 2014; Llop et al., 2011; Chaix et al., 2006b; Naess et al., 2007; Cesaroni et al., 2010; Goodman et al., 2011). Recent evidence showed the importance of considering SEP at both individual and area levels because they are independently associated with health outcomes (Hajat et al., 2015; Chaix et al., 2006a; Bell et al., 2005a; Stafford, 2003; Diez Roux, 2007).

More generally, the association between SEP and air pollution still needs to be investigated in Europe (Hajat et al., 2015; Miao et al., 2015) as SEP is one of the major potential determinants of variability in the association between air pollution and health (O'Neill et al., 2003; Bell et al., 2005b; Jerrett et al., 2011).

Within the framework of the multicenter European Study of Cohorts for Air Pollution Effects (ESCAPE) (Beelen et al., 2013), we had the opportunity to tackle this research gap using outdoor NO_2 annual concentrations at participants' home addresses estimated from standardized procedures across a large range of European cities (Beelen et al., 2013). The main objective of the present analysis was to test the environmental justice hypothesis that people with lower SEP (defined at both individual and neighborhood level) were more exposed to traffic related air pollution exposure than people with higher SEP in Western Europe.

2. Materials and methods

2.1. Study population

This cross-sectional study included participants of three multicenter epidemiological European cohorts that had previously collaborated together (Boudier et al., 2013) and were involved in the ESCAPE study: the French Epidemiological family-based study of the Genetics and Environment of Asthma (EGEA2) (2003–2007) (Siroux et al., 2009), and two population-based studies: the European Community Respiratory Health Survey (ECRHSII) (1999–2002) (Jarvis, 2002) and The Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA2) (2001 − 2003) (Ackermann-Liebrich et al., 2005). Details on each cohort are given elsewhere (Siroux et al., 2009; Jarvis, 2002; Ackermann-Liebrich et al., 2005) and summarized in the supplementary materials. For the three cohorts, information on participants were collected from detailed, standardized and validated questionnaires completed by face-to-face interviews.

Initially, the ESCAPE study included a subsample of the three cohorts ($n = 9556$ participants, Fig. 1) from 20 urban areas of eight Western European countries. Of these 20 areas, we were able to recover homogenized SEP data at individual and neighborhood level for 16 ($n = 5692$ participants: 4002, 1078 and 612 in ECRHS, EGEA and SAPALDIA respectively; Fig. 1) including Norwich, Ipswich (Great Britain; GB); Antwerp (Belgium; BE); Paris, Lyon, Grenoble, Marseille (France; FR); Geneva, (Switzerland; CH); Verona, Pavia, Turin (Italy; IT); Oviedo, Galdakao, Barcelona, Albacete, Huelva (Spain; SP) (Fig. S1). The areas covered by ESCAPE were of substantially different sizes (Table S1) with a range of density population from 152 to 21,154 inhabitants/km^2 (Cyrys et al., 2012). Most of them could be defined as metropolitan areas (large cities with surrounding smaller suburban communities) but some areas were restricted to a single city (municipality). For purposes of clarity, we refer to these different areas as “cities”.

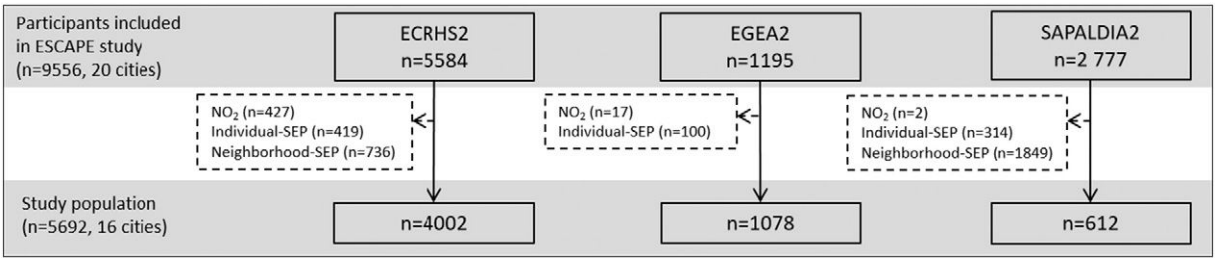

Fig. 1. Flow chart of the study population. Dotted frame: missing data. ESCAPE: European Study of Cohorts for Air Pollution Effects. ECRHS: European Community Respiratory Health Survey (1999–2002). EGEA: Epidemiological study on Genetics and Environment of Asthma (2003–2007). SAPALDIA: Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (2001–2003).

2.2. NO_2 exposure assessment

We considered nitrogen dioxide (NO_2) as a marker of near-road traffic-related air pollution (WHO Regional Office for Europe, 2005). The major sources of NO_2 are motorized road traffic, industry, shipping and heating (Cyrys et al., 2012). In the framework of ESCAPE, a single harmonized exposure assessment protocol has been developed to estimate the NO_2 annual concentrations. A common protocol described in detail in Beelen et al. was used to ensure high standardization of all procedures (i.e. measurement and estimation model) across the study areas (Beelen et al., 2013). Briefly, in each city covered, two-week integrated NO_2 measurements at approximately 40 urban sites were made in three different seasons over a one-year period between 2008 and 2011. City-specific land use regression (LUR) models (see Supplementary materials) were developed to explain the spatial variation of NO_2 using a variety of geographical data including traffic, population and land use variables. The model explained variances (R^2) of the LUR models ranged from 55% in Huelva to 92% in Pavia, 10 out of the 16 cities have a R^2 above 75% (Beelen et al., 2013). These LUR models were used to assign estimates of NO_2 annual average concentrations at each participant's geocoded residential address. Back-extrapolated estimates were also derived because ESCAPE measurement campaigns took place after the health surveys for the three cohorts (Beelen et al., 2014). Correlations between back-extrapolated and non-back-extrapolated concentrations were high (Pearson correlation coefficient = 0.95) so we only considered the non-back-extrapolated data in the present analysis.

2.3. Markers of socioeconomic position

We indexed SEP defined at two different levels.

2.3.1. Individual-level SEP

We characterized individual-level SEP based on educational level and occupational class. For the three cohorts, educational level corresponded to the age at completion of full-time education. We categorized the continuous educational variable into country-specific tertiles (high, medium and low). Occupational class was based on the longest job held between baseline and follow-up (in average 10–12 years), and categorized in five classes according to the International Standard Classification of Occupation (ISCO-1988) (International Standard Classification of Occupations, 1991): Manager and Professional (Occupational Class-I); Technician & associate (OC-II); Other non-manual (OC-III); Skilled, semi-skilled and unskilled manual (OC-IV) and "not in labor force".

2.3.2. Neighborhood-level SEP

To characterize the socioeconomic residential environment of the participants, we used the neighborhood unemployment rate (i.e. proportion of unemployed persons of the labor force). The neighborhood level corresponded to the smallest geographical level unit (with a population size ranging from 169 to 2000 inhabitants) with census-based data available in the different countries (see Table S2 for neighborhood specific characteristics). We obtained the unemployment rate variable from 2001 national censuses (except for France: 2008 and Switzerland: 2006). As the magnitude of the unemployment rate varied across European countries, we standardized it using country-specific z-scores to take this variability into account.

2.4. Strategy of analysis

2.4.1. Main analyses

The strategy of analysis aimed to test the hypothesis that the NO_2 annual concentration (dependent variable) differs according to the individual- and neighborhood-SEP of the participants (explanatory variables).

We performed analyses considering first the pooled dataset and then each city separately, due to the heterogeneity of the associations between SEP and air pollution among the cities (assessed with the Higgins' I-squared test (I^2) (Higgins et al., 2003)) We ran several multilevel linear regression models (Table S3) with neighborhood random effects (plus city random effects for the pooled dataset) including one individual SEP indicator (education or occupation) mutually adjusted for neighborhood unemployment rate. In the supplementary materials, we present the results for the single-level linear regression models that ignore the nested structure of the observations.

We transformed NO_2 using a natural log transformation to obtain a normally distributed variable. For ease of interpretation, we converted the regression coefficients (βs) into percent change (and 95% Confidence Interval (CI)) per one unit increase in the explanatory factor using the formula $[\exp(\beta) - 1] * 100$ (a 95% CI which does not include zero indicates the presence of significant differences). The considered unit for unemployment rate was 1 standard deviation (SD). For the individual-level SEP variables, we considered each subgroup and tested the statistical differences of the coefficients against the highest group (thus reference group were high educational level and OC-I for occupational class). We deliberately did not show results for participants who were not in the labor force as this class was too heterogeneous to draw any kind of conclusion (i.e. housepersons, unemployed, not working because of poor health, full-time student and retired). This category was excluded to assess the trend across the occupational groups.

2.4.2. Additional analyses

We ran a sensitivity analysis using logistic regression models considering high vs. low exposure (high exposure was defined as an exposure above the 75th percentile of the distribution for each city). All models were adjusted for cohort, age and sex. We checked for potential interactions between SEP and sex, SEP and age and between individual- and neighborhood-level SEP (Supplementary materials). Analyses were conducted using R statistical software (Version 3.0.3) and SAS 9.3.

As pointed out above some "cities" included in this analysis had a wide geographic coverage. For example, the city labelled "Paris" (FR) covered actually the metropolitan area of Paris-Region (i.e. 12,000 km^2). Therefore, we ran a sensitivity analysis by examining

more in detail this area: instead of considering participants of Paris in only one area, we considered three distinctive areas (i.e. City of Paris, the inner-suburbs and the outer-suburbs) defined by particular sociodemographic and geographic situations that could influence the association between SEP and air pollution. The methods and results are presented in detail in the Supplementary materials and discussed in the main article.

3. Results

3.1. Study population characteristics

The study population (Table 1a) was composed of 48% males, with a mean age (±standard deviation; ±SD) of 44 (±11) years. Regarding the NO_2 distribution, we found substantial variability between cities with a mean ranging from 21 (±5) (Pavia; IT) to 57 (±14) μg m^{-3} (Barcelona; ES). Substantial variability was also found within cities. The average range for NO_2 (difference between the highest and the lowest annual average) within each area was 50.3 μg m^{-3}. The largest variation for NO_2 was found in the two largest cities Paris (FR) (85.0) and Barcelona (SP) (92.8).

Regarding the socioeconomic characteristics of the population (Table 1b), participants completed their education on average at age 20 (±4) years. The proportion of manual workers ranged from 6% (Paris; FR) to 38% (Galdakao; SP) and was generally higher in the Spanish cities. On average, participants with lower educational attainment were employed in less skilled occupations (p-value for trend < 0.001) (Table S4). The neighborhood unemployment rate varied from 3% (Pavia; IT) to 22% (Huelva; SP). Participants with lower educational attainment or less skilled occupations were more likely to live in neighborhoods with higher unemployment rate. However, the associations did not reach the level of significance in 7 and 6 out of the 16 cities for education and occupation respectively (Tables S5a—S5b).

3.2. Pooled results

Pooled results are shown in Table 2. In the model taking into account only clustering within cities, low educational level and manual occupations were associated with a lower NO_2 exposure (Percent difference (95% CI) Low vs. high educational level = −6.9% (−9.1; −4.7); OC-IV vs. OC-I = −5.6% (−8.2; −3.0)). Conversely, higher neighborhood unemployment rate was associated with higher NO_2 exposure (7.3% (6.2; 8.5) per 1 SD increase in the unemployment rate). The introduction of individual- and neighborhood-SEP in the same model did not substantially alter effect estimates (Low vs. High educational level = −8.7% (−10.8; −6.5) and 7.8% (6.7; 8.9) per 1 SD increase in the unemployment rate). Accounting for both city and neighborhood clustering decreased the effect size of both the individual- and neighborhood-SEP. Associations remained significant for educational level and the unemployment rate.

Table 1a
Characteristics of the population (by city and data pooled).

City	Country	n	Sex	Age	NO_2 (μg ∗ m^{-3})	
			Men, %	Mean ± SD	Mean ± SD	Q1–Q3
Norwich[a]	UK	242	43.0	43.6 ± 6.5	25.6 ± 5.7	22.8–28.7
Ipswich[a]	UK	338	42.3	42.4 ± 6.8	24.2 ± 4.0	22.7–26.0
Antwerp[a]	Belgium	500	49.9	42.7 ± 6.9	39.4 ± 9.0	32.7–45.6
Paris[a,b]	France	785	48.3	41.7 ± 12.9	36.4 ± 13.4	27.4–42.6
Lyon[a]	France	210	46.7	48.4 ± 15.3	28.7 ± 13.5	16.9–40.6
Grenoble[a,b]	France	690	52.9	44.9 ± 13.4	27.5 ± 8.2	20.8–32.9
Marseille[b]	France	119	43.7	49.2 ± 15.8	26.1 ± 8.2	21.4–31.1
Geneva[c]	Switzerland	612	49.4	52.1 ± 11.3	26.5 ± 7.0	21.1–31.3
Verona[a]	Italy	179	44.1	42.6 ± 7.1	30.7 ± 13.8	22.6–40.2
Pavia[a]	Italy	188	53.7	44.2 ± 6.6	20.5 ± 4.8	17.6–21.8
Turin[a]	Italy	170	46.6	42.9 ± 7.0	54.9 ± 10.1	49.2–61.9
Oviedo[a]	Spain	315	49.8	42.9 ± 7.1	36.6 ± 12.5	29.3–43.9
Galdakao[a]	Spain	408	48.5	40.7 ± 7.3	23.9 ± 6.6	18.6–28.3
Barcelona[a]	Spain	284	44.4	41.9 ± 7.1	57.4 ± 14.1	49.6–62.4
Albacete[a]	Spain	419	46.8	40.8 ± 7.3	28.6 ± 14.8	19.5–38.1
Huelva[a]	Spain	233	50.2	41.1 ± 7.2	25.2 ± 6.4	20.6–29.8
Pooled data		5692	48.2	43.9 ± 10.6	31.8 ± 13.6	22.4–38.6

Cities are sorted from north to south.
Participants were from [a]ECRHS, [b]EGEA, [c]SAPALDIA; Paris: ECRHS n = 386, EGEA n = 399, Grenoble: ECRHS n = 350, EGEA n = 340.

3.3. City-specific results

In the city-specific analyses using standard linear regression models (Table S4), associations with NO_2 were highly heterogeneous for all SEP indicators (I^2 > 76%, p < 0.001). Using multilevel linear regression models, individual-SEP was weakly or not associated with NO_2 exposure for most cities (14 out of 16 cities). For educational level (Table 3a), significant associations were only found in Lyon (FR) (Low vs. High = −3.6 (−12.3; −5.9)) and Verona (IT) (−16.1 (−26.5; −4.3)). For occupational class (Table 3b), significant associations were found for the middle class in Paris (FR) (OC-III vs. OC-I = −3.3 (−6.4; −0.1)) and Oviedo (−8.7 (−15.7; −1.2)). Living in a neighborhood with higher unemployment rate was associated with higher NO_2 exposure (regardless of the individual-SEP marker included in the model) in 11 out of 16 cities. In Oviedo (ES) and Barcelona (ES) an inverse association was observed.

3.4. Additional analyses

Results from the logistic regression models (high vs. low exposure) were consistent with the linear regression ones for the educational level (Table S6a) as well for occupational class (Table S6b).

In Paris-Region (FR), when considering participants in three distinctive areas (i.e. city of Paris, inner suburbs and outer suburbs; supplementary materials), participants with lower educational level or occupational class were less exposed to air pollution (not significant) but those living in neighborhood with higher unemployment rate were more exposed. These results are consistent with those observed when considering participants in one area.

4. Discussion

We investigated, in three European cohorts, whether SEP evaluated at both individual- and neighborhood-level was associated with traffic related air pollution exposure across sixteen Western European cities. The pooled analyses masked important heterogeneity across the cities showing that city appeared to be the major predictor of the association between SEP and NO_2 exposure.

The associations between individual-SEP and NO_2 were generally weak and inconsistent across the cities. This is in accordance with those of the three studies that used a comparable approach to ours (Fernandez-Somoano & Tardon, 2014; Vrijheid et al., 2012; Hajat et al., 2013). Education and occupation showed the same pattern with NO_2 in the pooled data and in most cities, in the city specific analyses, showing that both indicators measured the same concept (Galobardes, 2001; Stronks et al., 1997). The associations between neighborhood-SEP and NO_2 were in the opposite direction (higher exposure in lower neighborhood-SEP) compared to the individual-SEP variables, both in the pooled data and in most cities in the city-specific models. This has also been observed in other studies in Europe (Goodman et al., 2011) and in Montreal, Canada (Crouse et al., 2009).

One possible explanation for the difference in direction is that the neighborhood-SEP is capturing aspects beyond the SEP of the population living in that area, such as how industrialized the neighborhood may be. Moreover, NO_2 variability was relatively small across the individual-SEP groups, and after adjusting for neighborhood-SEP there was little evidence of potential confounding by individual-SEP. Place of residence is strongly patterned by social position and outdoor air

Table 1b
Socioeconomic characteristics of the population (by city and data pooled).

City	*n*	Individual-level SEP						Neighborhood-level SEP
		Age at end of school	Occupational class, %					Unemployment rate*
		Mean ± SD	Managers and professionals (OC-I)	Technicians & associate professionals (OC-II)	Other non-manuals (OC-III)	Manuals (OC-IV)	*Not in labor force*	Mean ± SD (min-max)
Norwich[a]	242	17.6 ± 3.1	25.6	19.4	27.3	24.0	*3.7*	11.1 ± 7.2 (2.1–34.1)
Ipswich[a]	338	17.1 ± 2.6	22.5	16.6	30.8	22.2	*8.0*	10.4 ± 6.6 (2.4–32.0)
Antwerp[a]	500	20.2 ± 3.1	33.0	18.6	31.0	16.8	*0.7*	8.2 ± 5.9 (0.8–31.2)
Paris[a,b]	785	21.3 ± 3.6	41.7	23.6	18.5	6.2	*10.1*	10.6 ± 4.0 (3.0–28.0)
Lyon[a]	210	19.5 ± 3.7	20.5	24.8	26.2	21.0	*7.6*	9.1 ± 3.8 (3.4–25.1)
Grenoble[a,b]	690	20.8 ± 3.8	37.5	20.1	17.4	13.9	*11.0*	9.8 ± 4.5 (3.4–31.3)
Marseille[b]	119	20.6 ± 3.4	46.2	20.2	14.3	9.3	*10.1*	12.1 ± 5.5 (4.9–35.0)
Geneva[c]	612	20.5 ± 4.3	32.4	20.4	24.8	11.4	*11.0*	4.3 ± 1.4 (0.7–9.1)
Verona[a]	179	19.0 ± 4.7	25.8	13.7	29.0	23.7	*7.9*	4.5 ± 3.0 (1.0–15.4)
Pavia[a]	188	18.7 ± 4.6	25.8	13.7	29.0	23.7	*7.9*	3.4 ± 2.5 (0.7–14.3)
Turin[a]	170	19.5 ± 5.2	21.6	13.1	36.4	22.1	*6.8*	7.4 ± 4.1 (1.4–21.7)
Oviedo[a]	315	19.3 ± 4.6	26.7	10.8	29.2	28.6	*4.8*	14.0 ± 3.0 (7.5–33.3)
Galdakao[a]	408	18.2 ± 4.1	17.9	8.6	25.3	37.7	*10.5*	10.7 ± 3.5 (3.1–21.9)
Barcelona[a]	284	18.8 ± 4.9	28.9	14.4	29.6	21.1	*6.0*	10.9 ± 3.3 (4.1–26.4)
Albacete[a]	419	17.7 ± 4.9	17.0	10.0	29.4	33.2	*10.5*	14.6 ± 5.3 (7.7–60.4)
Huelva[a]	233	18.0 ± 4.6	17.6	9.4	27.9	30.5	*14.6*	21.8 ± 6.7 (10.7–41.4)
Pooled data	5692	19.5 ± 4.3	29.1	17.0	25.6	19.6	*8.7*	10.0 ± 6.0 (0.7–60.4)

Cities are sorted from north to south.
SD = standard deviation.
Participants were from [a]ECRHS, [b]EGEA, [c]SAPALDIA; Paris: ECRHS $n = 386$, EGEA $n = 399$, Grenoble: ECRHS $n = 350$, EGEA $n = 340$.
OC = occupational class. Not in labor force participants (in italics) included unemployed, retired, housepersons and students.
* The neighborhood unemployment rate has been assigned individually to participants using their residential addresses.

pollution is spatially located within cities, therefore the degree to which air pollution is socially patterned is likely to occur more at area-level as well (Diez Roux, 2007).

Accounting for both city and neighborhood clustering using a two level random intercept model drastically decreased the size effects of the associations for both individual- and area-SEP markers compared to the single level linear regression model (Table S7). This has been observed in other studies (Goodman et al., 2011; Jerrett et al., 2011; Havard et al., 2008) showing the importance to accounting for clustering in analyses including spatially nested data. With the multilevel approach the effect of unemployment rate remained in all cities but the effect of the individual-SEP decreased and even became null for several cities showing that variability was mainly explained by the city first then by the neighborhoods and for a smaller part by the individual-SEP. We looked at some socioeconomic variables at city level (e.g. population density, gross domestic product, etc.) to try to explain the heterogeneity of the association between SEP and NO_2 among the cities using a meta-regression. However, none of the tested variables explained this heterogeneity (not shown).

To the best of our knowledge this is the first study including a large sample of cities geographically representative of Western Europe, with important within- and between-area variability of air pollution

Table 2
Pooled results for the association between NO_2 concentration ($\mu g * m^{-3}$) and SEP markers ($n = 5692$) in percent change (95%CI).

		n	Multilevel model with city at level[a]			Multilevel model with neighborhood (level 2) and city (level 3)[b]		
			Adjusted for individual factors	Mutually adjusted for individual and neighborhood SEP		Adjusted for individual factors	Mutually adjusted for individual and neighborhood SEP	
Individual-level SEP								
Educational level	High (ref)	1917	–	–		–	–	
	Medium	2001	−4.5 (−6.6; −2.3)	−5.1 (−7.1; −3.0)		−1.3 (−2.7; −0.2)	−1.3 (−2.7; 0.2)	
	Low	1774	−6.9 (−9.1; −4.7)	−8.7 (−10.8; −6.5)		−1.7 (−3.2; −0.1)	−1.8 (−3.3; −0.2)	
p-value for trend			<0.0001	<0.0001		0.04	0.03	
Occupational class	OC-I (ref)	1657	–		–	–		–
	OC-II	967	−2.6 (−5.3; 0.2)		−2.7 (−5.4;0.01)	1.0 (−0.8; 2.9)		1.0 (−0.8; 2.9)
	OC-III	1457	−1.0 (−3.5; 1.6)		−2.0 (−4.1; 0.5)	−0.6 (−2.3;1.0)		−0.7 (−2.3; 1.0)
	OC-IV	1118	−5.6 (−8.2; −3.0)		−7.9 (−10.4; −5.3)	−0.6 (−2.5;1.2)		−0.8 (−2.6; 1.1)
p-value for trend			0.001		<0.0001	0.03		0.03
Neighborhood-level SEP								
Unemployment rate		5692	7.3 (6.2; 8.5)	7.8 (6.7; 8.9)[c]	7.7 (6.6; 8.8)[d]	3.33 (0.71; 6.01)	3.2 (1.5; 5.0)[c]	3.3 (1.5; 5.1)[d]

All models are adjusted for cohort, age and sex.
Results are expressed in percent change in NO_2 ($\mu g * m^{-3}$) concentration adjusted for cohort, age, sex. Negative value means a decrease in NO_2 (in percent) compared to the reference class for categorical variable and for 1 SD increase for the continuous variable; *p*-value for trend were calculated by introducing the categorical variables in continuous. The unemployment rate has been transformed in z-score, the change in NO_2 is showed for 1 standard deviation.
Occupational class (OC): OC-I: managers and professionals, OC-II: technician and associate professionals, OC-III: other non-manuals, OC-IV: skilled, semi-skilled and unskilled manuals.
[a] A multilevel model was performed with city at level-2 (random intercept for city level).
[b] A multilevel model was performed with neighborhood at level-2 and city at level-3 (random intercept for city and neighborhood levels).
[c] Mutually adjusted for educational level and neighborhood unemployment rate.
[d] Mutually adjusted for occupational class and neighborhood unemployment rate.

Table 3a
Percent change (95%CI) in NO_2 concentration ($\mu g * m^{-3}$) in association to educational level mutually adjusted for neighborhood unemployment rate ($n = 5692$).

City	n	Educational level (ref = high)			Neighborhood unemployment rate
		Medium	Low	p-value for trend	
Norwich	242	−0.9 (−5.7; 4.3)	−1.1 (−7.7; 6.0)	0.71	9.4 (5.1; 13.8)
Ipswich	338	2.0 (−0.6; 4.7)	0.5 (−2.8; 3.8)	0.69	4.9 (1.0; 8.9)
Antwerp	500	0.6 (−2.2; 3.4)	1.2 (−1.9; 4.3)	0.45	14.9 (11.8; 18.2)
Paris	785	0.1 (−2.6; 2.9)	−0.3 (−3.1; 2.6)	0.84	13.7 (9.7; 17.8)
Lyon	210	−9.4 (−17.0; −0.9)	−3.6 (−12.3; −5.9)	0.58	12.6 (2.2; 24.0)
Grenoble	690	0.5 (−2.1; 3.0)	0.8 (−1.9; 3.7)	0.56	9.3 (5.1; 13.7)
Marseille	119	−1.9 (−10.4; 7.3)	−7.1 (−16.1; 2.9)	0.13	12.1 (7.1; 17.4)
Geneva	612	−2.0 (−4.5; 0.6)	−1.8 (−4.4; 0.9)	0.18	9.5 (4.7; 14.6)
Verona	179	−0.9 (−15.8; 16.8)	−16.1 (−26.5; −4.3)	0.01	14.0 (3.6; 25.3)
Pavia	188	0.1 (−4.2; 4.6)	−1.4 (−5.4; 2.6)	0.48	2.6 (−1.0; 6.4)
Turin	170	2.8 (−5.9; 12.3)	5.9 (−3.9; 16.6)	0.22	2.3 (−1.4; 6.1)
Oviedo	315	−0.4 (−7.2; 7.0)	−5.0 (−12.3; 3.0)	0.25	−14.1 (−23.6; −3.3)
Galdakao	408	−1.3 (−5.1; 2.8)	−3.3 (−7.8; 1.5)	0.18	21.8 (14.1; 30.1)
Barcelona	284	3.3 (−2.7; 9.7)	3.7 (−3.3; 11.2)	0.28	−7.7 (−12.7; −2.4)
Albacete	419	−10.3 (−21.1; 1.9)	−8.4 (−18.4; 2.9)	0.11	−7.9 (−17.5; 2.9)
Huelva	233	−1.0 (−6.1; 4.3)	−2.6 (−8.5; 3.6)	0.39	1.9 (−2.3; 6.4)

Cities are sorted from north to south.
A multilevel linear regression model (PROC MIXED) was performed with neighborhood at level-2 (random intercept for neighborhood level); adjusted for cohort, age and sex.
Results are expressed in percent change in NO_2 ($\mu g * m^{-3}$) concentration. Negative value means a decrease in NO_2 (in percent) compared to the reference class for the categorical variable; p-value for trend were calculated by introducing the categorical variables in continuous. The unemployment rate has been transformed in z-score, the change in NO_2 is showed for 1 standard deviation.

exposure. We used NO_2 as a traffic-related pollutant known to have a great intra-urban variability and thus was the most appropriate to study socioeconomic differences at individual-level (Chaix et al., 2006a; Cyrys et al., 2012; Jerrett et al., 2005). The NO_2 annual concentrations have been estimated at participant's residential address with a single harmonized exposure assessment protocol across the cities. The measurement time of NO_2 does not overlap with the questionnaire data from the cohorts. However, we assume that spatial contrasts in outdoor NO_2 pollution were stable over time; an assumption supported from observations in different settings in European countries (Eeftens et al., 2011; Beevers et al., 2012). We used homogenized SEP indicators at both individual- and neighborhood-level. Recent evidence showed the importance of accounting SEP at both levels because they were independently associated with health outcomes (Stafford, 2003; Diez Roux, 2007; Bell et al., 2005b; Hajat et al., 2013; Chaix et al., 2010; Krieger et al., 2014) but this had rarely been investigated with air pollution exposure (Chaix et al., 2006a; Naess et al., 2007; Cesaroni et al., 2010). We used an area-based indicator defined at the smallest geographical unit available in each country to avoid MAUP as recommended (Crouse et al., 2009; Diez Roux, 2005; Maantay, 2002; Mujahid et al., 2007).

Our study has some limitations. Due to data confidentiality, we did not have access to participants' geographical coordinates for the present analysis and we were not able to analyze their spatial distribution. We applied an aspatial multilevel model to take into account the clustering of the participants within neighborhoods (Hajat et al., 2013; Havard et al., 2011) but the proportion of neighborhoods containing only one participant was relatively high in some cities (Bell et al., 2010). This highlights a common problem in studies that were not originally designed to study area-level determinants. We compared a large number of European cities, but the sample in some cities was quite small and could explain the absence of associations and large confidence intervals. The

Table 3b
Percent change (95%CI) in NO_2 concentration ($\mu g * m^{-3}$) in association to occupational class mutually adjusted for neighborhood unemployment rate ($n = 5692$).

City	n	Occupational class (ref = OC-I)				Neighborhood unemployment rate
		OC-II	OC-III	OC-IV	p-value for trend	
Norwich	242	−0.1 (−6.1; 6.2)	0.1 (−6.1; 6.7)	4.9 (−1.5; 11.8)	0.45	9.7 (5.3; 14.3)
Ipswich	338	2.3 (−1.2; 5.8)	1.6 (−1.4; 4.7)	0.6 (−2.5; 3.7)	0.99	5.0 (1.2; 9.1)
Antwerp	500	0.9 (−2.5; 4.4)	1.6 (−1.4; 4.6)	−1.7 (−5.0; 1.7)	0.63	15.1 (11. 9; 8.3)
Paris	785	−2.3 (−5.0; 0.6)	−3.3 (−6.4; −0.01)	−4.8 (−9.5; 0.1)	0.03	13.7 (9.7; 17.8)
Lyon	210	3.2 (−5.7; 12.9)	−3.9 (−12.5; 5.5)	−2.1 (−11.7; 8.6)	0.78	13.0 (2.5; 24.6)
Grenoble	690	1.8 (−1.1; 4.8)	1.1 (−2.1; 4.3)	3.1 (−0.4; 6.7)	0.20	9.1 (4.9; 13.5)
Marseille	119	−8.6 (−16.6; 0.1)	−6.9 (−15.2; 2.2)	−4.8 (−15.8; 7.7)	0.07	12.1 (7.0; 17.3)
Geneva	612	1.7 (−1.3; 4.8)	−1.0 (−3.7; 1.9)	−0.7 (−4.1; 2.8)	0.72	9.3 (4.4; 14.3)
Verona	179	1.9 (−20.8; 31.0)	−2.7 (−18.3; 15.8)	−12.9 (−28.1; 5.4)	0.07	13.3 (2.9;4.7)
Pavia	188	−2.6 (−8.2; 3.4)	−3.7 (−7.8; 0.7)	−2.5 (−7.6; 2.8)	0.17	2.7 (−0.9; 6.4)
Turin	170	9.5 (−3.6; 24.4)	9.6 (−0.6; 20.8)	11.7 (−0.1; 25.0)	0.07	2.3 (−1.3; 6.1)
Oviedo	315	0.8 (−9.5; 12.3)	−8.7 (−15.7; −1.2)	−5.9 (−13.2; 2.1)	0.07	−13.7 (−23.6; −2.8)
Galdakao	408	3.9 (−3.1; 11.4)	3.6 (−1.6; 9.0)	3.3 (−1.8; 8.6)	0.67	21.4 (13.6; 29.6)
Barcelona	284	3.4 (−4.8; 12.2)	3.4 (−2.8; 10.1)	4.1 (−2.6; 11.2)	0.16	−7.7 (−12.7; −2.5)
Albacete	419	−3.7 (−18.2; 13.5)	−6.1 (−18.2; 7.8)	−4.6 (−16.5; 9.1)	0.34	−8.3 (−18.0; 2.6)
Huelva	233	8.5 (−0.1; 17.9)	4.1 (−2.1; 10.8)	6.8 (0.1; 13.8)	0.15	1.0 (−3.2; 5.3)

Cities are sorted from north to south.
A multilevel linear regression model (PROC MIXED) was performed with neighborhood at level-2 (random intercept for neighborhood level); adjusted for cohort, age and sex. Results are expressed in percent change in NO_2 ($\mu g * m^{-3}$) concentration. Negative value means a decrease in NO_2 (in percent) compared to the reference class for the categorical variable; p-value for trend were calculated by introducing the categorical variables in continuous. The unemployment rate has been transformed in z-score, the change in NO_2 is showed for 1 standard deviation.
Occupational class (OC): OC-I: managers and professionals (ref), OC-II: technicians and associate professionals, OC-III: other non-manuals, OC-IV: skilled, semi-skilled and unskilled manuals. p-value for trend were calculated by introducing the categorical variables in continuous.

different areas were also of different sizes and with different population density. However, the additional analysis performed for the Paris-Region suggested that the results were not sensitive to this aspect.

We considered the unemployment rate, the sole indicator of neighborhood SEP uniformly available for most of the cities with ESCAPE NO_2 estimates. This single indicator does not fully describe participants' neighborhood-SEP (Diez Roux, 2007) but has been used in other studies that compared different countries regarding air pollution (Samoli et al., 2008) and has been associated with adverse health outcomes at neighborhood level (Samoli et al., 2008; van Lenthe et al., 2005; Bosma et al., 2001; Payne et al., 1993). We performed additional analyses with country-specific deprivation indices that were available at neighborhood level but only for 12 out of the 16 cities (Pornet et al., 2012; Carstairs & Morris, 1989; Alguacil Gómez et al., 2013; Caranci et al., 2010) and we found consistent results compared to the ones with the neighborhood unemployment rate (Table S8).

Finally, we did not have information on other type of exposures such as occupational and indoor exposures or time-activity patterns (Schweizer et al., 2007) which could contribute to create or reinforce environmental inequalities.

5. Conclusions

Unequal distribution to air pollution exposure according to SEP groups is complex in European cities and no general pattern exists across cities, but rather inequalities need to be specifically assessed in each city. Importantly, our results highlighted the importance of taking into account both individual- and neighborhood-SEP in order to fully describe and understand the complexity of current patterns of social inequalities relating to air pollution.

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Competing financial interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.envint.2016.12.026.

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9.3 Appendix 3 Supplementary material: Characterization of rhinitis according to the asthma status in adults using an unsupervised approach in the EGEA study

Methods

A lung function test with methacholine challenge was performed using a standardized protocol with similar equipment across centers according to the ATS/ERS guidelines (217). Methacholine challenge was performed unless baseline FEV1 <80% predicted.

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Table A. Comparison of the characteristics of the participants included and non-included in the analysis

		Not included (n=588)	Included (n=983)	p-value
age, mean± sd		43.1±16.6	42.6±16.5	0.52
Sex, women %		52.4	49.5	0.28
Tobacco status, %	Non smoker	50.4	49.6	0.40
	Ex smoker	28.2	26.3	
	Smoker	21.3	24.1	
BMI, %	<20	10.8	10.7	0.09
	[20-25]	56	49.6	
	[25-30]	23	29.4	
	>=30	10.2	10.3	
SPT	SPT=0	40.9	44.8	0.61
	SPT=1	20.3	17.9	
	SPT=2	12.8	12.9	
	SPT>2	25.9	24.4	
Ever asthma, %		40.8	40.8	0.99
FEV1, % predict		102.5±0.19	102.4±0.18	0.89
BHR, %		42.9 (n=203)	44.3 (n=663)	0.71
Report of nasal symptoms, %		63.3	58.9	0.09
Reports of AR, %		33.33	36.22	0.26
Reports of hay fever, %		35	38.76	0.14
Educational level, %	Low	24.6	24.5	0.94
	Med	26.9	27.7	
	high	48.5	47.8	

BMI= Body Mass Index, SPT: Skin Prick Test, BHR: Bronchial HyperResponsiveness (Methacholine test, PD20≤4 mg), FEV1= Forced Expiratory Volume in 1s , AR: allergic rhinitis

Table B. Missing values for each variables

	Variable	**Missing (N=)**
Nasal symptoms	Type (associated with eyes symptoms or not)	6
	Current or ever	12
	Persistence	103
	Disturbance	103
	Month profile	127
Report of other related disease	Report of allergic rhinitis	33
	Report of hay fever	25
	Report of conjunctivitis	30
	Report of sinusitis	9
	Report of eczema	10
Sensitivity to stimuli	Animals	64
	Hay/flowers	59
	Tobacco	2
	Cold air	53
	Effort	74
	Dust	58
	Weather	192
Drug consumption	Spray for nasal problem , last 12 month	13
	Other drugs for nasal problem(not spray), last 12 months	107
Report	Desensitization since first survey (EGEA1)	89
	Diagnosis of allergy (by a physician)	86
Allergic sensitization	SPT+	266
Asthma status		0

Table C. Description of the participants without asthma according to the four classical phenotypes (hypothesis driven)

		Phenotype 1: No symptoms, no SPT (n=228)	Phenotype 2: SPT only(n=89)	Phenotype 3: symptoms, no SPT(n=140)	Phenotype 4: Symptoms and SPT (n=125)
age, mean± sd		48.3±15.9	42.7±16.6	50.6±14.8	38.7±13.8
Sex, women %		49.1	40,5	61,4	52.8
Tobacco status, %	**Non-smoker**	45.8	50.6	47.9	50.4
	Ex-smoker	32.6	23.6	33.6	21.6
	Smoker	21.6	25.8	18.6	28
BMI, %	**<20**	9.2	12.4	5.7	12.8
	[20-25]	46.5	48.3	47.1	53.6
	[25-30]	32.9	34.8	36.4	24.8
	>=30	11.4	4.5	10.7	8.8
Nasal symptoms, %	**Symptoms without eye symptoms**			62.9	24.8
	Symptoms with eye symptoms			37.1	75.2
Type of nasal symptoms, %	**ever but not current**			2.9	1.6
	ever and current			97.1	98.4
Report of allergic rhinitis*, %		5.3	6.7	25.7	58.4
Report of hay fever*, %		6.6	21.4	17.9	68
Report of conjonctivitis*, %		12.3	16.9	27.1	44.8
Report of sinusitis*, %		35.1	33.7	58.6	52.8
Report of eczema*, %		17.5	33.7	35.7	31.2
Diagnostic of allergy*, %		13.2	21.4	30.7	60.0
Sensitivity to hay/flowers, %	**No sensitivity**	92.5	80.9	76.4	34.4
	Rhinorrhea or sneezing	6.1	13.5	18.6	28.8

	Rhinorrhea and sneezing	1.3	5.6	5	36.8
Sensitivity to animals, %	**No sensitivity**	98.3	97.8	99.3	78.4
	Rhinorrhea or sneezing	1.3	2.2	0.7	12.8
	Rhinorrhea and sneezing	0.4	0	0	8.8
Sensitivity to dust, %	**No sensitivity**	78.9	69.7	52.9	32
	Rhinorrhea or sneezing	23.3	27	40.7	45.6
	Rhinorrhea and sneezing	0.9	3.3	6.4	22.4
Sensitivity to tobacco smoke, %	**No sensitivity**	97.8	98.9	86.3	92
	Rhinorrhea or sneezing	1.8	1.12	11.5	7.2
	Rhinorrhea and sneezing	0.4	0	2.2	0.8
Sensitivity to cold air, %	**No sensitivity**	84.7	83.2	63.6	71.2
	Rhinorrhea or sneezing	14.9	15.7	32.1	25.6
	Rhinorrhea and sneezing	0.4	1.1	4.3	3.2
Sensitivity to weather, %	**No sensitivity**	97.8	96.6	86.4	84.8
	Rhinorrhea or sneezing	1.8	1.1	10.7	12
	Rhinorrhea and sneezing	0.4	2.3	2.9	3.2
Use of nasal spray in the last 12 months*, %		23.3	22.5	45.7	48
Use of other drug in the last 12 months*, %		16.2	21.4	36.4	53.6

***= p-value<0.001, BMI: Body Mass Index**

Table D. Description of the participants with asthma according to the four classical phenotypes (hypothesis driven)

		Phenotype 1: No symptoms, no SPT (n=17)	Phenotype 2: SPT only (n=70)	Phenotype 3: symptoms, no SPT (n=55)	Phenotype 4: Symptoms and SPT (n=259)
age, mean± sd		47.2±14.2	38.2±17.0	45.1±17.7	35.4±15.0
Sex, women %		58.8	41.4	52.7	46
Tobacco status, %	**Non-smoker**	47	52.9	41.8	54.1
	Ex-smoker	41.2	25.7	30.9	18.2
	Smoker	11.8	21.4	27.3	27.8
BMI, %	**<20**	0	10	7.3	14.7
	[20-25]	41.2	55.7	45.5	52.1
	[25-30]	41.2	21.4	30.9	23.9
	>=30	17.6	12.9	16.4	9.3
Nasal symptoms, %	**Symptoms without eye symptoms**			40.0	21.0
	Symptoms with eye symptoms			60.0	79.0
Type of nasal symptoms, %	**ever but not current**			0	0.8
	ever and current			100	99.2
Report of allergic rhinitis*, %		0	32.9	47.3	69.5
Report of hay fever*, %		11.8	41.4	38.2	71.4
Report of conjonctivitis*, %		11.8	30	32.7	55.6
Report of sinusitis, %		41.2	47.1	60	54.1
Report of eczema*, %		41.2	42.9	25.5	56
Diagnostic of allergy*, %		35.3	64.3	52.7	85.7
BHR=1, %		57.1	67.7	71.0	71.8
FEV1 % predict		1.06±0.19	0.94±0.22	0.97±0.21	0.97±0.16
Sensitivity to hay/flowers*, %	**No sensitivity**	94.1	72.9	81.8	31.7
	Rhinorrhea or sneezing	5.9	14.3	5.5	29.7
	Rhinorrhea and sneezing	0	12.9	12.7	38.6

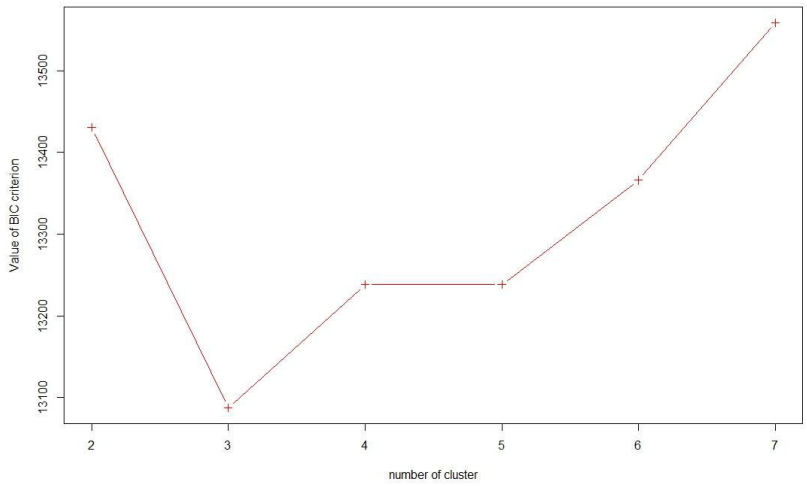
Sensitivity to animals*, %	**No sensitivity**	100	85.7	94.5	59.9
	Rhinorrhea or sneezing	0	8.6	3.6	18.5
	Rhinorrhea and sneezing	0	5.7	1.8	21.6
Sensitivity to dust*, %	**No sensitivity**	82.4	60	49.1	28.6
	Rhinorrhea or sneezing	17.6	27.1	34.6	41.7
	Rhinorrhea and sneezing	0	12.9	16.4	29.7
Sensitivity to tobacco smoke, %	**No sensitivity**	100	94.3	88.9	82.6
	Rhinorrhea or sneezing	0	5.7	7.4	12.7
	Rhinorrhea and sneezing	0	0	3.7	4.6
Sensitivity to cold air, %	**No sensitivity**	88.2	85.7	58.2	69.1
	Rhinorrhea or sneezing	11.8	14.3	38.2	26.3
	Rhinorrhea and sneezing	0	0	3.6	4.6
Sensitivity to weather, %	**No sensitivity**	94.1	94.3	85.5	76.5
	Rhinorrhea or sneezing	5.9	5.7	9.1	13.1
	Rhinorrhea and sneezing	0	0	5.5	10.4
Use of nasal spray in the last 12 months*, %		35.3	44.3	45.5	66.8
Use of other drug in the last 12 months, %		5.9	8.6	5.5	18.5

*= p-value<0.001, BMI= Body Mass Index, BHR: Bronchial HyperResponsiveness (Methacholine test, PD20≤4 mg), FEV1= Forced Expiratory Volume 1s

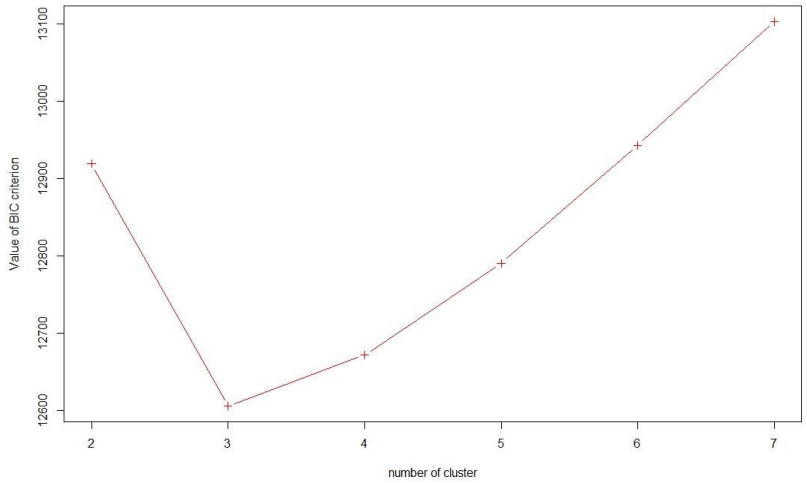
Figure legends

Fig S1: BIC criterion according to the number of cluster for participants without (Part A) and with (Part B) asthma

Part A



Part B



9.4 Appendix 4 Supplementary material: The sensitization pattern differs according to rhinitis and asthma multimorbidity in adults: the EGEA study

Respiratory phenotypes

A lung function test with methacholine challenge was performed using a standardized protocol with similar equipment across centers according to the ATS/ERS guidelines (E1). Methacholine challenge was performed unless baseline FEV_1 <80% predicted.

E1. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005 Aug;26(2):319–38.

Table E1 OR with different adjustments of the association between polysensitization (*versus* no or monosensitized) and the 6 groups

OR [95% CI]	No asthma, no rhinitis	NAR alone	AR alone	Asthma alone(As+)	Asthma +NAR	Asthma + AR
crude OR	1 (ref)	1.5[0.8-2.6]	7.8[4.9-12.4]	6.6[3.6-12.1]	5.5[3.1-9.8]	17.3[11.5-26.2]
aOR (on age, sex and education)	1 (ref)	1.6[0.9-2.8]	8.6[5.3-14.0]	6.0[3.2-11.3]	4.8[2.6-8.8]	15.2[9.9-23.3]
aOR (on age, sex, education, childhood life in farm, parental asthma)	1(ref)	1.7[0.9-3.1]	10.6[6.3-17.8]	6.8[3.5-13.1]	4.8[2.5-9.1]	17.2[10.9-27.1]
aOR (on age, sex, occupation, childhood life in farm, parental asthma)	1(ref)	1.7[0.9-3.2]	10.8[6.4-18.1]	7.2[3.7-13.9]	4.7 [2.4-8.9]	17.5[11.0-27.6]

aOR: adjusted Odd Ratio, NAR: non-allergic rhinitis, AR: allergic rhinitis**.**

Table E2: adjusted OR of the association between allergic sensitization to each of the 10 allergen and the 6 groups

	Group	aOR[95%]
Reference	**No asthma, no rhinitis**	**1.0 (reference)**
Cat	NAR	1.46 [0.72-2.97]
(n=255 with positive SPT)	AR	3.98 [2.21-7.17]
	Asthma	4.45 [2.15-9.22]
	Asthma+NAR	3.42 [1.65-7.08]
	Asthma+AR	10.49[6.39-17.22]
Cladosporium herbarum	NAR	0.74 [0.23-2.38]
(n=60 with positive SPT)	AR	1.48 [0.58-3.77]
	Asthma	4.12 [1.57-10.81]
	Asthma+NAR	1.71 [0.52-5.56]
	Asthma+AR	2.29 [1.09-4.80]
Olive tree	NAR	1.81 [0.85-3.86]
(n=221 with positive SPT)	AR	7.19 [3.91-13.22]
	Asthma	3.7[1.62 -8.43]
	Asthma+NAR	2.8[1.24 -6.32]
	Asthma+AR	9.32 [5.42-16.02]
Birch	NAR	0.91 [0.28-2.97]
(n=116 with positive SPT)	AR	3.92 [1.74-8.86]
	Asthma	4.12 [1.54-11.03]
	Asthma+NAR	2.74 [1 -7.54]
	Asthma+AR	6.8 [3.4 -13.57]
Ragweed	NAR	NC
(n=66 with positive SPT)	AR	5.34 [2.14-13.33]
	Asthma	1.44 [0.29-7.13]
	Asthma+NAR	1.8[0.45 -7.19]
	Asthma+AR	5.77 [2.51-13.26]
Dermatophagoides pteronyssinus	NAR	1.32 [0.78-2.24]
(n=393 with positive SPT)	AR	3.63 [2.3 -5.72]
	Asthma	4.94 [2.72-9.00]
	Asthma+NAR	4.06 [2.3 -7.15]
	Asthma+AR	6.46 [4.41-9.46]
Alternaria tenuis	NAR	1.87 [0.62-5.68]
(n=98 with positive SPT)	AR	4.78 [1.9-12.03]
	Asthma	9.14 [3.37-24.83]
	Asthma+NAR	2.97 [0.91-9.69]
	Asthma+AR	7.42 [3.3-16.69]
Timothy grass	NAR	1.33 [0.71-2.49]

(n=347 with positive SPT)	AR	8.48 [5.16-13.96]
	Asthma	2.62 [1.29-5.31]
	Asthma+NAR	2.91 [1.52-5.57]
	Asthma+AR	9.94 [6.45-15.33]
Parieteria judaica	NAR	0.69 [0.07-6.68]
(n=35 with positive SPT)	AR	3.39 [0.79-14.44]
	Asthma	NA
	Asthma+NAR	1.38[0.14-13.59]
	Asthma+AR	8.03[2.38-27.17]
Cypress	NAR	6.27[0.65-60.88]
(n=33 with positive SPT)	AR	19.68[2.47-157.14]
	Asthma	NC
	Asthma+NAR	13.24[1.35-130.21]
	Asthma+AR	16.99[2.23-129.27]

aOR: adjusted OR on age, sex, smoking status and educational level, NAR: non-allergic rhinitis, AR: allergic rhinitis, NC: not calculable (sample too small)

9.5 Appendix 5 Supplementary material: Association between air pollution and rhinitis incidence in two European cohorts

Air pollution exposure assessment

The European Study of Cohorts for Air Pollution Effects (ESCAPE, www.escapeproject.eu) is a European project who aimed to investigate of long-term exposure to air pollution effects on human health in Europe. ESCAPE was based on the collaboration between more than 30 existing European population studies including EGEA and ECRHS. The objectives of the ESCAPE were to develop a flexible methodology for assessment of long-term population exposure to air pollution focused primarily on fine particles, particle composition, and NOx, and to apply the exposure assessment methodology on existing cohort studies. Investigations focused on several health outcomes such as mortality, cardiovascular diseases, cancer, adverse perinatal outcomes and respiratory diseases.

Ambient concentrations of $PM_{2.5}$, PM_{10}, particle composition, NO_2 and NOx were measured in 36 study areas across Europe, selected because of the availability of informative cohort studies in these areas. NO_2 and NOx were measured in all 36 areas; PM was measured in 20 out of 36 areas. For each area, a mean of 40 measurement sites for NO_2 and NOx and a mean of 20 sites for PM were classified as regional background, urban background and street site. The objective was to capture the large diversity of potential sources of air pollution variability (e.g. population density, traffic intensity, industry, proximity to harbours …). Measurements were done between October 2008 and April 2011 in a 14-day period of each of three seasons (cold, warm and intermediate). Annual average concentrations for each monitoring site were calculated after adjustment for temporal variation using routine monitor background data.

For each cohort participants, home address has been geocoded and linked with individual annual exposure estimates based on predictions of LUR models, corresponding to the year of the questionnaire *(Hoek, Atmos Environ 2008)*. LUR models were based on air pollution measurements at monitoring site and geographic predictors including digital road network (traffic intensity data), land use, population density, altitude and study local area specific data (e.g. distance to the sea or wood smoke) *(Beelen Atmos Environ 2013*). Additionally, each participant also had indicators of traffic corresponding to home address from digital road networks: traffic intensity on the nearest road (traffic intensity, vehicles/day) and total traffic load on major roads in a 100 m buffer (traffic load, vehicles*m/day).

Figure S1 Association between NO_2 and incident rhinitis by city and meta-regression, separated by study

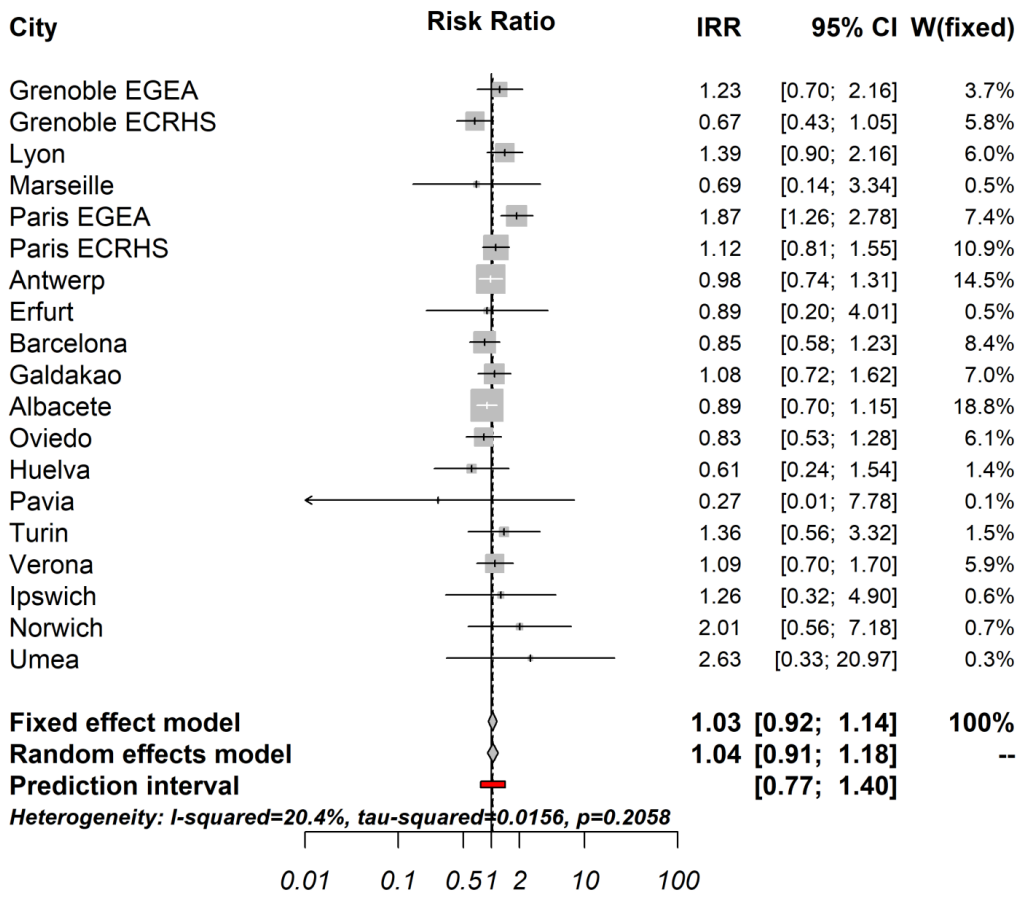


Table 1 Pearson's correlation coefficients for air pollution concentrations and and traffic variables

	NO_2	**PM_{10}**	**$PM_{2.5}$**	**PM_{coarse}**	**$PM_{2.5}$ absorbance**	**NOx**	**Traffic load in major road**	**Traffic intensity**
NO_2	1	0.71	0.70	0.87	0.80	0.87	0.55	0.39
PM_{10}		1	0.77	0.80	0.57	0.62	0.31	0.39
$PM_{2.5}$			1	0.66	0.68	0.56	0.46	0.53
PM_{coarse}				1	0.79	0.74	0.48	0.37
$PM_{2.5}$ absorbance					1	0.74	0.66	0.51
NOx						1	0.60	0.38
Traffic load in major road							1	0.46
Traffic intensity								1

Table 2 IRR of the associations between for NOx, PMcoarse, $PM_{2.5}$ absorbance, traffic measures and incident rhinitis

	No of subjects in adjusted model (No of cases)			crude IRR (95%CI)			aIRR (95%CI)		
Pollutant	NOx	PM coarse	$PM_{2.5}$ abs	NOx	PM coarse	$PM_{2.5}$ abs	NOx	PM coarse	$PM_{2.5}$ abs
	1372(353)	645 (187)	502(147)	1.00[0.92-1.09]	0.94[0.78-1.16]	0.97[0.78-1.22]	0.99[0.90-1.07]	0.91[0.76-1.12]	0.90[0.73-1.14]

aIRR : adjusted IRR on adjusted on 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 5 µg/m3 of $PM_{2.5}$ and PMcoarse, 10–5/m1 of $PM_{2.5}$absorbance and 20 µg/m3 of NOx

	No of subjects in adjusted model (No of cases)		crude IRR (95%CI)		aIRR (95%CI)	
Traffic measure	Traffic load in major road	Traffic intensity	Traffic load in major road	Traffic intensity	Traffic load in major road	Traffic intensity
	846(249)	890(241)	1.02[0.89-1.13]	1.00[0.94-1.05]	0.99[0.85-1.11]	0.98[0.91-1.04]

aIRR : adjusted IRR on adjusted on 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 5,000 vehicles/day for traffic intensity on the nearest road and four millions vehicles × m/day for traffic load in major roads within a 100-m buffer.

9.6 Appendix 6 Supplementary material: Air pollution increases the severity of rhinitis in two European cohorts

Table 1: Characteristics of the participants according to the study

Variable	ALL N=1550	EGEA N=386	ECRHS N=1164	p-value
Age, mean±sd	52.4±10.9	47.1±16.8	54.2±7.2	<0.001
Sex=women, %	54.5	50.3	55.8	0.056
Smoking status, %				<0.001
current	18.1	15.93	18.8	
ex-smoker	37.8	29.24	40.6	
never	44.1	54.83	40.6	
Educational level, %				<0.001
low	21.6	13.6	24.08	
medium	29.8	28.05	30.35	
high	48.5	58.36	45.57	
Asthma ever, %	29.2	52.6	21.3	<0.001
Asthma age of onset, mean±sd	16.4±14.0	12.9±14.3	19.3±13.1	<0.001
Report of allergic rhinitis or hay fever ever, %	58.8	68.2	55.8	<0.001
Allergic sensitization, %	48.1	66.2	42	<0.001
Score of severity, median[Q1-Q3]	4[2-6]	5[3-7]	4[2-6]	<0.001
NO_2, m g.m^{-3}, mean±sd	28.9±14.4	29.2±12.7	30.1±14.9	0.0008
PM_{10}, m g.m^{-3}, mean±sd	25.2±6.7	25.3±3.8	25.2±7.6	0.92
$PM_{2.5}$, m g.m^{-3}, mean±sd	15.3±3.7	15.3±1.9	15.3±4.2	0.94
Pmcoarse, m g.m$^{-3,}$ mean±sd	10.0±3.8	9.3±2.5	10.3±4.2	0.02
Traffic load, mean	1573040	1326526	1680559	0.07
Traffic intensity, mean±sd	5721±9994	6106±8176	5532±10774	0.36
Severity of runny nose				<0.001
no	26.3	20.5	28.1	
mild	36.8	33.7	37.8	
moderate/severe	36.9	45.8	34.1	
Severity of blocked nose				<0.001
no	31.9	24.4	34.06	
mild	25.2	23.21	25.74	
moderate/severe	43	52.38	40.21	
Severity of itchy nose				<0.001
no	44.1	32.72	47.35	
mild	31.6	33.95	30.98	
moderate/severe	24.2	33.33	21.67	
Severity of sneezing				<0.001
no	30.4	27.2	31.4	
mild	37.3	30.31	39.46	
moderate/severe	32.3	42.49	29.14	

Table 2: Odds Ratio of the associations between NO_2, PM_{10}, $PM_{2.5}$,PM coarse, traffic load and traffic intensity and the severity of rhinitis (according to the symptom and considering the score in quartile)

Outcome	Pollutant		OR (Odds Ratio)	CI-	CI+
Runny nose	NO_2	Mild	**1.12**	**1.02**	**1.23**
		Moderate/severe	1.09	0.96	1.23
	PM_{10}	Mild	1.23	0.91	1.65
		Moderate/severe	**1.48**	**1.01**	**2.16**
	$PM_{2.5}$	Mild	1.04	0.80	1.37
		Moderate/severe	1.26	0.88	1.79
	Pmcoarse	Mild	1.30	0.99	1.70
		Moderate/severe	**1.61**	**1.17**	**2.22**
	Traffic load	Mild	1.07	0.86	1.33
		Moderate/severe	1.03	0.82	1.30
	Traffic intensity	Mild	1.14	1.01	1.27
		Moderate/severe	1.09	0.97	1.23
Blocked nose	NO_2	Mild	**1.17**	**1.05**	**1.30**
		Moderate/severe	**1.16**	**1.03**	**1.30**
	PM_{10}	Mild	**1.39**	**1.03**	**1.89**
		Moderate/severe	**1.84**	**1.31**	**2.60**
	$PM_{2.5}$	Mild	**1.37**	**1.04**	**1.80**
		Moderate/severe	**1.69**	**1.22**	**2.35**
	Pmcoarse	Mild	1.27	0.96	1.68
		Moderate/severe	**1.57**	**1.16**	**2.12**
	Traffic load	Mild	0.97	0.77	1.23
		Moderate/severe	1.04	0.85	1.27
	Traffic intensity	Mild	**1.11**	**1.00**	**1.22**
		Moderate/severe	1.04	0.94	1.15
Itchy nose	NO_2	Mild	0.98	0.88	1.08
		Moderate/severe	0.88	0.77	1.02
	PM_{10}	Mild	1.15	0.86	1.52
		Moderate/severe	**1.56**	**1.02**	**2.40**
	$PM_{2.5}$*	Mild	0.97	0.76	1.25
		Moderate/severe	**1.23**	**0.85**	**1.77**
	Pmcoarse	Mild	1.03	0.77	1.36
		Moderate/severe	1.30	0.80	2.11
	Traffic load	Mild	1.07	0.89	1.28
		Moderate/severe	0.89	0.70	1.14

	Traffic intensity	Mild	1.04	0.96	1.12
		Moderate/severe	1.05	0.96	1.15
Sneezing	NO_2	Mild	1.11	0.99	1.23
		Moderate/severe	1.07	0.97	1.19
	PM_{10}	Mild	1.11	0.72	1.73
		Moderate/severe	**1.66**	**1.17**	**2.36**
	$PM_{2.5}$	Mild	1.10	0.75	1.60
		Moderate/severe	**1.67**	**1.21**	**2.32**
	Pmcoarse	Mild	1.28	0.83	1.99
		Moderate/severe	1.18	0.83	1.69
	Traffic load	Mild	1.08	0.88	1.33
		Moderate/severe	1.04	0.84	1.30
	Traffic intensity	Mild	0.99	0.90	1.09
		Moderate/severe	1.05	0.96	1.15
Score of severity	NO_2	Quartile 2	**1.14**	**1.02**	**1.27**
		Quartile 3	1.13	0.98	1.29
		Quartile 4	1.13	0.96	1.32
	PM_{10}	Quartile 2	**1.49**	**1.05**	**2.12**
		Quartile 3	**2.07**	**1.35**	**3.19**
		Quartile 4	**2.37**	**1.41**	**3.97**
	$PM_{2.5}$	Quartile 2	**1.67**	**1.22**	**2.29**
		Quartile 3	**1.95**	**1.31**	**2.88**
		Quartile 4	**1.95**	**1.21**	**3.15**
	Pmcoarse	Quartile 2	1.15	0.83	1.58
		Quartile 3	**1.52**	**1.02**	**2.27**
		Quartile 4	**1.95**	**1.26**	**3.02**
	Traffic load	Quartile 2	1.00	0.80	1.25
		Quartile 3	1.06	0.83	1.36
		Quartile 4	1.05	0.82	1.35
	Traffic intensity	Quartile 2	1.07	0.96	1.20
		Quartile 3	1.12	0.99	1.26
		Quartile 4	1.09	0.97	1.24

Reference: no problem (symptom not present) for the symptoms and quartile 1 for the score of severity. CI: Confidence Interval. Odds Ratio (OR) adjusted for age, sex, smoking status, number of siblings, family history of allergies, asthma, report of nasal allergies or hay fever (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/m3 for NO_2 and PM_{10} and 5 µg/m3 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.

*: Results not adjusted on allergic rhinitis/hay fever due to convergence problem.

9.7 Appendix 7: Substantial abstract in French

RHINITE : CARACTERISATION ET ASSOCIATION AVEC LA POLLUTION ATMOSPHERIQUE

1. Contexte scientifique, social et sociétal

La rhinite se définit par une inflammation des fosses nasales caractérisée par des éternuements, un nez qui coule ou qui gratte et/ou une congestion nasale (Bousquet et al. 2008). Elle se divise en deux grandes catégories, la rhinite allergique et la rhinite non allergique. La rhinite allergique résulte d'une réponse immunitaire médiée par les Immunoglobulines E (IgE) en réponse à la pénétration d'un allergène dans les fosses nasales, par exemple un grain de pollen (Bousquet et al. 2012). La rhinite allergique est souvent associée à une conjonctivite allergique, ou à d'autres maladies allergiques telles que l'asthme ou l'eczéma et elle présente souvent un caractère saisonnier (Quillen and Feller 2006). La rhinite non-allergique est généralement chronique même si elle peut aussi être aiguë, et regroupe un grand nombre de sous-phénotypes. Les mécanismes de la rhinite non-allergique sont moins bien connus et elle peut être déclenchée entre autres par l'air froid, un changement de température, des odeurs, ou par l'exercice physique. Il existe également un certain nombre de patients atteint de rhinite dite « mixte » qui associe des symptômes de la rhinite allergique et de la rhinite non allergique (Bernstein 2010). Le diagnostic de rhinite n'est de ce fait pas facile à établir (Bousquet et al. 2015) : il repose sur un entretien détaillé avec le patient portant sur les symptômes, les éléments déclencheurs, les comorbidités et les antécédents de la maladie ainsi que la réalisation d'un test de sensibilité allergique si nécessaire. En épidémiologie, il n'y a pas de standardisation de la définition de la rhinite et de ses différents phénotypes chez l'adulte, et les deux types de rhinite sont généralement distingués grâce à des tests de sensibilité allergique. Enfin la littérature sur le sujet traite majoritairement du phénotype de rhinite allergique. Selon les pays et la définition utilisée, la prévalence de la rhinite varie ainsi de 20 à 50%, et son incidence a fortement augmenté en 30 ans (Katelaris et al. 2012; Wang et al. 2014). La rhinite est souvent considérée comme anodine, mais a un fort impact sur la performance scolaire, la vie sociale, la performance au travail, et est associée à une forte augmentation des coûts des soins (Cardell et al. 2016; Linneberg et al. 2016). Par ailleurs, la rhinite est très fortement liée à l'asthme, et ce quelle que soit la sensibilité allergique (Shaaban et al. 2008).

De manière similaire à d'autres maladies respiratoires ou allergiques, l'augmentation de l'incidence de la rhinite durant les dernières décennies est probablement due à des interactions complexes entre prédisposition génétique et facteurs environnementaux. Parmi ceux-ci, la pollution atmosphérique représente le plus grand risque environnemental pour la santé, responsable d'environ 4.5 millions de décès chaque année (Cohen et al. 2017).

En Europe, la pollution atmosphérique liée à l'industrie a été contrôlée et les épisodes aigus majeurs ont disparu. Actuellement, la source principale de pollution atmosphérique est le trafic automobile. Avec la baisse des concentrations des polluants industriels dans les années 80, l'intérêt pour la pollution atmosphérique a diminué car les concentrations étaient considérées comme trop faibles pour avoir des effets néfastes sur la santé

(Brunekreef and Holgate 2002). Mais, dès le début des années 90's des études comme celle des « six villes » aux USA ont démontré que même des concentrations faibles pouvaient être associées à une augmentation de la mortalité toutes causes et cardio-respiratoire (Dockery et al. 1993). Depuis, il n'a pas été possible de mettre en évidence un seuil minimal de nocivité. Les polluants atmosphériques les plus étudiés actuellement sont le dioxyde d'azote (NO_2) et les particules qui sont issues principalement du trafic, et l'ozone (O_3) qui est formé secondairement. Les grosses particules (PM_{10} d'un diamètre aérodynamique inférieur ou égal à 10 µM) peuvent atteindre les voies respiratoires supérieures et les poumons. Les particules fines ($PM_{2,5}$) peuvent atteindre les alvéoles. Les particules ultrafines ($PM_{0,1}$) peuvent atteindre la circulation sanguine, expliquant en partie les observations d'effets néfastes sur le système cardiovasculaire résultant d'un effet systémique (Simkhovich et al. 2008). La population urbaine représente environ 2/3 de la population Européenne, et des estimations récentes montrent que l'exposition au-delà des valeurs maximales suggérées par l'Organisation Mondiale de la Santé (OMS) concernent une forte proportion de la population urbaine (50-62% pour les PM_{10}–moyenne-annuelle (ma)>20µg/m3, 82-85% pour les $PM_{2.5}$–ma>10µg/m3, 7%-9% pour NO_2–ma>40µg/m3, "European Environment Agency (EEA), 2017). En 2013, la pollution atmosphérique a été classée comme substance cancérigène groupe 1 par le Centre International de Recherche sur le cancer (CIRC, http://www.iarc.fr).

La pollution atmosphérique est un facteur de risque reconnue pour de nombreuses maladies et en particulier celles des voies respiratoires et cardiovasculaires (Pope 2003). L'exposition à long-terme à la pollution atmosphérique est aussi associée à une diminution de la fonction ventilatoire ainsi qu'à l'exacerbation de l'asthme (Li et al. 2016; Zheng et al. 2015). Seules quelques études se sont intéressées aux associations entre l'exposition à long-terme à la pollution atmosphérique et la prévalence de la rhinite, et portaient majoritairement sur la rhinite allergique avec des résultats différents selon les études (Heinrich et al. 2005; Lindgren et al. 2009; Wyler et al. 2000). La pollution atmosphérique pourrait jouer un rôle dans le développement des maladies allergiques mais à ce jour, il n'y a aucune étude évaluant l'effet de la pollution atmosphérique à long-terme sur l'incidence de la rhinite. De plus, comme suggéré dans le cas de la rhinite allergique (Annesi-Maesano et al. 2012), la pollution atmosphérique pourrait également être un facteur aggravant de la sévérité de la maladie.

2. Objectifs

L'objectif général de ce projet est d'identifier les différentes formes d'expression de la rhinite chez l'adulte et de mieux comprendre le rôle de la pollution atmosphérique dans le développement et la sévérité de la rhinite.

Les objectifs spécifiques du projet de thèse sont :

1) D'identifier différents phénotypes de rhinite chez l'adulte à l'aide d'approches non supervisées et d'étudier le lien entre phénotypes de rhinite, multimorbidité avec l'asthme et sensibilisation allergique.
2) D'étudier l'association entre l'exposition à long terme à la pollution atmosphérique et l'incidence de la rhinite et l'association entre l'exposition à long terme à la pollution atmosphérique et la sévérité des symptômes de rhinite.

3. Méthodes et techniques

Population

Ce projet repose sur les données de deux études épidémiologiques Européennes multicentriques sur la santé respiratoire, ayant un design similaire et des données détaillées sur la santé respiratoire de chaque participant :

L'étude EGEA (Etude épidémiologique des facteurs génétiques et environnementaux de l'asthme, https://egeanet.vjf.inserm.fr) est une étude multicentrique cas-témoin et familiale. La première enquête s'est déroulée entre 1991 et 1995 (EGEA1, n=2047). Un premier suivi de la cohorte initiale a été réalisé entre 2003 et 2007 (EGEA2, 92% de suivi, 1601 sujets avec examens complets dont 1570 adultes). Un deuxième suivi a été réalisé entre 2011 et 2013 (EGEA3, 79,2% de suivi, 1558 adultes). Tous les sujets ont été caractérisés en ce qui concerne les phénotypes cliniques et les facteurs environnementaux et de nombreux échantillons biologiques ainsi que des tests de sensibilités allergiques ont été recueillis à EGEA2 (Certification ISO 9001 depuis 2006 et renouvelée depuis).

L'étude **ECRHS** (European Community Respiratory Health Survey, http://www.ecrhs.org/) a été réalisée dans une population générale d'adultes Européens (>30 villes dans 14 pays) agés de 20 à 44 ans en 1990 (ECRHS I, n≈18000). Un premier suivi (ECRHS II) a eu lieu entre 1998 et 2002 (n≈11000 participants) et un deuxième suivi a eu lieu entre 2011 et 2013 (ECRHS III, n=7040 participants). Tous les sujets ont été largement caractérisés en ce qui concerne les phénotypes cliniques et les facteurs environnementaux et de nombreux échantillons biologiques ainsi que des tests de sensibilités allergiques ont été recueillis au cours des trois études.

Pour le premier objectif, nous avons utilisé les données à EGEA2 et pour le second objectif nous avons utilisé les données des deux cohortes à EGEA2 et 3 et ECRHSII et III.

Estimation à long terme de la pollution atmosphérique

Dans EGEA2 et ECRHS II, l'exposition à long terme à la pollution atmosphérique (NO_x et PM) a été estimée à l'adresse résidentielle des sujets, après géocodage, à l'aide de modèles d'estimations Land Use Regression (LUR,) dans le cadre du projet Européen ESCAPE (http://www.escapeproject.eu/) coordonné par B Brunekreef (IRAS, Utrecht).

Phénotypes cliniques

Il n'existe pas de questionnaires aussi standardisés pour la rhinite que pour l'asthme. Cependant, les questionnaires d'EGEA2 et d'ECRHS II sont similaires et fournissent des informations sur la survenue de la rhinite durant la vie, la notion de rhinite allergique ou non, la rhinite active, l'âge de début, la fréquence des symptômes, les facteurs déclencheurs, la sévérité et les traitements spécifiques.

La sensibilité allergique est disponible dans EGEA2 par la réponse allergique aux tests cutanés à 12 aéroallergènes et dans ECRHSII par un taux élevé d'IgE spécifiques à 4 allergènes. La monosensibilisation a été définie comme un test de sensibilisation positif et la polysensibilisation comme au moins deux tests de sensibilisation positifs.

La rhinite a été définie par une réponse positive à la question: *«Avez-vous déjà eu des problèmes d'éternuements, nez qui coule ou nez bouché quand vous n'étiez pas enrhumé€ ou n'aviez pas la grippe ?»*. Les autres maladies telle que l'eczéma, la rhinite allergique,

le rhume des foins, la sinusite ou la conjonctivite ont été définies par une réponse positive à la question suivante *« Avez-vous déjà eu … (une rhinite allergique/un rhume des foins/de l'eczéma/ une conjonctivite/une sinusite) ? »*.

Dans EGEA, l'asthme vie a été défini par une réponse positive à : *« Avez-vous déjà eu des crises d'essoufflement au repos avec des sifflements ? »* ou *«Avez-vous déjà eu une crise d'asthme ? »* ou si le participant avait été recruté comme cas asthmatique. Dans ECRHS, l'asthme vie a été défini par la réponse positive à la question « *Avez-vous déjà eu de l'asthme ?* ».

Pour identifier les phénotypes et sous-phénotypes de rhinite dans EGEA2 (Objectif 1), nous avons réalisé une analyse de clustering aussi nommée « Data driven » chez 983 adultes, séparément chez les non-asthmatiques (Asthme-, N=582) et les asthmatiques (Asthme+, N=401). Les réponses des participants à l'auto-questionnaire relatives à la rhinite portant sur les symptômes nasaux, le rhume des foins, la sinusite, la conjonctivite ainsi que les sensibilités ressenties face à différents stimuli (poussières, animaux, foin/fleurs, air froid) ont été utilisées. La sensibilité allergique a été définie par une réponse positive à un test cutané à au moins un des 12 allergènes par rapport au témoin. Nous avons comparé les clusters obtenus avec les phénotypes classiques (« Hypothesis driven ») définis uniquement à partir de la question sur les symptômes de rhinite et les tests de sensibilité allergique (i.e : rhinite non-allergique : symptôme de rhinite mais pas de sensibilisation et rhinite allergique : symptômes de rhinite et sensibilisation).

L'incidence de la rhinite (Objectif 2) a été définie par une réponse positive à *« Avez-vous déjà eu des problèmes d'éternuements, nez qui coule ou nez bouché quand vous n'étiez pas enrhumé(e) et n'aviez pas la grippe ? »* à EGEA3 et ECRHS III et une réponse négative à la même question à EGEA2/ ECRH II.

La sévérité de la rhinite a été définie à EGEA3 et ECRHS III de deux manières :

1) en fonction de la gêne due aux quatre symptômes de rhinite : nez qui coule comme de l'eau, nez bouché, éternuement, nez qui gratte, et catégorisée en 3 groupes : aucune (référence), sévérité légère ou sévérité importante
2) en utilisant un score général de sévérité incluant la gêne relative à tous les symptômes, variant de 0 à 12, ensuite divisé en quartile.

Analyses statistiques

Pour identifier les phénotypes et sous-phénotypes de rhinite dans EGEA2 (Objectif 1), des méthodes d'apprentissage non supervisé et plus particulièrement des modèles de mélange ont été utilisés. Le nombre de classes a été déterminé grâce à la plus petite valeur du critère BIC, ou Bayesian Information Criterion.

Afin d'étudier l'association entre la pollution atmosphérique et l'incidence de la rhinite (Objectif 2), nous avons utilisé le ratio du taux d'incidence, calculé en utilisant un modèle de Poisson, prenant en compte la ville comme un « intercept » aléatoire, et le temps de suivi entre les deux suivis comme « offset ». Dans un second temps, nous avons réalisé une analyse par ville et une méta-régression. Dans l'étude de l'association entre la pollution atmosphérique et la sévérité de la rhinite, nous avons également pris en compte la ville comme un « intercept » aléatoire.

Pour les autres analyses statistiques, des régressions logistiques ou linéaires -en fonction des variables d'intérêt- ont été utilisées.

Suivant le protocole ESCAPE, les coefficients sont estimés pour une augmentation de 10 µg/m3 pour NO_2 et les PM_{10}, et de 5 µg/m3 pour les $PM_{2.5}$.

3. Résultats

Le premier objectif de ma thèse était d'identifier différents phénotypes de rhinite chez l'adulte à l'aide d'approches non supervisées.

Dans un premier temps, j'ai utilisé une approche non supervisée (data-driven) afin d'identifier des phénotypes de rhinite chez 983 adultes de l'étude EGEA2. Comme la rhinite est fortement associée à l'asthme, j'ai réalisé ces analyses séparément chez les asthmatiques (N=401) et les non asthmatiques (N=582). Trois cluster distincts ont été mis en évidence, quel que soit le statut asthmatique : 1) Cluster A (55 % des Asthme-, et 22% des Asthme+) : caractérisé par l'absence de symptôme nasal et de sensibilité allergique, le cluster de référence, 2) Cluster B (23% des asthme- et 36% des asthme+) caractérisé par des symptômes nasaux tout au long de l'année, un faible taux de sensibilité allergique, un faible taux de déclaration de rhinite allergique, de rhume des foins et de conjonctivite et des facteurs déclencheurs associés aux phénotypes non-allergiques tels que l'air froid, le tabac ou le changement de temps et 3) Cluster C (22% des asthme- et 42% des asthme+) caractérisé par un pic des symptômes au printemps, un fort taux de sensibilité allergique et de déclaration de rhume des foins, de rhinite allergique et de conjonctivite.

Les participants ayant de l'asthme et une rhinite allergique (cluster C chez les participants avec de l'asthme) avaient le plus fort taux de polysensibilité définie précédemment comme la sensibilité allergique à au moins 2 allergènes. Ces clusters avaient des caractéristiques assimilables aux phénotypes connus dans la littérature de rhinite non-allergique (cluster B) et de rhinite allergique (cluster C) mais différaient en termes de caractéristiques et en particulier de sensibilité allergique. En effet, parmi les participants avec de la rhinite, 21% des non-asthmatiques et 30% des asthmatiques ne sont pas classés de manière identique selon les clusters et selon les phénotypes définis classiquement.

Pour conclure, cette étude a mis en évidence 3 clusters de rhinite et ce quel que soit le statut asthmatique : pas de rhinite, rhinite non-allergique et rhinite allergique. Cette étude a permis de valider et de confirmer les phénotypes souvent décrits dans la littérature. Elle a aussi permis de mettre en évidence la différence en terme de sensibilité allergique entre ces phénotypes classiques et les clusters identifiés qui pourrait laisser penser que les tests de sensibilisation peuvent être insuffisants pour distinguer le phénotype de rhinite allergique du phénotype de rhinite non-allergique. Ces clusters peuvent être facilement reconstruits en utilisant seulement quelques questions et sont donc d'intérêt aussi pour les cliniciens.

Ce premier travail a donné lieu a deux communications dont une orale (congrès de l'ERS, Munich, 2014) et à une publication (*Burte E, Bousquet J, Varraso R, Gormand F, Just J, Matran R, Pin I, Siroux V, Jacquemin B, Nadif R. Characterization of Rhinitis According to the Asthma Status in Adults Using an Unsupervised Approach in the EGEA Study. PLoS One. 2015 Aug26;10(8):e0136191. doi: 10.1371/journal.pone.0136191*).

Ce premier travail a aussi montré que la sensibilisation allergique, et en particulier le nombre de sensibilisation allergique, étaient très différents en fonction des phénotypes

d'asthme et de rhinite. J'ai donc voulu étudier plus en détail le niveau de sensibilisation allergique et en particulier la mono et poly sensibilisation et la comorbidité entre l'asthme et la rhinite. Pour cela, nous avons utilisé les données de 1199 adultes de EGEA2 et nous avons classé les participants en 6 groupes, en utilisant uniquement les données obtenues par questionnaire : asymptomatiques (ni asthme ni rhinite), rhinite non-allergique uniquement, rhinite allergique uniquement, asthme uniquement, asthme+ rhinite non-allergique et asthme+ rhinite allergique.

Les participants asymptomatiques étaient majoritairement non sensibilisés (environ 72%) et environ 12% d'entre eux étaient polysensibilisés. Parmi les participants ayant une rhinite allergique uniquement, un asthme uniquement ou un asthme+ rhinite non-allergique, de 32 à 43% d'entre eux étaient non sensibilisés et de 37 à 46 % d'entre eux étaient polysensibilisés. 65% des participants ayant de l'asthme+ rhinite allergique étaient polysensibilisés. Le niveau d'IgE totales suivait la même tendance que la sensibilisation allergique. Le taux d'éosinophiles était plus élevé chez les asthmatiques, et particulièrement chez ceux ayant asthme + rhinite allergique. Les participants de ce phénotype combiné asthme +rhinite allergique avaient des symptômes de rhinite plus sévères et déclaraient plus souvent de l'eczéma que ceux des autres groupes.

Cette étude a montré que le taux de polysensibilisation dépendait fortement de la présence concomitante ou non d'asthme et de rhinite. Nos résultats confirment que la sensibilisation ne doit pas être considérée comme une variable dichotomique.

Ce deuxième travail a donné lieu à une communication par poster (congrès de l'ERS, Amsterdam 2015) et à une publication *(Burte E, Bousquet J, Siroux V, Just J, Jacquemin B, Nadif R. The sensitization pattern differs according to rhinitis and asthma multimorbidity in adults: the EGEA study. Clin Exp Allergy. 2017 Apr;47(4):520-529. doi: 10.1111/cea.12897.PubMed PMID: 28236637).*

Mon deuxième objectif était d'étudier l'association entre l'exposition à long terme à la pollution atmosphérique et la rhinite.

Dans un premier temps, j'ai étudié l'association entre l'exposition à la pollution atmosphérique à long terme et l'incidence de la rhinite. J'ai utilisé les données des études EGEA2 et 3 et ECRHS II et III. Aucune association entre l'exposition annuelle individuelle à la pollution atmosphérique et l'incidence de la rhinite n'a été trouvée : Ratio du taux d'incidence ajusté (RTTa) pour une augmentation de 10 $\mu g.m^{-3}$ de NO_2 : 1,00 [0,91-1,09], pour une augmentation de 5$\mu g.m^{-3}$ de $PM_{2.5}$: 0,88 [0,73-1,04]). Des résultats similaires ont été trouvés dans le modèle bi-polluants prenant en compte le NO_2 et les $PM_{2.5}$: RTTa pour une augmentation de 10 $\mu g.m^{-3}$ de NO_2 :1,05 [0,92-1,22], pour une augmentation de 5$\mu g.m^{-3}$ de $PM_{2.5}$: 0,84 [0,66-1,04]). Les résultats étaient très différents en fonction des villes, mais aucune tendance géographique n'a été mise en évidence, et ce quel que soit le polluant. Dans les analyses stratifiées, l'augmentation du niveau de pollution était associée à un plus faible taux d'incidence parmi les participants avec une sensibilisation allergique et chez les hommes. Les résultats étaient similaires pour PM_{10}. Ces analyses ont aussi été réalisées sur les NOx, PM_{coarse} et deux variables de trafic : l'intensité du traffic et la distance à une route importante, et les résultats étaient

comparables. Nous avons aussi réalisé ces analyses en considérant l'incidence de la rhinite allergique et non la rhinite en général, et les résultats restaient identiques.

Ce travail a donné lieu à une communication par poster (congrès de l'ISEE, Rome 2016) et à la rédaction d'un article qui est actuellement en révision *(Burte Emilie, Leynaert Bénédicte, Bono Roberto, Brunekreef Bert, Bousquet Jean, Carsin Anne-Elie, De Hoogh Kees, Forsberg Bertil, Gormand Frédéric, Heinrich Joachim, Just Jocelyne, Marcon Alessandro, Künzli Nino, Nieuwenhuijsen Mark, Pin Isabelle, Stempfelet Morgane, Sunyer Jordi, Villani Simona, Siroux Valérie, Jarvis Deborah , Nadif Rachel, Jacquemin Bénédicte. Association between air pollution and rhinitis incidence in two European cohorts. En révision à Environment International).*

J'ai ensuite étudié l'association entre l'exposition à la pollution atmosphérique à long terme et les phénotypes de rhinite et en particulier la sévérité de la rhinite.

J'ai considéré 1550 adultes de EGEA3 (N=386) et ECRHS III (N=1164), âgés en moyenne de 52,4 ans, dont 45% d'Hommes. Le score moyen de sévérité de rhinite était de 4 avec une médiane et un intervalle [Q1-Q3] de 4 [2-6]. L'exposition au NO_2 était associée à une plus forte sévérité de nez qui coule ou nez bouché, et l'exposition au PM_{10} était associée à une plus forte sévérité des quatre symptômes. L'exposition au $PM_{2.5}$ était associée à une plus forte sévérité de nez bouché et d'éternuements et l'exposition au PMcoarse était associée à une sévérité importante pour le nez qui coule ou nez bouché. Les expositions au PM_{10}, $PM_{2.5}$ et PMcoarse étaient associées à une augmentation du score de sévérité de rhinite et particulièrement pour PM_{10} (Odds Ratio ajusté: ORa[95% CI], pour le quartile 2(qu2): 1.49 [1.05-2.12], pour le quartile 3(qu3): 1.35[2.07-3.19], pour le quartile 4(qu4): 1.41[2.37-3.97]).

Un résumé de ce travail a été soumis au congrès de l'ISEE (Munich, 2017) et un article est actuellement en cours de rédaction *(Burte Emilie, Leynaert Bénédicte, Bousquet J, Benmerad M, Bono Roberto, Brunekreef Bert, Carsin Anne-Elie, De Hoogh Kees, Forsberg Bertil, Gormand Frédéric, Heinrich Joachim, Just Jocelyne, Marcon Alessandro, Nieuwenhuijsen Mark, Pin Isabelle, Stempfelet Morgane, Sunyer Jordi, Villani Simona, Künzli Nino, Siroux Valérie, Jarvis Deborah , Nadif Rachel, Jacquemin Bénédicte. Air Pollution increases the severity of rhinitis in two European cohorts, rédaction en cours).*

4. Discussion

Cette thèse est basée sur les données de deux études épidémiologiques européennes ayant des phénotypes respiratoires détaillés ainsi que des données d'exposition individuelle à la pollution atmosphérique. Cela nous a permis de mieux comprendre les phénotypes de rhinite et d'étudier les associations entre la pollution atmosphérique et la rhinite.

La rhinite a été étudiée dans de nombreuses études épidémiologiques mais du fait de l'absence de définition standardisée de la rhinite construite à partir de questionnaires, l'épidémiologie de la maladie est finalement mal connue. De plus, la majorité des études se sont focalisée sur l'étude de la rhinite allergique, ne considérant pas le pan non-

allergique de la maladie. Or la prévalence de la rhinite augmente depuis plusieurs décennies, probablement en raison d'interactions complexes entre facteurs génétiques et environnementaux, dont la pollution. A ce jour, très peu d'études se sont intéressées aux effets de la pollution atmosphérique sur la rhinite.

Dans mes travaux, j'ai utilisé une approche non supervisée qui a identifié des classes/groupes similaires à celles/ceux des phénotypes de rhinite allergique et non-allergique connu(e)s dans la littérature, mais qui étaient plus contrasté(e)s en terme de sensibilité allergique. J'ai aussi montré que la sensibilisation allergique était très différente en fonction des phénotypes d'asthme et de rhinite, et qu'en particulier le phénotype combiné d'asthme et rhinite allergique était particulièrement sévère et polysensibilisé. J'ai ainsi montré que le fait d'avoir une sensibilité allergique n'était probablement pas suffisant pour définir les phénotypes de rhinite, et que le niveau de sensibilité allergique était très important dans la distinction des différents phénotypes combinés d'asthme et de rhinite. Mes principaux résultats soulignent le besoin d'une ligne directive pour la définition de la rhinite dans les études épidémiologiques afin de savoir quelles questions utiliser pour définir la rhinite, et les différents phénotypes de rhinite. Il semble également primordial de considérer la comorbidité de l'asthme et de la rhinite lors de l'étude d'une de ces maladies. D'un point de vue de santé publique, la prise en charge de la rhinite est d'autant plus difficile que la majorité des individus souffrant de rhinite considère leur maladie comme bénigne et donc ne cherche pas à obtenir des soins médicaux. La deuxième difficulté réside dans la complexité du diagnostic de la maladie, primordial pour un traitement et des recommandations adéquates. La mise en place d'un plan d'information semble donc essentielle, et il serait d'autant plus efficace s'il était intégré dans un plan de prévention multiniveau concernant les malades, mais aussi les pharmaciens, les généralistes et les spécialistes.

Dans une deuxième partie, j'ai étudié l'association entre l'exposition à long-terme à la pollution atmosphérique et la rhinite. Je n'ai pas mis en évidence d'effet de la pollution sur l'incidence de la maladie, et bien que l'association variait beaucoup selon les villes, il n'y avait pas clairement de différence entre les régions ou les pays. En revanche, j'ai montré qu'une plus forte exposition à la pollution était associé à une augmentation de la sévérité de la rhinite, et particulièrement pour le symptôme de nez bouché. Nous n'avions pas de données sur le climat ou la concentration en pollen qui pourrait jouer un rôle important dans l'association entre pollution et rhinite et dans le futur, il serait intéressant de prendre en compte ces différents facteurs environnementaux dans l'étude de la rhinite. Notre étude montre un effet de la pollution atmosphérique sur la rhinite, et contribue à l'importante littérature ayant montré l'impact de la pollution sur la santé. Il est important de poursuive les études sur le sujet, et plus particulièrement dans les pays avec les plus hauts niveaux de pollution tels que l'Inde ou la Chine où les résultats seront probablement encore plus frappants. Ceci afin que des mesures soient prises rapidement pour réduire le niveau de pollution dans le monde.

5. Conclusion

Dans ces travaux, nous avons montré que pour améliorer la caractérisation de la rhinite il était utile de prendre en compte à la fois les différentes caractéristiques de la maladie, la

sensibilité allergique, et la présence de comorbidité –en particulier celle de l'asthme-, et également de ne pas se restreindre à une seule question ou un seul test de sensibilité allergique. Une meilleure caractérisation de la maladie permettra d'améliorer la prise en charge et le traitement de la maladie. Nous n'avons pas mis en évidence d'effet de la pollution atmosphérique à long-terme sur l'incidence de la rhinite, mais nous avons montré une association entre l'exposition à long-terme à la pollution atmosphérique et la sévérité de la rhinite, soulignant l'importance de contrôler les niveaux de pollution.

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Titre : Rhinite : caractérisation et association avec la pollution atmosphérique

Mots clés : Environnement, phénotypes, pollution atmosphérique, rhinite, sensibilité allergique

Résumé : Alors que la rhinite a un fort impact sur la santé publique, chez l'adulte, il n'existe pas de définition standardisée de la rhinite dans les études épidémiologiques. De plus, les facteurs environnementaux de la rhinite sont mal connus et, en particulier, il existe très peu d'études sur les effets à long terme de la pollution atmosphérique sur la rhinite chez l'adulte. Pour combler ces lacunes, nous avons utilisé les données de deux études épidémiologiques multicentriques européennes ayant des données détaillées sur la santé respiratoire et d'exposition annuelle individuelle à la pollution atmosphérique. Nos résultats ont montré que pour mieux caractériser la rhinite, il faut considérer l'ensemble des caractéristiques des symptômes nasaux, les comorbidités et la sensibilisation allergique, et ne pas limiter la maladie à une question ou à un test de sensibilisation allergique. Nous n'avons trouvé aucune association entre la pollution atmosphérique à long terme et l'incidence de la rhinite, mais nous avons montré que l'exposition à long terme à la pollution était associée à une augmentation de la sévérité de la rhinite, soulignant le besoin de contrôler les niveaux de pollution atmosphérique.

Title: Rhinitis: characterization and association with air pollution

Keywords: air pollution, allergic sensitization, environment, phenotypes, rhinitis

Abstract: Whereas rhinitis has an important public health impact, in adults there is no standardized definition of rhinitis in epidemiological studies. Furthermore, environmental factors of rhinitis are barely known, and in particular, there are very few studies on the effects of long-term exposure to air pollution on rhinitis in adults. To fill these gaps, we used data from two European multicentre epidemiological studies with extensive data on respiratory health and individual estimated exposures to long-term air pollution. Our findings showed that to better characterize rhinitis, one need to consider together all the characteristics of the nasal symptoms, the comorbidities and the allergic sensitization, and not to restrict the disease to one question or one allergic sensitization test. We found no association between long-term air pollution and incidence of rhinitis, but we showed that long-term exposure to air pollution is associated to an increased severity of rhinitis, emphasising that air pollution needs to be controlled.