RHINITIS: CHARACTERISATION AND ASSOCIATION WITH AIR POLLUTION

Doctoral thesis in cotutorship between Université Paris-Saclay and Universitat Pompeu Fabra,

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Thesis presented and defended in Villejuif, the 2 of March of 2018 by

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Thèse de doctorat

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

1. 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 Aug 26;10(8):e0136191. doi: 10.1371/journal.pone.0136191. eCollection 2015. PubMed PMID: 26309034; PubMed Central PMCID: PMC4550236.

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asthma across the life cycle. Clin Transl Allergy. 2016 Dec 30;6:47. doi: 10.1186/s13601-016-0137-4. eCollection 2016. Review. PubMed PMID: 28050247; PubMed Central PMCID: PMC5203711.

Anto JM, Bousquet J, Akdis M, …, Burte E, ..., Varraso R, Wenzel K, Xu CJ. Mechanisms of the Development of Allergy (MeDALL): Introducing novel concepts in allergy phenotypes. J Allergy Clin Immunol. 2017 Feb;139(2):388-399. doi: 10.1016/j.jaci.2016.12.940. Review. PubMed PMID: 28183433.

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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.

Burte E, Bousquet J, Siroux V, Nadif R, Jacquemin B. Association between air pollution and rhinitis symptoms in two European cohorts. *28th annual conference of the ISEE (International Society for Environmental Epidemiology)*, Roma, 1-4 September 2016.

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).

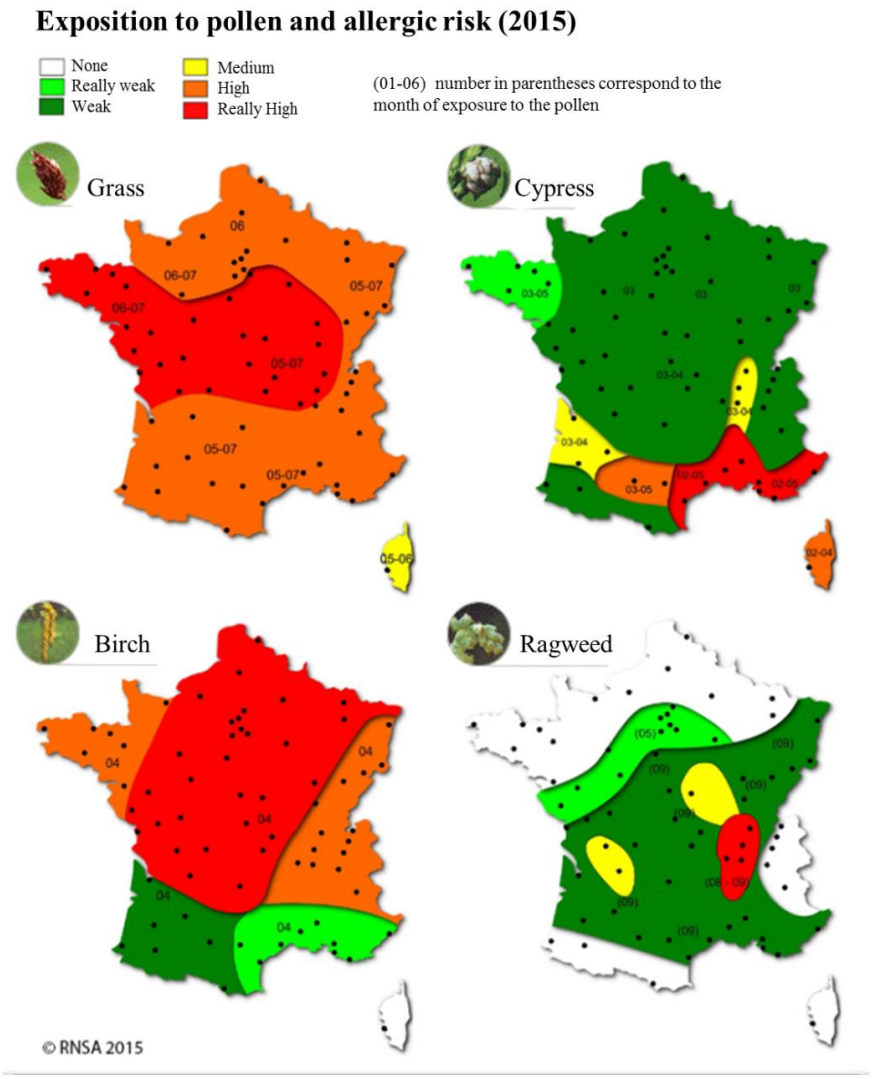


Figure 1 Exposition to pollen and allergic risk among French regions (adapted from Réseau National de Surveillance Aérobiologique (RNSA http://www.pollens.fr/en/) 2015)

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).

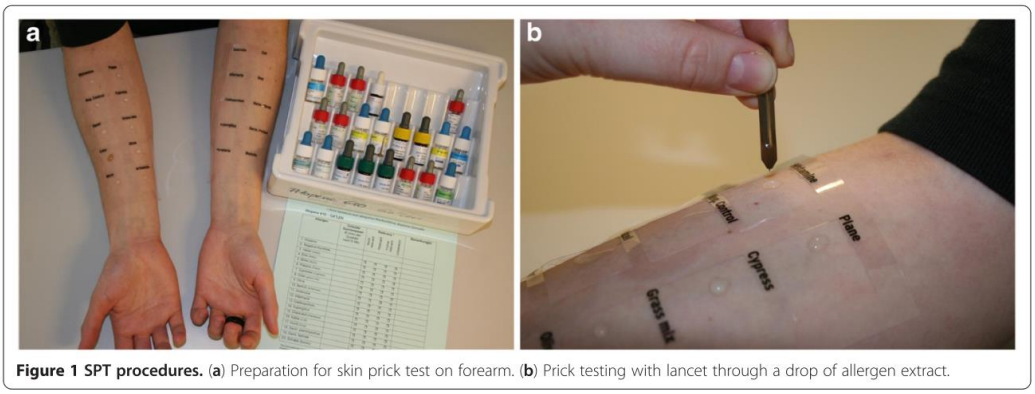


Figure 1 SPT procedures. (**a**) Preparation for skin prick test on forearm. (**b**) Prick testing with lancet through a drop of allergen extract.

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).

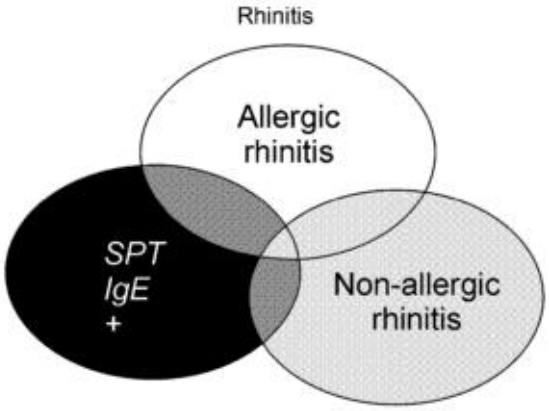


Figure 3 Schematic representation of allergic and non-allergic patients demonstrating skin test positivity from Bachert *et al.* (34) **)**

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

Questionnaire[a]	Outcome investigated	
	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.

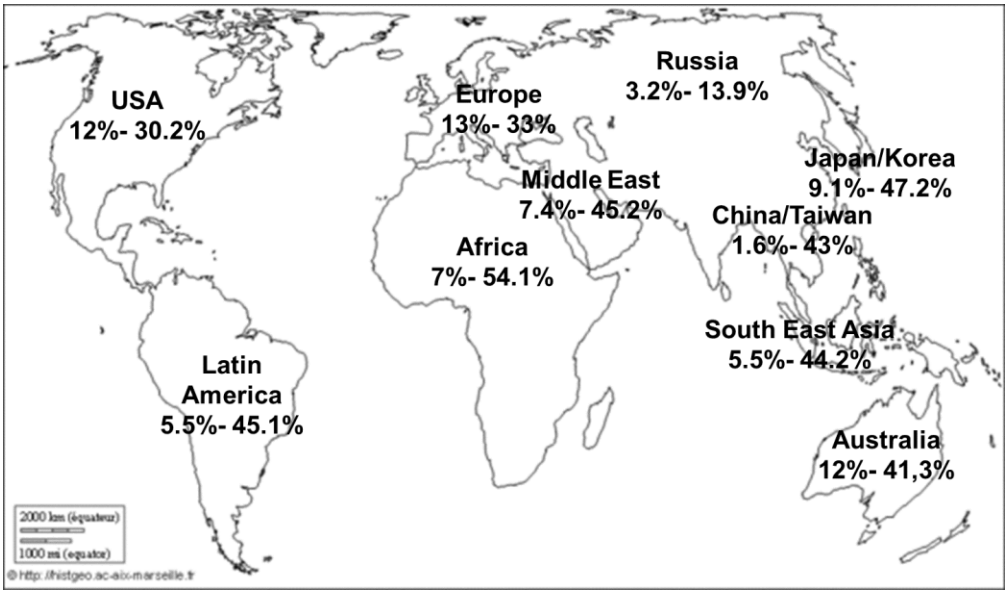
A detailed questionnaire (by physician, by examiner or self-reported) on symptom's triggers may be a good option to differentiate allergic from non-allergic rhinitis (47). In absence of medical diagnosis, it seems very difficult to identify other type of rhinitis than the allergic and non-allergic ones.

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*.

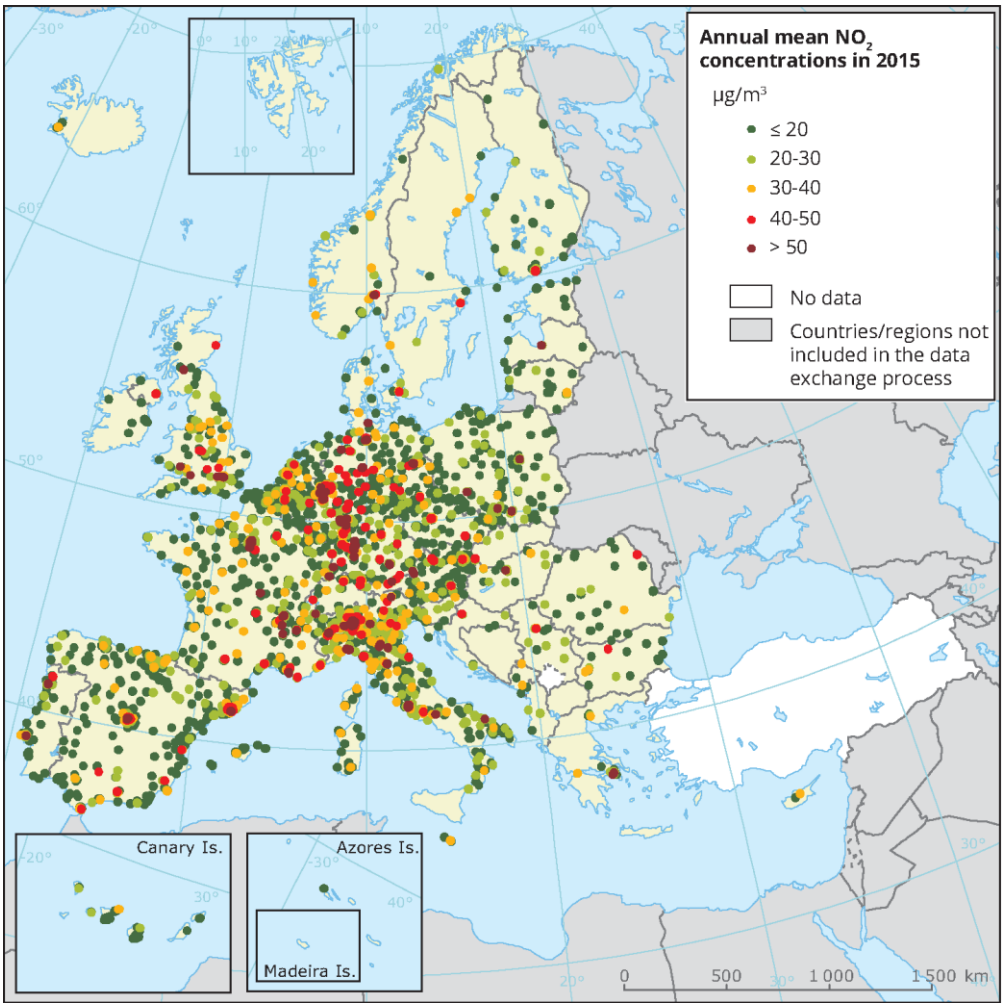


Figure 5 Concentration of NO_2 in 2015 in Europe (Based on Air Quality e-reporting database https://www.eea.europa.eu (116)**)**

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).

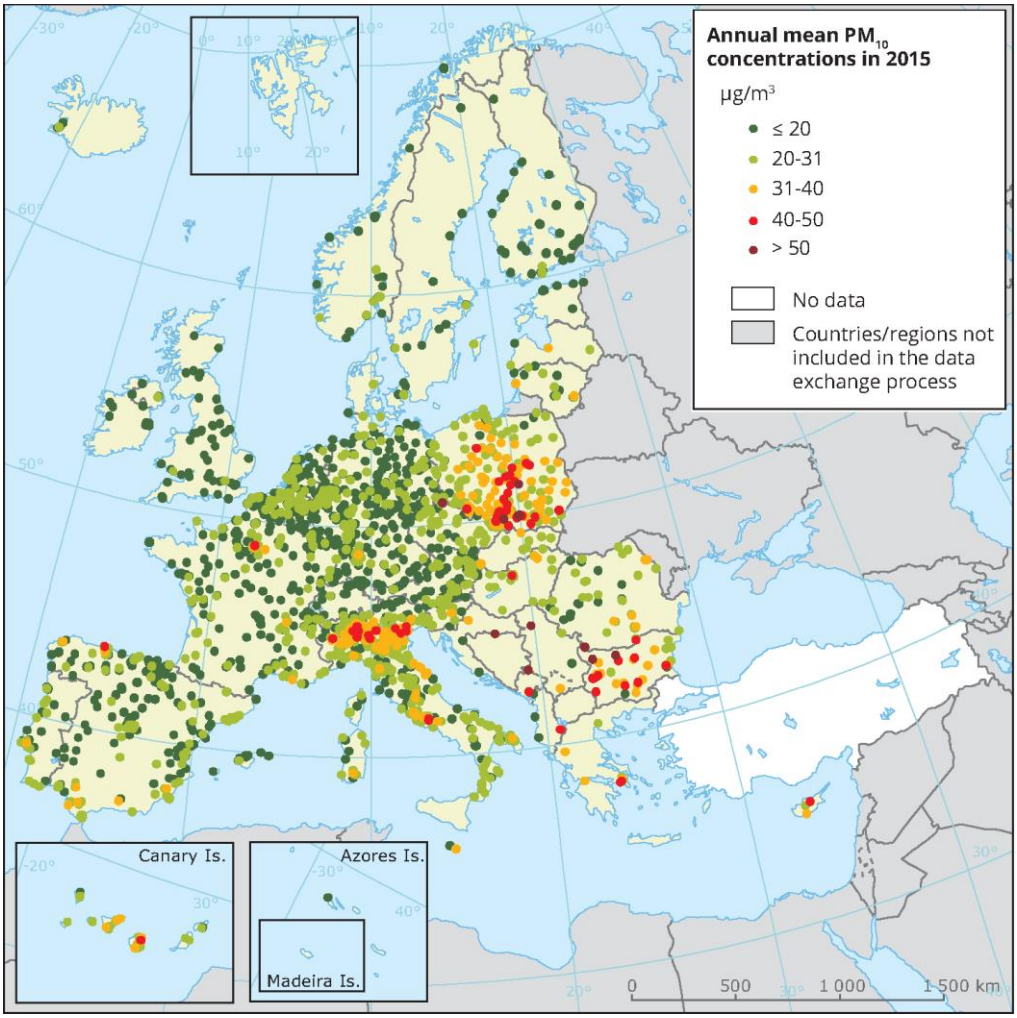


Figure 6 Concentration of PM_{10} in 2015 in Europe (Based on Air Quality e-reporting database https://www.eea.europa.eu/ (104))

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).

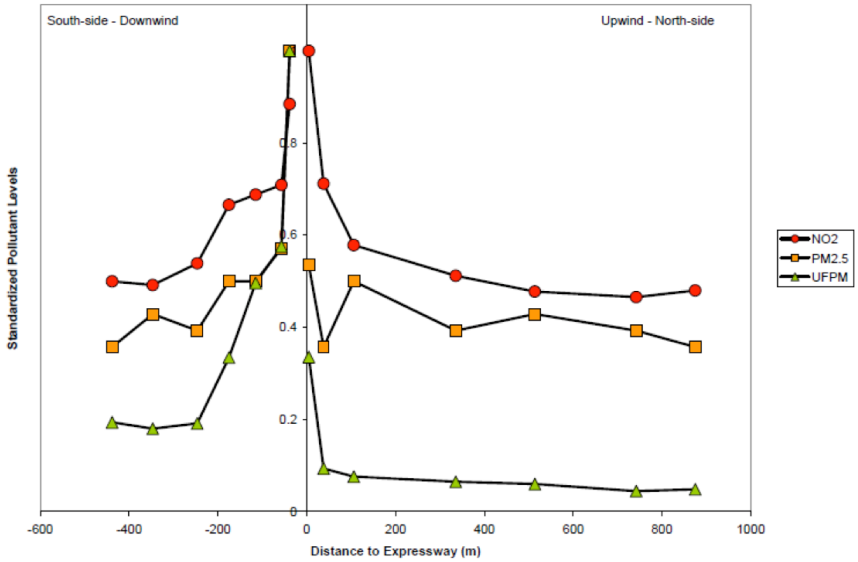


Figure 7 Concentration of pollutants according to the distance to expressway, from Beckerman et al. (122)

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).

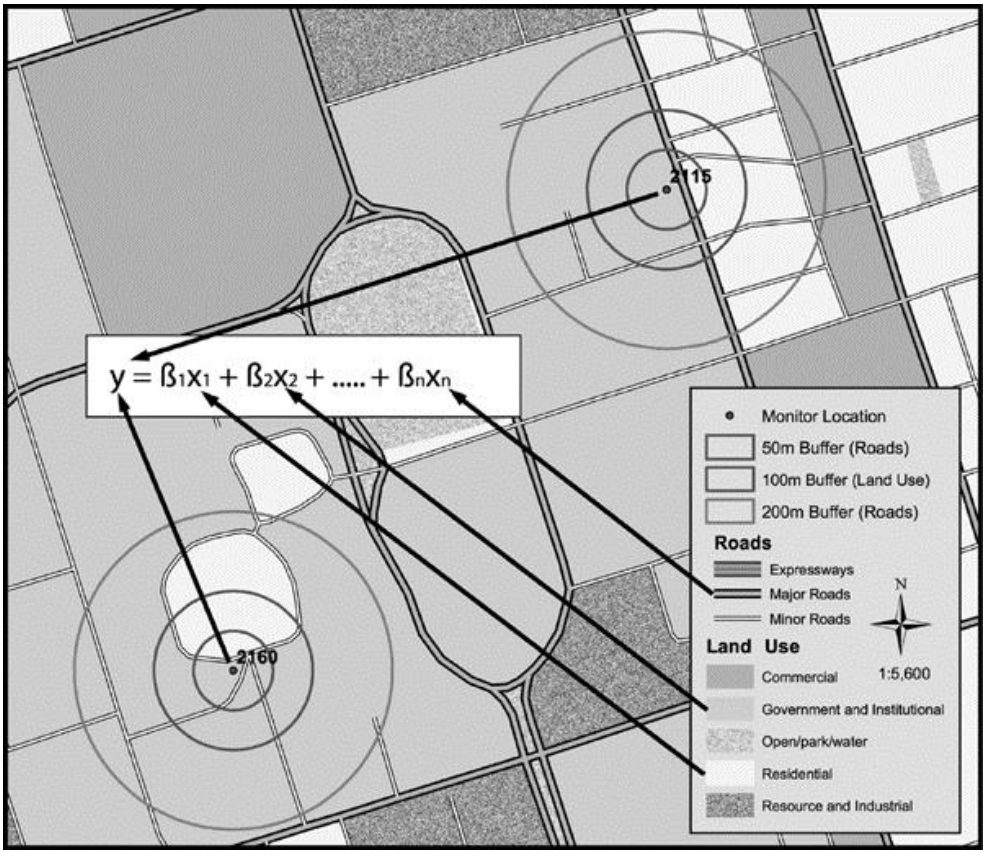


Figure 8 Illustration of elements of a LUR model from Jerret *et al.* 2005 (131)

-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 (169–171). A third study in Switzerland found no association between proximity to busy road and AR (172). 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) (171).

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 (171). 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.

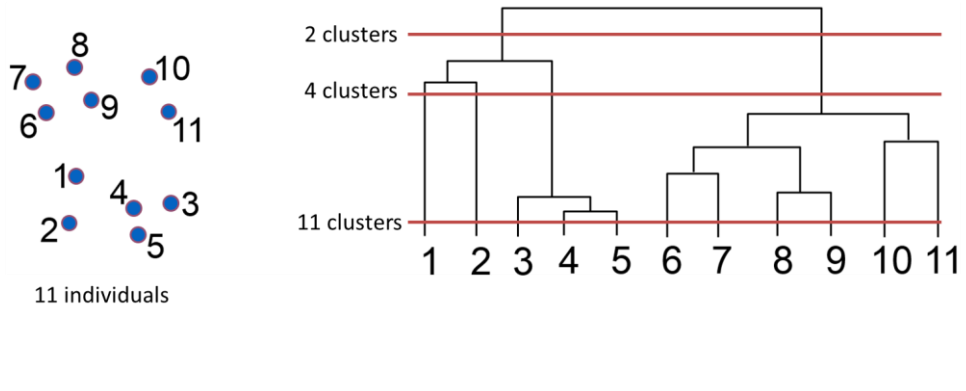
In supervised learning, the outcome disease is initially defined and the goal is to obtain a set of variables that can predict the outcome or to study the association between a set of variables and the specific disease. Supervised learning encompasses several methods used daily in epidemiology such as 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.

Published at PLoS One. 2015 Aug 26;10(8):e0136191. doi:

10.1371/journal.pone.0136191. eCollection 2015. PubMed PMID: 26309034;

Burte E, Bousquet J, Varraso R, Gormand F, Just J, Matran R, et al. Characterization of Rhinitis According to the Asthma Status in Adults Using an Unsupervised Approach in the EGEA Study. Liu Z, editor. PLoS One. 2015 Aug 26;10(8):e0136191. DOI: 10.1371/journal.pone.0136191

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

Published at Clin Exp Allergy. 2017 Apr;47(4):520-529. doi: 10.1111/cea.12897. PubMed PMID: 28236637.

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):520–9. DOI: 10.1111/cea.12897

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

In revision at Environment International.

Burte E, Leynaert B, Bono R, Brunekreef B, Bousquet J, Carsin A-E, et al. Association between air pollution and rhinitis incidence in two European cohorts. Environ Int. 2018 Jun;115:257–66. DOI: 10.1016/j.envint.2018.03.021

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 $\mu g/m^3$ for NO_2 and PM_{10}, 5 $\mu g/m^3$ for $PM_{2.5}$ and PMcoarse, 4,000,000 vehicles*m/day for traffic load on all major roads in a 100m buffer and 5,000 vehicles/day for traffic density on the nearest road, following ESCAPE protocol.

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

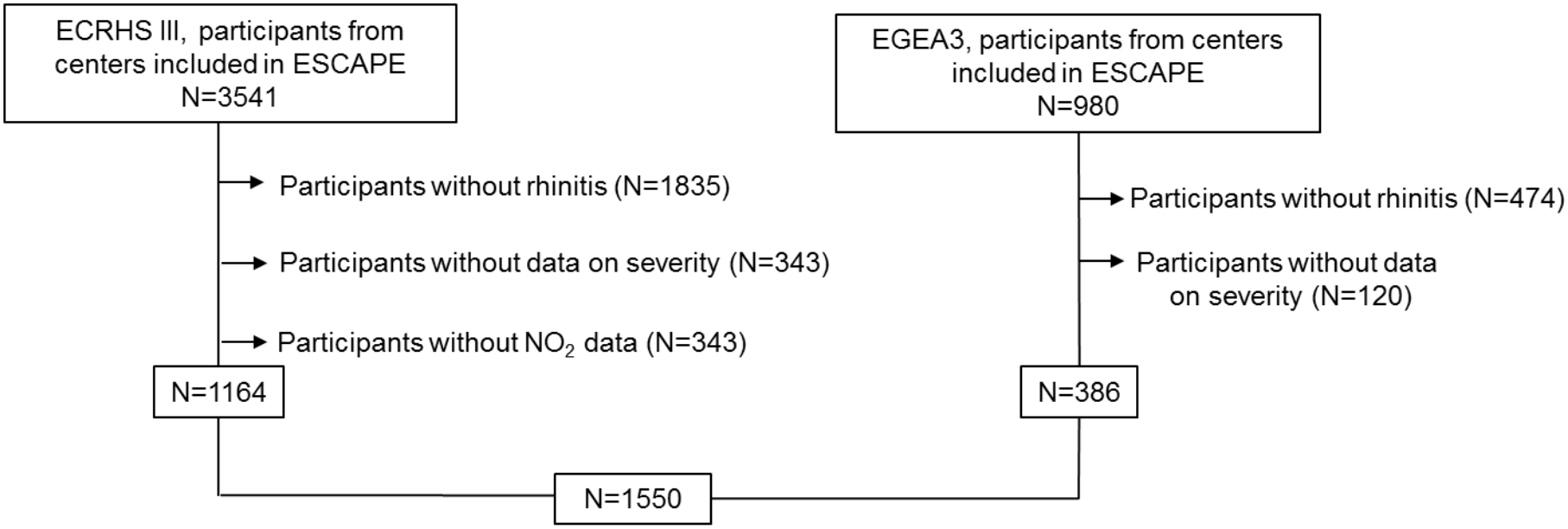
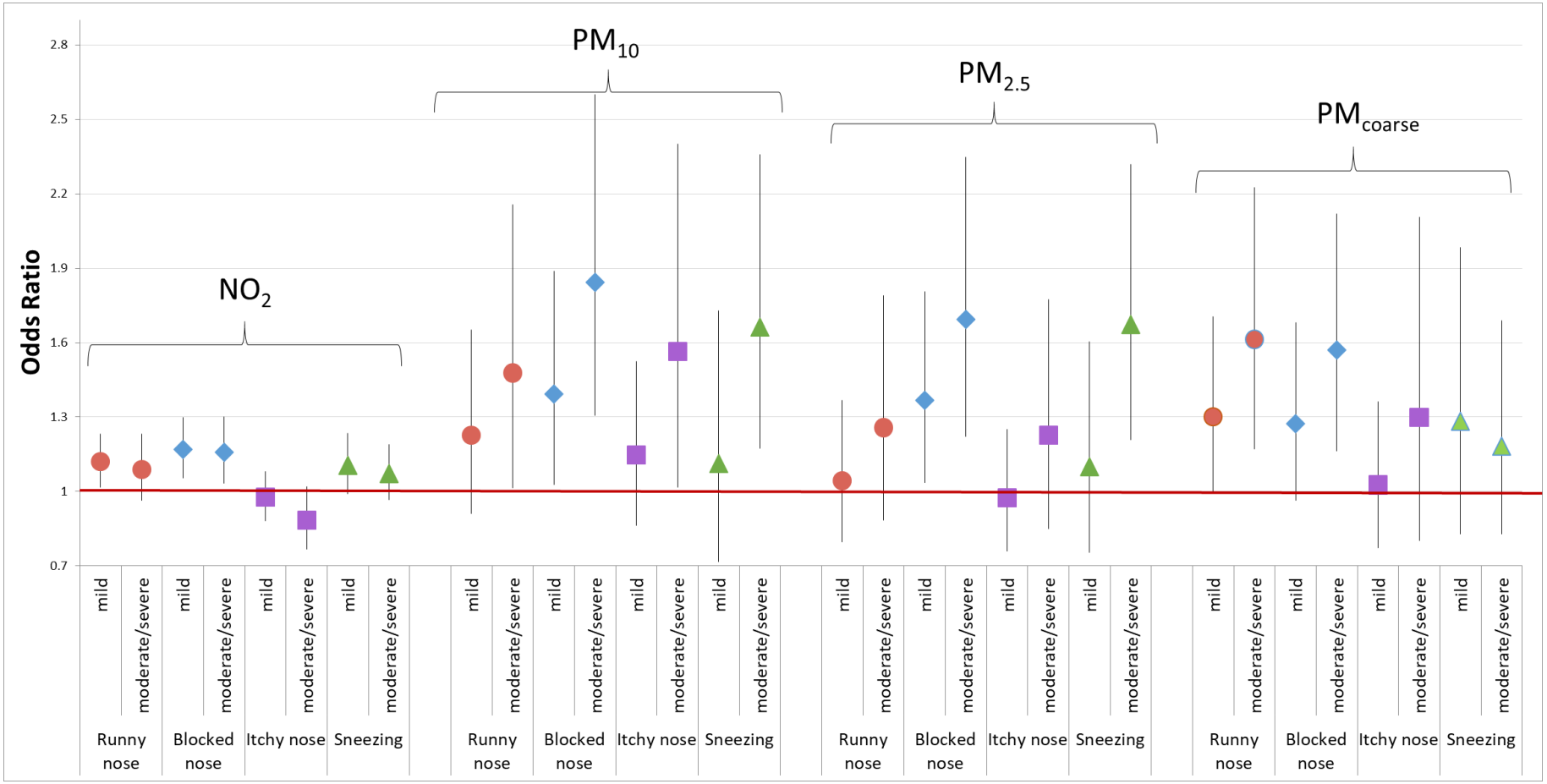
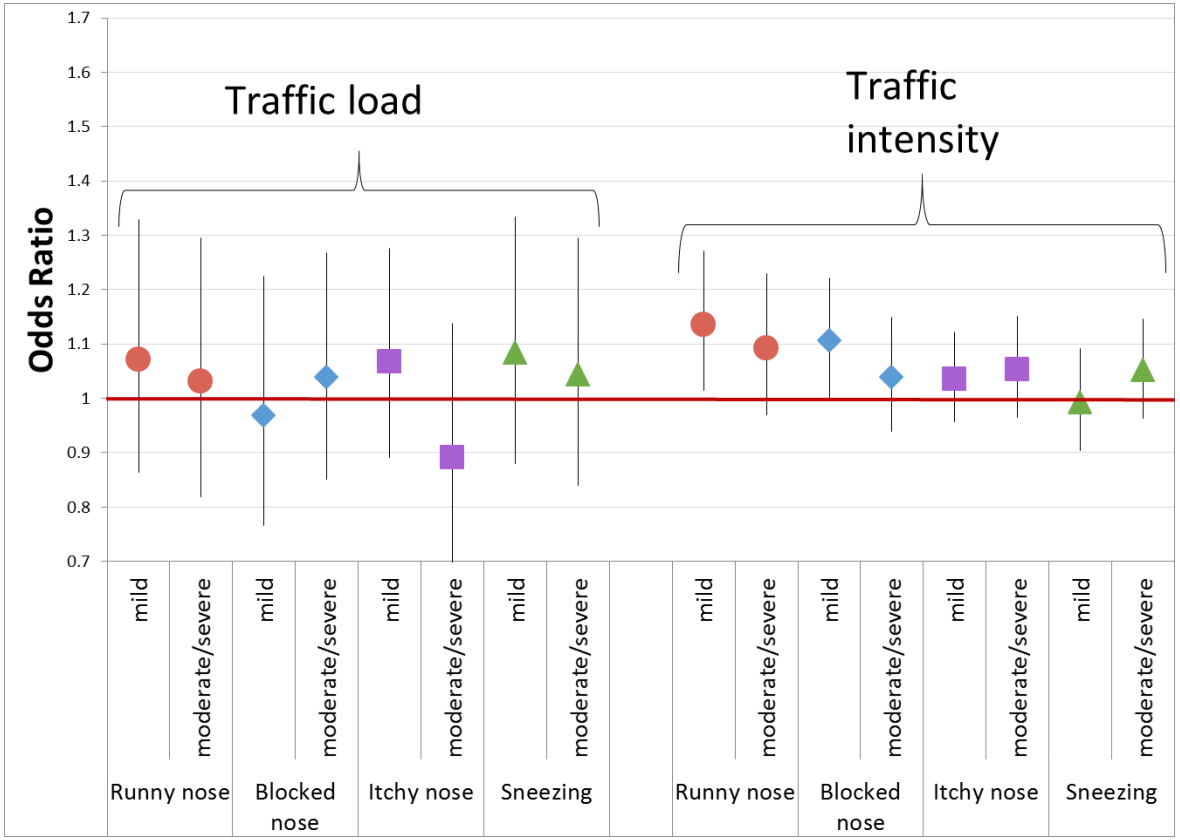


Figure 2: Association between exposure to NO_2, PM_{10}, $PM_{2.5}$ and PM coarse and the severity of the four main symptoms of rhinitis



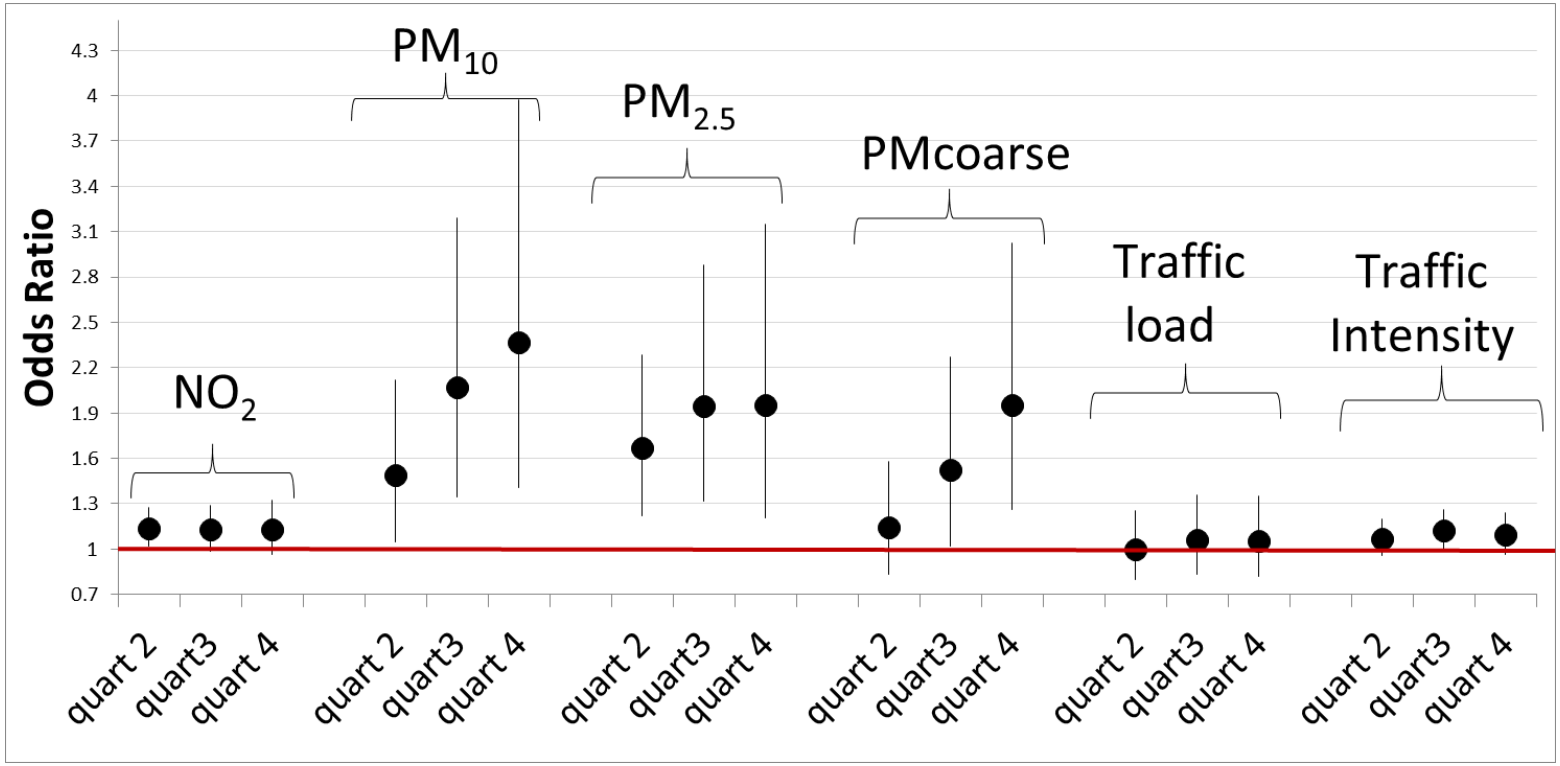
Reference : no problem (symptom not present), Odds Ratio adjusted for age, sex, smoking status, number of siblings, family history of allergies, asthma, and report of nasal allergies or hay fever, with city as a random intercept. Estimates are presented for an increase of 10 µg/m3 for NO_2 and PM_{10}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

Curr Environ Health Rep. 2016 Mar;3(1):23-39. doi: 10.1007/s40572-016-0084-1. Review. PubMed PMID: 26820569.

Burte E, Nadif R, Jacquemin B. Susceptibility Factors Relevant for the Association Between Long-Term Air Pollution Exposure and Incident Asthma. Curr Environ Heal Reports. 2016 Mar 28;3(1):23–39. DOI: 10.1007/s40572-016-0084-1

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

Environ Int. 2017 Apr;101:117-124. doi: 10.1016/j.envint.2016.12.026. Epub 2017 Feb 1. PubMed PMID: 28159394.

Temam S, Burte E, Adam M, Antó JM, Basagaña X, Bousquet J, et al. Socioeconomic position and outdoor nitrogen dioxide (NO2) exposure in Western Europe: A multi-city analysis. Environ Int. 2017 Apr;101:117–24. DOI: 10.1016/j.envint.2016.12.026

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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S1. 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.

Burte E, Bousquet J, Varraso R, Gormand F, Just J, Matran R, et al. Characterization of Rhinitis According to the Asthma Status in Adults Using an Unsupervised Approach in the EGEA Study. Liu Z, editor. PLoS One. 2015 Aug 26;10(8):e0136191. DOI: 10.1371/journal.pone.0136191

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

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):520–9. DOI: 10.1111/cea.12897

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

Burte E, Leynaert B, Bono R, Brunekreef B, Bousquet J, Carsin A-E, et al. Association between air pollution and rhinitis incidence in two European cohorts. Environ Int. 2018 Jun;115:257–66. DOI: 10.1016/j.envint.2018.03.021

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.