Phenotypes of rhinitis : identification and association with long-term exposure to air pollution in two French studies

Marine Savouré

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THÈSE DE DOCTORAT

NNT : 2023UPASR002

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Phenotypes of rhinitis: identification and association with long-term exposure to air pollution in two French studies

Phénotypes de la rhinite : identification et association avec l'exposition à long terme à la pollution atmosphérique dans deux études françaises

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École doctorale n°570, santé publique (EDSP)
Spécialité de doctorat : Épidémiologie
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Thèse préparée dans **l'équipe d'épidémiologie respiratoire intégrative du CESP (Université Paris-Saclay, UVSQ, Inserm)** sous la direction de **Bénédicte JACQUEMIN**, CR, et de **Rachel NADIF**, CR

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Phenotypes of rhinitis: identification and association with long-term exposure to air pollution in two French studies

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Thèse préparée dans le cadre du réseau doctoral en santé publique animé par l'EHESP
Thesis prepared in the framework of the doctoral network of public health led by the EHESP

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LIST OF SCIENTIFIC PRODUCTIONS

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Abbreviations and acronyms

8-iso	8-isoprostanes
95% CI	95% Confidence Interval
AQG	Air Quality Guidelines
AR	Allergic Rhinitis
ARIA	Allergic Rhinitis and its Impact on Asthma
BC	Black Carbon
BDR	Bronchodilator Reversibility
BHR	Bronchial Hyperresponsiveness
BMI	Body Mass Index
CC-16	Clara Cell protein-16
CO	Carbone monoxide
COPD	Chronic Obstructive Pulmonary Disease
CRP	C-Reactive Protein
DC	Dendritic Cell
DNA	Deoxyribonucleic Acid
EBC	Exalte Breath Condensate
ECP	Eosinophil Cationic Protein
ECRHS	European Community Respiratory Health Survey
EDN	Eosinophil Derived Neurotoxin
EGEA	Epidemiological study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy
EU	European Union
FAMD	Factorial Analysis of Mixed Data
FDep	French Deprivation index
FeNO	Fraction Exhaled Nitric Oxide
FEV_1	Forced Expiratory Volume in the first second
FlOP	Fluorescent Oxidation Products
FVC	Forced Vital Capacity
GDP	Gross Domestic Product
GIS	Geographical Information System
GPX	Glutathione peroxidase
GWAS	Genome-Wide Association Studies
H1	Histamine 1
HCA	Hierarchical Clustering Analysis
HR	Hazard Ratio
HSC	Health Screening Centre
ICAM-1	Intercellular Adhesion Molecule-1
IFN	Interferon
IgE	Immunoglobulin E
IL	Interleukin
INCS	Intranasal Corticosteroids

IRR	Incidence Rate Ratio
ISAAC	International Study on Asthma and Allergy in Childhood
LAR	Local Allergic Rhinitis
LCA	Latent Class Analysis
LUR	Land Use Regression
MCA	Multiple Correspondence Analysis
MCH PD20	Provocative Dose of Methacholine that results in a 20% fall in FEV_1
MPO	Myeloperoxidase
NAR	Non-Allergic Rhinitis
NARES	Non-Allergic Rhinitis with Eosinophilia Syndrome
NO_2	Nitrogen dioxide
NOx	Nitrogen oxide
O_3	Ozone
OAH	Oral Antihistamines
OTC	Over The Counter medicine
PCA	Principal Component Analysis
PM	Particulate Matter
PM_{10}	Particulate Matter with 10 µm median cut-off aerodynamic diameter
$PM_{2.5}$	Particulate Matter with 2.5 µm median cut-off aerodynamic diameter
RNA	Ribonucleic Acid
SD	Standard Deviation
SES	Socioeconomic status
SO_2	Sulphur dioxide
SOD	Superoxide dismutase
SPT	Skin Prick Test
TARC	Thymus and Activation-Regulated Chemokine
Th2	Lymphocytes T helper 2
TNF	Tumor Necrosis Factor
TRAP	Traffic Related Air Pollutant
TSLP	Thymic Stromal Lymphopoietin
TNSS4	Total Symptom Score 4
VAS	Visual Analogue Scale
VOC	Volatile Organic Compound
WBC	White Blood Cell count
WHO	World Health Organisation

1. INTRODUCTION

The etymology of the word rhinitis comes from the ancient Greek *rhinos* "nose" combined with the suffix *itis* "inflammation". In practice, rhinitis is a generic term used to describe nasal symptoms such as nasal congestion/obstruction, rhinorrhoea, sneezing and itching resulting from inflammation but also dysfunction of the nasal mucosa (1). Behind the apparent simplicity of its clinical definition, rhinitis is in fact a complex and heterogeneous disease: there is not one rhinitis but several rhinitis phenotypes. Many classifications have been proposed to cover the whole spectrum of rhinitis, firstly based on observed clinical features -referred as phenotypes- and subsequently based on the underlying biological or mechanistic pathways -referred as endotypes. Among the phenotypes of rhinitis, beyond infectious rhinitis (common cold, flue, or COVID-19), the most well-known phenotype is undoubtedly the pollen-induced allergic rhinitis, commonly called "hay fever". While "hay fever" may seem like an old term, its first description was reported in 1819 by John Bostock a London doctor who was suffering of "a periodical affection of the eyes and chest" and who called it "summer catarrh" which soon became known as hay fever (2). In 1859, Charles Blackley who also suffered from rhinitis, established the clear link between pollens and hay fever (3). At that time, extremely few cases of hay fever were reported, Bostock reported only 28 cases in 1828 and by the end of 19th century, hay fever was popularly known as the "aristocrats' disease" following the Bostock's observations that it mainly affected the upper classes. People suffering from it were called "Hayfeverites," a mocking description of rich young people eager to make their symptoms a matter of concern. Since then, the prevalence of rhinitis has drastically increased, and it is one of the most common diseases in the world with economic as well as daily life of patients' consequences. However, rhinitis is still underestimated, under-diagnosed and often trivialised and many gaps remain regarding its prevalence, characterisation and its risk factors. The appearance of the term hay fever during the industrial revolution and the increasing prevalence of rhinitis since then raises questions about the impact of environmental factors and in particular of air pollution. As the nose is the first organ in contact with air pollution, it may seem obvious that air pollutants increase the risk of rhinitis, but there are surprisingly few epidemiological studies on the association between long-term exposure to air pollution and rhinitis.

The main objective of this thesis was to study, in adults, the characteristics of rhinitis and its phenotypes and the associations between long-term exposure to air pollution and rhinitis.

The first part of this thesis will be devoted to the introduction of the current knowledge on rhinitis and its link with air pollution. In the next sections, the overall method used will be described and then for each of the objectives the specific method, results and discussion will be detailed. An overall discussion on the key results and their potential implications for public health will conclude this thesis.

1.1. RHINITIS

Although rhinitis may appear to be a well-known disease, its classification and clinical characterisation are not so straightforward, and this fact has consequences on its management. In this first introductive section, the current clinical and epidemiological knowledge on rhinitis, their link, and the remaining gaps in the study of rhinitis will be presented.

1.1.1. Clinical knowledge on rhinitis

1.1.1.1. Rhinitis phenotypes

A phenotype, in its clinical sense, refers to a combination of observable traits that result in clinical differences such as symptoms, severity, disease control, or response to treatment and that allow differentiation between individuals with a given disease, in this case rhinitis (4,5).

Rhinitis is classically divided into two major phenotypes[1]: allergic rhinitis (AR) and non-allergic rhinitis (NAR). According to ARIA, rhinitis can also be described based on: 1) its severity (mild, moderate, severe), 2) its duration (persistent or intermittent), 3) its seasonality (seasonal or perennial), 4) the predominant symptoms (nasal congestion or rhinorrhoea), 5) disease control (controlled, partially controlled, or uncontrolled), 6) its triggers (allergens, infectious agents, drugs, and others) and 7) the response to specific treatments (steroid-responsive or non-responsive) (6).

Efforts to harmonise rhinitis phenotypes have been made, notably by the World Health Organisation's (WHO) Allergic Rhinitis and its Impact on Asthma (ARIA) working group which is a landmark in the field.

This thesis will focus on the main phenotypes of rhinitis according to the ARIA classification: AR and NAR, rhinitis according to its duration and rhinitis according to its severity. These classifications are not mutually exclusive and may therefore overlap (Figure 1).

[1] There is also the infectious rhinitis phenotype, which is mostly an acute viral infection. Infectious rhinitis is a separate phenotype with different mechanisms, risk factors and epidemiology from AR and NAR, and it will not be covered in this thesis.

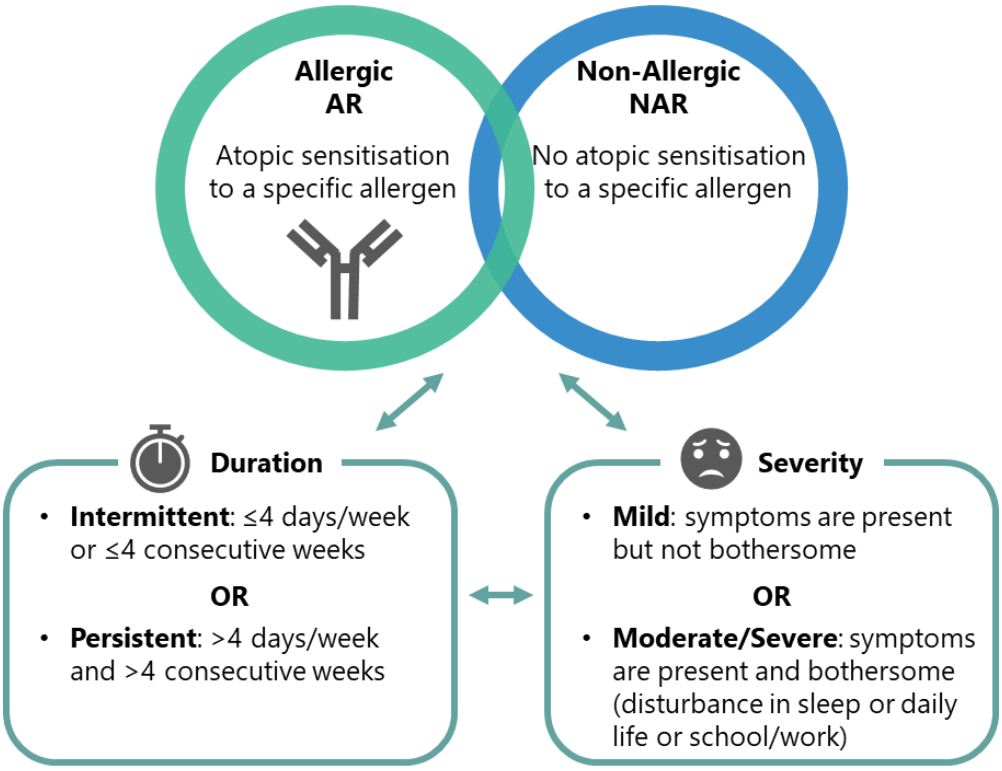


Figure 1: Phenotypes of rhinitis

1.1.1.1.1. AR and NAR

1.1.1.1.1.1. Definition

AR is the best known and the most studied phenotype of rhinitis. It is clinically defined as a symptomatic disorder of the nose induced after exposure to an allergen via Immunoglobulin E (IgE) mediated inflammation (7). The pathophysiological mechanism involves a hypersensitivity reaction with a sensitisation and an effective phase (Figure 2). The sensitisation phase is the first contact with environmental allergens such as pollen, dust mites or animal dander. The sensitisation phase is followed by an asymptomatic latency period which may last for varying lengths of time. On a subsequent contact with the same allergen, the effective phase is triggered. It comprises two response steps: an early and a late (8). The early step begins with the recognition of the allergen by specific IgE antibodies present on the mast cells and basophils of sensitised individuals. This step is rapidly (within minutes) associated with acute nasal symptoms (sneezing and rhinorrhoea) and frequently with the appearance of associated-eyes symptoms (pruritus, conjunctivitis and lacrimation). Approximately six hours later, mast cell activation leads to the delayed production of lipid mediators which leads to the maintenance of early effects and the initiation of delayed effects. Finally, twelve to twenty-four hours later, a last late step takes place and contributes to the establishment of an inflammatory reaction. This inflammatory response is associated with tissue remodelling, oedema and the development and perpetuation of nasal congestion. As a result of mucosal inflammation, the tissues are more sensitive and will react more strongly to exposure to the allergen.

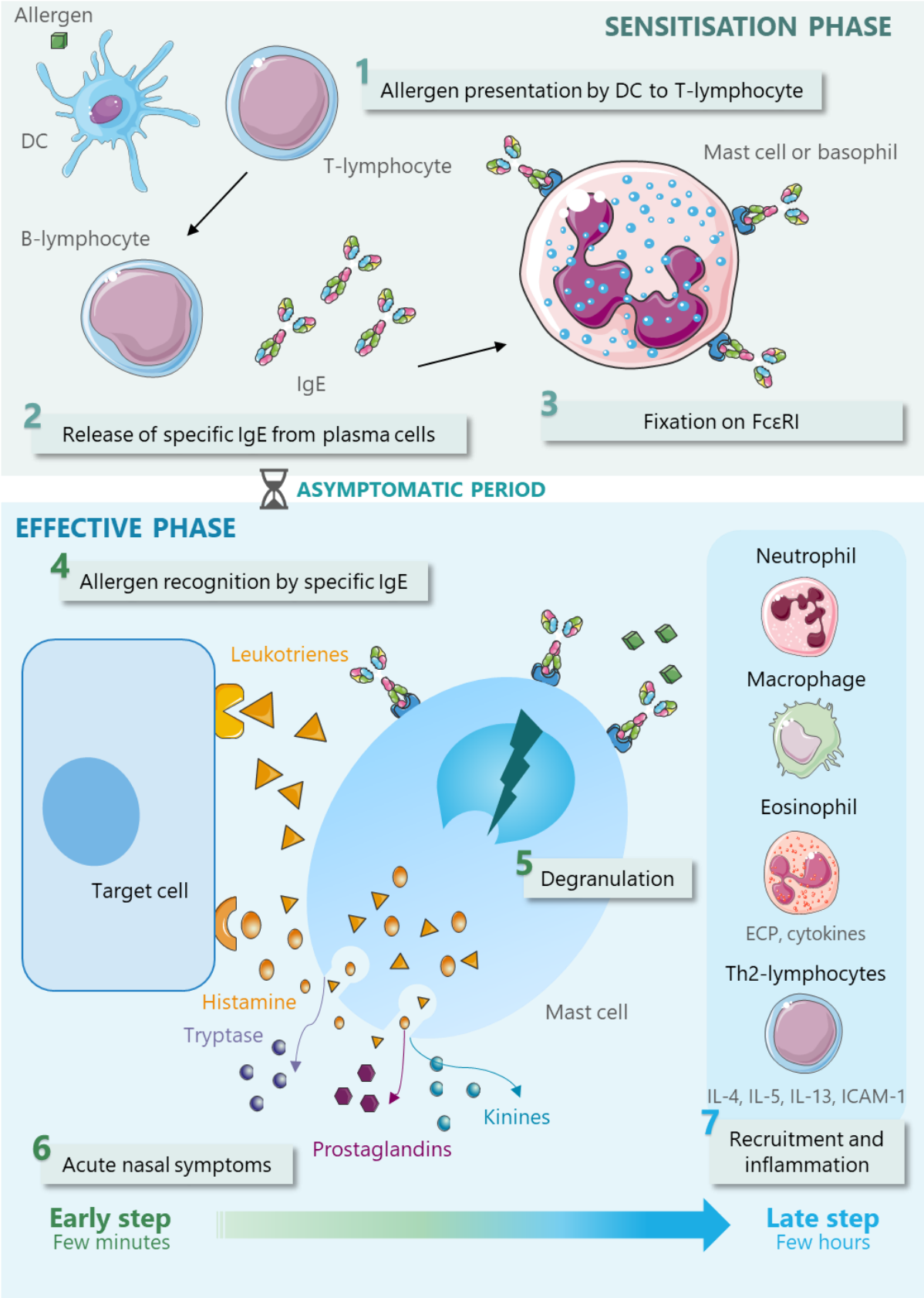


Figure 2: Physiopathology of AR

DC: Dendritic Cell, ECP: Eosinophil Cationic Protein, ICAM-1: Intercellular Adhesion Molecule-1, IgE: Immunoglobulin E, IL: Interleukin

NAR is a heterogeneous group of nasal conditions with rhinitis symptoms. There are different subtypes of NAR, the most described are hormone-induced rhinitis, rhinitis of the elderly, drug-induced rhinitis and idiopathic rhinitis.

1) **Hormonal rhinitis**, mainly found in women, can be due to hormonal changes due to hormonal cycle, pregnancy or hypothyroidism (9,10). An increase in oestrogen concentration would be the cause of nasal congestion through vascular congestion. Other potential mechanisms could involve vasodilation by increased beta-oestradiol or progesterone concentration, which could affect mucosal Histamine 1 (H_1) receptors and eosinophil function.
2) **Elderly rhinitis** is characterised by persistent clear rhinorrhoea, not associated with a specific trigger. Although the pathophysiology is unclear, age-related changes in connective tissues, such as collagen atrophy or weakening of the septal cartilage, and/or vascular deficiencies, may be involved (6).
3) Drugs, due to their pharmacological properties, can induce **rhinitis medicamentosa.** This rhinitis can be subdivided according to the treatments involved. 1) Local inflammatory rhinitis/rhinosinusitis caused by aspirin and non-steroidal anti-inflammatory drugs (N-ERD). The pathogenesis of this rhinitis, although still poorly understood, would involve the inhibition of cyclooxygenase-1 (COX-1) leading to an overproduction of sulphidopeptide leukotrienes which would be the cause of the symptoms (11). 2) Neurogenic rhinitis medicamentosa mediated by the vascular effects of alpha- and beta-adrenergic antagonists, and by selective phosphodiesterase-5 inhibitors (6). 3) Rhinitis medicamentosa resulting from prolonged use of decongestants (alpha-adrenergic agonist vasoconstrictors) via a possible rebound effect (6). 4) Idiopathic rhinitis medicamentosa caused by different drug classes (e.g. converting enzyme inhibitors, antipsychotics...) without clear identified mechanisms (6).
4) **Idiopathic rhinitis** is the most prevalent subtype of NAR and has been called by many different names over the years: idiopathic rhinitis, non-allergic perennial rhinitis, intrinsic rhinitis, vasomotor rhinitis or non-allergic rhinopathy. Due to its inconsistent terminology, its prevalence is difficult to estimate but may account for up to 70% of NAR cases (12–14). Symptoms can be triggered by a wide variety of stimuli: tobacco smoke, odours, changes in temperature, climate, pressure, humidity, traffic emissions, or even no identifiable trigger.

1.1.1.1.1.2. Diagnosis

The diagnosis of rhinitis is based on the presence of nasal symptoms such as nasal congestion/obstruction, rhinorrhoea, sneezing and itching resulting from inflammation but also dysfunction of the nasal mucosa (1).

The diagnosis of AR and NAR phenotypes is more difficult and is made by a combination of biological tests and patient's history. **Skin prick tests** (SPTs) and **serum specific IgE** are the biological tests commonly used in clinical practice to distinguish AR from NAR (15). However, both SPT and specific IgE tests have their limitations. It is

impossible to test for all existing allergens and only the major ones are tested. Furthermore, evidence of systemic sensitisation by SPTs or specific IgE does not necessarily mean that nasal symptoms are triggered by an allergic mechanism (16). In addition, **local AR** is characterised by symptoms similar to AR, associated with a positive nasal provocation test to allergens and elevated local (nasal) specific IgE, despite negative SPTs and non-elevated serum specific IgE (6). Due to their cost and complexity, nasal provocation tests and the measurement of specific IgE in nasal secretions are not recommended as first-line tests in clinical practice (6). Therefore, a large percentage of patients with local AR are classified as NAR (17). In this context, the **anamnesis** is an essential element of the diagnosis (16). Although sharing common symptoms, AR and NAR have different clinical features (18). AR usually starts in childhood, whereas NAR often appears later, after the age of 20. AR tends to decrease with advancing age, and age may be a susceptibility factor for the development of NAR (19). No sex differences were observed for AR. However, there may be more women with NAR than men (20,21). Most patients with AR have family members with asthma, rhinitis or atopic dermatitis and the presence of a familial predispostion for NAR varies between studies (22). Patients with AR may also have a seasonal exacerbation of symptoms, mainly due to aeroallergens. AR is characterised by the presence of nasal congestion, rhinorrhoea, sneezing and nasal itching, frequently associated with allergic conjunctivitis. Patients with NAR have, in the majority of cases, year-round symptoms triggered by a wide range of irritants and not by exposure to an allergen. The most common symptom of NAR is nasal congestion, while eye complaints are uncommon. Thus an atopic background, associated allergies, and a predominance of symptoms such as sneezing and nasal pruritus support the diagnosis of AR (6). Conversely, symptoms such as nasal congestion and rhinorrhoea without itching or sneezing and without correlation with exposure to an allergen support the diagnosis of NAR (6). However, AR and NAR should not be considered mutually exclusive. Indeed, studies have shown that up to 50% of patients with chronic rhinitis may have **mixed rhinitis** (23). Mixed rhinitis is characterised by persistent or intermittent rhinitis that is not fully explained by specific IgE sensitisation, and is triggered by a combination of allergic and non-allergic triggers (23).

Beyond the allergic or non-allergic characteristics of rhinitis, two others essential features to consider are the duration and the severity of rhinitis.

1.1.1.1.2. Rhinitis according to its duration

In 2001, ARIA proposed to categorise AR by presumed cause and seasonality. Seasonal AR (hay fever) triggered by outdoor allergens such as pollens was thus distinguished from peri-annual AR triggered by indoor allergens present throughout the year such as dust mites, moulds or animal dander (7). However, this classification was problematic because patients with peri-annual AR did not necessarily have symptoms all year round even if triggers are present all year long. Similarly, patients with seasonal rhinitis could have symptoms in different seasons depending on the number of pollens they were

sensitised to. Therefore, in 2008, ARIA proposed a new classification based on the **duration** and recurrence of symptoms defining persistent and intermittent rhinitis. This distinction originally applied to AR (1). But it can also be applied to NAR, as persistent rhinitis does not necessarily result from an allergic origin (24).

According to the ARIA classification:

- **Intermittent rhinitis** refers to symptoms that occur less than four days per week or less than four consecutive weeks
- **Persistent rhinitis** refers to symptoms present for more than four days per week and for more than four consecutive weeks.

1.1.1.1.3. Rhinitis according to its severity

ARIA proposes to classify rhinitis as "mild" and "moderate/severe" according to the severity of symptoms and their impact on social life, work and school (12):

- **Mild rhinitis**: symptoms are present but not bothersome, i.e. none of the following disturbances are present
  - Disturbance in sleep
  - Disturbance in daily activities, leisure or sport
  - Disturbance in school or work
- **Moderate/severe rhinitis**: symptoms are present and bothersome, one or more of the following disturbances are present
  - Disturbance in sleep
  - Disturbance in daily activities, leisure or sport
  - Disturbance in school or work

This classification is used to define and monitor treatment strategies in daily clinical practice, in clinical trials and in epidemiological studies.

1.1.1.2. Rhinitis endotypes

Within each phenotype there is variability in the clinical features that is not totally explained. Considering the underlying biological pathways or mechanisms could explain some of the observed variability, this approach consists of studying the **endotypes** of rhinitis (25).

There are relatively few literature reviews on the endotypes of rhinitis (15,26,27). The endotypes most frequently found in the literature involve the following mechanisms/pathways: IgE-mediated inflammation, non-IgE inflammation, structural abnormalities, infectious mechanisms, neurogenic mechanisms and unknown mechanisms. Endotypes should be seen as providing an additional level of understanding to phenotypes, like a wallpaper on which phenotypes are based (Figure 3). It is therefore sometimes difficult to distinguish phenotypes from endotypes.

The **IgE-mediated inflammation** endotype corresponds to AR. This endotype can be divided into two subtypes based on biomarkers which will differ depending on whether the AR is local or not. Non-local AR presents markers of IgE-mediated inflammation in

the nasal fluids and the serum: eosinophils, total IgE, specific IgE, eosinophil cationic protein (ECP), interleukin (IL)-5, IL-4, IL-13. Whereas for local AR biomarkers are only in the nasal fluids (15,26,27).

The **non-IgE inflammation** endotype is characterized by the following biological markers: neutrophils, IL-1β, IL-6, IL-8, myeloperoxidase (MPO), interferon (IFN) γ, tumor necrosis factor (TNF), Th17, IL-17A, IL-17F, IL-21, and IL-22. There is also the **non-allergic rhinitis with eosinophilia syndrome** (NARES) where the levels of eosinophils, IL-4, IL-17, IL-10 are high (15,26,27).

For endotypes based on infectious mechanisms, neurogenic mechanisms, unknown mechanisms and structural abnormalities there are no biomarkers associated with, which makes their identification complex. For the **infectious endotype**, the pathogen involved needs to be investigated, these are mainly viruses such as rhinovirus, adenovirus, coronavirus including SARS-CoV-2, influenza viruses (15,26,27). The **neurogenic endotype** includes several phenotypes of NAR with a neurological component. A neuronal hyper-responsiveness may trigger an exacerbation of parasympathetic and sympathetic reflexes leading to symptoms of rhinitis. This endotype can be identified by provocation tests like cold dry air (15,26,27). There are also **structural abnormalities endotype** like septal deviation, that can cause rhinitis and particularly symptoms of nasal obstruction. The identification of this endotype is based on a clinical examination (15,26,27). Finally, the endotype based on **unknown mechanisms** is defined on the exclusion of all previous endotypes (15,26,27). However, to date there has been little research into the endotypes of rhinitis and it is possible that new mechanisms may be discovered in future research.

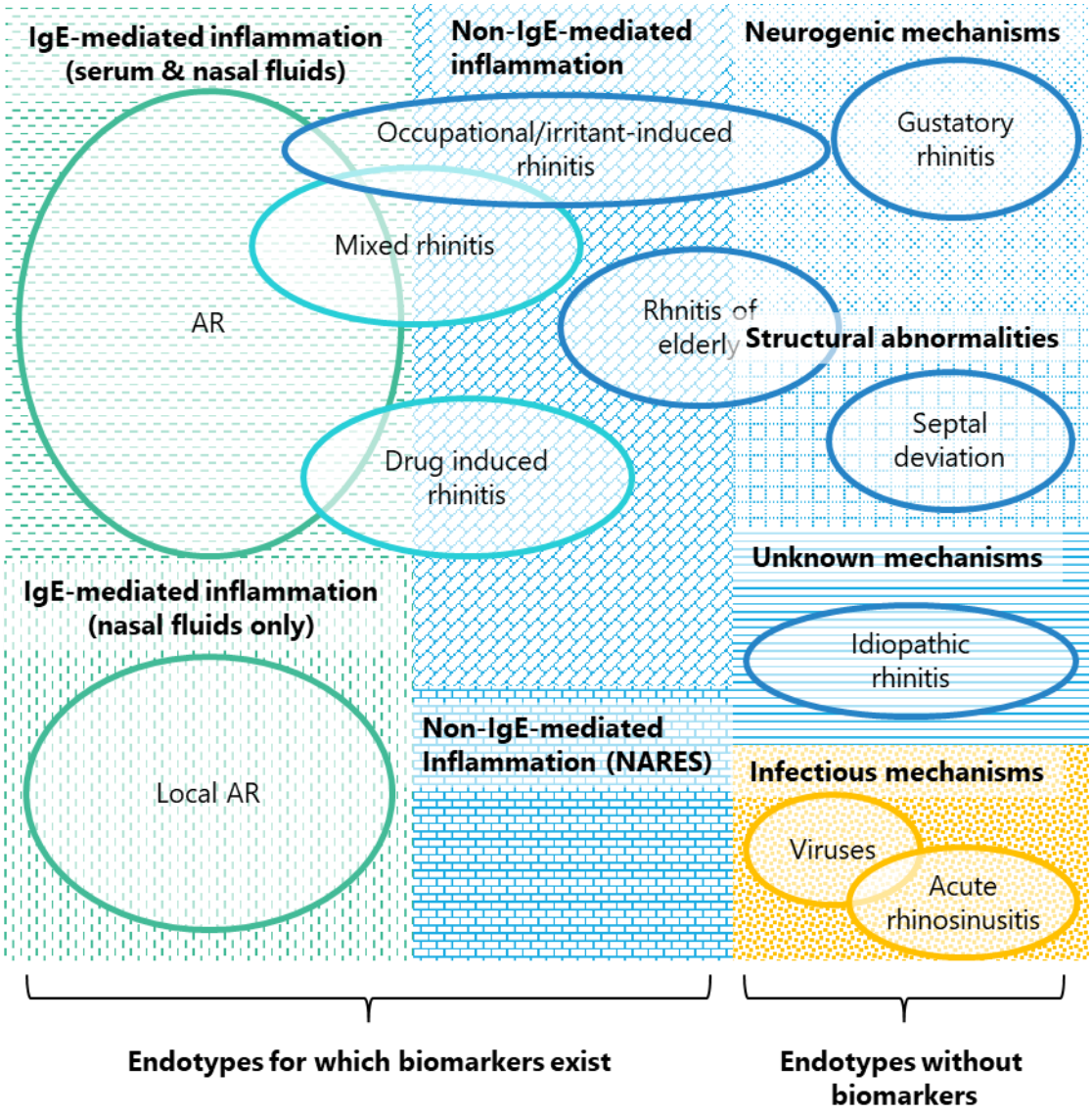


Figure 3: The different endotypes (background) on which rhinitis phenotypes (circles) are superposed

AR: Allergic Rhinitis, IgE: Immunoglobulin E, NARES: Non-Allergic Rhinitis with Eosinophilia Syndrome

1.1.1.3. Multimorbidities of rhinitis

To add an additional level of complexity, rhinitis often coexists with other health conditions. Several diseases have been shown to be associated with rhinitis via common mechanistic pathways -notably those of allergies- or disorders anatomically related to the nose.

Of all the multimorbidities of rhinitis, **asthma** is probably the most widely studied. Asthma is a complex and heterogeneous disease manifesting with reversible bronchial hyperresponsiveness and characterised by respiratory symptoms such as wheezing, shortness of breath, tightness, and cough (28). The definition of asthma has evolved over time and there is no one asthma, but there are many asthmas that manifest

through different phenotypes and/or endotypes (29). Asthma and rhinitis often co-exist: over 80% of patients with asthma have rhinitis and 10-40% of patients with AR have asthma (1). Allergic asthma and AR share common mechanisms that can involve both the upper and lower airways. This fact led to the concept of "one airway, one disease" that suggests that rhinitis and asthma are in fact one and same disease (30). However, this concept needs to be nuanced as not all patients with asthma have rhinitis and especially not all patients with rhinitis have asthma. One hypothesis is that rhinitis without asthma, and rhinitis with asthma could be different diseases with different clinical features and also different risk factors.

Allergic conjunctivitis is a conjunctivital reaction that occurs following exposure to allergens and is an important multimorbidity of AR: 50-70% of patients with AR have ocular symptoms (31,32). Rhinitis associated with conjunctivitis symptoms may be more severe and have higher impacts on quality of life than rhinitis without conjunctivitis (33).

AR can be directly associated with food allergies but AR is more frequently indirectly associated with food allergies via the **pollen-food allergen syndrome** (32,33). This is a cross-reactivity allergy where patients sensitised to a pollen will also be sensitised to a specific food that have similar antigens. The best-known example is when patients allergic to birch pollens are also allergic to apples.

Atopic dermatitis also known as atopic eczema is an inflammation of the skin associated with pruritus, scratching, and eczematous lesions. Although the multimorbidity of AR/atopic dermatitis is recognized in clinical practice, particularly in children (32), the level of evidence for the association between these two diseases is limited due to the lack of epidemiological studies (33).

Rhinitis and **rhinosinusitis** can co-exist and AR may be a risk factor of acute rhinosinusitis (32,33). The symptoms of rhinitis and rhinosinusitis may overlap which complicates the differential diagnosis between the two diseases, especially when distinguishing NAR from chronic rhinosinusitis with nasal polyps CRSwNP) (1). Furthermore, in some classifications of rhinitis, rhinosinusitis is included as a possible phenotype of rhinitis (15).

Rhinitis may be associated with dysfunction of the **sense of smell**: loss of sense of smell, hyposmia and odour distortion (34–36). This may be explained by multifactorial mechanisms involving obstruction of odorant transmission in the olfactory cleft due to mucosal inflammation (34). Loss of smell may be greater in cases of more severe rhinitis (35,36).

Nasal congestion, which is one of the most common symptoms of rhinitis, can lead to **sleep disturbances**, more difficulty in falling asleep and also **sleep apnoea** (32,33).

These morbidities will potentially play on the symptomatology of rhinitis. However, the multimorbidities of rhinitis have so far been relatively little considered, whether for classification by phenotype or by endotype.

1.1.1.4. Management of rhinitis

In order to optimize the management of rhinitis, the best possible therapeutic strategy should consider the different potential phenotypes and endotypes as well as the associated multimorbidities (32).

The main management options for rhinitis are summarised in Table 1.

Table 1: Summary of the main management options for rhinitis

Management option	Rhinitis phenotypes	Comments
Avoidance of the trigger	AR and NAR	First management element. Primary management of NAR (when trigger is known).
Oral H_1 Antihistamines	AR	First line of drug treatment for AR. Second generation antihistamines drugs are recommended.
Intranasal corticosteroids	AR and +/- NAR	First line of drug treatment for AR. Possible efficacy on NAR.
Leukotriene receptor antagonists	AR	May have additional benefit over anti-H1 drugs when AR is associated with asthma.
Decongestants	AR and NAR	Act only on nasal congestion. Beware of significant side effects and the risk of inducing rhinitis medicamentosa with prolonged use.
Saline solutions	AR and NAR	Low level of evidence but good safety profile.
Allergenic immunotherapy	Severe AR with identifiable specific IgE	Very restrictive, recommended especially in cases of severe rhinitis.

Regardless of the type of rhinitis, the first element of management is the **avoidance of the trigger**, including allergens. Avoidance may involve: environmental control measures, avoidance of certain foods, medications, and/or lifestyle/workplace changes. Even if very effective in reducing symptoms, total avoidance of most environmental factors is almost impossible (37,38). Moreover, this measure requires to know the trigger, which is not necessarily the case, especially for NAR.
The first-line drug treatments for AR are **second-generation oral H_1 antihistamines** (OAH) or **intranasal corticosteroids** (INCS). Oral H_1 antihistamines are all effective for AR by acting on rhinorrhoea, nasal itching and sneezing symptoms and have less effect on nasal congestion. Antihistamines have a limited effect on NAR (12,39). Intranasal corticosteroids are effective for AR by acting on both nasal and conjunctival symptoms. NAR may benefit from their anti-inflammatory effect, but studies are inconclusive regarding their effectiveness (6,40). The choice between OAH and INCS treatments is debated, with some recommendations preferring OAH as the first choice and others

INCS (41,42). The choice of treatment can be made according to the patient's preference for the nasal or oral route, and patients tend to prefer the oral route. The choice of treatment for the patient can also be made according to its availability without a prescription. Indeed many patients self-diagnose their rhinitis symptoms and treat themselves with over-the-counter (OTC) medications (43). In France, OAH are mostly available in OTC, while INCS are not available over the counter, except for *Humex rhume des foins©* (beclomethasone), which may be available without prescription in adults in the event of a recurrence of symptoms already diagnosed by a doctor (44).

Among **other treatments**, leukotriene receptor antagonists (montelukast) have comparable efficacy to OAH in AR, and in NARES (45). For patients with AR and asthma, they may have an additional benefit by acting on both conditions (46). Decongestants or vasoconstrictors (pseudoephedrine) are sometimes mentioned as treatment options and are available OTC. However, they have significant side effects. Prolonged use (>10 days) may induce rhinitis medicamentosa by rebound effect. They are also likely to cause cardiovascular, neurological or glaucoma side effects (1). The level of evidence for saline washes, irrigations or sprays is low but they are well tolerated, safe and inexpensive (47). Alternative medicines (acupuncture, homeopathy, yoga and other physical techniques) are often used by patients, and while many are satisfied with them, from a scientific point of view, there is no evidence of their effectiveness in rhinitis (48).

Allergen immunotherapy (or specific allergen desensitisation) is defined as the repeated administration of specific allergens to patients with IgE-mediated conditions in order to provide protection against allergic reactions to natural exposure to these allergens (49). Allergenic immunotherapy has been shown to be effective in the treatment of patients with AR with identifiable specific IgE. The effect of the treatment is maintained for years and can prevent the development of sensitisation to other allergens or even asthma (50). Despite this, the use of immunotherapy is very low, probably due, in the case of subcutaneous immunotherapy, by their restrictive treatment regimen with a subcutaneous injection every 4-8 weeks for 3-5 years (51). These repeated injections can also appear expensive but unlike other treatments that only act on the symptoms, this treatment is the only one with a long-term effect on rhinitis.

Recommendations for the treatment of AR have had a significant impact on its management (46) but there are still many gaps to find/establish the optimal management of rhinitis. For NAR, there are very few recommendations and even fewer effective treatments (16). The endotypes of rhinitis involving specific biological pathways, could allow to have targeted treatments. However, research on rhinitis endotypes is currently quite limited and specific treatments even more so, despite the development of new treatments, notably via allergen-specific immunotherapy (52). While the multimorbidities of rhinitis should be considered in the management of rhinitis (32), they are too often not taken into account. As an example, there is currently no plan to detect and prevent asthma in patients with AR (53), although this is one of

the first ARIA's management recommendations (54). Overall, many patients still do not achieve sufficient control of their rhinitis symptoms which can have a significant impact on their quality of life.

1.1.1.5. Burden of rhinitis

1.1.1.5.1. Health and social burden

Uncontrolled rhinitis is associated with a **deterioration of the quality of life**, both in terms of work/school and social life. Having rhinitis significantly increases fatigue and may even lead to cognitive impairment, depression and anxiety (1). Symptoms of rhinitis will lead to sleep disturbances including difficulty in falling asleep, insomnia, sleep apnoea or nighttime awakenings. These sleep disorders lead to lack of concentration, memory problems and difficulties in performing everyday tasks (55).
The impacts of rhinitis on **work productivity** can be classified into two categories: lost work time (i.e. absenteeism) or reduced work performance (i.e. presenteeism). A systematic review of the literature showed that rhinitis was associated with a loss of productivity with a high impact in terms of presenteeism, the impairment of performance being estimated at 35.9%, while the impact on absenteeism was minimal (3.6%) (56). The impairment of work productivity due to rhinitis would be at least as important as that reported for other chronic diseases such as asthma, arthritis, diabetes, cardiac problems, musculoskeletal disorders, depression, high stress or anxiety disorders (56). Finally, the severity of rhinitis impacts work productivity with a 24.9% higher loss of productivity for moderate-severe rhinitis compared to mild rhinitis (56).

1.1.1.5.2. Economic burden

Beyond the individual impacts on the lives of patients, rhinitis generates costs at the society level. Cost estimates can be divided into two main categories: direct costs or indirect costs and vary from country to country. **Direct costs** are attributable to the disease or its management, whether they are medical costs related to health goods and services (drugs, hospitalisation, biology and radiology) or wether they are non-medical costs attributable to the treatment, but which concern non-health resources (transport, for example). **Indirect costs** are the non-medical resources consumed not directly related to the treatment. They reflect essentially the time lost due to the disease itself: loss of productivity due to work stoppages, time spent with relatives, and the human and psychological costs associated with the disease (57). It is therefore more difficult to estimate indirect costs and they are less frequently evaluated.
It is estimated that **direct costs of rhinitis are low** because its treatments are inexpensive and medical consultations for rhinitis are infrequent (58). In France, Belhassen *et al.* estimated that, for a patient with perennial AR without asthma, the median annual cost reimbursed by social security system was €159 (59). Cardell *et al.* estimated in 2014 the AR total cost (direct and indirect) in Sweden to be €961.1 per individual per year (60). In this study, the average direct and indirect costs were €210.3

and €750.8 respectively, showing the **major contribution of indirect costs**. Presenteeism was the main indirect cost of rhinitis and accounted for more than two-thirds of total costs. Furthermore, the total cost per patient varied according to the ARIA classification of symptom severity. For moderate to severe rhinitis, the estimated total cost was €1,756.6 per person per year, while for mild rhinitis it was about a quarter of this amount (€464.4 per person per year). The total cost of self-reported AR in Sweden has been estimated at €1.3 billion (60). Considering that the demographics and costs of care are similar between Sweden and other European countries, the annual cost of AR in France could be estimated to be between 9.4 and 9.9 billion euros per year (60). Similar results were also found by Colás *et al.* in Spain which showed that the total cost of rhinitis was €2326 per year with 76% of the costs being indirect and the costs were increased by the severity of the rhinitis (61). The importance of the indirect costs of rhinitis -in particular those associated with lost productivity at work- has been confirmed in a systematic review of the literature (56). The costs of presenteeism was 2.2 to 18.7 times greater than those of absenteeism, and the total costs of lost productivity (absenteeism and presenteeism) was 3.2 to 13.5 times greater than direct medical costs (56). The indirect costs of rhinitis may be higher than or similar to those of other chronic diseases such as asthma or diabetes traditionally considered 'more important' from a medical point of view (56).
Beyond the direct and indirect costs there are also **"hidden" costs** of rhinitis. The multimorbidities associated with rhinitis will generate costs that may not be accounted for in medico-economic studies. For example, in the study of Belhassen *et al.*, the cost of perennial AR alone was €159 and the cost of rhinitis combined with asthma was between €266 and €375 (59). In addition, most studies are based on medico-administrative data which can also lead to an underestimation of the real costs as many patients use OTC drugs which are not accounted for in these databases (43).

In conclusion, despite low direct costs, the overall cost of rhinitis is high due to the presence of indirect and hidden costs. These costs are even more impactful as rhinitis is one of the most frequent diseases in the world, as we will see in the following part.

1.1.2. Epidemiology of rhinitis

1.1.2.1. Definitions and worldwide prevalences of rhinitis

Results from this section were published as a literature review in Clinical and Translational Allergy (62)*, see Appendix 1 for full text.*

Although there are many different definitions of rhinitis in epidemiology, there was no review of the literature listing them. The reviews of the literature on the prevalences of rhinitis have been limited to AR and the most recent review that has considered all regions of the world was published in 2008. For these reasons, we decided to conduct a review of the literature on the different definitions of rhinitis and its prevalence

worldwide in the general adult population which is the population of interest of this thesis.

1.1.2.1.1. Methods

The literature search used the computerised bibliographic databases PubMed and Scopus and included all the existing literature up to October 13, 2020.
The terms "*rhinitis*" or "*hay fever*" combined with "*epidemio**" or "*preval**" were searched in the title or abstract. The only limitation applied was that the studies had to be written in English, French or Spanish language. Additional records from the references of the literature reviews and of the eligible publications identified in the search were included. Articles were first screened based on their title and abstract, and then the articles of interest were read in detail to assess their eligibility.
Articles were selected according to the following criteria: the articles should 1) be an original epidemiological study, 2) include prevalence data on rhinitis, AR and/or NAR, 3) be based on a general adult population or a population including all ages. As this review focused on rhinitis prevalence in general populations, studies focusing only on specific subpopulations such as children, students, farmers, exclusively in men or in women were excluded. We also excluded studies that were conducted in specific health centres or allergy clinics and studies that did not contain any information on the definition of rhinitis, or that did not provide any data to calculate the rhinitis prevalence in the general population.

After excluding duplicates, a total of 5,878 records were identified. Altogether 184 articles were included in the present review.

1.1.2.1.2. Results

1.1.2.1.2.1. Definitions of rhinitis

A total of 156 different definitions of rhinitis were identified. Because of the large number of definitions, we grouped them into several categories which are presented in Table 2, thus are: unspecified rhinitis, AR and NAR. In addition, we further subcategorized them according to the method on which the definition was based: symptoms, doctor diagnosis or IgE/SPT-based definition. Finally, we subcategorized unspecified rhinitis, AR and NAR into 1) ever rhinitis (lifetime prevalence), or 2) current rhinitis (period prevalence). In addition, the International Study of Asthma and Allergies in Childhood (ISAAC) and European Community Respiratory Heath Survey (ECRHS) definitions are also provided in this table as they were the definitions most frequently used in the literature to define rhinitis.
Among the 156 different definitions, 58 were for unspecified rhinitis, 86 for AR, and 12 for NAR. It is interesting to note that the most used definitions to defined AR and NAR in the literature are those based on self-report, and those based on SPTs and IgE are much less frequent, even if they are the gold standard in clinical practice.

Table 2: Categorisation of rhinitis definitions and number of associated prevalences

Category	Definition	n prevalences
Main categories		
Unspecified rhinitis	A definition of rhinitis that did not specify whether it was allergic or non-allergic	103
AR	A definition including the term "allergic rhinitis" and/or "hay fever" and/or including triggers known to induce an allergic inflammation of the airways, such as pollen, furry animals, or house dust mites; and/or assessment of allergic sensitization by skin tests and/or serum specific IgE	311
NAR	A definition excluding AR and/or referred to triggers known to induce a non-allergic rhinitis, such as cold and dry air, temperature change, airborne chemical irritants, spicy food, alcoholic beverages, exercise, use of tobacco, anti-inflammatory drugs, stress, and/or printer ink	13
According to the method used		
Symptoms-based definitions	A definition that is based on a question asking from the participant himself/herself about the presence of rhinitis or nasal symptoms	Unspecified: 88 AR: 187 NAR: 7 Total: 282
Doctor diagnosis-based definitions	A definition that is based on a previous self-reported medical diagnosis of rhinitis or on a diagnosis made by a physician for the study	Unspecified: 15 AR: 81 NAR: 0 Total: 96
IgE/SPT-based definition	Definition based on either of symptoms or doctor diagnosis in combination with the assessment of the IgE-mediated sensitization with measurements of specific IgE and/or skin prick tests (SPTs). Participants with positive SPTs and/or positive specific IgE were defined as AR IgE/SPT-based definition, those with negative IgE/SPT results were defined as NAR IgE/SPT-based definition	AR: 42 NAR: 6 Total: 48
Lifetime and period prevalences		
Ever	A definition that refers to the presence of rhinitis ever in the study participant's lifetime (i.e. lifetime prevalence)	Unspecified: 34 AR: 98 NAR: 1 Total: 133
Current	A definition that refers to the presence of rhinitis at the time of the study or in the last few months (i.e. point or months/one-year period prevalence)	Unspecified: 69 AR: 212 NAR: 12 Total: 293
ISAAC and ECRHS definitions		
ISAAC: ever self-reported unspecified rhinitis	*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?*	6
ISAAC: current self-reported unspecified rhinitis	*In the past 12 months, have you had a problem with sneezing, or a runny, or a blocked nose when you did not have a cold or the flu?*	15
ECRHS: current self-reported AR	*Do you have nasal allergies including hay fever?*	87

1.1.2.1.2.2. Overall prevalences

Table 3 describes the rhinitis prevalences for the three main categories and their subcategories. The median rhinitis prevalences were: 29.4% (ranging from 1.1% to 63.3% based on 103 reported prevalences) for unspecified rhinitis, 18.1% (from 1.0% to 54.5% based on 310 reported prevalences) for AR, and 12.0% (from 4.0% to 31.4% based on 13 reported prevalences) for NAR. The median prevalence of current AR was 21.6% based on symptoms-based definition and 16.4% based on IgE/SPT-based definition. For NAR, the median prevalence was 16.4% based on symptoms-based definition and 31.4% based on IgE/SPT-based definition. In adults of all ages, NAR was reported from 24.4% to 67.1% of participants with rhinitis (20,63–72).

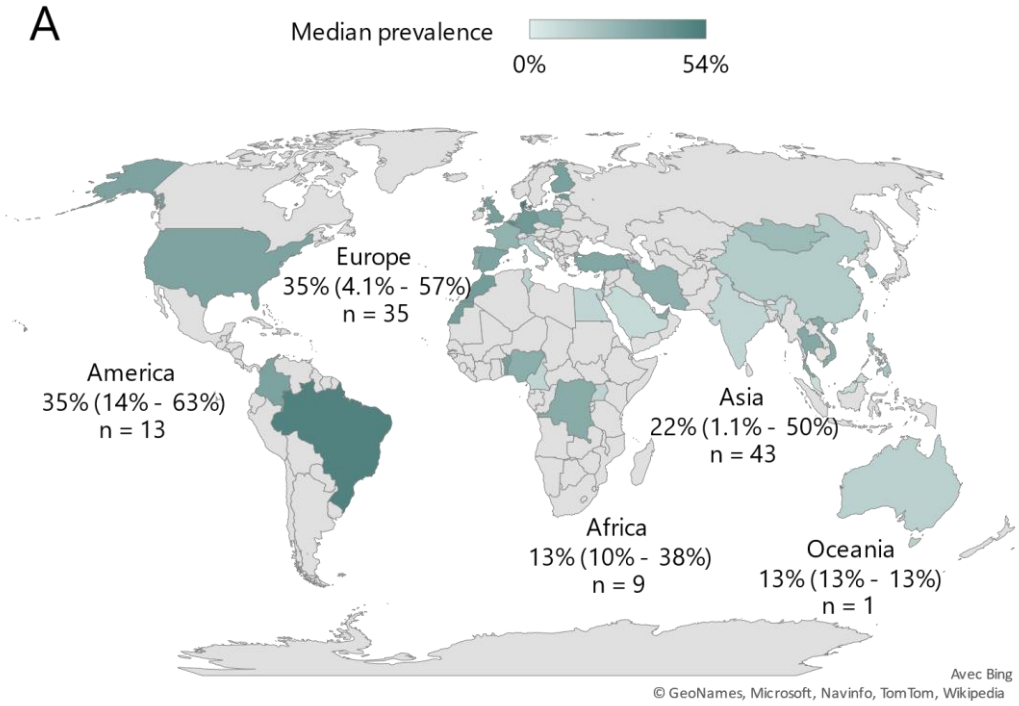
Table 3: Rhinitis prevalences according to the different definitions

	n	Mean	Med	SD	$CI_{95\%}$		Min	Max
All definitions								
Unspecified rhinitis	103	27.0%	29.4%	14.0%	(24.3%,	29.7%)	1.1%	63.3%
AR	311	19.1%	18.1%	10.2%	(18.0%,	20.3%)	1.0%	54.5%
NAR	13	14.6%	12.0%	8.3%	(9.6%,	19.6%)	4.0%	31.4%
Symptoms-based definitions								
Unspecified rhinitis								
Ever	20	28.1%	30.4%	12.8%	(22.1%,	34.0%)	10.8%	50.2%
Current	68	30.8%	32.3%	12.5%	(27.8%,	33.8%)	4.1%	63.3%
AR								
Ever	42	21.4%	20.7%	10.9%	(18.0%,	24.8%)	4.2%	52.0%
Current	145	23.5%	21.6%	9.7%	(21.9%,	25.1%)	3.6%	54.5%
NAR								
Ever	1	7.9%	-	-	-	-	-	-
Current	6	10.0%	16.4%	4.4%	(5.4%,	14.6%)	4.0%	16.4%
Doctor diagnosis-based definitions								
Unspecified rhinitis								
Ever	14	9.0%	9.1%	3.3%	(7.2%,	10.9%)	2.5%	14.0%
Current	1	1.1%	-	-	-	-	-	-
AR								
Ever	53	12.8%	13.0%	6.9%	(10.9%,	14.7%)	1.0%	30.9%
Current	28	7.9%	7.9%	1.4%	(7.4%,	8.5%)	3.9%	11.4%
IgE/SPT-based definitions								
AR								
Ever	3	15.5%	28.5%	11.3%	-	-	8.9%	28.5%
Current	39	17.4%	16.4%	7.3%	(15.1%,	19.8%)	3.7%	44.2%
NAR								
Ever	0	-	-	-	-	-	-	-
Current	6	20.4%	31.4%	8.5%	11.5%,	29.3%)	5.5%	31.4%

AR: Allergic Rhinitis, CI: Confidence Interval, Current: combination of point and period prevalences, Ever: Lifetime prevalences, IgE: Immunoglobulin E, Max: highest reported prevalence, Med: Median, Min: lowest reported prevalence, n: number of reported prevalences, NAR: Non-Allergic Rhinitis, SD: Standard Deviation, SPT: Skin Prick Test

1.1.2.1.2.3. Rhinitis prevalences worldwide

World maps showing the average prevalences of unspecified rhinitis, AR and NAR are presented in Figure 4. There was a wide variation in the reported prevalences even within the same continent for all categories of rhinitis. Indeed, prevalence of unspecified rhinitis ranged from 10.4% to 37.8% in Africa, from 14.0% to 63.3% in America, from 1.1% to 50.2% in Asia, from 4.1% to 56.6% in Europe, and was of 13.2% in Oceania based on a single study (73). Prevalence of AR ranged from 3.6% to 22.8% in Africa, from 3.5% to 54.5% in America, from 1.0% to 47.9% in Asia, from 1.0% to 43.9% in Europe, and from 19.2% to 47.5% in Oceania. A few prevalences of NAR have been reported, and no data was reported from America, Africa or Oceania; for Asia, the six reported prevalences ranged from 4.0% to 31.4%, and for Europe, the six reported prevalences ranged from 5.5% to 23.5%.



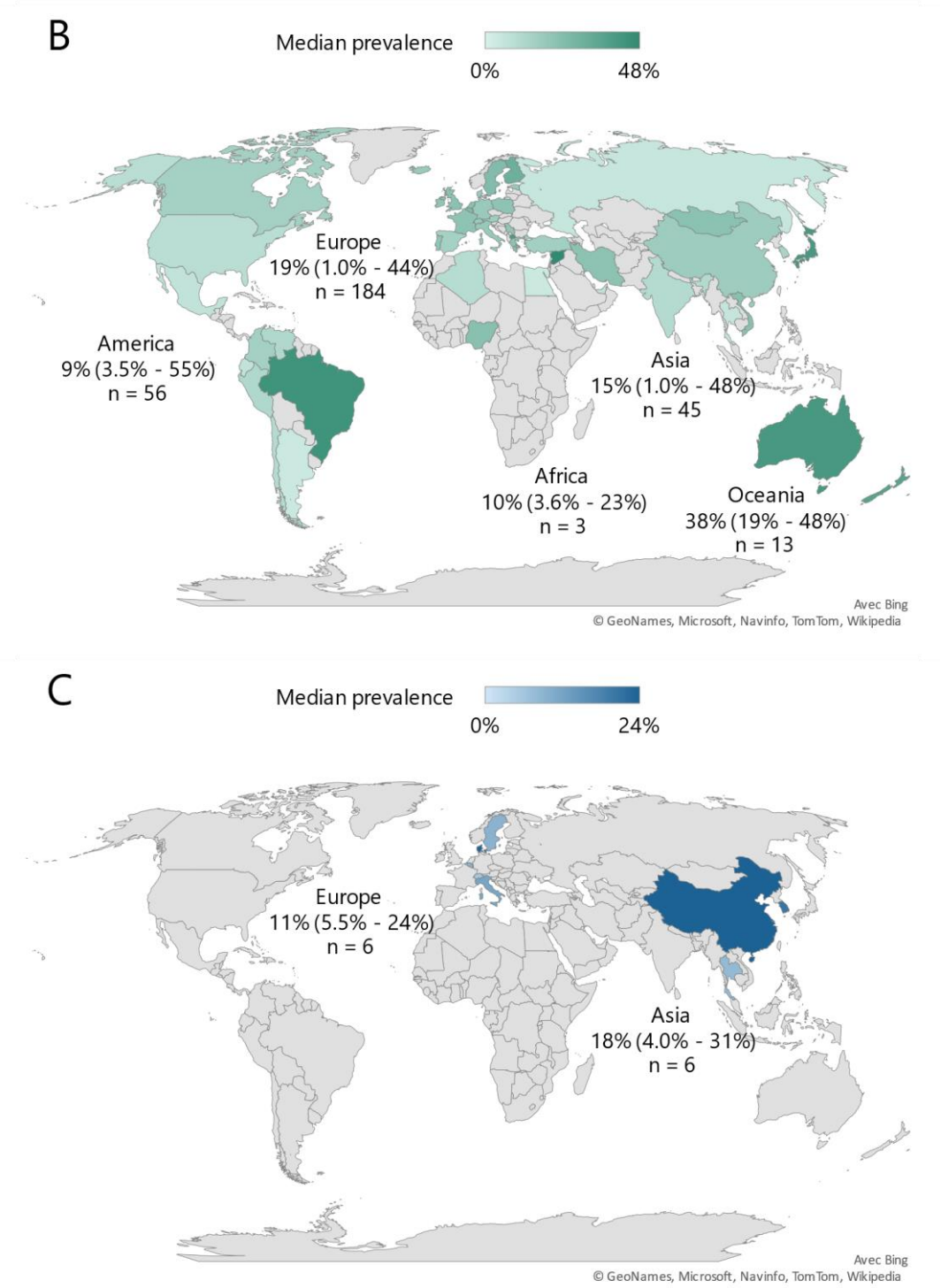


Figure 4: Rhinitis prevalences from different regions of the world (62)

A: Unspecified Rhinitis, B: Allergic Rhinitis, C: Non-Allergic Rhinitis.
The data for continents are presented as follows: median (minimum reported - maximum reported), n = number of reported prevalences. Coloured countries are those for which data are available. The darkest countries are those for which the median prevalence is the highest.

1.1.2.1.2.4. Evolution in the rhinitis prevalences over time

The evolution of rhinitis prevalences over time within the same or similar populations using the same definition is presented in
Figure 5.

In America, in Brazil a 10% decrease in the rhinitis prevalence was reported between 2011 and 2018 (74). In the United States, the National Health and Nutrition Examination Survey (NHANES) reported that episodes of hay fever in the past 12 months increased from 11.8% to 13.6% between 2007 and 2012. In the National Health Interview Survey (NHIS), the prevalence of AR decreased from 9.3% to 7.3% between 1997 and 2018. In Asia, the Korean National Health and Nutrition Examination Survey reported that the prevalence of AR increased from 1.0% to 17.1% between 1998 and 2017 (75,76).

In Europe, studies from Denmark (77,78), Finland (79,80), France (81,82), Germany (83), Italy (84), Russia (79), Scotland (85), and Sweden (86–88) reported increases in the prevalence of rhinitis. In Poland, the results varied depending on the definition used: between 2003 and 2012 a slight decrease was observed for rhinitis based on "*Problem with sneezing or a runny or blocked nose or itchy eyes in April, May, June, or July* " and " *In last 12 months, have you had a problem with sneezing or a runny or blocked nose or itchy eyes when you (your child) did not have a cold or flu?*" (89). Conversely, in the same study, an increase from 4.8% to 7.7% was observed when rhinitis was defined by "*Has a physician ever told you that you have hay fever?*" (89).

For Oceania, one study in Australia showed that hay fever prevalence increased from 21.9% to 46.7% between 1981 and 1990 (90). No studies were found on the evolution of rhinitis prevalence over time from the African continent.

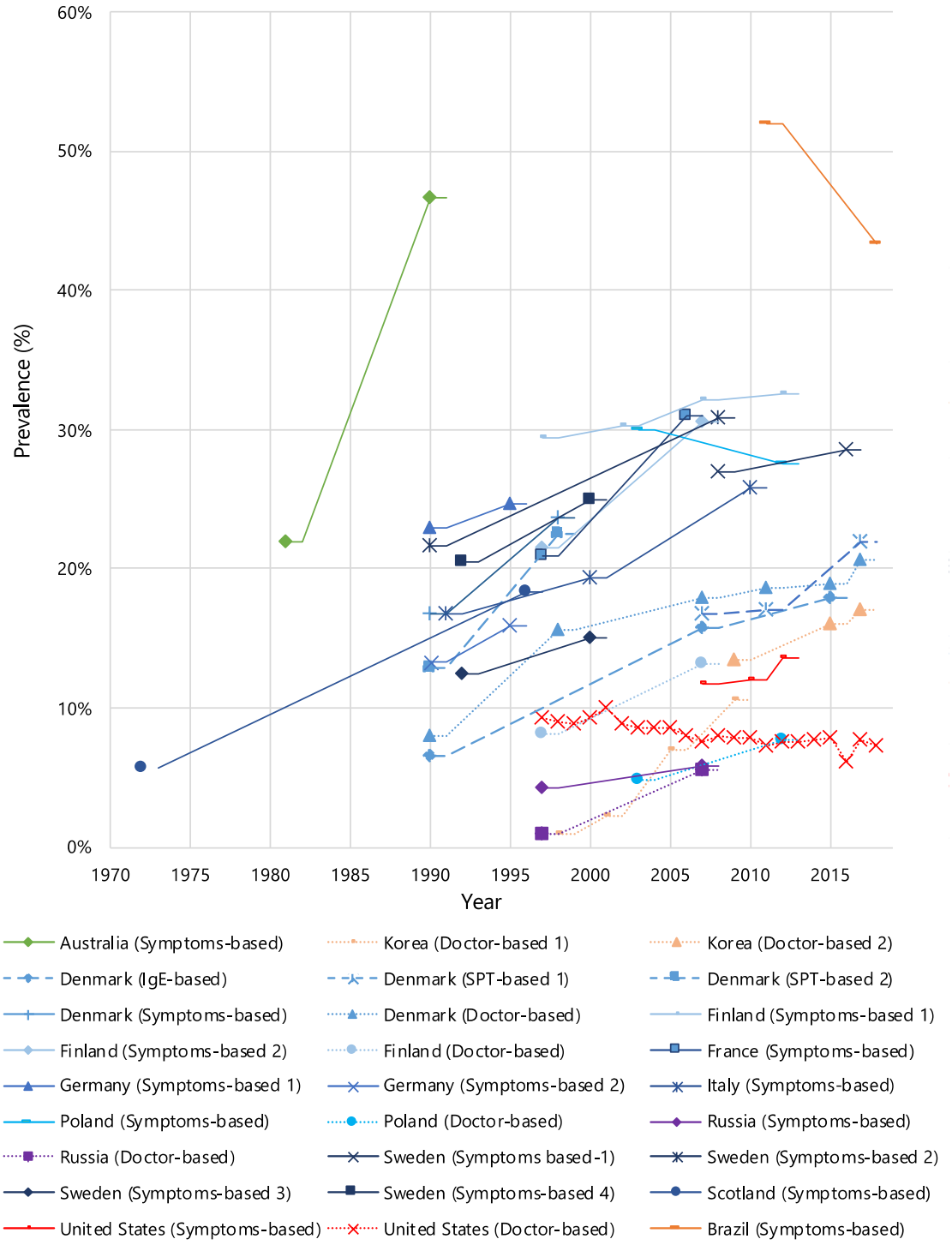


Figure 5: Evolution of allergic rhinitis prevalence worldwide over time (62)

1.1.2.1.3. Discussion

In this review, a total of 184 articles that included data on rhinitis prevalence among adults were identified and contributed to **156 different definitions** of rhinitis. Depending on the definition used and the geographical area studied, rhinitis prevalence ranged from 1% to over 60%. The **median worldwide prevalences of unspecified rhinitis, AR and NAR were 27.0%, 19.1% and 14.6%**. A geographical variability was observed in the prevalences of subtypes of rhinitis. Irrespective of the definition used, most of the studies reported an increase in the rhinitis prevalence over the last decades.

The wide variability in definitions of rhinitis detected in this extensive review highlights the need to find a consensus on which definitions should be used in epidemiological studies. We recommend to define rhinitis in epidemiological studies applying a question that is easily understandable by all participants, that refers to the main symptoms of rhinitis, and that does not include specific medical terms. The ARIA recommends to use a question including symptoms of "*sneezing, runny nose and/or blocked nose when the patient does not have a cold*" (7). The definitions of current and ever rhinitis should not include any ambiguous terms, such as "often", "several" or "most of the time". Instead, it would be better to refer to clear time periods, for example "in the last 12 months" or "during your lifetime". The two questions in the ISAAC study (91) comply with these suggestions, and could be accurate questions to define current and ever unspecified rhinitis. In clinical practice, to define AR and NAR, the measurement of specific IgE or SPTs combined with a medical history by the doctor is 'the gold standard'. However, as these diagnostic tools are not always easily available in large epidemiological studies, it could be useful to have a proxy for AR and NAR using a definition based on questionnaire, using questions about the main triggers of nasal symptoms. Specific allergens triggering rhinitis symptoms, such as pollen or animal exposure, or the presence of eye symptoms in combination with rhinitis symptoms have been shown to have a moderately high positive predictive value for AR in participants with SPT positivity to common aeroallergens (92). These triggers as well as associated-eye symptoms emerged as important discriminative variables in a clustering analysis that was performed without any *a priori* hypothesis to identify AR or NAR (93). An expert consensus and/or methodological research comparing different definitions with a clinical diagnosis of rhinitis is needed to establish the best definitions for rhinitis, AR and NAR, to be used in epidemiological studies.

Overall, this review highlights the wide variability in the definitions used to identify the phenotypes of rhinitis and underlines the urgent need for a consensus on standardized definitions for rhinitis to be used in epidemiological studies.

Worlwide, the median prevalence of unspecified rhinitis was 29%, which is close to the prevalence of 31.7% reported for children aged 13-14 years in the ISAAC phase 3 study (94). However, a large variability of rhinitis prevalence was observed between the studies. This variability is probably partly explained by heterogeneity in the definitions used in the studies. Indeed, within the same population the prevalence was found to vary greatly depending on the definition used: for example, in the study by Bauchau *et al*. rhinitis prevalence in Belgium varied by more than 30% depending on whether rhinitis was defined based on doctor diagnosis or on reported symptoms (95). Considering all the studies, I found that the average prevalence of doctor diagnosis-based definitions was lower compared to the other definitions. This could be partly explained by the fact that rhinitis prevalence is often underestimated when based on the doctor diagnosis. Indeed, it is recognized that patients with rhinitis often tend to self-diagnose their rhinitis and treat themselves (47), and those who consult a doctor are likely to have more often moderate to severe rhinitis (54). In addition, access to health professionals may be heterogeneous according to the geographic location, healthcare system, or socioeconomic status (SES) of the patient. Large variabilities in reported prevalences were also observed for AR and NAR. The median prevalence of AR calculated in this literature review based on all definitions was 18%, with a higher average prevalence being detected with the symptoms-based definitions compared to the IgE/SPT-based definitions. The median prevalence of NAR was 12%, which is lower than the prevalence obtained for AR. Nevertheless, based on this literature review, compared to AR, NAR could represent 20 to 80% of rhinitis cases in adults. As only 13 studies had evaluated the prevalence of NAR, it is rather difficult to make conclusions on the "true" prevalence of NAR.

The geographical variability in rhinitis prevalence could be partly explained by different access to healthcare, different environmental exposures, such as different species of pollen, different lifestyle factors, including dietary habits and keeping of pets indoors, or different host risk factors (96). As in this review we have reported rhinitis prevalences without considering these risk factors, these hypotheses need to be tested in future studies. It should be noted that these factors were rarely considered and/or investigated in the studies identified by this literature review.

Rhinitis appears to be a common disease in the European and American countries, which is consistent with some previous reports (1,96). In other parts of the world, far fewer studies have been reported on the prevalence of different types of rhinitis, which makes it more difficult to calculate reliable estimates and make firm conclusions. It is noteworthy that the global distribution of rhinitis prevalence was found to be similar to that of global distribution of asthma prevalence, for which the literature is more extensive (97). Further studies that apply standardized definitions of rhinitis from different parts of the world would add knowledge on "true" differences in rhinitis prevalence and on their related risk factors.

This extensive review also showed that most studies reported an increase in rhinitis prevalence over time. One explanation could be that the awareness of rhinitis has improved in parallel in different populations around the world due to advertising of

OTC medicines for rhinitis, and with the development of the internet making it easier to get information on rhinitis. In addition, medical examinations may have become more accessible and thus, the rhinitis diagnosis may also be more easily done. Despite this fact, rhinitis prevalence seems to have increased in many parts of the world, whatever the definition of rhinitis used. Concerning the trend of increasing prevalence of different types of rhinitis, potential impact of risk factors, including global warming, changes in seasonal patterns, and air pollution, have been proposed (98). However, a few studies have investigated potential impact of such factors on rhinitis prevalence over time.

In conclusion, this review highlights a geographical variability of rhinitis prevalences, pointing out the scarcity or even lack of data for NAR prevalence.

To better understand rhinitis, beyond the studies on its prevalence, it is essential to describe the characteristics of rhinitis in population-based epidemiological studies in complement to the clinical knowledge. The added value of the descriptive epidemiological approach and the remaining gaps are discussed below.

1.1.2.2. Characterisation and classification of rhinitis in epidemiological settings

The clinical population from which the main knowledge on rhinitis is issued is a highly selected population. Indeed, few patients with rhinitis consult a doctor because most patient trivialise their symptoms and OTC medications are available (99,100). An assessment in France of patients with clinically confirmed symptoms of AR showed that 43% did not know they had AR and 54% had not been diagnosed by their doctor (95). Furthermore, in the same study, 29% of the patients who were aware of their symptoms had never consulted a doctor and had therefore not been officially diagnosed with rhinitis (95). In addition, the majority of patients who consult a doctor have moderate to severe rhinitis (54). Thus, population-based studies offer the opportunity to study rhinitis under "real" conditions and to consider all cases of rhinitis, even the mildest and/or those who do not consult their doctor for their symptoms. However, there are no recent studies in the general population in adults that have assessed characteristics of phenotypes of rhinitis. Furthermore, few of them have assessed NAR (16).
Moreover, as we saw earlier, the clinical practice suggests that there may be different AR phenotypes depending on the presence of multimorbidity, especially asthma and conjunctivitis. Although there are studies looking at the characteristics of asthma in relation to the presence or absence of rhinitis, there are surprisingly no population-based epidemiological studies in adults that have looked at the characteristics of rhinitis in relation to the presence or absence of asthma or conjunctivitis (32,33).
Several population-based studies have described AR according to its duration and indicate that persistent rhinitis is different from intermittent rhinitis (65,101–103). Particularly, persistent AR could be associated with more severe AR (103). In this

context, it is questionable whether the different characteristics observed between intermittent and persistent rhinitis are independent of its severity. Characterising the severity of rhinitis, its progression and response to treatment could help identify the best treatments for each patient and therefore facilitate the therapeutic management of rhinitis (54). The ARIA classification has been validated in clinical practice (1,104–106) but few population-based studies have looked at the severity of rhinitis according to the ARIA definition, and the data used to describe rhinitis were limited (65,107–109). Therefore, the severity of rhinitis according to ARIA remains to be validated in the general population. Furthermore, the association between asthma and severity of rhinitis is unclear: some studies, suggest that asthma is more common in patient with moderate-severe rhinitis than those with mild rhinitis while other studies show no association (1,110). No population-based study has been conducted in adults to describe rhinitis according to its severity associated to its duration and no study assessed the impact of asthma multimorbidity in ARIA classes.

Beyond this lack of data on rhinitis, to date, classifications of rhinitis based on a candidate approach [2] are inconsistent and subjective, leading to difficulties in communication in research or clinical practice (6). An unsupervised approach[3], which does not require an *a priori* knowledge, could identify rhinitis phenotypes or endotypes, while avoiding problems related to subjectivity. This approach could confirm some clinical classifications and/or allow the identification of new classes of rhinitis. However, to date the unsupervised approaches have been little used to identify the phenotypes or endotypes of rhinitis. As presented in Table 4, most studies were conducted among patient's cohorts and only three studies have identified phenotypes by unsupervised approach in case-control (93) or population-based studies (111,112). No study has identified endotypes by unsupervised approach using a wide variety of biological markers.

[2] A candidate approach is a "classical" approach where rhinitis is defined on the basis of established knowledge, using a questionnaire definition or a combination of clinical diagnosis and biological tests, in this sense we refer to an approach based on *a priori* hypotheses.

[3] unsupervised approach which does not rely on established definitions to identify the different groups of rhinitis but on classification algorithms, in this sense we refer to an approach without *a priori* hypotheses.

Table 4: Summary of the main studies identifying phenotypes or endotypes of rhinitis by unsupervised approach

Author	Population	Method	Variables	Results
Bousquet *et al.* 2015 (113)	825 patients consulting for AR and treated as per clinical practice, France	Ward's minimum-variance HCA + VARCLUS cluster analysis	18 variables in 6 clusters - Cluster 1: oral/nasal antihistamines, corticoids, ocular antihistamine, OTC - Cluster 2: TNSS4, VAS, ARIA classes - Cluster 3: antileukotriene, concomitant respiratory disease, concomitant skin disease, documented allergy - Cluster 4: duration of diagnostic, age - Cluster 5: cromoglycate-like drugs, decongestant, SES - Cluster 6: gender, residential area	4 phenotypes clusters which partly followed the ARIA classes
Burte *et al.* 2015 (93)	983 adults from a case-control study on asthma (EGEA), France	Mixture model	- Report of nasal symptoms - Current/ever symptoms - Persistence and disturbance of these symptoms, - Seasonal pattern - Sensitivity to seven triggers - Report of AR, hay fever, conjunctivitis, sinusitis and eczema - Report of diagnostic of allergy by a physician - SPTs - Report of spray, report of drug except spray, and allergic immunotherapy since the last survey	3 phenotypes clusters: - Cluster 1 (55% in Asthma-, and 22% in Asthma+): absence of nasal symptoms - Cluster 2 (23% in Asthma-, 36% in Asthma+): nasal symptoms all over the year, sinusitis and a low prevalence of positive SPTs - Cluster 3 (22% in Asthma-, 42% in Asthma): peak of nasal symptoms during spring, a high prevalence of positive SPTs and a high report of hay fever, AR and conjunctivitis
Kurukulaaratchy *et al.* 2015 (111)	468 participants (18 years) whole population birth cohort on the Isle of Wight, United Kingdom	K-means	- Atopic status at age 18 years - Asthma at age 18 years - Eczema at age 18 years - Age at which rhinitis appeared - Seasonality of rhinitis symptoms - Total IgE level - BDR - BHR dose response slope - mean FeNO value - FEV_1 - FVC	4 endotypes clusters: - Cluster 1 (27.4%): moderate childhood-onset rhinitis - Cluster 2 (42.5%): mild adolescence-onset female rhinitis - Cluster 3 (12.6%): severe earliest-onset rhinitis with asthma - Cluster 4 (17.5%): moderate childhood-onset male rhinitis with asthma

Author	Population	Method	Variables	Results
			- FEV_1/FVC ratio - FEF_{25-75}	
Lee *et al.* 2016 (114)	512 children from the Children's Health and Environment Research cohort with current rhinitis, Korea	LCA	- Sex - BMI - Income - Maternal educational level - Prior exposure to environmental tobacco smoke - Parental history of allergic diseases (AD, AR, and/or asthma) - Presence of allergic disease - Comorbidities at the time of enrollment - Treatment of rhinitis within the previous 12 months - SPTs - Total serum IgE, - Blood eosinophil percentages - Pulmonary function test results at the time of enrollment - Presence of rhinitis at the time of enrollment	4 endotypes clusters: - Cluster 1 (25%): non-atopy and a low SES - Cluster 2 (36%): high-atopic burden but normal lung function - Cluster 3 (22%): high-atopic burden and impaired lung function - Cluster 4 (17%): low atopy and a high SES
Caimmi *et al.* 2018 (115)	28,109 adult patients with a previous medical diagnosis of seasonal AR and consulting a physician, France	K-means or Agglomerative HCA	- Nasal congestion - Nasal obstruction - Rhinorrhea - Nasal itching - Sneezing - Headache, - Tiredness, - Loss of appetite, - Irritability, - Lacrimation, - Eye itching, - Painful throat, - Cough, - Itching throat, - Earache, - Alteration of daily activity - Sleep alteration	3 phenotypes clusters: - Cluster 1 (40.4% or 28.4%): mild AR - Cluster 2 (36.2% or 44.1%): moderate AR - Cluster 3 (23.4% or 27.3%): severe AR
Amaral *et al.* 2019 (112)	728 adults from a cross-sectional study in the Portuguese general population	LCA	19 dichotomic variables - Mite sensitization - Epithelium (cat/dog) sensitization - Mold sensitization - Tree sensitization - Grass sensitization	6 phenotypes clusters: - Cluster 1 (25%): non-allergic participants without bronchial or ocular symptoms - Clusters 2 (22%) and 3 (11%): nasal and ocular (low

Author	Population	Method	Variables	Results
			- Weed sensitization - Runny nose - Sneezing - Nasal congestion - Itchy nose - Impaired sleep by nasal symptoms - Impaired work/school by nasal symptoms - Impaired daily activities by nasal symptoms - Watery eyes - Itchy eyes - Dyspnea - Dyspnea at night - Wheezing - Chest tightness	levels) symptoms without nasal impairment, monosensitized (Cluster 2) or polysensitized (Cluster 3) - Cluster 4 (13%): polysensitized participants with high levels of nasal and ocular symptoms, and nasal impairment - Clusters 5 (16%) and 6 (14%): high level of nasal, bronchial and ocular symptoms with nasal impairment (non-allergic or polysensitized, respectively)
Ciprandi *et al.* 2019 (116)	724 patients suffering from AR, Navy soldiers, United States of America	Ascending HCA	- Gender - Age - Disease duration - Smoking - FVC - FEV_1 - FEV_1/FVC ratio - FEF_{25-75} - FeNO - VAS - MCH PD20 - BHR - Sensitization to dermatophagoides, cat, dog, gramineae, parietaria, olea, alder, hazel, betulaceae, compositae, cypress, alternaria, cladosporium, aspergillus	5 endotypes clusters: - Cluster 1 (52.9%): frequent sensitization to Dermatophagoides - Cluster 2 (14.8%): short disease duration, almost all non-smokers, normal FEF_{25-75} values, low FeNO levels, almost no BHR and are sensitized to perennial allergens - Cluster 3 (13.1%): longer disease duration and a high frequency of sensitization to pollens - Cluster 4 (16.9%): frequent sensitization to Grass pollens - Cluster 5 (2.1%): the longest disease duration, generally smokers, low FEF_{25-75} levels, BHR and high FeNO levels; patients frequently sensitized to moulds
Meng *et al.* 2019 (117)	259 patients with chronic rhinitis and 20 control, China	HCA with Euclidean similarity and Ward minimum-variance linkage	- Age - Gender - Asthma history - FeNO - Serum IgE - local nasal IgE - Local eosinophils - Nasal obstruction score - Rhinorrhea score	6 endotypes clusters: - Cluster 1 (38.6%): AR without asthma - Cluster 2 (13.5%): AR with asthma - Cluster 3 (18.6%): NARES without asthma - Cluster 4 (4.6%): Local AR - Cluster 5 (5.0%): NARES

Author	Population	Method	Variables	Results
			- Nasal itching score - Sneezing score - VAS	with asthma - Cluster 6 (19.7%): Idiopathic rhinitis
Yavuz *et al.* 2021 (118)	510 children with physician-diagnosed AR, Turkey	LCA	- Allergic conjunctivitis - Eczema - Asthma - Family history of asthma - Family history of AR - SPTs to 8 common allergens - Tonsillectomy - Adenoidectomy	4 phenotypes clusters: - Cluster 1 (70.8%): AR with grass mono-sensitization and conjunctivitis - Cluster 2 (14.7%): AR with house dust mite sensitization and asthma - Cluster 3 (6.9%): AR with pet and grass polysensitization and conjunctivitis - Cluster 4 (7.6%): AR among children with tonsils and adenoids removed

AD: Atopic Dermatitis, AR: Allergic Rhinitis, BDR: Bronchodilator Reversibility, BHR: Bronchial Hyperresponsiveness, BMI: Body Mass Index, FEF_{25-75}: Forced Expiratory Flow at 25% to 75%, FeNO: Fraction of exhaled Nitric Oxide, FEV_1: Forced Expiratory Volume in the first second, FVC: Forced Vital Capacity, HCA: Hierarchical Clustering Analysis, IgE: Immunoglobulin E, LCA: Latent Class Analysis, MCH PD20: provocative dose of methacholine that results in a 20% fall in FEV_1, NARES: Non-Allergic Rhinitis with Eosinophilia Syndrom, OTC: Over The Counter Medicine, SES: Socioeconomic Status, SPT: Skin Prick Test, TNSS4: Total Symptom Score 4, VAS: Visual Analogue Scale

A better characterisation of rhinitis allows a better identification of its risk factors and a better understanding of its etiology.

1.1.2.3. Risk and protective factors of rhinitis

In this section only the main factors and those for which the level of evidence is highest will be presented. These factors can be grouped into several categories: non-modifiable individual factors, factors related to early childhood exposure, social factors, occupational exposures and environmental factors.

1.1.2.3.1. Individual non-modifiable factors

Various genes have been found to be related to rhinitis, some involved in the development of allergic diseases, and others common to AR and NAR (31). The strongest risk factor for developing AR is the presence of first-degree family members with AR, and the heritability of AR has been estimated to be from 35% to 80% across studies, highlighting the role of genetic factors (33,119).
The relationship between **sex** and AR is complex. AR seems to be more frequent among boys than girls in childhood, then more frequent among women than men in adolescence. In adulthood, according to the reviews, AR was reported to be more frequent among women than men or no differences between women and men were

found (21,120). NAR seems to be more frequent among women than men, and an interaction between sex, age, and rhinitis was observed (20,21). Overall, the results could be partly explained by sex-differences such as hormones, and also by gender-differences such as lifestyles (120).
As mentioned above, AR is more likely to start in childhood, whereas NAR is more likely to start at a later age of onset. **Age** may be a susceptibility factor for the development of NAR. There is a sub-phenotype of NAR called "rhinitis of elderly" that occurrs in patients over the age of 65 and which is clinically characterised by a clear rhinorrhoea not associated with any specific trigger (121).

Although non-modifiable factors -especially genetic- play a major role in the risk of developing rhinitis -especially AR- the increase in the prevalence of rhinitis in the last decades cannot be explained by genetic factors. It is likely that early life and environmental risk factors have played a role.

1.1.2.3.2. Early life factors

Breastfeeding may have protective effects against the development of AR (122). Owning a cat in early childhood may also be a protective factor for the development of allergic sensitivity to it later in life, on the other hand no statistical association was found for keeping a dog or a horse (123). Overall, **early exposure to allergens** and the subsequent development of AR is still a subject to debate, with some studies showing a protective effect while others show a deleterious effect (33).
Early exposure to allergens can be linked to the **hygiene hypothesis** that assumes that a high level of hygiene in early childhood would increase the risk of developing allergies later in life (124). Exposure to infections, particularly early in life, helps to develop and adapt the immune system to the environment. A lack of exposure to infections would cause the immune system to malfunction later in life, leading to allergic diseases such as AR. However, there is some scepticism about the hygienist hypothesis in the scientific community because the underlying biological mechanisms remain unclear. Recently, this hypothesis was reinterpreted through the pathways of the **microbiome** whose diversity could be protective, but the causal links between microbiome diversity, environment and rhinitis are yet unknown and more studies are needed (123).

1.1.2.3.3. Social factors

Most studies show an association between high **SES** and rhinitis but this is not a consistent finding (33). SES is probably a proxy for various exposures such as number of siblings, viral infections, exposure to tobacco smoke, housing conditions and location, exposure to allergens, food factors and nutrition, including breastfeeding and general diet. The association between rhinitis and SES could also be partly explained by the hygienic/microbiome diversity hypothesis (125).

1.1.2.3.4. Occupational exposures

Various occupational exposures can lead to the subsequent development of AR or NAR, which is called **occupational rhinitis** (126). AR and NAR can occur in individual exposed to irritants and AR can also occurs in individual exposed to allergens/sensitizers.

1.1.2.3.5. Environmental factors

1.1.2.3.5.1. Indoor

The association between **tobacco** and rhinitis is unclear: some reviews have highlighted a deleterious effect of tobacco on rhinitis (127) while others have not (33).
A recent systematic review provided an overview of the literature published from 2006 to 2017 on the associations between indoor **mould exposure** and rhinitis, with sufficient evidence of an association with AR (128). Additional evidence is needed from longitudinal studies, especially population-based studies.

1.1.2.3.5.2. Outdoor

The prevalence of rhinitis varies by **geography** (62). Several hypotheses have been proposed to explain this disparity. Regarding seasonal allergens, **allergenic plant species** may tend to grow in certain geographical areas and pollen concentrations of various species depend on the climatic conditions of the region (33). There is also a possible relationship between rhinitis and **urban area** although this is inconsistent (123,127). Urban dwellers may be involved in more indoor activities, which may increase their exposure to dust and mites and thus their sensitisation to these perennial allergens, and there could also be relationships between urbanity with SES, and the hygienic/microbiome hypothesis (33). Another hypothesis is that urban areas are more exposed to air pollution. In parallel with the increase in the prevalence of rhinitis, exposure to **air pollution** has evolved as the population has become more urbanised. It is clearly established that air pollution has adverse effects on health and it is the first ranking environmental risk factor for mortality (129). Since the nose is the first place that air pollution passes through, it is logical to think that air pollution is a risk factor of rhinitis. However, the literature on the association between long term exposure to air pollution and rhinitis remains scarce.
The next section will provide an in-depth overview of this risk factor and what is currently known about its association with rhinitis.

1.2. AIR POLLUTION

In this section, the main air pollutants and the methods used in epidemiology to estimate their long-term exposure will be first outlined. Then, the main results found in the literature regarding the association between air pollution exposure and rhinitis will be described, with a specific focus on long-term exposure in adults. Finally, susceptibility factors and potential mechanisms of this association will be introduced.

1.2.1. Definitions and main air pollutants

1.2.1.1. Definitions and sources

Air pollution is characterised by the presence of gases and particles in the air that have adverse effects on human health in terms of both mortality and morbidity, and on the environment (130). Air pollutants are mainly the result of human activities such as agriculture, industry, transport or residential heating, but also of natural phenomena such as volcanic eruptions, forest fires, sea spray, or sand mists (131,132) (Figure 6).
Epidemiological evidence linking exposure to air pollutants and health has mainly focused on traffic related air pollutant (TRAP), ozone (O_3), and sulfur dioxides (SO_2). **TRAP** is a complex mixture of pollutants such as particulate matter (PM) or nitrogen oxide (NO_X), derived from vehicle exhausts, secondary pollutants formed in the atmosphere, and non-combustion emissions (e.g., brakes, road dust, tire wear). **PM** consists of mixture of solid and liquid particles of organic and inorganic substances suspended in the air. PM are classified according to their median cut-off aerodynamic diameter in micrometers. PM with a median cut-off aerodynamic diameter of 10 micrometers (PM_{10}) can penetrate up to the bronchioles, fine particles (median cut-off aerodynamic diameter of 2.5 micrometers, $PM_{2.5}$) can reach the gas exchange regions of the lung (alveolus) and ultrafine particles (<100 nanometers) may pass from the lungs to the blood stream and then reach other organs and organ systems (132). **Black carbon** (BC), also known as soot, is a major fraction of PM resulting from the incomplete combustion of fossil fuels and biomass (i.e. wood). The health impact of BC has been little studied but it is suggested that it is one of the most harmful compounds of PM (133). NO_X are gaseous compounds, among which **nitrogen dioxide** (NO_2) is the most studied as it has often been used as a traffic marker although it can have effects by itself. NO_2 is a pollutant emitted mainly from fossil fuel combustion especially heating and transport. O_3 and SO_2 are also gaseous components. O_3 is formed in the atmosphere by a cycle of photo-chemical reactions in the presence of sunlight and of precursor pollutants, such as the NO_X or Volatile Organic Compounds (VOCs), subsequently O_3 can reform NO_2. SO_2 is emitted when fuels containing sulphur are combusted and are mainly emitted by industrial activity or home heating with coal.

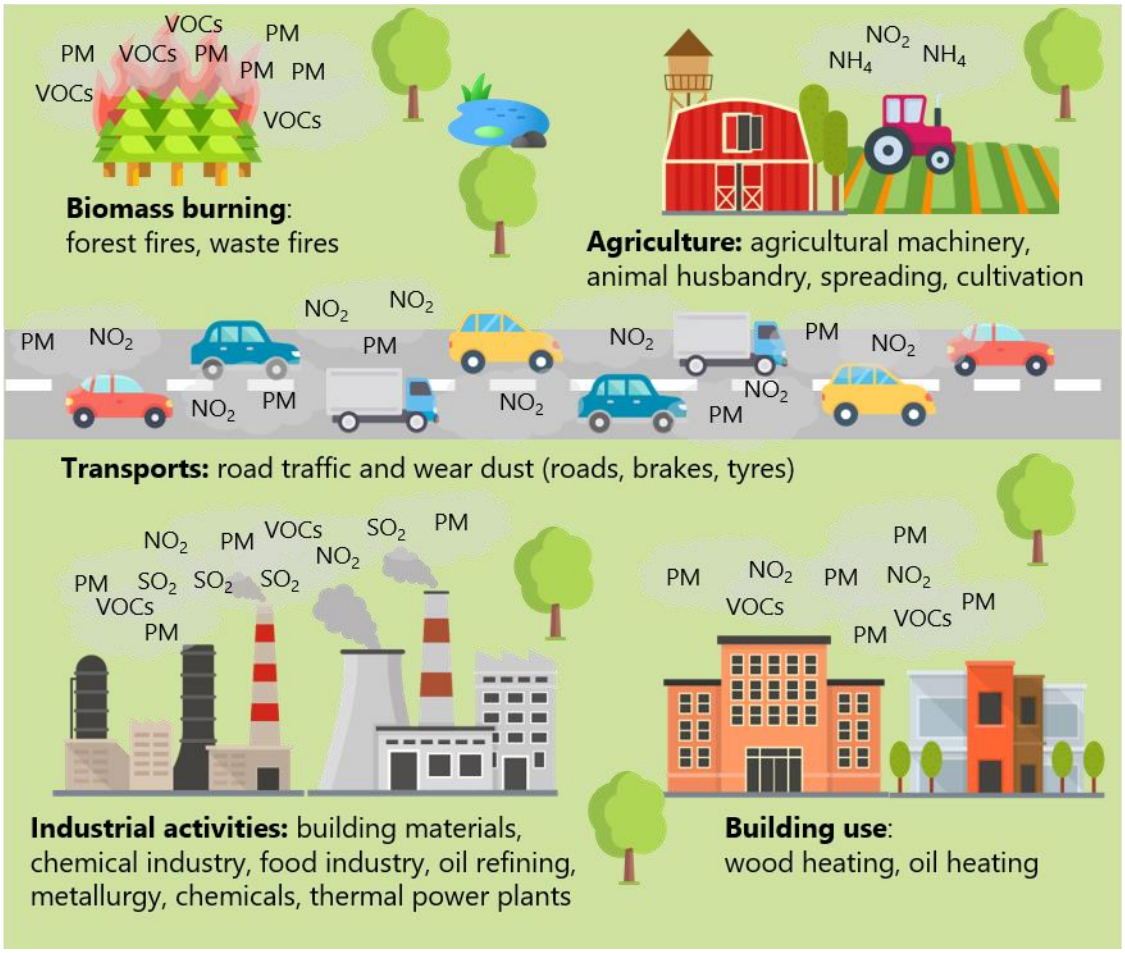


Figure 6: The main sources of air pollutants

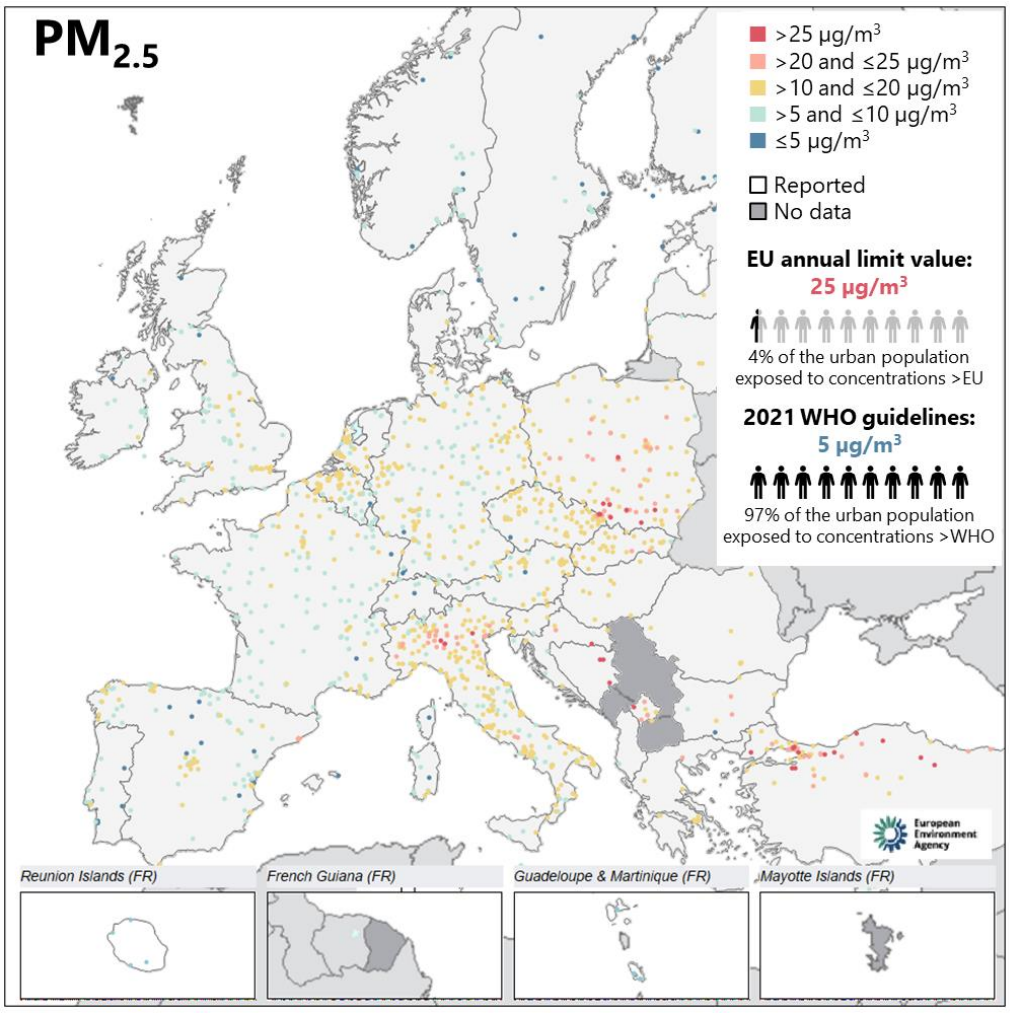
PM: Particulate Matter, NH_4; ammoniac, NO_2: Nitrogen Dioxide, SO_2: Sulphur Dioxide VOC: Volatile Organic Compound, Icons: flaticon.com

Due to the adverse effects of air pollution, the WHO provides a set of guideline levels for specific air pollutants to protect the health of citizens. For over 15 years, the air quality guidelines (AQG) used were those of 2005. In 2021, the WHO provided new AQG given the evidence of health-harmful effects of air pollution even at low concentrations (134). These guidelines values do not imply any regulatory constraints. In European Union (EU) the concentrations of pollutants are monitored and there are legal standards set by the European Commission. The EU legal standards are much higher than the WHO AQG (Table 5). Thus, in 2019, although only 4% of the EU urban population was exposed to concentrations of $PM_{2.5}$ and NO_2 above the EU legal standards, more than 90% was exposed to concentrations of $PM_{2.5}$ and NO_2 above the 2021 WHO AQG (135) (Figure 7). In october 2022, the European Commission published proposals for new air quality standards for deployment in 2030, although these limits are more restrictive than the previous ones, they are not aligned with the 2021 WHO AQG (136).

Table 5: Recommended WHO 2005 and 2021 Air Quality Guidelines (AQG) and European Union (EU) legal standards for air pollutants

Pollutant	Averaging time	2005 WHO AQG	2021 WHO AQG	Current EU legal standards	EU 2030 proposal
$PM_{2.5}$, µg/m^3	24h-hour	25[a]	15[a]	-	25
	Annual	10	5	25	10
PM_{10}, µg/m^3	24h-hour	50[a]	45[a]	50[b]	45[c]
	Annual	20	15	40	20
O_3, µg/m^3	8-hour	100[a]	100[a]	120[e]	120[f]
	Peak season	-	60[d]	-	-
NO_2, µg/m^3	24-hour	-	25[a]	-	50[c]
	Annual	40	10	40	20
SO_2, µg/m^3	24-hour	20[a]	40[a]	125[g]	50
	Annual	-	-	-	20
CO, mg/m^3	24-hour	-	4	-	4

[a] 99th percentile (i.e. 3-4 exceedance days per year), [b] as a daily average not to be exceeded > 35 days per year, [c] as a daily average not to be exceeded > 18 days per year, [d] Average of daily maximum 8-hour mean O_3 concentration in the 6 consecutive months with the highest 6-month running-average O_3 concentration, [e] Average of daily maximum 8-hour mean O_3 concentration not to be exceeded > 25 days over 3 years, [f] Average of daily maximum 8-hour mean O_3 concentration not to be exceeded > 18 days over 3 years, [g] as a daily average not to be exceeded > 3 days per year



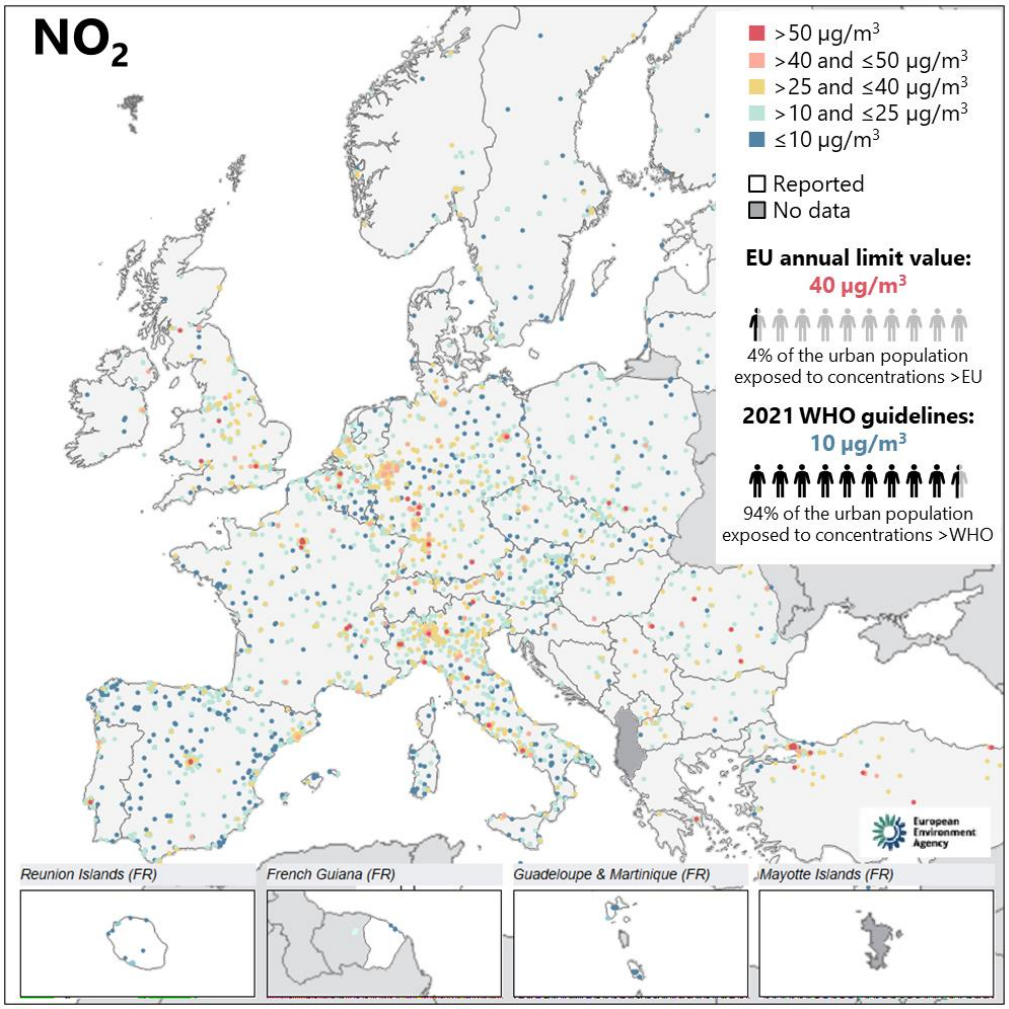


Figure 7: Concentrations of $PM_{2.5}$ and NO_2 in 2019 in relation to the EU annual limit values and the 2021 WHO air quality guidelines

Based on data from the European Environment Agency (135)

1.2.1.2. Air pollution exposure assessment in epidemiology

The WHO guideline values are notably based on the level of evidence provided by epidemiological studies and one of the challenges of epidemiological studies is exposure estimation. The short-term exposure is mainly estimated using daily or weekly variations at fixed monitoring stations, assuming those variations are similar for all those living in a determined geographical area. The estimation of long-term exposure is more challenging as spatial variability on long term averages, such as yearly or even life-time scales, is very important. The methods for assessing long term exposure to air pollution in epidemiology are diverse and have evolved over time (137).

One of the first methods to assess long-term exposure was the use of **air quality monitoring stations**. Air pollution is routinely measured by station and then the average measurements over the wanted time lapse from the station closest to the participant's place of residence are assigned to the participant. Even if nowadays, there are many air quality monitoring stations that continuously measure exposure levels to

major pollutants in cities from developed countries, the precision of the estimate is too rough. Indeed, the exposure is assessed in an ecological way and is the same for all participants living in the surroundings of the station, and the number of stations is never enough to capture the spatial variability on a fine scale. Moreover, these stations are less present in rural areas and in less developed countries.
Another method to directly measure exposure to air pollution is to provide each participant with **personal monitors**. This method allows the mobility of participants to be considered if the monitors are portable. However, portable personal monitors are usually less accurate than air quality monitoring stations and have significant variability in measurements. In addition, they have a high cost and require complex logistics which makes them usable only in small populations for short times.
To overcome some of the limitations of these exposure assessments, **exposure modelling** based on Geographic information systems (GIS) has been developing for the past decades. GIS are a set of techniques and data that can be used to build exposure maps. The objective is to generate estimates of exposure to air pollutants at sites other than the monitoring stations based on statistical models. The maps of estimated exposure to the different pollutants are then linked to the location of the participants, providing an estimate of individual exposure for each participant. Numerous GIS-based models are used. GIS-based interpolation modelling, GIS-based dispersion modelling or GIS-based regression modelling are the most commonly used in epidemiology (138). For the interpolation models, kriging is the most used technique: measurements of pollutants are obtained at a set of monitoring stations and the model exploits spatial dependence in the data to develop continuous surface of air pollution. The dispersion model is based on deterministic modelling i.e. on the empirical data of the chemical, physical, and biological mechanisms; it uses data on pollution, emissions, meteorological conditions and topography to model air pollutant concentrations. As its name suggests, regression-based modelling uses a regression model to estimate the concentration of pollutants. In particular, **Land Use Regression** (LUR) models uses measured pollution concentrations at a given location as the response variable and land use types (park, water, industrial...), the distance from road traffic, altitude from the sea and/or population density, as predictors of the measured concentrations.

1.2.2. Air pollution and rhinitis

It is now established that air pollution has adverse effects on almost every systems and organs, the respiratory tract being among the first and most studied ones (130). Scientific societies have given statements on the effects of air pollution on asthma and chronic obstructive pulmonary disease (COPD) (139,140). In a recent systematic review and meta-analysis conducted by the Health Effects Institute, the overall confidence in the evidence for an association of the long-term exposure to TRAP was moderate to high for asthma onset in children and adults, and moderate for asthma ever and active asthma in children (141). For COPD, the confidence was low in part due to the small

number of qualifying studies (141). However, rhinitis has received much less attention and there is currently no report from a scientific society on the effects of air pollution on rhinitis.

Throughout my thesis I conducted and updated a literature review on the short- and long-term effects of air pollution on prevalence and incidence of rhinitis.

On June 14th, 2022, **eight literature reviews and meta-analyses** have been identified and are presented in Table 6. Six of the eight reviews were published in the last two years, reflecting the growing interest in the subject. Four reviews considered both child and adult populations and four considered paediatric populations only. Out of the four reviews considering both children and adults, only one conducted analyses in adult and children subpopulations separately and reported meta-ORs for $PM_{2.5}$ and AR risk that were significant in both populations with a higher meta-OR among adults (142). For the other three reviews, the authors pointed out that there were not enough studies in adults to do separate analyses (143–145). Among the paediatric populations, five of six reviews showed a significant effect of air pollution on AR, in particular $PM_{2.5}$, PM_{10}, and NO_2 were almost always associated with an increased risk of AR prevalence or incidence (142,145–148). The only meta-analysis showing no significant effect of $PM_{2.5}$ and NO_2 on AR risk was that conducted by Heinrich *et al.* using data from six birth cohorts (149). The meta-analysis by Wang *et al.* was the only one to present both long-term and short-term results (144): short-term exposure to PM_{10} and NO_2 showed a significant deleterious effect on AR, whereas no association was found with exposure to $PM_{2.5}$, SO_2, CO and O_3 (144); long-term exposure to $PM_{2.5}$ showed a significant deleterious effect on AR, whereas no association was found with exposure to PM_{10}, NO_2, SO_2, CO, and O_3 (144).
However, the results of the literature review should be interpreted with caution due to **methodological shortcomings**. As shown by Heinrich *et al.* in his letter to the editor (150), the review by Li *et al.* (143) conducted in 2022 did not present all the existing studies in the literature, mixed long-term and short-term effects and has methodological shortcomings for the meta-analysis of ORs. The meta-analysis conducted in 2022 by Jia *et al.* (142) also combined short-term and long-term effects and did not present all the existing studies in the literature. Although the review by Wang *et al.* (144) covered both short-term and long-term effects separately, some studies are missing. The meta-analysis conducted by Rosario *et al.* pooled estimates of differente pollutants to obtain a unique meta-OR (145). Furthermore, all the literature reviews so far did not study the associations between air pollutants and NAR.

Table 6: Summary of meta-analyses on the effect of air pollution on rhinitis

Author	Population	Included studies	Exposure	Outcome	n	Key-findings
Zou *et al.* 2018 (147)	Children (0-18 years)	Cross-sectional, cohort or case-control studies	$PM_{2.5}$, PM_{10}, NO_2, SO_2	AR	13	- Meta-OR $PM_{2.5}$: **1.17 (1.09-1.25)** - Meta-OR PM_{10}: **1.13 (1.06-1.19)** - Meta-OR NO_2: **1.14 (1.05-1.23)** - Meta-OR SO_2: **1.09 (1.01-1.16)**
Heinrich *et al.* 2019 (149)	Children	Birth cohort	$PM_{2.5}$ and NO_2	AR	6	- Meta-OR $PM_{2.5}$: 1.02 (0.72-1.43) - Meta-OR NO_2: 1.01 (0.85-1.19)
Zhang *et al.* 2021 (148)	Chinese children (0-18 years)	Cross-sectional, cohort or case-control studies	$PM_{2.5}$, PM_{10}, NO_2, SO_2 and O_3	AR	11	- Meta-OR $PM_{2.5}$: **1.15 (1.03-1.29)** - Meta-OR PM_{10}: **1.02 (1.01-1.03)** - Meta-OR NO_2: **1.11 (1.05-1.18)** - Meta-OR SO_2: **1.03 (1.01-1.05)** - Meta-OR O_3: 0.98 (0.67-1.41)
Rosario *et al.* 2021 (145)	Children and adults from Latin American countries	Cross-sectional and cohort studies	Air pollutants	AR	22 (12 in statistical analyses)	- Meta-OR: **1.43 (1.03-1.98)**
Lin *et al.* 2021 (146)	Children (0-18 years)	Cross-sectional, cohort or case-control studies	PM	AR	21	- Meta-OR $PM_{2.5}$: **1.09 (1.01-1.17)** - Meta-OR PM_{10}: **1.06 (1.02-1.11)**
Wang *et al.* 2022 (144)	Children and adults	Original studies reported effect estimates in human (no design restrictions)	$PM_{2.5}$, PM_{10}, NO_2, SO_2, CO and O_3	AR	31	Long-term: - Meta-RR $PM_{2.5}$: **1.06 (1.01-1.22)** - Meta-RR PM_{10}: 1.00 (0.99-1.02) - Meta-RR NO_2: 1.00 (0.99-1.01) - Meta-RR SO_2: 1.01 (0.99-1.03) - Meta-RR CO: 1.13 (0.89-1.42) - Meta-RR O_3: 1.00 (0.99-1.02) Short-term: - Meta-RR $PM_{2.5}$: 1.05 (0.99-1.11) - Meta-RR PM_{10}: **1.03 (1.01-1.05)** - Meta-RR NO_2: **1.02 (1.01-1.03)** - Meta-RR SO_2: **1.01 (1.00-1.02)** - Meta-RR CO: **1.00 (1.00-1.00)** - Meta-RR O_3: 1.01 (0.99-1.02)
Li *et al.* 2022 (143)	Children and adults	Cross-sectional, cohort or case-control studies	$PM_{2.5}$, PM_{10}, NO_2, SO_2, CO and O_3	AR	35	- Meta-OR $PM_{2.5}$: **1.12 (1.05-1.20)** - Meta-OR PM_{10}: **1.13 (1.04-1.22)** - Meta-OR NO_2: **1.13 (1.07-1.20)** - Meta-OR SO_2: **1.13 (1.01-1.12)** - Meta-OR CO: 1.07 (0.99-1.17) - Meta-OR O_3: **1.07 (1.01-1.12)**
Jia *et al.* 2022 (142)	Children and adults	Original studies in human (no design restrictions)	$PM_{2.5}$	AR	14	- Meta-OR $PM_{2.5}$: **1.14 (1.00-1.29)** - Meta-OR $PM_{2.5\ children}$: **1.08 (1.04-1.13)** - Meta-OR $PM_{2.5\ other\ ages}$: **1.50 (1.24-1.81)** - Meta-OR $PM_{2.5\ Asia}$: **1.20 (1.01-1.44)** - Meta-OR $PM_{2.5\ Out\text{-}Asia}$: 1.04 (0.82-1.31)

AR: Allergic Rhinitis, CO: Carbon monoxide, NO_2: Nitrogen dioxide, O_3: Ozone, OR: Odds Ratio, PM: Particulate Matter, $PM_{2.5}$: Particulate Matter ≤2.5 µm, PM_{10}: Particulate Matter ≤ 10 µm, RR: Risk Ratio, SO_2: Sulphur dioxide. OR data in bold means statistical significance.

Thus, I conducted a literature review including original articles on the short- and long-term effects of air pollution on rhinitis, AR or NAR prevalence or incidence in children and/or adult populations. Cross-sectional, case-control, cohort, ecological or time series studies, as well as individual, semi-ecological or ecological air pollution measures were considered. Studies had to focus on an identified outdoor air pollutant or on a measure of road traffic intensity. Rhinitis could be defined based on diagnosis, register, or by questionnaire.

On June 14th, 2022, 115 original studies were identified, 24 on short-term effects and 91 on long-term effects, 74 studies were conducted in paediatric populations, 21 in adult populations, and 20 in mixed (adult and child) populations. In order to summarize the results, and in line with the subject of this thesis, in this section only the 17 long-term effect studies carried out in adult or mixed populations will be presented. Table 7 and Figure 8 summarise the results of studies that have investigated associations between air pollution and the prevalence or incidence of rhinitis in adults.

Most studies on the long-term effects of air pollution have focused on the **AR prevalence**. The associations varied across studies and air pollutants. On the basis of five studies on traffic intensity (70,151–154), seven of them showed no significant effect and five showed a deleterious effect on rhinitis prevalence. NO_2 and PM were the pollutants for which there were the most measurements of association, with discordant results between studies. Excluding our study in Constances -that will be presented later-, only one study had investigated the effects of BC (155). In this study, lifetime exposure was not significantly associated with AR prevalence but exposure in the year prior to study participation was significantly associated with AR (155). Furthermore, only two studies (70,152) had considered NAR and AR prevalences with discordant results. The study by Montnémery *et al.* showed that exposure to heavy traffic was only associated with non-allergic nasal symptoms (152), whereas the study by Lindgren *et al.* showed that traffic intensity was only related to AR and not to NAR prevalence (70).

Only two studies have investigated the effects of air pollution on **rhinitis incidence** in adults (156,157). Burte *et al.* did not find any significant associations between exposure to NO_2, PM_{10} or $PM_{2.5}$ and rhinitis incidence (156), whereas Fasola *et al.* showed a significant association with $PM_{2.5}$ but not PM_{10} (157).

In conclusion, there are numerous gaps in the current knowledge of the association between long-term exposure to air pollution and rhinitis in adults. There are few studies with rhinitis prevalence, only two has considered NAR and only one has considered BC. Regarding the incidence, only two studies exist and they show discordant results.

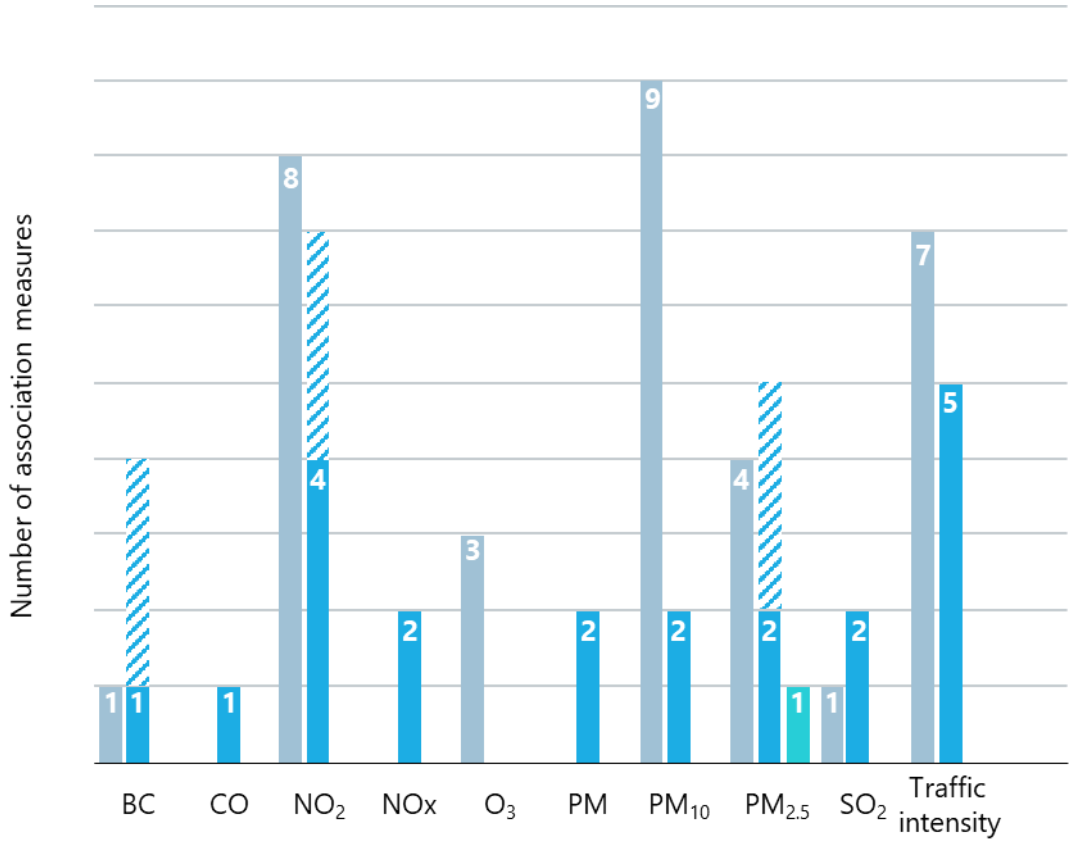


Figure 8: Summary of association measures between long-term exposure to air pollution and rhinitis in adults (from 17 studies)

No significant result *Deleterious effect* *Protective effect*

The striped filling corresponds to the results published in Constances (158)

Table 7: Main studies that have investigated the associations between long-term exposure to air pollution and the prevalence or incidence of rhinitis in adults

Author	Study design	Population	Exposure assessment	Outcome(s) Definition	Key findings
Wyler *et al.* 2000 (151)	Cross-sectional	820 adults (18-60 years) from the SAPALDIA study, in Basel, Switzerland	Traffic inventory at residential address	- Hay fever: "*Did you have hay fever this year or last year?*" - seasonal rhinitis or conjunctivitis symptoms: yes to "*When you are near trees, grass or flowers, or when there is a lot of pollen about, do you ever get a runny or stuffy nose or start to sneeze?*" or "*Do you ever get itchy or watering eyes?*"	Hay fever and seasonal rhinitis or conjunctivitis were not associated with motor vehicle traffic
de Marco *et al.* 2002 (159)	Cross-sectional (semi-ecological)	18,873 adults (20-44 years) from Italy	Annual mean of NO_2 at the closest monitoring station from the residential address	"*Do you have any nasal allergies, including hay fever?*"	NO_2 (per 18.3 µg/m^3 increase): OR 1.10 (0.95-1.27)
Montnémery *et al.* 2003 (152)	Cross-sectional	8,469 adults (20-59 years) living in the southern part of Sweden	Heavy traffic: "*Do you live close to a road with heavy traffic?*"	"*Recurrent or permanent nasal symptoms (including ''nasal discharge'', ''thick yellow nasal discharge'', ''a blocked nose'', and ''sneezing and itching'')*"	- Nasal symptoms: OR **1.3 (1.1-1.5)** - Only allergic nasal symptoms: OR non-significant - Only non-allergic nasal symptoms: **1.3 (1.1-1.6)**
Heinrich *et al.* 2005 (153)	Cross-sectional	7,124 adults (18-79 years) from East German Area	Traffic Intensity "*Is your home located at an extremely busy road, considerably busy side street, not busy side street, or on a street with no or very rare traffic?*" The first two and the last two categories were combined and so three categories representing low, moderate, and high traffic intensity were created	"*Do you currently have nasal allergy including hay fever?*"	- Moderate traffic exposure: OR 1.10 (0.84-1.44) - High traffic exposure: OR 1.16 (0.94-1.42)
Cesaroni *et al.* 2008 (154)	Cross-sectional	9,488 adults (25-59 years) from Rome, Italy	- Self-reported traffic intensity - Average PM exhaust emissions at each subject's census block of residence - NO_2 at residential address with LUR model	Self-report of ever rhinitis	- Self-reported traffic (high vs absent): OR **1.30 (1.05-1.62)** - Distance from high traffic roads (<50m vs >200m): OR 1.18 (0.96-1.44) - PM emissions (4th vs 1st): OR 1**.37 (1.14-1.64)** - NO_2 (50.3-62.6 µg/m^3 vs 21.0-37.3 µg/m^3): OR **1.30 (1.08-1.56)**
Bhattacharyya 2009 (160)	Cross-sectional (semi-ecological)	313,982 adults from the	CO, NO_2, SO_2 and PM from the EPA website	Had hay fever, past 12 months	Standardized β: - CO: **0.012 (pval <0.001)**

Author	Study design	Population	Exposure assessment	Outcome(s) Definition	Key findings
		National Health Interview Survey in United States			- NO_2: **0.013 (pval <0.001)** - SO_2: **0.012 (pval <0.001)** - PM: **0.016 (pval <0.001)**
Lindgren *et al.* 2009 (70)	Cross-sectional	9,319 adults (18-77 years) from Sweden	- Distance to roads with specified traffic intensity: the individual was assigned the road with the heaviest traffic intensity within a radius of 100 m from residence. - NO_X: annual mean concentration at residential address	- AR: Yes to "*Do you have nasal symptoms provoked or worsened by environmental factors? A) Tree-pollen b) grass-pollen c) Animals d) House-dust e) Mould*" NAR: No to "*Do you have nasal symptoms provoked or worsened by environmental factors? A) Tree-pollen b) grass-pollen c) Animals d) House-dust e) Mould*" and yes to "*f) damp and/or cold air g) dry air h) tobacco fumes i) strong-smelling scents j) spicy food k) red wine/alcoholic beverage l) drugs m) other food n) stress or discomfort o) printer ink p) other factors*"	AR: - Heavy traffic: OR **1.13 (1.01-1.26)** - Heaviest road radius <100m (no heavy road vs >10 cars/min): OR **1.30 (1.05-1.61)** - NO_X (0-8 µg/m^3 vs >19): OR **1.33 (1.13-1.57)** NAR: - Heavy traffic: OR 0.99 (0.83-1.18) - Heaviest road radius <100m (no heavy road vs >10 cars/min): OR 1.07 (0.73-1.56) - NO_X (0-8 µg/m^3 vs >19): OR **1.37 (1.03-1.81)**
Zhang *et al.* 2009 (161)	Cross-sectional (semi-ecological)	38,203 participants from 11 cities in China	NO_2, PM_{10}, and SO_2 from the National Bureau of Statistics of China	Problem with symptoms such as sneezing, or runny, blocked, or itchy nose within the last 12 months unrelated to suffering from an upper respiratory infection	SO_2 correlation coefficient: **r^2 = 0.614**, p = 0.04, no correlation with NO_2 and PM_{10}
Karakatsani *et al.* 2010 (162)	Cross-sectional (semi-ecological)	299 mail carriers in Athens, Greece	Mean annual concentration for NO_2, O_3 and PM_{10} at the closest monitoring station from the residential and employment addresses	Nasal catarrh or congestion without common cold or all the nasal problems accompanied by eye irritation and being in tears	- NO_2 (>44.1 µg/m^3 vs ≤44.1 µg/m^3): OR 1.28 (0.78-2.10) - O_3 (>48.94 µg/m^3 vs ≤48.94 µg/m^3): OR 1.44 (0.88-2.35) - PM_{10} (>39.35 µg/m^3 vs ≤39.35 µg/m^3): **1.67 (1.01-2.75)**
Pindus *et al.* 2016 (163)	Cross-sectional	905 adults (39-63 years) from Tartu in Estonia	Annual concentration of $PM_{2.5}$ and PM_{10} at residential address calculated using a dispersion model	Yes to "*Do you have any nasal allergies including hay fever?*" and "*Have you ever experienced nasal symptoms such as nasal congestion, rhinorrhoea (runny nose) and/or sneezing attacks without having a cold?*"	- PM_{10} (per 2.9 µg/m^3 increase): OR 1.09 (0.79-1.45) - $PM_{2.5}$ (per 3.8 µg/m^3 increase): OR 0.93 (0.67-1.30)
Burte *et al.* 2018 (156)	Longitudinal	1,533 adults from EGEA and ECRHS	Annual average concentration at residential address using LUR for NO_2, PM_{10} and $PM_{2.5}$	- Rhinitis incidence: "*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?*"	Rhinitis incidence: - NO_2 (per 10 µg/m^3 increase): IRR 1.00 (0.91-1.09) - PM_{10} (per 10 µg/m^3 increase): IRR 0.88 (0.72-1.08) - $PM_{2.5}$ (per 5 µg/m^3 increase):

Author	Study design	Population	Exposure assessment	Outcome(s) Definition	Key findings
				(not at inclusion and yes at follow-up) - AR: rhinitis + atopic sensitization - NAR: rhinitis + no atopic sensitization	IRR 0.87 (0.68-1.08) AR incidence: - NO_2 (per 10 µg/m^3 increase): IRR 0.95 (0.77-1.14) - PM_{10} (per 10 µg/m^3 increase): IRR 0.73 (0.42-1.15) - $PM_{2.5}$ (per 5 µg/m^3 increase): IRR **0.52 (0.29-0.87)** NAR incidence: - NO_2 (per 10 µg/m^3 increase): IRR 1.05 (0.95-1.15) - PM_{10} (per 10 µg/m^3 increase): IRR 0.90 (0.72-1.15) - $PM_{2.5}$ (per 5 µg/m^3 increase): IRR 0.93 (0.76-1.14)
Fasola *et al.* 2020 (157)	Longitudinal	305 adults from Pisa, Italy	PM_{10} and $PM_{2.5}$ at residential address through a Random Forest Machine Learning Approach	Reported hay fever or other conditions causing runny or blocked nose, apart from common colds (first survey) or if the subjects reported hay fever or problems with sneezing or a runny or blocked nose, apart from common colds (second survey)	- $PM_{2.5}$ (per 1 µg/m^3 increase): OR **2.25 (1.07-4.98)** - PM_{10} excluded by the stepwise selection procedure (non-significant result).
Hsieh *et al.* 2020 (164)	Cross-sectional (semi-ecological)	140,365 National Health Insurance of Taiwan cohort	Environmental monitoring stations in the neighbourhoods of the subjects' clinics/hospitals, annual mean concentration of O_3, SO_2, NO_2, PM_{10}, $PM_{2.5}$	ICD-9 CM codes	- O_3 8h (per 10 ppb increase): OR 1.00 (0.99-1.00) - SO_2 (per 10 ppb increase): OR 1.00 (0.99-1.00) - NO_2 (per 10 ppb increase): OR **1.08 (1.06-1.09)** - PM10 (per 10µg/m^3 increase): OR 1.00 (0.99-1.00)
Nordeide Kuiper *et al.* 2020 (155)	Cross-sectional	3,428 adults (18-40 years) from the RHINESSA study in Norway and Sweden	Annual average concentration at residential address using LUR for NO_2, $PM_{2.5}$, PM_{10}, O_3 and BC	"*Do you have any nasal allergies including rhinitis?*"	Lifetime: - NO_2 (per 10 µg/m^3 increase): OR 1.12 (0.98-1.27) - $PM_{2.5}$ (per 10 µg/m^3 increase): OR 1.18 (0.94-1.48) - PM_{10} (per 10 µg/m^3 increase): OR 1.21 (0.95-1.55) - BC (per 1 µg/m^3 increase): OR 1.32 (0.97-1.78) - O_3 (per 10 µg/m^3 increase): OR 1.09 (0.80-1.48) The last year before participation: - NO_2 (per 10 µg/m^3 increase): OR **1.25 (1.08-1.45)** - $PM_{2.5}$ (per 10 µg/m^3 increase): OR **1.35 (1.02-1.77)** - PM_{10} (per 10 µg/m^3 increase): OR **1.45 (1.08-1.94)** - BC (per 1 µg/m^3 increase): OR **1.50 (1.15-1.96)** - O_3 (per 10 µg/m^3 increase): OR 1.22 (0.95-1.57)

Author	Study design	Population	Exposure assessment	Outcome(s) Definition	Key findings
Wang *et al.* 2021 (165)	Cross-sectional (semi-ecological)	40,279 young parents in China	Annual PM_{10} and NO_2 on a city level	By questionnaire: allergies in the nose/eyes	- NO_2 (per 10 µg/m^3 increase): OR **1.17 (1.06-1.31)** - PM_{10} (per 10 µg/m^3 increase): OR 1.06 (0.96-1.17)
Savouré *et al.* 2021 (158)	Cross-sectional	127,108 adults (18-69 years) from the French Constances cohort	Annual average concentration at residential address using LUR for NO_2, $PM_{2.5}$, and BC	- Current rhinitis: "*In the past 12 months, have you had a problem with sneezing, or a runny, or blocked nose when you did not have a cold or the flu?*" - Current AR: current rhinitis + yes to "H*ave you ever had nasal allergies including hay fever*?" - Current NAR: current rhinitis + no to "*Have you ever had nasal allergies including hay fever?*"	Current rhinitis: - $PM_{2.5}$ (per 4.85 µg/m^3 increase): OR **1.13 (1.08-1.17)** - BC (per 0.88 10^{-5} m^{-1} increase): OR **1.12 (1.07-1.17)** - NO_2 (per 17.3 µg/m^3 increase): OR **1.11 (1.06-1.17)** Current AR: - $PM_{2.5}$ (per 4.85 µg/m^3 increase): OR **1.15 (1.09-1.21)** - BC (per 0.88 10^{-5} m^{-1} increase): OR **1.15 (1.09-1.21)** - NO_2 (per 17.3 µg/m^3 increase): OR **1.13 (1.06-1.16)** Current NAR: - $PM_{2.5}$ (per 4.85 µg/m^3 increase): OR **1.13 (1.10-1.17)** - BC (per 0.88 10^{-5} m^{-1} increase): OR **1.09 (1.04-1.14)** - NO_2 (per 17.3 µg/m^3 increase): OR **1.11 (1.06-1.16)**
Han *et al.* 2022 (166)	Cross-sectional (semi-ecological)	27,863 adults of the Korean National Health and Nutrition Examination Survey (KNHANES)	SO_2, NO_2, O_3 and PM_{10} concentrations of geographic districts were matched to each participant's residence	AR	PM_{10}: OR **1.15 (1.04-1.26)**

AR: Allergic Rhinitis, BC: Black Carbon, CO: Carbon monoxide, LUR: Land Use Regression, NAR: Non-Allergic Rhinitis, NO_X: Nitrogen oxide, NO_2: Nitrogen dioxide, O_3: Ozone, OR: Odd Ratio, $PM_{2.5}$: Particulate Matter ≤2.5 µm, PM_{10}: Particulate Matter ≤10 µm, RR: Risk Ratio, SO_2: Sulphur dioxide. OR data in bold means statistical significance.

1.2.3. Susceptibility factors

Specific populations may be more susceptible to the effects of air pollution on rhinitis. There are not enough studies that have investigated susceptibility factors in the association between air pollution and rhinitis. This section therefore discusses the main potential susceptibility factors based on what is known about air pollution on general health and asthma (167).

Extreme ages i.e. young children and the elderly, appear to be more sensitive to the effects of air pollution (168).

Women may be more sensitive to air pollution than men (168). Women have slightly higher airway reactivity than men, as well as smaller airways. Therefore, dose-response relationships may be more easily detected in women than in men. Particle deposition also varies by sex, with more pulmonary deposition in women.

The link between pollution and **smoking** has been debated for many years. Air pollution and tobacco may share similar underlying biological mechanisms and tobacco smoke may increase the toxicity of key air pollutants (169).

The literature on the relationship between **SES** and pollution is inconclusive (168). In the French context, the association with social level is city-specific: in Paris, the higher social categories are exposed to a higher average level of NO_2, whereas in Marseille and Lille the opposite is observed (170).

Pollutant emissions come mainly from road transport, industry, urbanisation and agriculture, which also depend on **geography**. **Pollens** and air pollution could interact with each other. Depending on the plant species and the type of pollutant and its concentration, this interaction could alter the properties of pollen grains. Air pollutants could potentiate the allergenicity of pollens, increase the bioavailability of pollen allergens and facilitate the penetration of pollens into the respiratory system (171).

1.2.4. Underlying mechanisms

A key factor to consider when discussing the causality of associations observed in epidemiological studies is the biological plausibility (172).

Three major underlying biological pathways have been proposed to support the associations between long-term exposure to air pollution and rhinitis: **inflammation**, **oxidative stress**, and **allergy**. These pathways interact with each other, and can be local, by acting specifically on the nasal epithelium, and/or systemic. The inflammatory effect of air pollutants can be neutrophilic or eosinophilic (173,174). Inflammation can lead to an increase in the permeability of the nasal epithelial barrier leading to an easier access of allergens to the immune system (175). PM, BC and NO_2 can induce the production of reactive oxygen and nitrogen species in the airway epithelium and the activation of macrophages, which can subsequently maintain the inflammatory effect and increase/activate the immune response (176–179). Finally, regarding AR, air pollutants, in particular diesel particles, could act as adjuvant in synergy with allergens to increase the allergic response which can subsequently induce inflammation (178,180,181).

To date, the biological pathways involved in the association between air pollution and rhinitis have been poorly investigated, and due to the lack of epidemiological studies, there is no clear conclusion on causality in the association between air pollution exposure and rhinitis.

1.3. SCIENTIFIC QUESTIONS

In summary, rhinitis is one of the most common medical conditions. Nevertheless, a significant number of patients do not consult a doctor because they believe that their symptoms are mild or insignificant despite their negative impact on social life, school, or work. Many patients still do not achieve sufficient control of their symptoms and the costs to society are significant, particularly due to the impact of rhinitis symptoms on work productivity. Despite the public health importance of rhinitis, there are still many gaps in current knowledge, particularly in epidemiology. The questions concerning rhinitis in epidemiological studies are standardised, but there is currently no consensus on the choice of questions to be used to define rhinitis, and the prevalences of rhinitis are therefore difficult to compare between studies. Furthermore, most studies to date have focused on AR, and there is very little data on NAR. Beyond the prevalence, the characteristics of AR and NAR have been little studied in the general population. Moreover, while the combination of rhinitis with asthma and/or conjunctivitis could constitute different phenotypes from rhinitis alone, no population-based study in adults had investigated the rhinitis characteristics in relation to its multimorbities. In population-based study, there is currently a lack of data on the severity and the duration of rhinitis. As the candidate approach may have some subjectivity in choosing which classifications to consider, an unsupervised approach may be complementary to it, but to date very few studies have used it to identify phenotypes or endotypes of rhinitis in the general population.
The increasing prevalence of rhinitis raises questions about the effects of environmental factors such as air pollution. However, there is limited knowledge on the link between long-term exposure to air pollution and rhinitis in adults: very little consideration was given to NAR and only one study has considered BC exposure despite the growing body of literature showing its harmful effect.

1.4. HYPOTHESES

The following research hypotheses have been identified:

- A questionnaire definition is a good proxy for AR and NAR in the absence of biological measures.
- In the general population, the clinical characteristics of AR and NAR are found but more cases of mild rhinitis are identified.
- The characteristics of rhinitis differ for participants with and without asthma.
- The ARIA classification of rhinitis is relevant in the general population and including asthma status in the classification provides additional information.

- An unsupervised approach based on questionnaire data identifies different rhinitis phenotypes.
- An unsupervised approach based on questionnaire and biological data identifies different rhinitis endotypes.
- Air pollution is associated with an increased risk of rhinitis.
- The association between air pollution and rhinitis is not the same depending on whether asthma status is taken into account.

2. OBJECTIVES

The overarching objective of this thesis was to study, in adults, the characteristics of rhinitis and its phenotypes and their associations with long-term exposure to air pollution.

The first objective was devoted to the identification and description of rhinitis, its phenotypes and endotypes. For this purpose, two different and complementary approaches were used.

1) A candidate approach based on *a priori* hypotheses derived from current knowledge of rhinitis.
2) An unsupervised approach without *a priori* hypothesis based on clustering algorithms to identify rhinitis.

The second objective was to investigate associations between long-term exposure to air pollution (in particular: $PM_{2.5}$, BC, and NO_2) and rhinitis phenotypes.

3. OVERALL MATERIALS AND METHODS

3.1. STUDY POPULATIONS

To address the objectives, data from two French studies were used: the EGEA case-control study on asthma and the Constances population-based cohort.

3.1.1. EGEA

3.1.1.1. Study design

The Epidemiological study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy (EGEA) is a cohort study based on an initial group of asthma cases recruited in chest clinics from five French cities (1991-1995) along with their first-degree relatives, and a group of controls. Briefly, 2,047 children (<16 years) and adult participants were enrolled at baseline, including 348 participants with current asthma from chest clinics, their 1,244 first-degree relatives, and 415 population-based controls. The protocol and descriptive characteristics of the EGEA study have been previously published in detail (182,183).
A 12-year follow-up of the initial cohort was conducted between 2003 and 2007 (EGEA2). Among the alive cohort (n = 2,002), 92% (n = 1,845) completed a short-self-administered questionnaire, and among them 1,601 (n = 1,571 adults aged ≥16 years) had a complete examination. As a follow-up study of EGEA2, the third survey (EGEA3, 2011-2013, n = 1,558) was conducted using self-completed questionnaire only. An additional follow-up (EGEA 4) is ongoing.

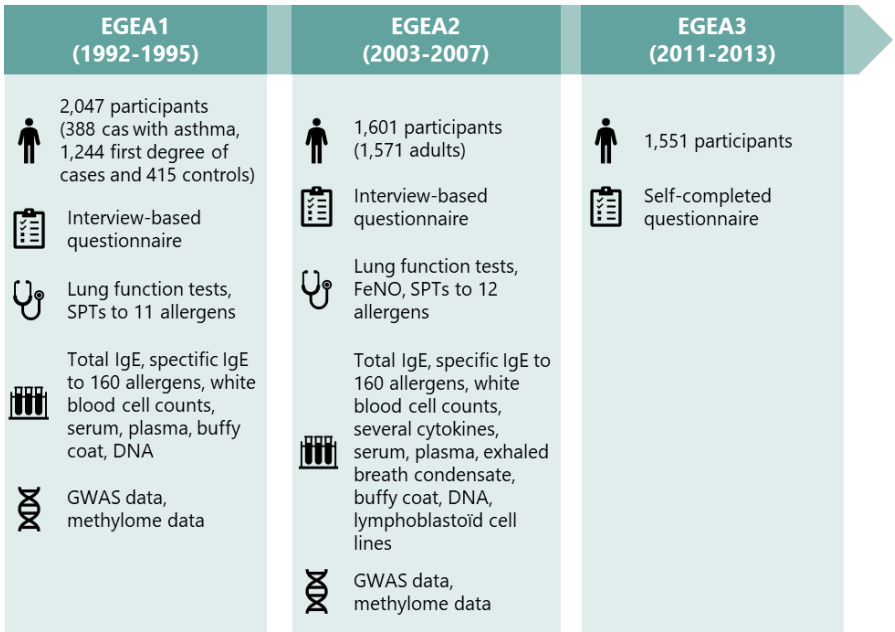


Figure 9: EGEA timeline adapted from Nadif *et al.* 2017 (184)

DNA: Deoxyribonucleic Acid, FeNO: Fraction Exhaled Nitric Oxide, GWAS: Genome-Wide Association Studies, IgE: Immunoglobulin E, SPTs: Skin Prick Tests

The analyses of this thesis were performed using data from adults at EGEA2.

3.1.1.2. Variables of interest at EGEA2

3.1.1.2.1. Definitions and characterisation of rhinitis

The definitions of rhinitis were based on the questions from the detailed questionnaire on respiratory health that were previously used and validated in epidemiological studies (91,183,185).

Current rhinitis was defined by a positive response to: "*Have you had problems with sneezing, runny nose or stuffy nose when you didn't have a cold or a flu in the last 12 months?*".
Among the participants with current rhinitis, participants who responded positively to "*Have you ever had allergic rhinitis?*" or "*Have you ever had hay fever?*" were classified as **AR** otherwise as **NAR**.

Age of onset of rhinitis: reporting of ever rhinitis and age reported to "*How old were you the first time?*".

Triggers were considered as dichotomous variables (yes/no) depending on whether the participant reported the trigger at the question "*In the last 12 months, what factors have triggered or increased these nose problems?*" *a. Dust mites or house dust, or b. Pollens, or c. Animals, or d. Other*.

Reported months of rhinitis symptoms were considered as dichotomous variables (yes/no) depending on whether the participant reported for each month "*During which of the last 12 months did you have these nose problems?*". The months were also categorized into seasons: winter symptoms if the participant reported symptoms in December or January or February; spring symptoms if the participant reported symptoms in March or April or May; summer symptoms if the participant reported having symptoms in June or July or August; and autumn symptoms if the participant reported symptoms in September or October or November.

Duration of rhinitis was defined into three classes (less than one month per year/more than one month per year and less than 4 days per week/more than one month per year and more than 4 days per week) following the answer to the question "*In the last 12 months, how often on average did you have nose problems?*".

Disturbance due to nasal symptoms was defined into four class (no/low/medium/high) following the answer to the question "*In the last 12 months, have these nose problems interfered with your daily activities?*".

Rhinorrhea, sneezing and eye symptoms after a stimulus correspond to having checked "runny nose", "sneezing" or "itchy or watery eyes" at least once in one of the following situations: smoky room, cold air contact, heavy physical effort, hay/cut flowers, animals, dust, occupational exposure, air pollution, weather, emotion, wine/alcohol, aspirin, other.

3.1.1.2.2. Multimorbidities of rhinitis

Ever nasal allergies: yes to "*Have you ever had allergic rhinitis?*" or yes to "*Have you ever had hay fever?*"

Ever asthma: yes to: "*Have you ever had attacks of breathlessness at rest with wheezing?"* or yes to "*Have you ever had asthma attacks?"* or if the participants were recruited as asthmatic cases at the first survey (183).

Ever conjunctivitis: yes to *"During your lifetime, have you ever had allergic conjunctivitis?"*

Ever eczema: yes to *"During your lifetime, have you ever had eczema?"*

3.1.1.2.3. Socio-demographic variables

Tobacco status was evaluated into three categories: never smoker, ex-smoker and current smoker.

Educational level was evaluated into three categories: less than high school, high school or university.

3.1.1.2.4. Biological variables

SPTs to 12 aeroallergens (indoor: cat, *Dermatophagoides pteronyssinus*, *Blattela germanica*; outdoor: olive, birch, *Parieteria judaica*, timothy grass, and ragweed pollen; moulds: *Aspergillus*, *Cladosporium herbarum*, *Alternaria tenuis*, Cupressus) were performed.
The EGEA2 biological collection include deoxyribonucleic acid (DNA), ribonucleic acid (RNA), lymphoblastoid cell lines, serum, plasma, erythrocytes, exhaled breath condensate as well as exhaled fraction of nitric oxide (FeNO). All sampling and storage processes of EGEA biobank were standardised (184). For the analyses included in this thesis, the **biological markers** measured in serum, plasma, erythrocytes, or in exhaled breath condensate (EBC) and FeNO were considered. These biomarkers correspond to biological pathways of allergy, inflammation or oxidative/nitrosative stress (Table 8).

Table 8: Biomarkers available at EGEA2

Biological pathway	Biomarkers	Biological compartment	n*
Allergy	Total Immunoglobulin E (IgE)	Serum	1,422
	Interleukin (IL)-1 receptor antagonist (RA)	Serum	828
	IL-5	Serum	828
	IL-7	Serum	828
	IL-8	Serum	828
	IL-10	Serum	828
	IL-13	Serum	828
Inflammation	Eosinophils	Blood	1,419
	Neutrophils	Blood	1,419
	Fraction Exhaled Nitric Oxide (FeNO)	Breath	722
	Eosinophil Cationic Protein (ECP)	Plasma	1,027
	Eosinophil Derived Neurotoxin (EDN)	Plasma	1,041
	C-reactive protein (CRP)	Serum	1,275
	Clara Cell protein-16 (CC-16)	Serum	1,298
	Tumour Necrosis Factor alpha (TNF-α)	Serum	828
	Thymus and Activation-Regulated chemokine (TARC)	Plasma	1,060
	Thymic Stromal Lymphopoietin (TLSP)	Plasma	1,060
	Leptin	Serum	828
Oxidative/Nitrosative stress	Nitrite/nitrate (NO_2/NO_3) levels	Plasma	1,192
	NO_2/NO_3	EBC	976
	Fluorescent oxidation products (FIOPs)	Plasma	1,327
	8-isoprostanes (8-iso)	EBC	696
	Superoxide dismutase (SOD)	Erythrocyte	1,380
	Glutathione peroxidase (GPX)	Erythrocyte	1,381
	Catalase	Erythrocyte	1,371

**n among 1,601 participants*

The differences in the number of biomarkers measurements are explained either by the avaibility of the analyser (FeNO), or by the quality criteria (blood versus EBC), or by the involment in specific project (IL).

3.1.2. Constances

3.1.2.1. Study design

Constances is a population-based cohort of almost 220,000 adults aged 18 to 69 years at inclusion, randomly selected from social security affiliates in France (https://www.constances.fr) (186–188). The participants were enrolled from 2012 to 2020 in 20 administrative districts ("departments") covered by one of the 24 Health Screening Centre (HSC) participating in Constances (Table 9, Figure 10).

Table 9: The 24 Health Screening Centres (HSCs) participating in Constances and corresponding departments

HSC	Departments	Year of addition in Constances
Angouleme	Charente	2012
Auxerre	Yonne	2017
Bordeaux	Gironde	2012
Caen	Calvados	2016
Colmar, Mulhouse (2 centres)	Haut-Rhin	2017
Le Mans	Sarthe	2016
Lille	Nord	2012
Lyon	Rhône	2012
Marseille	Bouches-du-Rhône	2012
Nancy, Longwy (2 centres)	Meurthe-et-Moselle	2012
Nimes	Gard	2012
Orleans	Loiret	2012
Paris (3 centres)	Paris	2012
Pau	Pyrénées-Atlantiques	2012
Poitiers	Vienne	2012
Rennes	Ille-et-Vilaine	2012
Saint-Brieuc	Côtes-d'Armor	2012
Saint-Nazaire	Loire-Atlantique	2012
Toulouse	Haute-Garonne	2012
Tours	Indre-et-Loire	2012

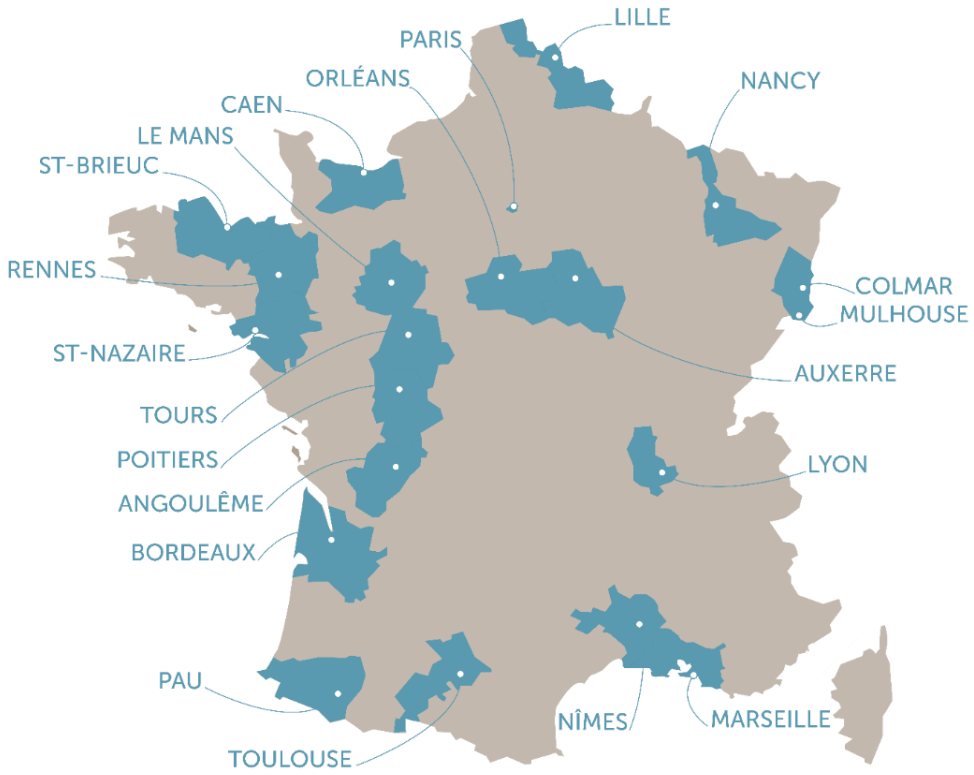


Figure 10: The 20 administrative districts and the cities where the participating Health Screening Centres were located

Three health screening centres were located in Paris.

The target population corresponds to individuals aged 18 to 69, affiliated to the general health insurance fund and residing in a department covered by a HSC participating in Constances. Participants considered as eligible due to their age and place of residence were drawn randomly by stratified sampling with unequal probabilities, and the size of the samples drawn differ each year. Random sampling was performed by the French national Old-Age insurance fund (Cnav) from the French national inter-scheme registry of health insurance beneficiaries, linked to the National careers management system.

At inclusion, each participant completed standardized questionnaires on occupational exposures, lifestyle and health including a detailed one on respiratory health, and had a complete medical examination.

An annual follow-up is done through a postal or on-line self-questionnaire. This annual follow-up focuses on different research topic each year. All participants recruited until the end of 2013 have received the 2014 annual follow-up questionnaire that includes two pages of detailed, validated, and standardized questions on rhinitis based on those of the ECRHS and the EGEA study (Appendix 2).

Every four years, a follow-up consisting of questionnaires and a complete medical eximation at one of the HSCs is carried out.

The questionnaires at inclusion and at four-year follow-up both have the same general questions on rhinitis. The 2014 follow-up questionnaire presents in addition to these questions detailed questions on rhinitis symptoms (Figure 11).

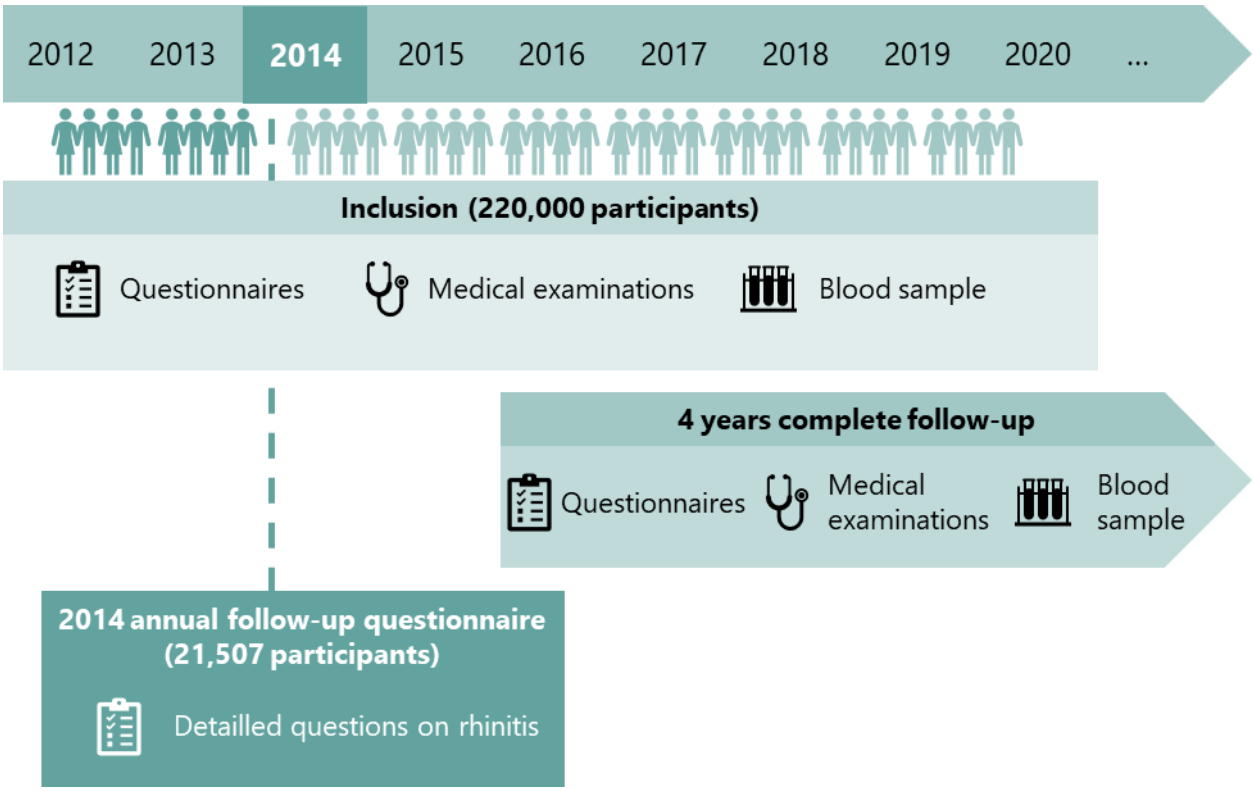


Figure 11: Constances timeline

The analyses of this thesis were performed using data from inclusion or data from the 2014 follow-up questionnaire.

3.1.2.2. Definitions and characterisation of rhinitis

3.1.2.2.1. At inclusion

Participants were considered as having **ever rhinitis** if they answered yes to "*During your lifetime, 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?*", otherwise as never having rhinitis.
Among those with ever rhinitis, participants were classified as having **current rhinitis** if they answered yes to "*Have you had these problems in the last 12 months?*", otherwise as having non-current rhinitis.

Participants with rhinitis who answered yes to "*Have you ever had nasal allergies in your lifetime, including hay fever?*" were classified as **AR**, otherwise as **NAR**.

3.1.2.2.2. At the follow-up questionnaire of 2014

The question and definition for **ever**, **current rhinitis**, **AR** and **NAR** were the same as those at inclusion.

The follow-up questionnaire of 2014 additionally presents detailed questions about rhinitis that defined the following variables:

Age of onset of rhinitis: reporting of ever rhinitis and age reported to "*How old were you the first time?*".

The following variables were defined among participants with current rhinitis:

Triggers were considered as dichotomous variables (yes/no) depending on whether the participant reported the trigger at the question "*What factor triggered or increased these nose problems? (Several answers possible)" Dust mites or house dust, Animals, Air pollution, Change in weather, Tobacco, Pollens, Cold air, Other, Unknown*. The variable "**number of triggers"** refers to the number of triggers reported.

Reported months of rhinitis symptoms were considered as dichotomous variables (yes/no) depending on whether the participant reported the month at the question ""*In which month did you have these nose problems? (Several answers possible)*". The months were also categorized into seasons: winter symptoms if the participant reported symptoms in December or January or February; spring symptoms if the participant reported symptoms in March or April or May; summer symptoms if the participant reported having symptoms in June or July or August; and autumn symptoms if the participant reported symptoms in September or October or November.

Duration of rhinitis was defined according to the ARIA recommendations (1), rhinitis was persistent if symptoms occur more than four days per week and more than four consecutive weeks. Otherwise, rhinitis was defined as intermittent.

For **rhinorrhoea, nasal itching, nasal obstruction, sneezing, and associated eye symptoms**, participants answered to the question: "*For each of the following problems, indicate whether you have had it in the last 12 months and whether it has been bothersome. If you have not been affected by any of them, indicate this in the first column of the table.*". Each symptom was scored on a scale from 0 to 3: 0 = no symptom, 1 = a symptom that is present but not bothersome, 2 = a symptom that is bothersome but does not affect daily activities or sleep, and 3 = a symptom that is bothersome and affects daily activities or sleep.
Each of the symptoms was also considered dichotomously: symptom absent (score = 0) or symptom present (score ≥ 1). The variable "**number of symptoms**" refers to the number of symptoms present (score ≥ 1), considering rhinorrhoea, nasal itching, nasal obstruction, sneezing, and associated eye symptoms (ranges from 0 to 5).

The **total nasal symptom score 4** (TNSS4) is a score based on the severity of four rhinitis symptoms: rhinorrhoea, nasal itching, nasal obstruction and sneezing and is expressed as the sum of these four symptoms (ranges from 0 to 12) (110).
Severity of rhinitis was defined following the ARIA recommendations (1), rhinitis was moderate-severe if at least one of the four symptoms of rhinitis (rhinorrhea, nasal obstruction, nasal itching, sneezing) had a score of 3. Otherwise, rhinitis was defined as mild if all the symptoms had a score lower than 3.

The **ARIA classification** in four classes corresponds to the crossing of the answers between the duration and the severity of the rhinitis leading to the following classes: mild/intermittent, mild/persistent, moderate-severe/intermittent, moderate-severe/persistent.

The **treatments of rhinitis** were considered in a four-class variable based on the answers to the questions on oral antihistamines (OAH): "*Have you used any oral antihistamines/anti-allergic treatments to treat these nose problems? (Aerius, Xyzall, Clarityne, Kestin, Virlix, Zyrtec, Cetirizine, Loratadine, Desloratadine…)"* and on intranasal corticosteroids (INCS): "*Have you used nasal corticosteroid sprays to treat these nose problems? (Nasacort, Nasonex, Avamys, Rhinocort, Beconase, Beclometasone…)"*. A participant who answered "no" to both questions was categorised as neither OAH nor INCS. A participant who answered "yes" to the question on OAH and "no" to question on INCS was categorized as OAH only. A participant who answered "no" to question on OAH and "yes" to question on INCS was categorised as INCS only. Finally, a participant who answered "yes" to both questions was categorised as OAH and INCS.

3.1.2.3. Definition of multimorbidities

3.1.2.3.1. At inclusion

Ever nasal allergies: yes to "*Have you ever had nasal allergies in your lifetime, including hay fever?*"

Participants who answered yes to "*Have you ever had asthma?*" were considered as having **ever asthma**, otherwise as never having asthma.
Among participants with ever asthma, those who reported at least one of the following five asthma symptoms in the last 12 months: wheezing accompanied by shortness of breath, waking up with a feeling of breathlessness, waking up with shortness of breath, shortness of breath after intense effort, breathlessness attack at rest or reported an asthma attack in the last 12 months or reported current asthma treatment were classified as having **current asthma** otherwise as having non-current asthma.

3.1.2.3.2. At the follow-up questionnaire of 2014

Ever nasal allergies: yes to "*Have you ever had nasal allergies in your lifetime, including hay fever?*"

Ever asthma: yes to "*Have you ever had asthma?*" at inclusion or answer "asthma" to: "*Here is a list of health problems. Indicate here the ones you have suffered from in the last 12 months (whether or not there was a work interruption, whether or not there is a treatment)"* at the follow-up questionnaire of 2014.

Ever conjunctivitis: yes to *"During your lifetime, have you ever had allergic conjunctivitis?"*

Ever eczema: yes to *"During your lifetime, have you ever had eczema?"*

3.1.2.4. Socio-demographic variables

3.1.2.4.1. At inclusion

Tobacco status was evaluated into three categories: never smoker, ex-smoker and current smoker.

Body Mass Index (BMI) was defined as the body mass divided by the square of the body height. Height and weight were measured for each participant at the health screening centre at inclusion.

Educational level was evaluated into three categories: less than high school (no diploma/grade school), high school (baccalauréat or equivalent) or university (≥ baccalauréat +2).

The **French Deprivation index** (FDep) is an indicator at the area level constructed at the smallest geographical division in France (IRIS - Regrouped statistical information blocks with 2000 inhabitants in average). Four variables were used to construct it: the median income per consumption unit in the household, the percentage of baccalaureate holders in the population over 15 years old, the percentage of workers in the active population and the unemployment rate. The FDep was defined as the first component of the principal component analysis (PCA) of these four variables (189).

Level of urbanity was considered in two classes: if the participant's municipality of residence has at least 2,000 inhabitants, the participant is considered to live in an urban area, otherwise in a rural area (190).

3.1.2.4.2. At the follow-up questionnaire of 2014

Tobacco status was evaluated into three categories: never smoker, ex-smoker and current smoker.

Body Mass Index (BMI) was defined as the body mass divided by the square of the body height. Height was measured at the health centre at inclusion and weight was reported by participants in the follow-up questionnaire of 2014.

3.1.2.5. Biological variables at inclusion

White blood cell count (WBC): a WBC count was performed for each participant in each Health Preventive Centre by an accredited laboratory. Participants were instructed to fast for 12 hours before the blood test which was performed between 8 AM and 10 AM. The WBC results indicate the total count of leukocytes, expressed as 10^9/L, and the percentage of each of the five leukocyte components: lymphocytes, monocytes, basophils, **eosinophils**, and neutrophils. From the eosinophils and neutrophils, expressed as a percentage of total leukocytes, the numbers of eosinophils and neutrophils, expressed in 10^9/L were generated (191).

3.2. AIR POLLUTION EXPOSURE ASSESSMENT IN CONSTANCES

Exposure assessment for $PM_{2.5}$, BC and NO_2 was based on estimated annual concentration data from **LUR** models. These models were developed for Western Europe using a supervised linear regression approach based on data from a large regulatory network (192). The LUR models were calibrated and validated using annual average $PM_{2.5}$ and NO_2 concentration data derived for 2010 from the AirBase v8 dataset (192). For BC, which is not available in AirBase, the annual mean BC concentrations, measured as $PM_{2.5}$ absorbance based on reflectance measurement of the filters, were obtained from the ESCAPE study[4] for the time period 2009-2010 (193). The LUR models included various predictors. $PM_{2.5}$ satellite data was offered as a predictor to the $PM_{2.5}$ model. Similarly, NO_2 satellite data was offered for the NO_2 model. There were no satellite data for BC but since BC is a major component of $PM_{2.5}$, $PM_{2.5}$ satellite data was offered as a predictor to the BC model. Chemical transport modelled estimates were also used. The GIS predictor variables were road data, land cover data, population density, and elevation. An annual average was modelled for $PM_{2.5}$, NO_2 and BC and the models were applied on a 100 x 100 m grid across Western Europe (192).

[4] European Study of Cohorts for Air Pollution Effects (ESCAPE) is a coloboration of more than 30 European cohort and aims to investigate relationships between long-term exposure to outdoor air pollution and health. PM measurements were made at 20 sites across Europe using a standardised protocol.

The grid was then linked to the geocoded residential addresses of Constances participants allowing to obtain an individual exposure for each participant.
In the present analyses, we used **annual averages for each pollutant from year 2010 models at the participant's residential address of inclusion** as a proxy for participants' long-term exposure to air pollution.

4. RESULTS

4.1. OBJECTIVE 1: IDENTIFICATION AND CHARACTERISATION OF PHENOTYPES AND ENDOTYPES OF RHINITIS

Objective 1 was performed using data from EGEA and Constances and is divided into six specific objectives:

1) To investigate whether a questionnaire definition could be an alternative to SPTs to differentiate AR from NAR in epidemiological studies and compared the SPTs and questionnaire definitions in EGEA.
2) To estimate the prevalences of rhinitis, AR and NAR in the general population of adults based on data from Constances.
3) To describe the characteristics of rhinitis, AR and NAR and to explore phenotypic differences between rhinitis alone and its association with asthma and/or conjunctivitis based on data from Constances and EGEA.
4) To describe AR according to its severity and duration defined by the ARIA classification with a special focus on asthma multimorbidity based on data from Constances.
5) To identify phenotypes of rhinitis with an unsupervised approach based on data from Constances.
6) To identify endotypes of rhinitis with an unsupervised approach based on data from EGEA.

4.1.1. Questionnaire as an alternative of SPTs to differentiate AR from NAR in epidemiological studies

Results from this section were published as a letter to the editor in Allergy (194)*, see Appendix 3 for full text.*

4.1.1.1. Introduction

Defining AR and NAR in epidemiological studies is complex. SPTs or serum specific IgE are the gold-standard to differentiate AR from NAR (6), but they are not often available in large cohorts as the Constances cohort.
This first objective is devoted to compare SPT-based versus questionnaire-based definitions for AR and for NAR using data among adults from the first follow-up (EGEA2) of the EGEA study.

4.1.1.2. Materials and methods

Among the participants with current rhinitis, two definitions of AR and NAR were used: one based on SPTs and one on questionnaire. Participants who had at least one positive SPT were classified as SPT-based AR (AR-SPT), otherwise as SPT-based NAR (NAR-SPT). Participants who responded positively to "*Have you ever had allergic rhinitis?*" or "*Have you ever had hay fever?*" were classified as questionnaire-based AR (AR-Q), otherwise as questionnaire-based NAR (NAR-Q). Due to the EGEA design, analyses were separately conducted among participants with never asthma and ever asthma. Characteristics of AR or NAR were compared between SPTs and questionnaire definitions using a marginal logistic model to account for matched pair data.

4.1.1.3. Results

Among the 696 participants included in the analyses (mean 42 years), 53.6% were women, 51.4% non-smokers, and 57.5% had ever asthma (Figure 12).

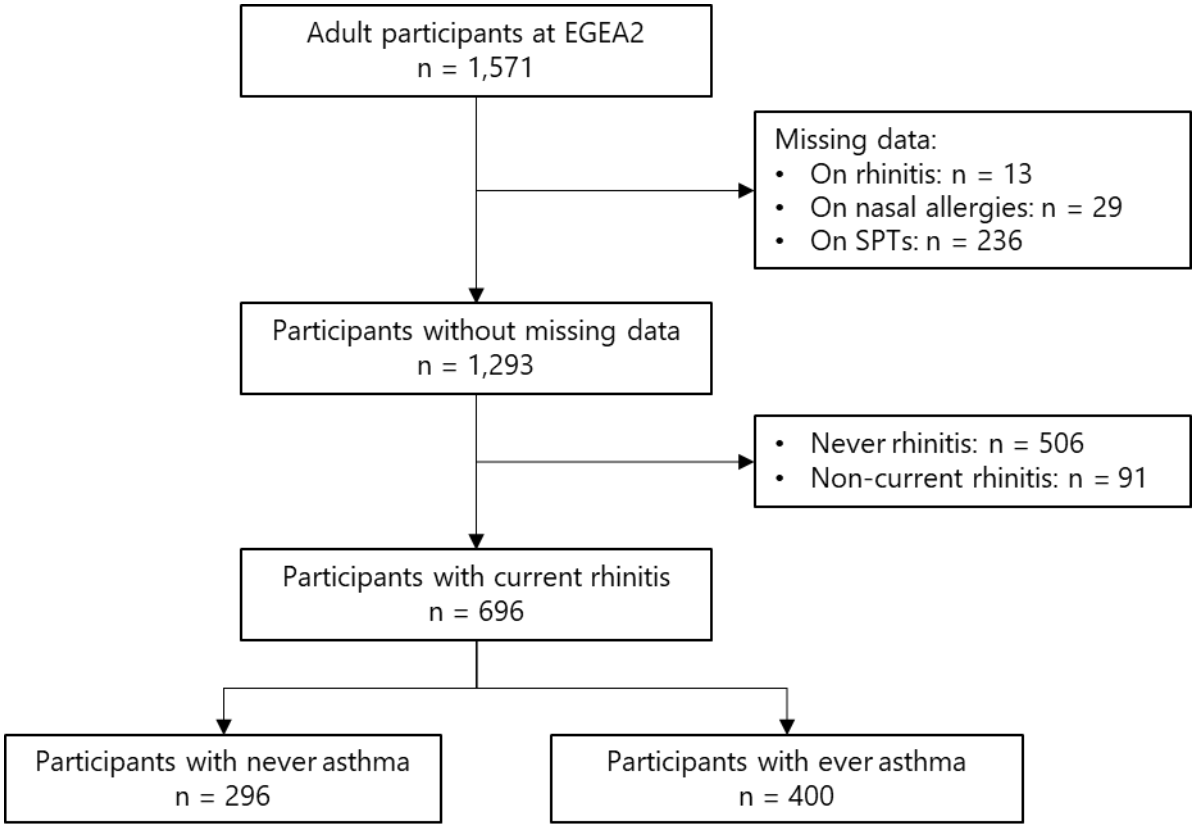


Figure 12: Flowchart of objective 1.1

Agreement measures between SPTs and questionnaire definitions were satisfactory for participant with never asthma. For participants with ever asthma, sensitivity and Positive Predictive Value were high but specificity, Negative Predictive Value, Youden's index and Cohen's Kappa coefficient were rather low (Table 10).

Table 10: Number of participants classified as AR or NAR according to SPT-based and questionnaire-based (Q) definitions

	Never asthma			**Ever asthma**		
	AR-SPT	NAR-SPT	Total	AR-SPT	NAR-SPT	Total
AR-Q	**109**	45	154	**282**	53	335
NAR-Q	32	**110**	142	38	**27**	65
Total	141	155	296	320	80	400
	Estimation ($CI_{95\%}$)			**Estimation ($CI_{95\%}$)**		
Sensitivity	0.77 (0.70 – 0.84)			0.88 (0.85 – 0.92)		
Specificity	0.71 (0.64 – 0.78)			0.34 (0.23 – 0.44)		
PPV	0.71 (0.64 – 0.78)			0.84 (0.80 – 0.88)		
NPV	0.77 (0.71 – 0.84)			0.42 (0.30 – 0.54)		
Youden Index	0.48			0.22		
Cohen's Kappa	0.48 (0.38 – 0.58)			0.24 (0.12 – 0.35)		

PPV: Positive Predictive Value, CI: Confidence Interval; NPV: Negative Predictive Value

Among pariticipants with never asthma, differences in participants' characteristics between questionnaire and SPTs were observed for age for both AR and NAR, and for age of onset and one trigger for AR (Table 11).

Table 11: Comparison of characteristics between SPT-based and questionnaire-based (Q) definitions for AR and for NAR in participants with never asthma

	AR-SPT (n=141)	**AR-Q (n=154)**	**p†**	**NAR-SPT (n=155)**	**NAR-Q (n=142)**	**p‡**
Age (year), mean ± SD	40.6 ± 14.3	44.2 ± 15.0	<.0001	51.3 ± 14.8	48.4 ± 15.8	0.002
Sex, women %	57.5	58.4	0.76	63.9	63.4	0.93
Tobacco status, %			0.18			0.25
Never smoker	51.1	50.0		50.3	51.4	
Ex-smoker	24.1	28.6		31.6	27.5	
Current smoker	24.8	21.4		18.1	21.1	
Ever conjunctivitis, %	44.9	46.4	0.67	28.1	25.0	0.27
At least one positive SPT, %	100	70.8		0.00	22.5	
Serum IgE, GM (Q1-Q3)	95.8 (46.7–209)	83.5 (36.3–201)	0.08	40.5 (15.4–91.3)	43.6 (15.4–105)	0.39
Age of onset of rhinitis, mean ±SD	21.7 ± 13.1	24.5 ± 15.3	0.007	36.1 ± 18.2	34.3 ± 18.5	0.17
Associated eye symptoms, %	78.7	77.9	0.67	36.8	33.8	0.29
Trigger(s) of rhinitis symptoms§, %						
Dust mites or house dust	37.6	31.8	0.03	20.7	25.4	0.10
Pollens	68.1	69.5	0.91	27.1	21.8	0.07
Animals	18.4	16.9	0.36	2.58	2.82	1.00
Other	9.22	13.0	0.16	31.6	29.6	0.46
No trigger reported	4.96	5.84	0.60	29.0	30.3	0.47

SD: Standard Deviation, IgE: Immunoglobulin E; GM: Geometric Mean; Q1–Q3: Quartile 1–Quartile 3
†: P-values for the comparison of the characteristics of AR between SPTs and questionnaire definitions, ‡: P-values for the comparison of the characteristics of NAR between SPTs and questionnaire definitions, §: Several possible answers

Among participants with ever asthma, differences were observed for age, sex, smoking and IgE level for both AR and NAR, for age of onset and one trigger for AR, and for ever allergic conjunctivitis, associated eye-symptoms and two triggers for NAR (Table 12).

Table 12: Comparison of characteristics between SPT-based and questionnaire-based (Q) definition for AR and for NAR in participants with ever asthma

	AR-SPT (n=320)	**AR-Q (n=335)**	**p†**	**NAR-SPT (n=80)**	**NAR-Q (n=65)**	**p‡**
Age (year), mean ± SD	35.9 ± 15.1	38.4 ± 15.9	<.0001	47.9 ± 16.7	37.9 ± 17.7	<.0001
Sex, women %	45.3	49.3	0.007	60.0	43.1	0.02
Tobacco status, %			0.04			0.03
Non-smoker	53.4	51.0		46.3	56.9	
Ex-smoker	19.1	22.4		28.8	13.9	
Smoker	27.5	26.6		25.0	29.2	
Ever allergic conjunctivitis, %	54.8	56.8	0.20	40.3	25.8	0.02
At least one positive SPT, %	100.0	84.2		0.0	58.5	
Serum IgE, GM (Q1-Q3)	197 (86.1–451)	160 (68.7–373)	<.0001	49.8 (16.7–138)	112 (28.4–338)	0.01
Age of onset of rhinitis, mean ± SD	13.3 ± 11.9	14.4 ± 12.5	0.01	24.3 ± 16.6	22.0 ± 17.9	0.95
Associated eye symptoms, %	79.1	81.5	0.16	61.3	44.6	0.009
Trigger(s) of rhinitis symptoms§, %						
Dust mites or house dust	56.9	54.9	0.18	30.0	33.9	0.60
Pollens	65.0	66.3	0.55	31.3	16.9	0.02
Animals	38.8	34.9	0.002	3.75	15.4	0.05
Other	7.81	8.36	0.61	21.3	21.5	0.93
No trigger reported	5.31	5.97	0.55	27.5	29.2	0.49

SD: Standard Deviation, IgE: Immunoglobulin E; GM: Geometric Mean; Q1–Q3: Quartile 1–Quartile 3
†: P-values for the comparison of the characteristics of AR between SPTs and questionnaire definitions, ‡: P-values for the comparison of the characteristics of NAR between SPTs and questionnaire definitions, §: Several possible answers

AR-Q participants reported more symptoms during the spring than AR-SPT participants and this being even significant for participants with ever asthma, conversely to what is observed for NAR (Figure 13).

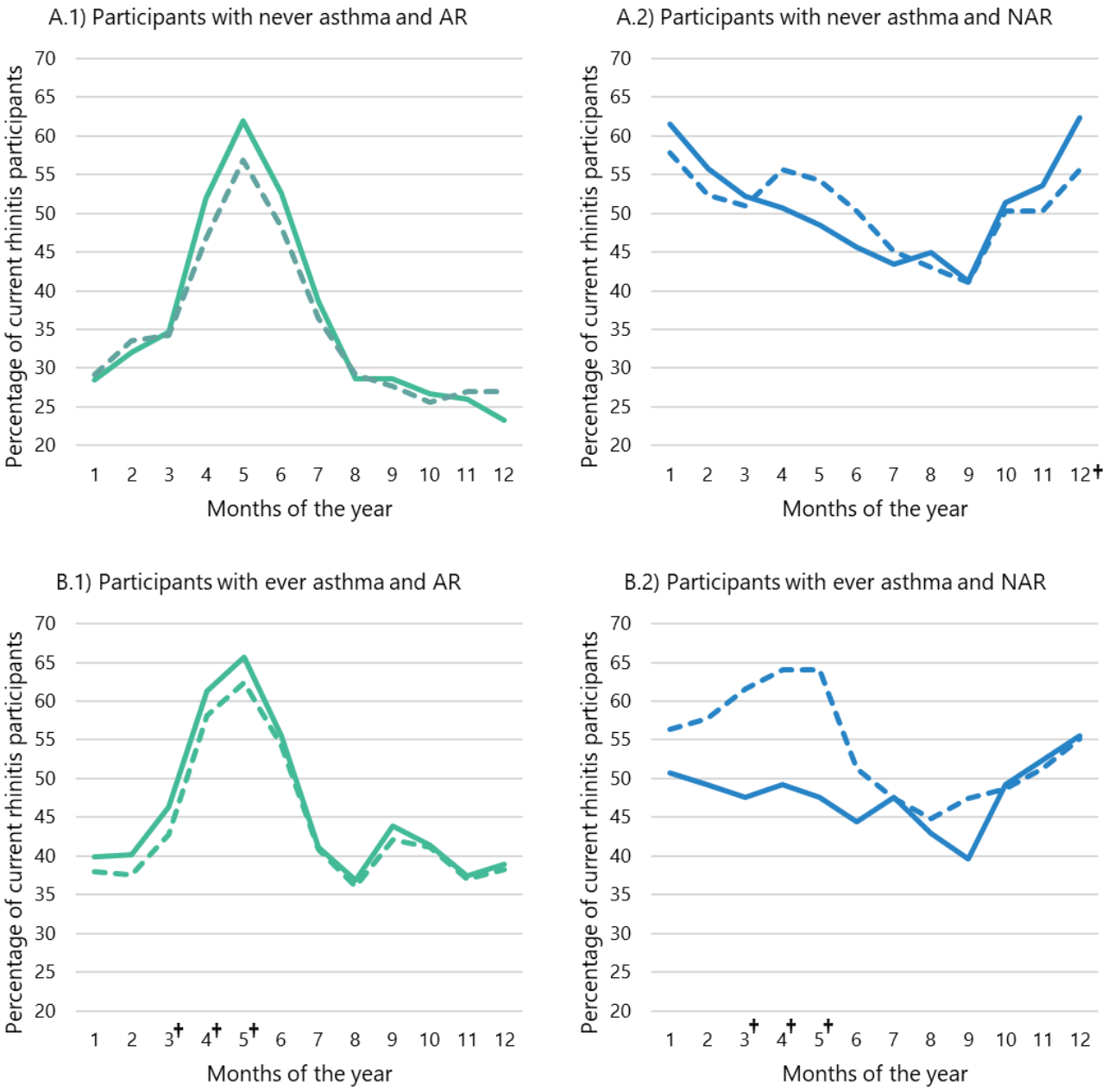


Figure 13: Comparison of seasonality between SPT-based and questionnaire-based definitions for AR and for NAR

A: In participants with never asthma, B: In participants with ever asthma
1: AR participants; 2: NAR participants
- - - SPT-based definition — Questionnaire-based definition
† P-values of comparison between SPTs and questionnaire definitions < 0.05

4.1.1.4. Discussion

We acknowledge that the best possible diagnosis of AR and NAR is achieved with a specific clinical diagnosis: anamnesis and SPTs/specific IgE, by a specialized health professional. As we did not have anamnesis, our definition of current rhinitis is based on the ISAAC definition (91) as suggested by the ARIA (7). To distinguish AR from NAR by questionnaire, we used an adaptation of the ECRHS definition (185). Although SPTs are the gold-standard for distinguishing AR from NAR, SPT positivity is not systematically associated with nasal symptoms (195). Indeed, among EGEA participants with never rhinitis, 29% of those with never asthma and 67% of those with ever asthma had at least one positive SPT (196). Also, SPT negativity does not systematically reflect NAR, as observed for local allergic rhinitis (17). The questionnaire approach has the advantage of relying on what participants directly identify as nasal allergies and could therefore consider the forms of local allergic rhinitis that the SPTs approach does not. This could partly explain the higher reports of pollen trigger, associated eye-symptoms and symptoms in spring observed in the NAR group with the SPT-based definition compared to the questionnaire-based definition. Based on this, the moderate agreement observed between SPTs and questionnaire would not necessarily reflect a false classification of AR/NAR by questionnaire.

In conclusion, these results suggest that a simple definition of AR and NAR based on a validated and standardized questionnaire could be a suitable proxy for AR and NAR in the absence of biological measures.

4.1.2. Prevalences of rhinitis, AR and NAR in the general population

Results from this section will be published as a letter to editor (in preparation).

4.1.2.1. Introduction

In adults, there is limited recent data on rhinitis prevalence, and there is overall scarce data on NAR (62). This objective aimed to estimate the prevalences of rhinitis, AR and NAR in the general population.

4.1.2.2. Materials and methods

Cross-sectional analyses were carried out in Constances with the data from the inclusion. The definitions of rhinitis, AR and NAR were similar to the questionnaire-based definition previously used in EGEA and are those presented in the overall material and methods section 3.1.2.2.1.

The prevalences were estimated using weighted data, thereby allowing inference to the target population: French population aged 18 to 69 years, affiliated to the general health insurance fund and residing in one of the participating departments. For each year of invitation from 2013 to 2017, a random sample has been drawn and robust annual weights have been calculated.
The reference distribution is estimated from the invited participants of year n. The weighting depended on the probability of inclusion (i.e. the survey weight) and the estimated probability of participation for each weightable participant (non-response correction factor). To calculate the corrective factor for non-participation, sociodemographic variables were used: sex, age, primary health insurance fund, affiliation, passive data from medical-administrative databases (SNIIRAM and CNAV).
The final weight considered both the survey weight and the non-participation correction factor and were calibrated using the target population margins.
Cross-sectional analyses were performed by invitation year. Stratifications by level of urbanity of the participant's commune (rural/urban), and by department were also performed.

4.1.2.3. Results

Among the 108,827 participants, those with missing data on rhinitis (n = 6,059) were excluded and 102,768 participants were included in the analyses (Figure 14, Table S1 Appendix 4).

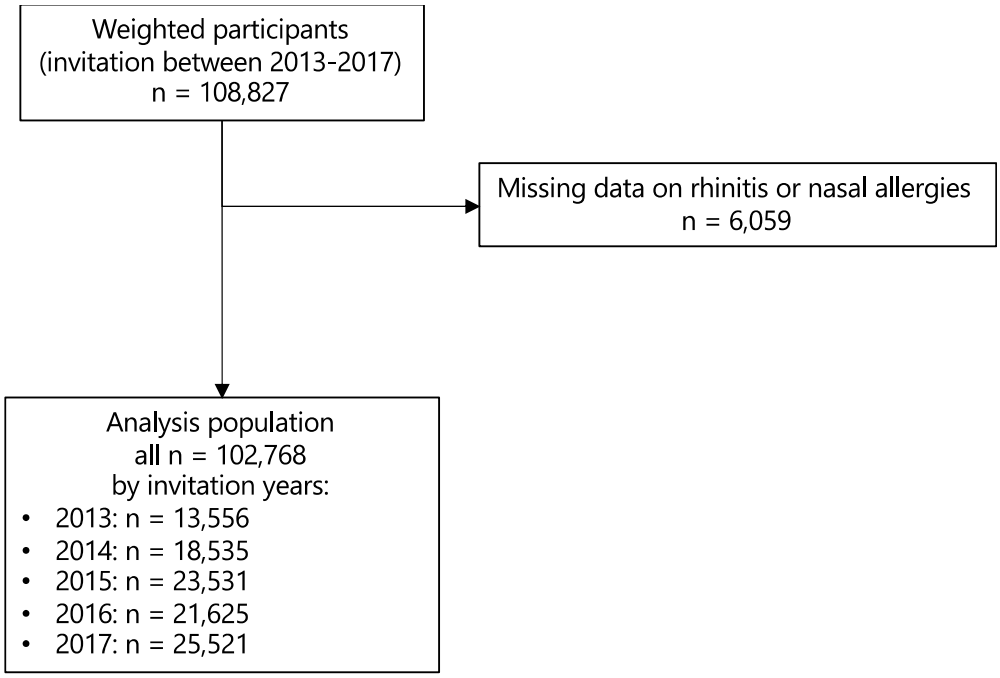


Figure 14: Flowchart of objective 1.2

According to the invitation year, the weighted prevalences of current rhinitis, AR and NAR ranged from 33.7% to 34.7%, 23.0% to 24.2% and 10.2% to 11.4%, respectively (Table 13). Regardless of the invitation year, participants living in urban areas reported more current rhinitis than those in rural areas (Table 14) and the prevalences varied according to departments (Figure 15, Table S2 Appendix 4).

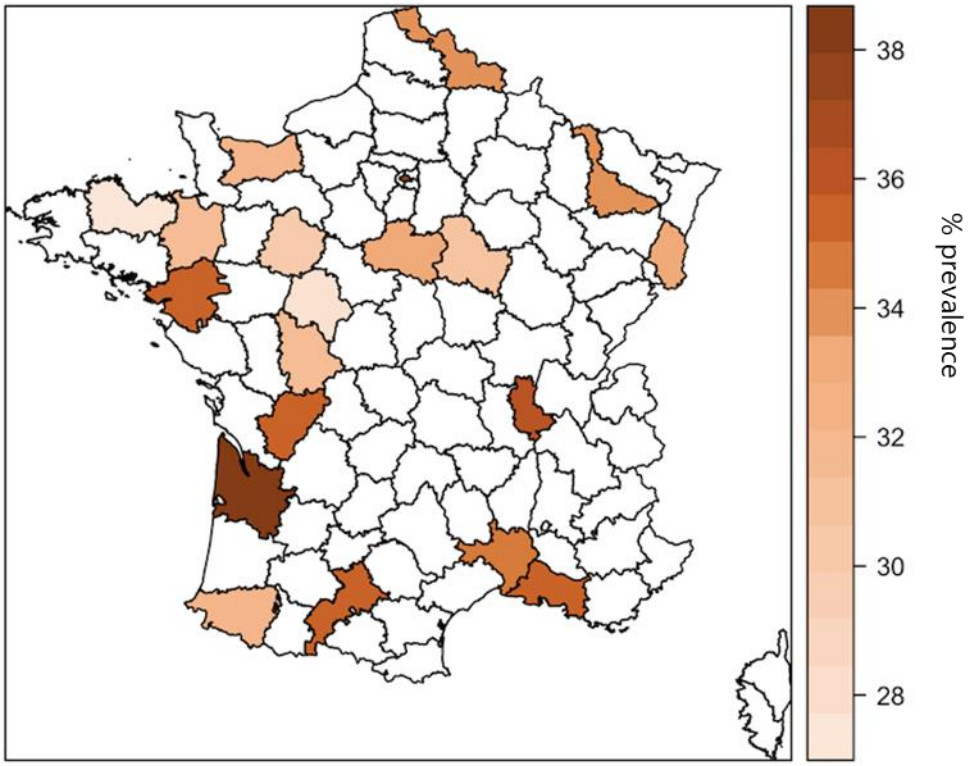
Table 13: Weighted prevalences of current rhinitis according to the year of invitation

	Year of invitation				
	2013	2014	2015	2016	2017
Never rhinitis	55.0	53.5	54.8	54.0	55.1
Non-current	11.0	11.8	10.8	11.3	11.2
Current rhinitis	34.0	34.7	34.5	34.7	33.7
Current NAR	11.0	11.4	10.2	10.8	10.7
Current AR	23.0	23.3	24.2	24.0	23.0

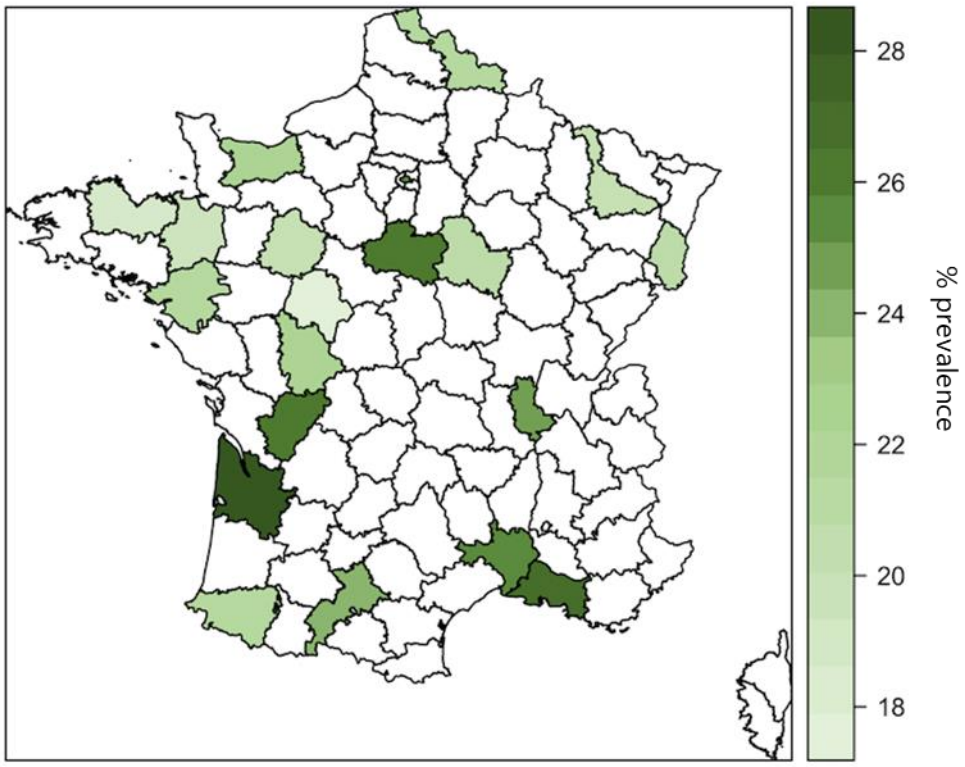
Table 14: Weighted prevalences of current rhinitis according to the year of invitation and the level of urbanity

	2013		**2014**		**2015**		**2016**		**2017**	
	Rural	Urban	Rural	Urban	Rural	Urban	Rural	Urban	Rural	Urban
Never rhinitis	58.4	54.4	55.1	53.3	58.4	54.2	58.3	53.2	57.0	54.7
Non-current rhinitis	11.5	11.0	12.4	11.7	11.0	10.7	11.4	11.3	11.4	11.2
Current rhinitis	30.0	34.6	32.5	35.0	30.6	35.1	30.2	35.6	31.7	34.2
Current NAR	11.5	10.9	9.7	11.7	10.7	10.1	10.1	10.9	9.5	11.0
Current AR	18.6	23.7	22.8	23.4	19.9	25.0	20.1	24.7	22.2	23.2

Current rhinitis prevalence (Invitation Year = 2017)



Current allergic rhinitis prevalence (Invitation Year = 2017)



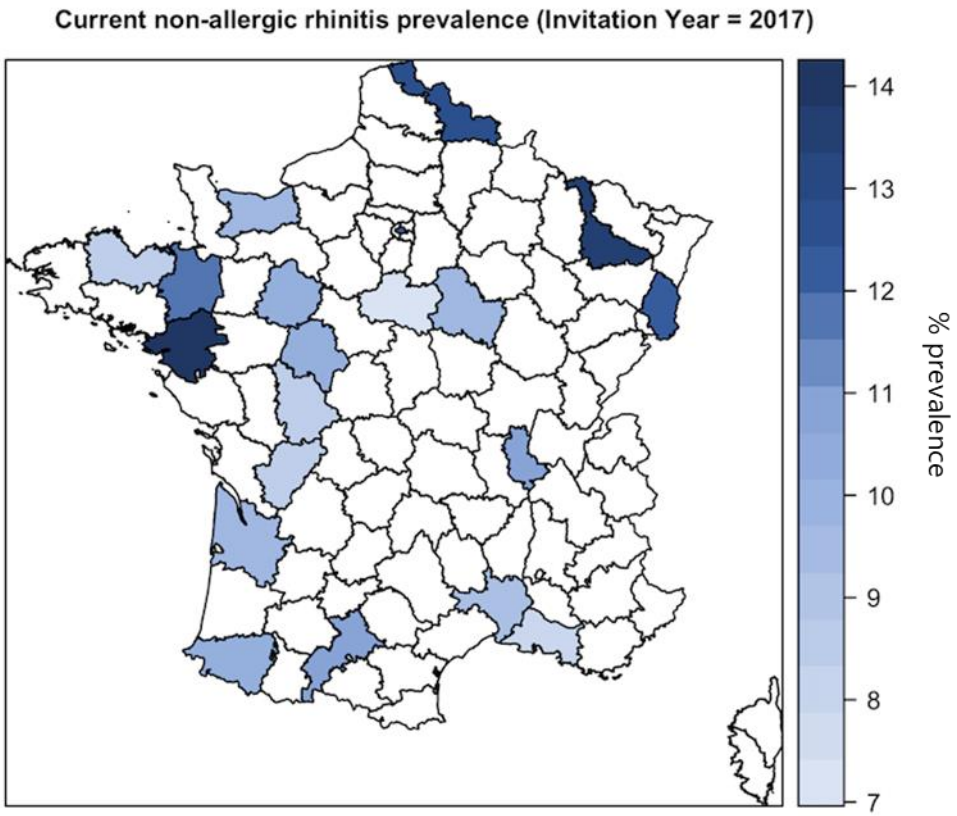


Figure 15: Prevalences of current rhinitis for participants invited to participate in Constances in 2017

A: Current rhinitis, B: Current AR, C: Current NAR
The darker the colour, the higher the prevalence of rhinitis, blank department: no data available

4.1.2.4. Discussion

This study shows that current rhinitis affected about one third of French adults from the Constances cohort.

The strengths of the study are the large size of the cohort and the use of weighted prevalences. However, Constances is not fully representative of the French adult population as 1) participants were randomly selected from the beneficiaries of the general health insurance fund that covered around 85% of the French population, and 2) some geographical areas of France were not included.
Although the SPTs and/or serum specific IgE measurements were not available, rhinitis, AR and NAR definitions were based on validated and standardised questions that we showed to be a suitable proxy for defining AR and NAR in epidemiologic studies (194). However, classification errors may remain.
In our literature review summarizing rhinitis prevalence worldwide, the overall median prevalences of current rhinitis, AR and NAR were 29.4%, 18.1% and 12.0% (62). These figures are close to those observed in the present study.
In the present study, the prevalences were stable over the 5-year period. Results suggest a north-south gradient with higher prevalences of NAR in the North and higher

prevalences of AR in the South, a pattern fitting with pollen maps (197). Higher prevalences of current rhinitis in urban versus rural areas were also found, a result that points towards the effect of environmental factors on rhinitis such as air pollution or exposure to greenspaces.

In conclusion, this study highlights that around one third of French adults had current rhinitis. AR was reported by two third of the participants with rhinitis and NAR by one third. These results add epidemiological knowledge, especially for NAR.

4.1.3. Characterisation of rhinitis phenotypes and multimorbidities

Results from this section were published as an original article in the European Respiratory Journal (198)*, see Appendix 5 for full text.*

4.1.3.1. Introduction

Beyond their prevalence, the characteristics of AR and NAR are poorly known in the general population.
This objective aimed to 1) describe rhinitis, AR and NAR, and 2) explore how asthma and conjunctivitis may lead to the identification of novel rhinitis phenotypes.

4.1.3.2. Materials and methods

4.1.3.2.1. Study design and definitions

Cross-sectional analyses were carried out in Constances with the data from the follow-up questionnaire of 2014. The definitions of rhinitis and the variables of interest are those presented in the overall material and methods section 3.1.2.

4.1.3.2.2. Statistical methods, biases and sample size

Analyses in complete-cases i.e. by excluding participants with missing data were carried out, and no imputation was performed.
Pearson Chi-2 tests for categorical variables, and Student' t tests (when comparing two groups) or ANOVA comparison of variances (when comparing more than two groups) for continuous variables were used.
As asthma is a major multimorbidity of AR and NAR, we described AR or NAR according to whether or not participants had reported ever asthma in addition to their rhinitis symptoms. Subsequently, we described sub-phenotypes of AR including ever conjunctivitis: participants who reported only AR, those who reported AR + ever conjunctivitis only, those who reported AR + ever asthma only, and those who reported AR + ever conjunctivitis + ever asthma. This step was done for AR as there was not enough participants with NAR reporting both ever asthma and ever conjunctivitis. The characteristics were compared across the four groups defined above.
All analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC).

4.1.3.2.3. Replication study

To validate the findings, the analyses were replicated in the EGEA study. Very similar questions were used to define rhinitis, and participants in EGEA also had biomarkers and test of allergic sensitization (total IgE and SPTs to 12 allergens).

4.1.3.3. Results

4.1.3.3.1. Demographic characteristics of the participants

Among the 26,737 participants included in the cohort by 2013, 21,507 (80%) of them completed the follow-up questionnaire of 2014. Participants with missing data regarding the definitions of rhinitis (n = 497) or nasal allergies (n = 238) were excluded from the analyses (Figure 16).

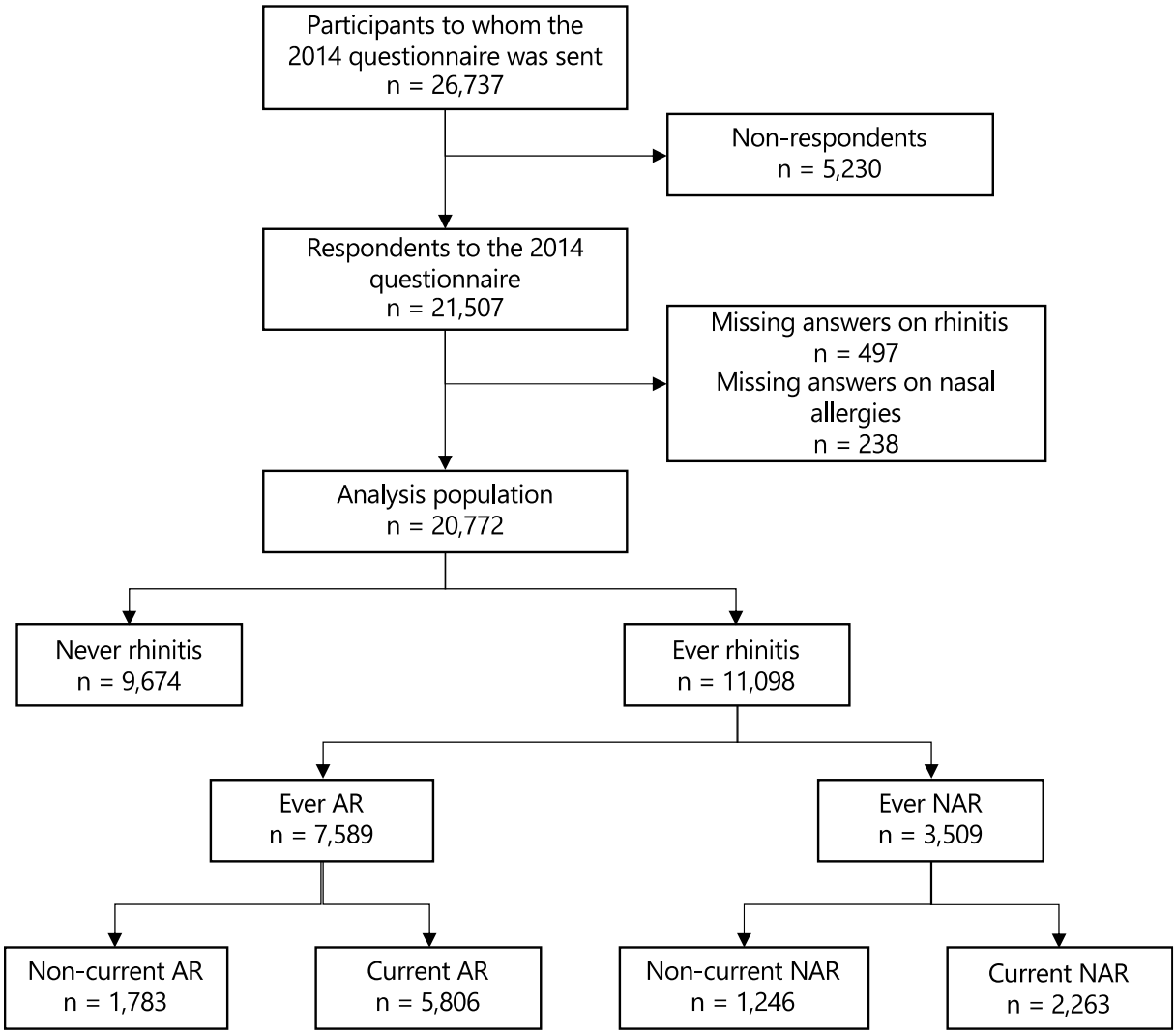


Figure 16: Flowchart of objective 1.3

Non-included participants were on average more often male, younger, smoker, with a lower level of education and a higher body mass index (BMI) and reported more asthma than included participants (Table S1 Appendix 5B).

The main analyses included 20,772 participants with a mean age of 52.6 years and 55.2% were women. Among them, 13.5% were current smokers, 12.7% reported ever asthma and 29.2% ever conjunctivitis (Table 15).

Table 15: Description of the participants according to their rhinitis status

	All (n=20,772)	Never rhinitis (n=9,674)	Non-current rhinitis (n=3,029)	Current rhinitis (n=8,069)	p
Sex					<0.0001
Men	9,297 (44.8%)	4,358 (45.0%)	1,459 (48.2%)	3,480 (43.1%)	
Women	11,475 (55.2%)	5,316 (55.0%)	1,570 (51.8%)	4,589 (56.9%)	
Age, years	52.6 (12.6)	52.9 (12.4)	53.5 (12.2)	51.9 (12.9)	<0.0001
Tobacco status					0.06
Never smoker	9,164 (46.4%)	4,353 (47.3%)	1,323 (46.0%)	3,488 (45.5%)	
Ex-smoker	7,904 (40.0%)	3,588 (39.0%)	1,157 (40.2%)	3,159 (41.2%)	
Current smoker	2,675 (13.5%)	1,259 (13.7%)	398 (13.8%)	1,018 (13.3%)	
Educational level					<0.0001
Less than high school	1,938 (9.4%)	927 (9.7%)	316 (10.6%)	695 (8.7%)	
High school	6,755 (32.9%)	3,321 (34.7%)	1,036 (34.8%)	2,398 (30.1%)	
University	11,825 (57.6%)	5,316 (55.6%)	1,625 (54.6%)	4,884 (61.2%)	
BMI, kg/m^2					0.02
<18.5	460 (2.3%)	222 (2.3%)	66 (2.2%)	172 (2.2%)	
[18.5-25[	11,510 (56.5%)	5,327 (56.2%)	1,610 (54.1%)	4,573 (57.9%)	
[25-30[	6,283 (30.9%)	2,970 (31.3%)	966 (32.5%)	2,347 (29.7%)	
≥30	2,104 (10.3%)	968 (10.2%)	332 (11.2%)	804 (10.2%)	
Asthma					<0.0001
Never asthma	17,793 (87.3%)	8,948 (94.2%)	2,485 (83.8%)	6,360 (80.4%)	
Ever asthma	2,579 (12.7%)	549 (5.8%)	481 (16.2%)	1,549 (19.6%)	
Conjunctivitis					<0.0001
Never conjunctivitis	13,354 (70.8%)	7,582 (85.3%)	1,803 (65.9%)	3,969 (54.8%)	
Ever conjunctivitis	5,509 (29.2%)	1,308 (14.7%)	931 (34.1%)	3,270 (45.2%)	
Eczema					<0.0001
Never eczema	13,631 (71.9%)	7,166 (79.4%)	1,883 (68.7%)	4,582 (63.7%)	
Ever eczema	5,337 (28.1%)	1,863 (20.6%)	858 (31.3%)	2,616 (36.3%)	
Eosinophil count, cells/mm^3	185.5 (126.2)	172.0 (112.2)	189.7 (125.5)	199.8 (139.7)	<0.0001
Age of onset of rhinitis, year	26.3 (16.1)	-	25.2 (15.1)	26.7 (16.5)	0.0002

Data are mean (SD) or n (%), BMI: Body Mass Index

4.1.3.4. Main results

The crude prevalences of ever rhinitis, ever AR and ever NAR were 53.4% ($CI_{95\%}$: 52.8%-54.1%), 36.5% (35.9%-37.2%) and 16.9% (16.4%-17.4%). The crude prevalences of current rhinitis, current AR and current NAR were 38.9% (38.2%-39.5%), 28.0% (27.3%-28.6%) and 10.9% (10.5%-11.3%).

The description of the participants according to their rhinitis status (never, non-current or current) is presented in Table 15. Participants with current rhinitis were more often women, younger, with a higher education level, had higher eosinophil count, and had more multimorbidities: ever asthma, ever conjunctivitis, and ever eczema than participants with never rhinitis or with non-current rhinitis.

Table 16 compares participants with current AR to those with current NAR. Participants with current AR reported significantly more often ever asthma, ever conjunctivitis, and ever eczema than those with NAR. The age of onset of rhinitis was on average 10 years earlier for AR compared to NAR. Participants with AR reported more nasal symptoms than participants with NAR, the highest differences between the two groups were observed for associated-eye symptoms (68.8% *vs* 35.3%) and nasal itching (67.0% *vs* 39.7%). Furthermore, they reported more persistent symptoms (31.6% *vs* 25.1%) and more moderate-severe rhinitis (40.1% vs 24.2%) than participants with NAR. Differences were also observed between participants with AR or NAR regarding triggers of rhinitis symptoms: the largest differences were observed for pollens (52.3% *vs* 10.2%), dust mites/house dust (33.4% *vs* 10.4%), and unknown triggers (27.1% *vs* 48.6%). Treatment by OAH and INCS were reported by 32.0% of participants with AR, and 6.0% of those with NAR.
The seasonality of symptoms differed between AR and NAR, participants with AR reporting symptoms mainly during the Spring whereas those with NAR reporting symptoms mainly during the Winter (Figure 17).

Table 16: Characteristics of participants with current rhinitis, current AR or current NAR

	All current rhinitis (n=8,069)	AR (n=5,806)	NAR (n=2,263)	p
Sex				0.072
Men	3,480 (43.1%)	2,468 (42.5%)	1,012 (44.7%)	
Women	4,589 (56.9%)	3,338 (57.5%)	1,251 (55.3%)	
Age, years	51.9 (12.9)	51.7 (12.8)	52.4 (13.3)	0.036
Tobacco status				0.0044
Never smoker	3,488 (45.5%)	2,534 (46.0%)	954 (44.3%)	
Ex-smoker	3,159 (41.2%)	2,289 (41.5%)	870 (40.4%)	
Current smoker	1,018 (13.3%)	688 (12.5%)	330 (15.3%)	
Educational level				0.77
Less than high school	695 (8.7%)	495 (8.6%)	200 (8.9%)	
High school	2,398 (30.1%)	1,717 (29.9%)	681 (30.4%)	
University	4,884 (61.2%)	3,528 (61.5%)	1,356 (60.6%)	
BMI, kg/m^2				0.34
<18.5	172 (2.2%)	124 (2.2%)	48 (2.2%)	
[18.5 - 25[	4,573 (57.9%)	3,264 (57.5%)	1,309 (59.0%)	
[25 - 30[	2,347 (29.7%)	1,690 (29.8%)	657 (29.6%)	
≥30	804 (10.2%)	599 (10.6%)	205 (9.2%)	
Asthma				<0.0001
Never asthma	6,360 (80.4%)	4,304 (75.7%)	2,056 (92.5%)	
Ever asthma	1,549 (19.6%)	1,383 (24.3%)	166 (7.5%)	
Conjunctivitis				<0.0001
Never conjunctivitis	3,969 (54.8%)	2,317 (44.7%)	1,652 (80.4%)	
Ever conjunctivitis	3,270 (45.2%)	2,868 (55.3%)	402 (19.6%)	
Eczema				<0.0001
Never eczema	4,582 (63.7%)	3,021 (59.2%)	1,561 (74.5%)	
Ever eczema	2,616 (36.3%)	2,081 (40.8%)	535 (25.5%)	
Eosinophil count, $cells/mm^3$	199.8 (139.7)	208.6 (146.4)	177.3 (117.9)	<0.0001
Age of onset of rhinitis, year	26.7 (16.5)	24.3 (15.3)	34.6 (17.5)	<0.0001
Reported triggers of rhinitis symptoms†				
Dust mites or house dust	2,172 (26.9%)	1,937 (33.4%)	235 (10.4%)	<0.0001
Animals	732 (9.1%)	677 (11.7%)	55 (2.4%)	<0.0001
Pollens	3,266 (40.5%)	3,035 (52.3%)	231 (10.2%)	<0.0001
Air pollution	1,847 (22.9%)	1,560 (26.9%)	287 (12.7%)	<0.0001
Change in weather	2,278 (28.2%)	1,677 (28.9%)	601 (26.6%)	0.037
Tobacco	452 (5.6%)	359 (6.2%)	93 (4.1%)	0.0003
Cold air	2,050 (25.4%)	1,423 (24.5%)	627 (27.7%)	0.0030
Other	1,017 (12.6%)	735 (12.7%)	282 (12.5%)	0.81
Unknown	2,673 (33.1%)	1,573 (27.1%)	1,100 (48.6%)	<0.0001
Reported symptoms†				
Rhinorrhoea	5,266 (70.7%)	4,051 (75.1%)	1,215 (59.0%)	<0.0001
Nasal congestion/obstruction	5,257 (72.4%)	4,000 (76.3%)	1,257 (62.1%)	<0.0001
Nasal itching	4,212 (59.5%)	3,445 (67.0%)	767 (39.7%)	<0.0001
Sneezing	5,128 (69.4%)	4,073 (75.9%)	1,055 (52.2%)	<0.0001
Associated-eye symptoms	4,391 (59.8%)	3,693 (68.8%)	698 (35.3%)	<0.0001
Number of reported symptoms	3.2 (1.4)	3.6 (1.3)	2.3 (1.3)	<0.0001

	All current rhinitis (n=8,069)	AR (n=5,806)	NAR (n=2,263)	p
Rhinitis severity				<0.0001
Mild	4,253 (64.3%)	2,862 (59.9%)	1,391 (75.8%)	
Moderate/severe	2,358 (35.7%)	1,913 (40.1%)	445 (24.2%)	
Rhinitis duration				<0.0001
Intermittent	5,422 (70.2%)	3,798 (68.4%)	1,624 (74.9%)	
Persistent	2,302 (29.8%)	1,758 (31.6%)	544 (25.1%)	
Rhinitis treatment				<0.0001
Neither OAH nor INCS	3,507 (45.1%)	1,911 (34.1%)	1,596 (73.5%)	
OAH only	1,322 (17.0%)	1,204 (21.5%)	118 (5.4%)	
INCS only	1,025 (13.2%)	700 (12.5%)	325 (15.0%)	
OAH and INCS	1,925 (24.7%)	1,794 (32.0%)	131 (6.0%)	

Data are mean (SD) or n (%), BMI: Body Mass Index, INCS: Intranasal Corticosteroids, OAH: Oral Antihistamines, †: several possible answers

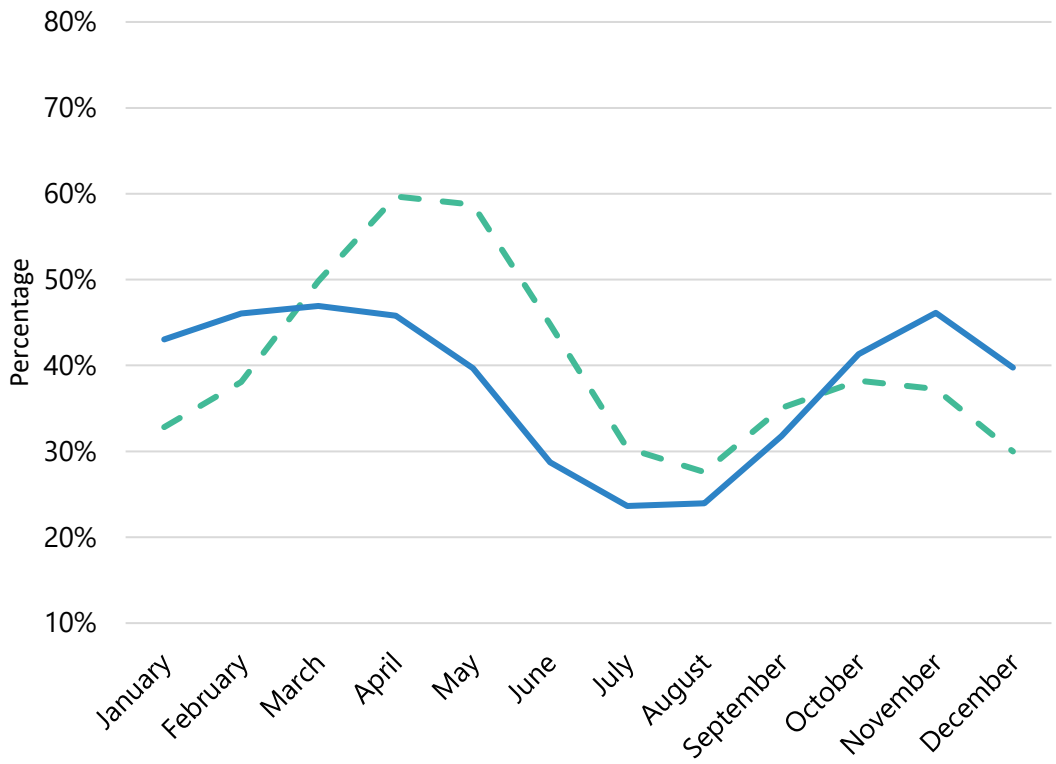


Figure 17: Percentage of participants with AR or NAR reporting symptoms by months

4.1.3.5. Rhinitis phenotypes including ever asthma and ever conjunctivitis status

Among participants with current AR, 1,383 reported ever asthma (24.3%), and among those with current NAR, 166 reported ever asthma (7.5 %) (Table 17). Both among participants with AR or with NAR, those who reported ever asthma had higher eosinophil count, an earlier age of onset of rhinitis and more moderate-severe rhinitis than those with never asthma. Participants with AR and ever asthma also reported more ever conjunctivitis and ever eczema than those with AR only. These differences were not significant for participants with NAR, even if the tendency was the same.
For replication analyses in EGEA, 842 participants with current rhinitis were included: 174 with AR and never asthma, 380 with AR and ever asthma, 176 with NAR and never asthma, and 83 with NAR and ever asthma (Table S4 Appendix 5B). Furthermore, participants who reported ever asthma had higher serum IgE levels and allergen sensitization assessed by SPT. Participants with ever asthma had on average a higher mean number of positive SPTs than those with never asthma for both AR (2.6 *vs* 1.9) and NAR (1.6 *vs* 0.4). When using the SPT definition instead of the questionnaire definition the results were almost identical (Table S5 Appendix 5B).

Table 17: Characteristics of participants with current AR or current NAR including ever asthma status

	AR			**NAR**		
	Never asthma (n=4,304)	Ever asthma (n=1,383)	p	Never asthma (n=2,056)	Ever asthma (n=166)	p
Sex			0.09			0.25
Men	1,851 (43.0%)	559 (40.4%)		925 (45.0%)	67 (40.4%)	
Women	2,453 (57.0%)	824 (59.6%)		1131 (55.0%)	99 (59.6%)	
Age, years	52.5 (12.6)	48.9 (12.7)	<0.0001	52.7 (13.3)	48.6 (13.8)	0.0001
Tobacco status			0.65			0.18
Never smoker	1,883 (46.1%)	613 (46.4%)		879 (44.8%)	59 (37.8%)	
Ex-smoker	1,702 (41.7%)	536 (40.6%)		786 (40.1%)	67 (42.9%)	
Current smoker	498 (12.2%)	172 (13.0%)		297 (15.1%)	30 (19.2%)	
Educational level			0.17			0.70
Less than high school	380 (8.9%)	104 (7.6%)		177 (8.7%)	17 (10.5%)	
High school	1,285 (30.1%)	396 (28.9%)		619 (30.4%)	50 (30.9%)	
University	2,604 (61.0%)	868 (63.5%)		1242 (60.9%)	95 (58.6%)	
BMI, kg/m^2			0.13			0.001
<18.5	95 (2.3%)	26 (1.9%)		42 (2.1%)	5 (3.1%)	
[18.5-25[	2,446 (58.1%)	760 (56.0%)		1,200 (59.6%)	83 (50.9%)	
[25-30[	1,244 (29.6%)	407 (30.0%)		599 (29.7%)	49 (30.1%)	
≥30	423 (10.1%)	165 (12.2%)		174 (8.6%)	26 (16.0%)	
Conjunctivitis			<0.0001			0.19
Never conjunctivitis	1,855 (48.6%)	418 (33.0%)		1,511 (80.8%)	113 (76.4%)	
Ever conjunctivitis	1,958 (51.4%)	848 (67.0%)		360 (19.2%)	35 (23.6%)	

	AR			NAR		
	Never asthma (n=4,304)	Ever asthma (n=1,383)	p	Never asthma (n=2,056)	Ever asthma (n=166)	p
Eczema			<0.0001			0.36
Never eczema	2,329 (62.0%)	639 (51.3%)		1,426 (74.8%)	110 (71.4%)	
Ever eczema	1,426 (38.0%)	607 (48.7%)		481 (25.2%)	44 (28.6%)	
Eosinophil count, cells/mm^3	194.6 (133.7)	252.1 (175.1)	<0.0001	173.8 (114.1)	224.2 (150.9)	<0.0001
Age of onset of rhinitis, year	26.4 (15.4)	18.3 (13.4)	<0.0001	35.2 (17.6)	28.8 (16.2)	0.0004
Reported triggers of rhinitis symptoms†						
Dust mites or house dust	1,167 (27.1%)	729 (52.7%)	<0.0001	194 (9.4%)	38 (22.9%)	<0.0001
Animals	338 (7.9%)	331 (23.9%)	<0.0001	39 (1.9%)	14 (8.4%)	<0.0001
Pollens	2,119 (49.2%)	861 (62.3%)	<0.0001	199 (9.7%)	26 (15.7%)	0.01
Air pollution	1,083 (25.2%)	443 (32.0%)	<0.0001	257 (12.5%)	27 (16.3%)	0.16
Change in weather	1,189 (27.6%)	442 (32.0%)	0.002	549 (26.7%)	46 (27.7%)	0.78
Tobacco	210 (4.9%)	142 (10.3%)	<0.0001	83 (4.0%)	9 (5.4%)	0.39
Cold air	1,026 (23.8%)	359 (26.0%)	0.11	565 (27.5%)	48 (28.9%)	0.69
Other	534 (12.4%)	186 (13.4%)	0.31	254 (12.4%)	20 (12.0%)	0.91
Unknown	1,301 (30.2%)	240 (17.4%)	<0.0001	1,019 (49.6%)	63 (38.0%)	0.004
Reported symptoms†						
Rhinorrhoea	2,951 (74.1%)	1,022 (78.3%)	0.002	1,096 (58.5%)	90 (62.1%)	0.39
Nasal congestion/obstruction	2,861 (74.3%)	1,056 (82.2%)	<0.0001	1,131 (61.3%)	103 (70.5%)	0.02
Nasal itching	2,456 (65.0%)	918 (72.7%)	<0.0001	683 (38.9%)	69 (49.3%)	0.02
Sneezing	2,945 (74.4%)	1,039 (79.6%)	0.0002	951 (51.8%)	80 (54.4%)	0.54
Associated-eye symptoms	2,621 (66.1%)	990 (76.3%)	<0.0001	615 (34.1%)	71 (49.3%)	0.0002
Number of reported symptoms	3.4 (1.3)	3.8 (1.2)	<0.0001	2.3 (1.3)	2.7 (1.4%)	0.0004
Rhinitis severity			<0.0001			0.0042
Mild	2,198 (62.8%)	609 (51.5%)		1,285 (76.6%)	83 (65.4%)	
Moderate/severe	1,301 (37.2%)	574 (48.5%)		392 (23.4%)	44 (34.6%)	
Rhinitis duration			0.003			0.74
Intermittent	2,853 (69.5%)	870 (65.1%)		1,481 (75.1%)	116 (73.9%)	
Persistent	1,252 (30.5%)	467 (34.9%)		492 (24.9%)	41 (26.1%)	
Rhinitis treatment			<0.0001			<0.0001
Neither OAH nor INCS	1,618 (39.0%)	259 (19.3%)		1,475 (74.6%)	94 (60.3%)	
OAH only	869 (20.9%)	307 (22.8%)		102 (5.2%)	15 (9.6%)	
INCS only	552 (13.3%)	132 (9.8%)		293 (14.8%)	23 (14.7%)	
OAH and INCS	1,113 (26.8%)	646 (48.1%)		106 (5.4%)	24 (15.4%)	

Data are mean (SD) or n (%), BMI: Body Mass Index, INCS: Intranasal Corticosteroids, OAH: Oral Antihistamines, †: several possible answers

In Constances, accounting for ever asthma and ever conjunctivitis, the characteristics of 1,855 participants with AR only, 1,958 with AR + ever conjunctivitis, 418 with AR + ever asthma, and 848 with AR + ever conjunctivitis + ever asthma are shown in Table 18. Statistically significant differences were observed for almost all the characteristics. In particular, participants with AR + ever conjunctivitis + ever asthma, had an earlier age of onset of rhinitis symptoms, more moderate-severe rhinitis, reported more comedication (INCS + OAH), and higher eosinophil count than participants from the other groups.

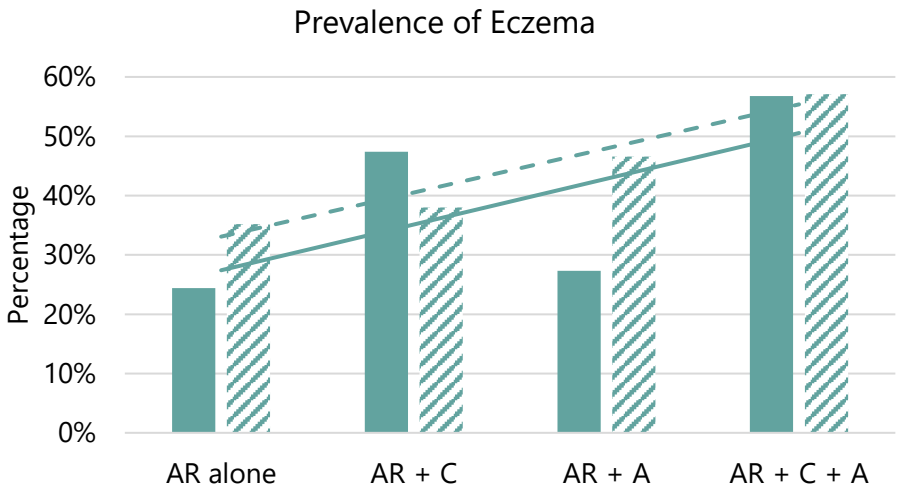
The results observed in the EGEA study were almost identical (Table S6 Appendix 5B, Figure 18). In addition, we observed that participants with AR + ever-conjunctivitis + ever-asthma had the highest mean number of positive SPTs. When using the SPT definition the results were also almost identical (Table S7 Appendix 5B).

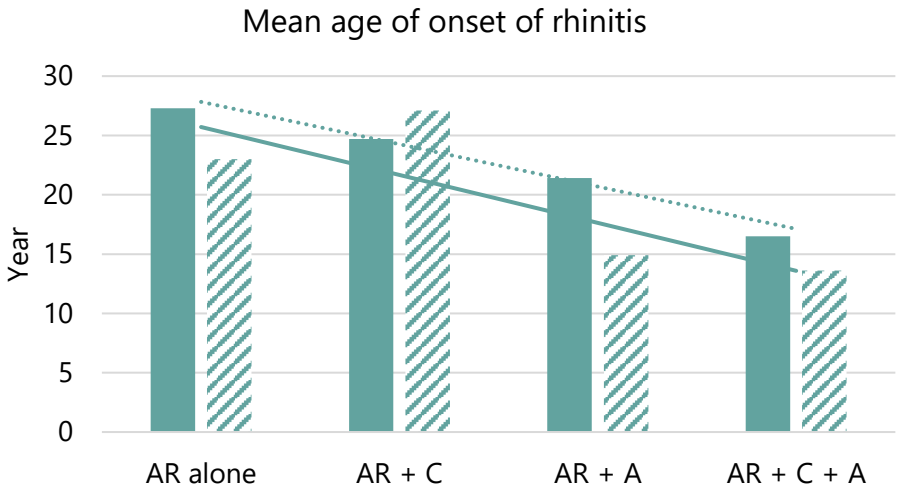
Table 18: Characteristics of participants with current AR including ever asthma (A) and ever conjunctivitis (C) status

	AR alone (n=1,855)	**AR + C (n=1,958)**	**AR + A (n=418)**	**AR + C + A (n=848)**	**p**
Sex					<0.0001
Men	941 (50.7%)	671 (34.3%)	196 (46.9%)	308 (36.3%)	
Women	914 (49.3%)	1,287 (65.7%)	222 (53.1%)	540 (63.7%)	
Age, years	51.9 (12.9)	51.6 (12.5)	48.7 (12.7)	48.1 (12.6)	<0.0001
Tobacco status					0.003
Never smoker	775 (43.9%)	920 (49.4%)	167 (42.0%)	397 (48.7%)	
Ex-smoker	756 (42.8%)	740 (39.7%)	169 (42.5%)	321 (39.4%)	
Current smoker	236 (13.4%)	202 (10.8%)	62 (15.6%)	97 (11.9%)	
Educational level					0.03
Less than high school	148 (8.0%)	154 (7.9%)	34 (8.2%)	54 (6.4%)	
High school	573 (31.1%)	519 (26.7%)	123 (29.8%)	229 (27.3%)	
University	1,120 (60.8%)	1,270 (65.4%)	256 (62.0%)	556 (66.3%)	
BMI, kg/m^2					0.09
<18.5	32 (1.8%)	50 (2.6%)	6 (1.5%)	18 (2.2%)	
[18.5-25[	1,041 (57.6%)	1,151 (59.9%)	249 (60.6%)	455 (54.4%)	
[25-30[	548 (30.3%)	530 (27.6%)	109 (26.5%)	265 (31.7%)	
≥30	187 (10.3%)	189 (9.8%)	47 (11.4%)	98 (11.7%)	
Eczema					<0.0001
Never eczema	1,398 (75.6%)	915 (52.6%)	301 (72.7%)	334 (43.2%)	
Ever eczema	450 (24.4%)	823 (47.4%)	113 (27.3%)	440 (56.8%)	
Eosinophil count, cells/mm^3	196.8 (134.0)	191.6 (134.2)	260.9 (183.3)	247.4 (169.1)	<0.0001
Age of onset of rhinitis, year	27.3 (15.7)	24.7 (14.4)	21.4 (14.6)	16.4 (12.1)	<0.0001
Reported triggers of rhinitis symptoms†					
Dust mites or house dust	441 (23.8%)	620 (31.7%)	210 (50.2%)	470 (55.4%)	<0.0001
Animals	118 (6.4%)	200 (10.2%)	91 (21.8%)	224 (26.4%)	<0.0001
Pollens	789 (42.5%)	1,149 (58.7%)	217 (51.9%)	591 (69.7%)	<0.0001
Air pollution	412 (22.2%)	571 (29.2%)	114 (27.3%)	292 (34.4%)	<0.0001
Change in weather	474 (25.6%)	568 (29.0%)	135 (32.3%)	271 (32.0%)	0.001
Tobacco	78 (4.2%)	107 (5.5%)	42 (10.0%)	88 (10.4%)	<0.0001
Cold air	445 (24.0%)	459 (23.4%)	111 (26.6%)	220 (25.9%)	0.35
Other	225 (12.1%)	247 (12.6%)	49 (11.7%)	126 (14.9%)	0.22
Unknown	617 (33.3%)	492 (25.1%)	87 (20.8%)	114 (13.4%)	<0.0001
Reported symptoms†					
Rhinorrhoea	1,230 (70.3%)	1,394 (76.5%)	291 (74.2%)	651 (80.0%)	<0.0001
Nasal congestion/obstruction	1,198 (71.0%)	1,364 (76.9%)	308 (79.8%)	656 (82.1%)	<0.0001
Nasal itching	982 (58.7%)	1,235 (71.0%)	251 (65.2%)	614 (77.2%)	<0.0001
Sneezing	1,231 (71.1%)	1,395 (77.0%)	297 (74.6%)	669 (82.2%)	<0.0001
Associated-eye symptoms	912 (53.1%)	1,488 (80.3%)	245 (62.0%)	689 (84.7%)	<0.0001
Number of reported symptoms	3.2 (1.3)	3.7 (1.2)	3.5 (1.3)	4.0 (1.1)	<0.0001

	AR alone (n=1,855)	AR + C (n=1,958)	AR + A (n=418)	AR + C + A (n=848)	p
Rhinitis severity					<0.0001
Mild	1,047 (66.1%)	947 (58.8%)	196 (54.4%)	377 (50.1%)	
Moderate/severe	537 (33.9%)	664 (41.2%)	164 (45.6%)	375 (49.9%)	
Rhinitis duration					0.002
Intermittent	1,268 (70.9%)	1,275 (68.4%)	284 (70.1%)	521 (63.4%)	
Persistent	520 (29.1%)	590 (31.6%)	121 (29.9%)	301 (36.6%)	
Rhinitis treatment					<0.0001
Neither OAH nor INCS	819 (45.5%)	603 (31.9%)	114 (28.2%)	120 (14.5%)	
OAH only	329 (18.3%)	472 (24.9%)	91 (22.5%)	207 (25.0%)	
INCS only	272 (15.1%)	200 (10.6%)	44 (10.9%)	60 (7.2%)	
OAH and INCS	380 (21.1%)	617 (32.6%)	155 (38.4%)	442 (53.3%)	

Data are mean (SD) or n (%), BMI: Body Mass Index, INCS: Intranasal Corticosteroids, OAH: Oral Antihistamines, †: several possible answers





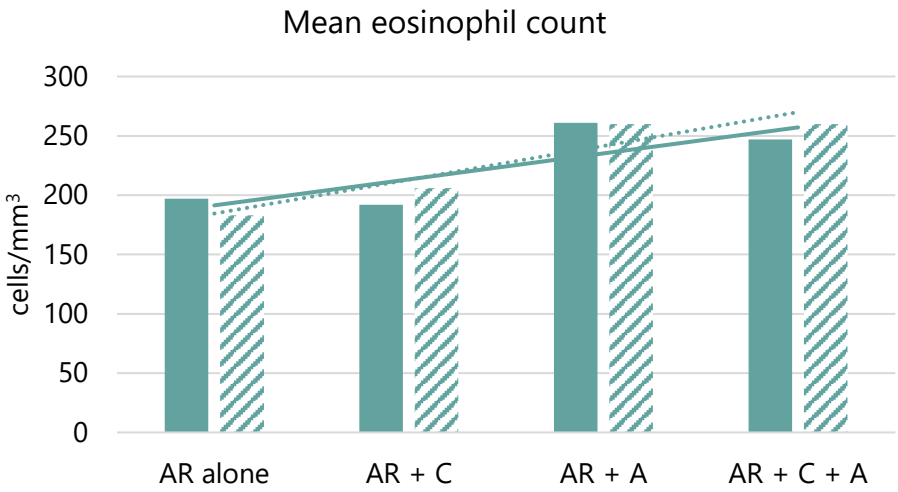


Figure 18: Comparison between Constances and EGEA for prevalence of ever eczema, mean age of onset, and mean eosinophil count

Results from Constances *Results from EGEA*

AR alone: current AR alone, AR + C: current AR and ever conjunctivitis without ever asthma, AR + A: current AR and ever asthma without ever conjunctivitis, AR + C + A: current AR and ever conjunctivitis and ever asthma

4.1.3.6. Discussion

In the large population-based study Constances, using questionnaire-based definitions of rhinitis, we observed the well-known characteristics of AR and NAR, and that 30% of participants with rhinitis reported moderate to severe symptoms. AR and NAR alone, or with asthma, or with asthma and conjunctivitis were associated with different characteristics.

For the first-time in a population-based study, given the large number of participants, we were able to identified and characterised phenotypes of rhinitis accounting for asthma and conjunctivitis. However, as previously stated, Constances is not fully representative of the French adult population. Furthermore, the 2014 population is even more selected mainly regarding age with few participants under 30 years old. This may have slightly impacted the characterization and identification of our phenotypes. Recall bias is possible, likely more for ever asthma than for current rhinitis as the questions on current rhinitis characteristics covered the last 12 months, limiting memory issues.
As mentioned earlier, it is possible that the questionnaire definition involves misclassifications. We observed that a few participants classified as NAR reported allergic triggers and we could not exclude that they could have AR without knowing it. By using alternate definitions of AR and NAR, the prevalence and characteristics of AR and NAR were very similar regardless of the definitions used, showing the robustness of our results. Considering asthma status, we observed that, even among NAR, participants with ever asthma reported more allergic triggers of rhinitis symptoms,

compared to those with never asthma. It is possible that among those with ever asthma, some participants with AR were misclassified as NAR. Even if misclassifications exist, it could not explain by itself the contrasted results observed between the four groups. The present study did not distinguish local AR and mixed rhinitis from other forms of AR. We also acknowledge that the rhinitis definition based on symptoms did not distinguish rhinitis from chronic rhinosinusitis which share some symptoms including nasal congestion.
We defined ever-asthma based on a validated and standardized question used in ECRHS (185), and recently published in Constances (191,199).

Most of the current knowledge about AR and NAR is derived from clinical knowledge. Few population-based studies have described the rhinitis characteristics. We confirmed the main differences observed in clinical practice (18): AR participants reported on average more allergic multimorbidities, an earlier age of onset, more allergic triggers than NAR participants.
We observed that the seasonal pattern of AR and NAR are different. Indeed, NAR showed a peak of declarations during the cold months in France and fewer declarations during the summer months. For AR there was a major peak during the spring season which is when the main pollens are released. It is interesting to note that there is also a second, smaller peak for AR in autumn, which corresponds to the season when ragweed pollens (notably *Ambrosia artemisiifolia*) are released in France. About half of AR participants reported antihistamine treatments. The majority of NAR participants did not report antihistamine or corticosteroid treatments, consistent with the lack of effective treatments for NAR.(200) The seasonality, triggers and treatments we observed for AR or NAR are consistent with the literature and clinical settings, suggesting that the questionnaire-based definition used is a good proxy to identify AR and NAR.
We observed that the age of AR onset was on average lower than that of NAR, even if it is often reported that AR starts in childhood whereas in our study the average age of AR onset was 24 years. We cannot exclude the possibility that a memory bias exists for age of onset, as some participants with childhood rhinitis may not remember it. Regarding the symptoms, we also found well-known differences: AR participants reported more sneezing, nasal itching and eye symptoms than NAR ones. Itching and eye symptoms are commonly described as rare in NAR.(18) In our study, over 30% of participants with NAR reported these symptoms. Similar results were found in many studies that have considered definitions of AR and NAR based on medical diagnosis or biological tests.(13,17) There are still many gaps in knowledge about NAR, but it is possible that some of its forms present symptoms usually considered as allergic. Another explanation could be that AR and NAR are not necessarily mutually exclusive, as up to 50% of rhinitis patients may have mixed rhinitis combining AR and NAR.(201) There are few epidemiological studies in adults that estimate the proportion of persistent and severe rhinitis in general population, especially for NAR. In the present study, the prevalence of persistent rhinitis represents 31% of AR and 25% of NAR.

Moderate-severe rhinitis was found in 40% for AR and 24% for NAR. These figures are lower than those found in clinical practice as most patients who consult a physician have severe rhinitis.(105) This shows that studies in the general population are needed to reflect the actual situation of rhinitis.

For the first time in adults from a population-based study, we described phenotypes of AR and NAR accounting for ever-asthma status. We observed contrasted characteristics across the groups. Our results showed that by comparison with AR participants without ever-asthma, those with ever-asthma reported (i) earlier onset of the disease, (ii) more frequent moderate-severe rhinitis, (iii) more conjunctivitis and eczema multimorbidities, (iv) a higher level of blood eosinophils and (v) more comedication. This latter finding suggests a more severe AR.(202) We validated these results by finding similar characteristics for all groups in the EGEA study. Moreover, allergen sensitization is available in EGEA and there was an increased number of sensitizations in AR with asthma.(203) It therefore appears that rhinitis alone and rhinitis and asthma represent two different diseases as found in real-life (204,205) and genetic studies, rhinitis alone being associated with Toll-like receptors and rhinitis and asthma multimorbidity with IL-5 (associated with eosinophilia) and IL-33.(206) However, biological pathways that are involved in rhinitis alone versus rhinitis with asthma are only partly understood, and further studies are needed to understand the underlying biological mechanisms involved in the aetiology of these phenotypes.

We further described the AR characteristics including ever-asthma and ever-conjunctivitis status. There was an extreme rhinitis phenotype in terms of rhinitis severity (symptoms and treatment) and eosinophil counts with the three multimorbidities associated. It is possible that the natural history of rhinitis alone or in multimorbidity differs. Based on our results, another potential explanation is that the intensity of allergic sensitization increases the risk of having more than one condition or conversely. It is of paramount importance that these newly described phenotypes can be observed in this large population-based study.

The high rhinitis prevalence is an issue for health policy, especially as more than a third of the participants reported having symptoms that interfered with their daily activities or sleep in the past 12 months. In this context, it is important to study the risk factors that could explain the increase in the rhinitis prevalence. These factors are not all clearly identified at present, in particular environmental factors. Further studies on the rhinitis etiology are needed.

We showed that AR and NAR alone, or with asthma, or with asthma and conjunctivitis had different characteristics, and thus may have different etiologies. This raises the question of how best to manage rhinitis and its multimorbidities in terms of natural history, impact on ageing processes or management. Furthermore, studying the evolution of these rhinitis phenotypes over time is an essential research perspective, especially in adults for whom data are scarce. How does rhinitis evolve with advanced age? How does the rhinitis severity evolve over time? Does rhinitis lead to

multimorbidities or vice versa? Do other morbidities appear over time? There is an unmet need to answer these questions.

In a large population-based cohort among adults, the well-known clinical characteristics of AR and NAR were found, with, as expected but never shown before, a lower prevalence of moderate-severe rhinitis than in clinical practice. Whether in Constances or in the EGEA study, including asthma and conjunctivitis in the analysis allows to identify new subphenotypes of rhinitis with specific characteristics. These subphenotypes provide new research perspectives for a better management of rhinitis.

4.1.4. Influence of asthma on severity and duration of AR

Results from this section will be published as an original article (in preparation).

4.1.4.1. Introduction

To go further in the characterisation of rhinitis, this objective aimed to describe AR according to its severity and duration and taking asthma multimorbidity into account among adults from the Constances cohort.
Indeed, although the ARIA classification of rhinitis is a reference in the field, few population-based studies have described AR according to its duration or severity and none has described AR according to the combination of both. Moreover, no study assessed the impact of asthma multimorbidity in the ARIA classes.

4.1.4.2. Material and methods

4.1.4.2.1. Study design and definitions

Cross-sectional analyses were carried out in Constances with the data from the follow-up questionnaire of 2014. The definitions of rhinitis and the variables of interest are those presented in the overall material and methods section 3.1.2.
Only participants with current AR were included in the analyses.

4.1.4.3. Statistical analyses

Analyses in complete-cases i.e. by excluding participants with missing data were carried out, and no imputation was performed.
First, we described AR according to the ARIA classification of severity (mild *versus* moderate-severe) or duration (intermittent *versus* persistent) separately. Pearson Chi-2 tests for categorical variables and Student' t tests were used to compare mild AR with moderate-severe AR or intermittent AR with persistent AR. In order to be not limited by a dichotomous definition of rhinitis severity, the severity of rhinitis was also considered according to the Total Symptom Score 4 (TNSS4) in four classes corresponding to the quartiles ([0-2], [3-4], [5-6], ≥7), as previously done (207). To determine whether the increase in TNSS4 led to a linear increase or decrease in the characteristics of AR, Mantel-Haenszel Chi-2 tests were performed and p values for trend were calculated.
In a second step, the severity and duration of rhinitis were combined according to the ARIA classification into four classes: mild/intermittent, mild/persistent, moderate-severe/intermittent, and moderate-severe/persistent. Pearson Chi-2 tests for categorical variables and ANOVA comparison of variances for continuous variables were used.
Because both duration and severity influence AR characteristics, multivariate logistic analyses were performed to determine whether the observed differences between

classes were due to severity, duration, or both, the interactions between severity and duration being tested for each of the AR characteristics. If the p value of the interaction coefficient was less than 0.05, stratified analyses were performed. Otherwise, logistic analyses comparing moderate-severe to mild AR were performed for each of the AR characteristics by adjusting for AR duration. Similarly, logistic analyses comparing persistent to intermittent AR were performed for each of the AR characteristics by adjusting for AR severity.
Finally, to investigate if asthma could influence the four ARIA classes, we stratified by ever asthma status, and for each of the ARIA classes the characteristics of the participants with ever or never asthma were compared.

All analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC).

4.1.4.4. Results

4.1.4.4.1. Demographic characteristics of the participants

Among the 26,737 participants included in the cohort by 2013, 21,507 (80%) of them completed the follow-up questionnaire of 2014. Participants with missing data regarding the definition of AR (n = 735) were excluded from the analyses. Among participants with current AR, participants with missing data regarding severity (n = 1,031), duration (n = 100), and ever asthma (n = 91) were also excluded. Finally, 4,584 participants with AR were included in the analyses (Figure 19).
Compared to participants with missing data for severity and duration, participants included in the analyses were younger and had a higher level of education (Table S1 Appendix 6).

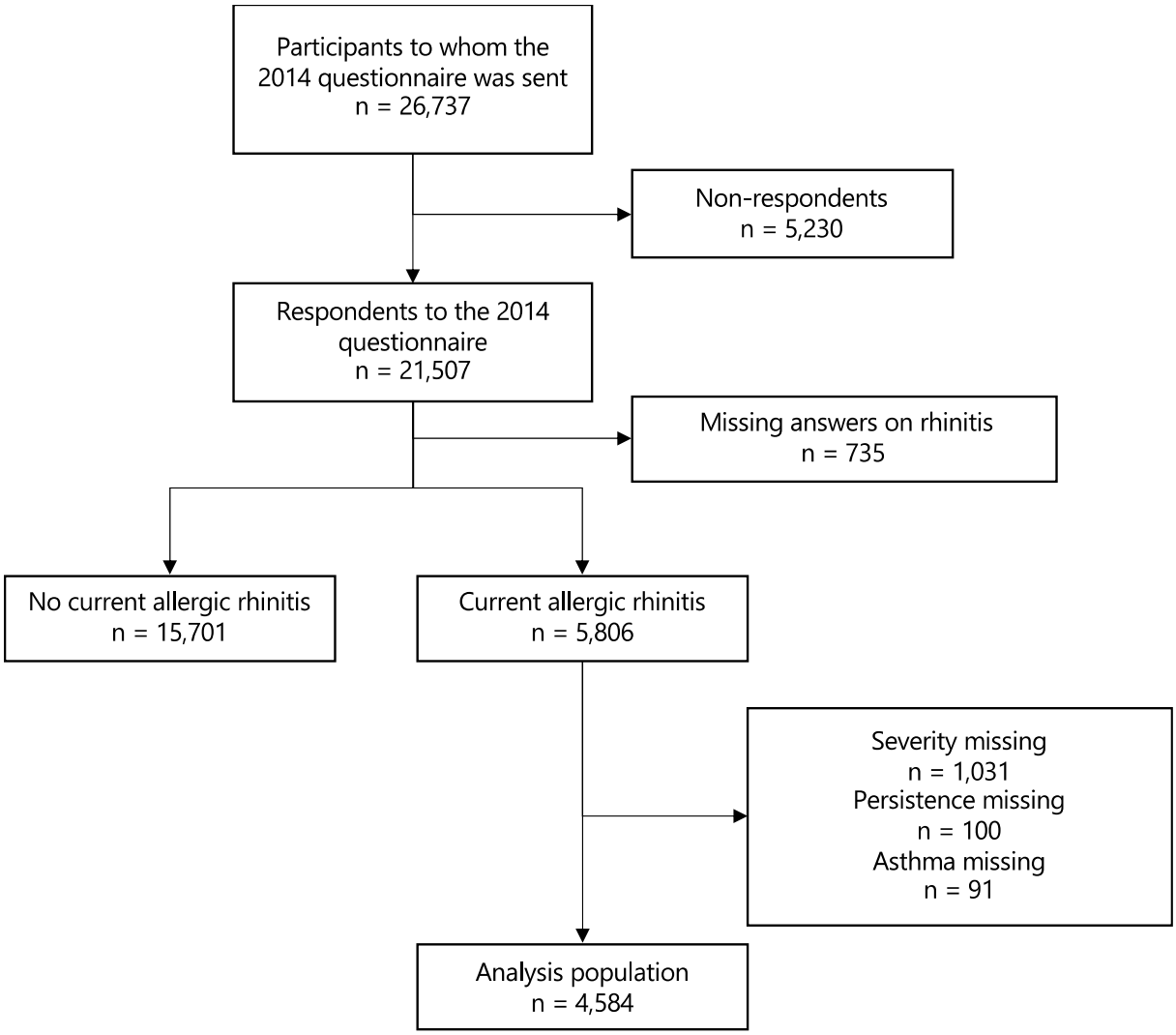


Figure 19: Flowchart of objective 1.4

Table 19 shows the demographic characteristics of the study population, 57.2% of the participants were women, 25.3% reported ever asthma and the mean age was 50.1 years. Based on the ARIA severity classification, 60.0% of the participants were classified as mild and 40.0% as moderate-severe rhinitis. The mean TNSS4 was 5.8. Based on the ARIA duration classification, 68.7% of the participants were classified as intermittent and 31.3% as persistent rhinitis. By crossing the two classifications, 44.0% of participants were classified as mild/intermittent, 15.9% as mild/persistent, 24.7% as moderate-severe/intermittent, and 15.3% as moderate-severe/persistent.

Table 19: Demographic characteristics, and ARIA classification of participants with AR

	Analysis population (n=4,584)
Sex	
Men	1,964 (42.8%)
Women	2,620 (57.2%)
Age, years	50.1 (12.7)
Tobacco status	
Never smoker	2,053 (46.6%)
Ex-smoker	1,791 (40.7%)
Current smoker	559 (12.7%)
Educational level	
Less than high school	319 (7.0%)
High school	1,274 (28.0%)
University	2,957 (65.0%)
Asthma	
Never asthma	3,424 (74.7%)
Ever asthma	1,160 (25.3%)
Rhinitis severity	
Mild	2,750 (60.0%)
Moderate to severe	1,834 (40.0%)
TNSS4	5.8 (2.8)
TNSS4	
[0-2]	604 (13.2%)
[3-4]	1,030 (22.5%)
[5-6]	1,183 (25.8%)
≥7	1,767 (38.5%)
Rhinitis duration	
Intermittent	3,150 (68.7%)
Persistent	1,434 (31.3%)
ARIA classification	
Mild/Intermittent	2,019 (44.0%)
Mild/Persistent	731 (15.9%)
Moderate-severe/Intermittent	1,131 (24.7%)
Moderate-severe/Persistent	703 (15.3%)

Data are mean (SD) or n (%), TNSS4: Total Symptom Score 4

4.1.4.5. AR severity

The characteristics of participants with AR according to rhinitis severity are presented in Table 20. There were more women with moderate-severe AR than with mild AR. Participants with moderate-severe AR had a higher mean eosinophil count and a higher TNSS4 as well as an earlier age of onset of rhinitis symptoms than those with mild AR. Participants with moderate-severe AR also reported more multi-morbidities (ever asthma, ever conjunctivitis, or ever eczema), nasal symptoms, triggers of rhinitis symptoms (except unknown triggers) and persistent rhinitis (all p-values < 0.05) than those with mild AR. Regarding treatments, participants with moderate-severe AR reported more co-medication (OAH + INCS) than those with mild AR (42.4% *vs* 25.7%). Considering a definition of severity in four classes based on the TNSS4, the same characteristics as with the ARIA dichotomous classification were observed with a gradation between the four classes (p trend < 0.05, Table S2 Appendix 6).

Table 20: Characteristics of participants with AR according to rhinitis severity

	Mild (n=2,768)	**Mod-Severe (n=1,834)**	**p**
Sex			<0.0001
Men	1,268 (46.1%)	696 (37.9%)	
Women	1,482 (53.9%)	1,138 (62.1%)	
Age, years	51.8 (12.5)	47.6 (12.5)	<0.0001
Tobacco status			0.08
Never smoker	1,220 (46.2%)	833 (47.3%)	
Ex-smoker	1,106 (41.8%)	685 (38.9%)	
Current smoker	317 (12.0%)	242 (13.8%)	
Educational level			0.64
Less than high school	183 (6.7%)	136 (7.4%)	
High school	765 (28.1%)	509 (27.9%)	
University	1,776 (65.2%)	1,181 (64.7%)	
BMI, kg/m^2			0.61
<18.5	55 (2.0%)	45 (2.5%)	
[18.5-25[	1,602 (59.1%)	1,037 (57.9%)	
[25-30[	780 (28.8%)	519 (29.0%)	
≥30	272 (10.0%)	191 (10.7%)	
Asthma			<0.0001
Never asthma	2,155 (78.4%)	1,269 (69.2%)	
Ever asthma	595 (21.6%)	565 (30.8%)	
Conjunctivitis			<0.0001
Never conjunctivitis	1,228 (48.7%)	686 (40.3%)	
Ever conjunctivitis	1,292 (51.3%)	1017 (59.7%)	
Eczema			<0.0001
Never eczema	1,557 (62.4%)	922 (55.1%)	
Ever eczema	938 (37.6%)	751 (44.9%)	
Eosinophil count, cells/mm^3	203.2 (139.0)	218.5 (162.3)	0.004
TNSS4	4.5 (2.1)	7.8 (2.3%)	<0.0001

	Mild (n=2,768)	Mod-Severe (n=1,834)	p
Rhinitis duration			<0.0001
Intermittent	2,019 (73.4%)	1,131 (61.7%)	
Persistent	731 (26.6%)	703 (38.3%)	
Reported symptoms†			
Rhinorrhoea	1,885 (68.5%)	1,508 (82.2%)	<0.0001
Nasal congestion/obstruction	1,750 (63.6%)	1,691 (92.2%)	<0.0001
Nasal itching	1,680 (61.1%)	1,307 (71.3%)	<0.0001
Sneezing	1,902 (69.2%)	1,487 (81.1%)	<0.0001
Associated-eye symptoms	1,693 (62.1%)	1,348 (73.9%)	<0.0001
Number of reported symptoms	3.2 (1.3)	4.0 (1.1%)	<0.0001
Age of onset of rhinitis, year	24.6 (15.5)	21.4 (13.6)	<0.0001
Reported triggers of rhinitis symptoms†			
Dust mites or house dust	900 (32.7%)	720 (39.3%)	<0.0001
Animals	296 (10.8%)	291 (15.9%)	<0.0001
Pollens	1,451 (52.8%)	1,033 (56.3%)	0.02
Air pollution	667 (24.3%)	571 (31.1%)	<0.0001
Change in weather	692 (25.2%)	620 (33.8%)	<0.0001
Tobacco	146 (5.3%)	153 (8.3%)	<0.0001
Cold air	630 (22.9%)	487 (26.6%)	0.005
Other	307 (11.2%)	274 (14.9%)	0.0002
Unknown	735 (26.7%)	459 (25.0%)	0.20
Number of reported triggers	2.1 (1.2)	2.5 (1.4)	<0.0001
Rhinitis treatment			<0.0001
Neither OAH nor INCS	1,100 (40.5%)	405 (22.4%)	
OAH only	617 (22.7%)	398 (22.0%)	
INCS only	303 (11.1%)	239 (13.2%)	
OAH and INCS	698 (25.7%)	770 (42.5%)	

Data are mean (SD) or n (%), BMI: Body Mass Index, INCS: Intranasal Corticosteroids, OAH: Oral Antihistamines, TNSS4: Total Symptom Score 4, †: several possible answers

4.1.4.6. AR duration

The characteristics of participants with AR according to rhinitis duration are presented in Table 21. No significant differences were observed for gender, age, smoking status, education level and BMI between groups. Participants with persistent AR had a higher mean eosinophil count, a higher TNSS4 and reported more moderate-severe rhinitis than those with intermittent AR. Participants with persistent AR also reported significantly more ever asthma or ever conjunctivitis, but not ever eczema. Regarding treatment, participants with persistent AR reported more co-medication (OAH + INCS) than those with intermittent AR (42.6% *vs* 27.8%).

Table 21: Characteristics of participants with AR according to rhinitis duration

	Intermittent (n=3,150)	**Persistent (n=1,434)**	**p**
Sex			0.10
Men	1,375 (43.7%)	589 (41.1%)	
Women	1,775 (56.3%)	845 (58.9%)	
Age, years	50.3 (12.5)	49.8 (13.0)	0.28
Tobacco status			0.35
Never smoker	1,415 (46.6%)	638 (46.8%)	
Ex-smoker	1,224 (40.3%)	567 (41.6%)	
Current smoker	400 (13.2%)	159 (11.7%)	
Educational level			0.46
Less than high school	217 (6.9%)	102 (7.1%)	
High school	892 (28.6%)	382 (26.8%)	
University	2,014 (64.5%)	943 (66.1%)	
BMI, kg/m^2			0.07
<18.5	58 (1.9%)	42 (3.0%)	
[18.5-25[	1,805 (58.3%)	834 (59.4%)	
[25-30[	905 (29.2%)	394 (28.0%)	
≥30	328 (10.6%)	135 (9.6%)	
Asthma			0.002
Never asthma	2,396 (76.1%)	1,028 (71.7%)	
Ever asthma	754 (23.9%)	406 (28.3%)	
Conjunctivitis			0.002
Never conjunctivitis	1,359 (47.0%)	555 (41.8%)	
Ever conjunctivitis	1,535 (53.0%)	774 (58.2%)	
Eczema			0.15
Never eczema	1,721 (60.2%)	758 (57.9%)	
Ever eczema	1,137 (39.8%)	552 (42.1%)	
Eosinophil count, cells/mm^3	203.4 (139.7)	222.1 (166.3)	0.001
TNSS4	5.6 (2.7)	6.4 (2.8)	<0.0001
Rhinitis severity			<0.0001
Mild	2,019 (64.1%)	731 (51.0%)	
Moderate-Severe	1,131 (35.9%)	703 (49.0%)	

	Intermittent (n=3,150)	Persistent (n=1,434)	p
Reported symptoms†			
Rhinorrhoea	2,289 (72.7%)	1,104 (77.0%)	0.002
Nasal congestion/obstruction	2,299 (73.0%)	1,142 (79.6%)	<0.0001
Nasal itching	2,030 (64.4%)	957 (66.7%)	0.13
Sneezing	2,301 (73.1%)	1,088 (75.9%)	0.04
Associated-eye symptoms	2,066 (66.0%)	975 (68.7%)	0.08
Number of reported symptoms	3.5 (1.3)	3.7 (1.3)	<0.0001
Age of onset of rhinitis, year	23.0 (14.6)	23.7 (15.2)	0.21
Reported triggers of rhinitis symptoms†			
Dust mites or house dust	1,095 (34.8%)	525 (36.6%)	0.22
Animals	401 (12.7%)	186 (13.0%)	0.82
Pollens	1,691 (53.7%)	793 (55.3%)	0.31
Air pollution	790 (25.1%)	448 (31.2%)	<0.0001
Change in weather	937 (29.7%)	375 (26.2%)	0.01
Tobacco	180 (5.7%)	119 (8.3%)	0.001
Cold air	774 (24.6%)	343 (23.9%)	0.63
Other	378 (12.0%)	203 (14.2%)	0.04
Unknown	757 (24.0%)	437 (30.5%)	<0.0001
Number of reported triggers	2.2 (1.2)	2.4 (1.5)	0.0002
Rhinitis treatment			<0.0001
Neither OAH nor INCS	1,179 (37.8%)	326 (23.1%)	
OAH only	722 (23.2%)	293 (20.7%)	
INCS only	350 (11.2%)	192 (13.6%)	
OAH and INCS	865 (27.8%)	603 (42.6%)	

Data are mean (SD) or n (%), BMI: Body Mass Index, INCS: Intranasal Corticosteroids, OAH: Oral Antihistamines, TNSS4: Total Symptom Score 4, †: several possible answers

4.1.4.7. Four classes ARIA classification

4.1.4.7.1. Descriptive analysis

The characteristics of participants with AR according to the four ARIA classes are presented in Table 22.
The four classes had different characteristics: participants with mild AR, whether it was intermittent or persistent, had the lowest prevalences for ever asthma (21.2%), ever conjunctivitis (50.6%), and ever eczema (37.4%), the highest proportion of participants with neither OAH nor INCS (43.7%), and the lowest mean eosinophil counts (201 ± 138). In contrast, participants with moderate-severe/persistent AR had the highest prevalences for ever asthma (34.1%), ever conjunctivitis (63.4%), and ever eczema (46.3%), the highest proportion of participants with co-medication (OAH + INCS) (52.3%), and the highest mean eosinophil count (235 ± 188). Participants with mild/persistent rhinitis had the latest age of onset of symptoms and the higher percentage of participants reporting not knowing what triggered their symptoms. In contrast participants with moderate-severe/persistent rhinitis had the earliest age of onset of symptoms and the lower percentage of participants reporting not knowing what triggered their symptoms.

Table 22: Characteristics of AR according to the ARIA classification

	Mild Intermittent (n=2,019)	**Mild Persistent (n=731)**	**Mod-Severe Intermittent (n=1,131)**	**Mod-Severe Persistent (n=703)**	**p**
Sex					<0.0001
Men	937 (46.4%)	331 (45.3%)	438 (38.7%)	258 (36.7%)	
Women	1,082 (53.6%)	400 (54.7%)	693 (61.3%)	445 (63.3%)	
Age, years	51.9 (12.3)	51.8 (13.2)	47.4 (12.4)	47.8 (12.6)	<0.0001
Tobacco status					0.06
Never smoker	889 (45.7%)	331 (47.6%)	526 (48.2%)	307 (46.0%)	
Ex-smoker	821 (42.2%)	285 (40.9%)	403 (36.9%)	282 (42.2%)	
Current smoker	237 (12.2%)	80 (11.5%)	163 (14.9%)	79 (11.8%)	
Educational level					0.76
Less than high school	134 (6.7%)	49 (6.7%)	83 (7.4%)	53 (7.6%)	
High school	564 (28.2%)	201 (27.7%)	328 (29.2%)	181 (25.8%)	
University	1,300 (65.1%)	476 (65.6%)	714 (63.5%)	467 (66.6%)	
BMI, kg/m^2					0.36
<18.5	34 (1.7%)	21 (2.9%)	24 (2.2%)	21 (3.1%)	
[18.5-25[	1,175 (59.1%)	427 (59.3%)	630 (56.9%)	407 (59.4%)	
[25-30[	572 (28.8%)	208 (28.9%)	333 (30.1%)	186 (27.2%)	
≥30	208 (10.5%)	64 (8.9%)	120 (10.8%)	71 (10.4%)	
Asthma					<0.0001
Never asthma	1,590 (78.8%)	565 (77.3%)	806 (71.3%)	463 (65.9%)	
Ever asthma	429 (21.2%)	166 (22.7%)	325 (28.7%)	240 (34.1%)	
Conjunctivitis					<0.0001
Never conjunctivitis	913 (49.4%)	315 (46.8%)	446 (42.6%)	240 (36.6%)	
Ever conjunctivitis	934 (50.6%)	358 (53.2%)	601 (57.4%)	416 (63.4%)	

	Mild Intermittent (n=2,019)	Mild Persistent (n=731)	Mod-Severe Intermittent (n=1,131)	Mod-Severe Persistent (n=703)	p
Eczema					<0.0001
Never eczema	1,144 (62.6%)	413 (61.9%)	577 (56.0%)	345 (53.7%)	
Ever eczema	684 (37.4%)	254 (38.1%)	453 (44.0%)	298 (46.3%)	
Eosinophil count, cells/mm^3	200.7 (138.0)	209.9 (141.3)	208.1 (142.7)	234.7 (188.0)	<0.0001
TNSS4	4.3 (2.1)	4.8 (2.2)	7.7 (2.3)	8.0 (2.5)	<0.0001
Reported symptoms†					
Rhinorrhoea	1,346 (66.7%)	539 (73.7%)	943 (83.4%)	565 (80.4%)	<0.0001
Nasal congestion/obstruction	1,263 (62.6%)	487 (66.6%)	1,036 (91.6%)	655 (93.2%)	<0.0001
Nasal itching	1,240 (61.4%)	440 (60.2%)	790 (69.8%)	517 (73.5%)	<0.0001
Sneezing	1,387 (68.7%)	515 (70.5%)	914 (80.8%)	573 (81.5%)	<0.0001
Associated-eye symptoms	1,241 (61.9%)	452 (62.7%)	825 (73.4%)	523 (74.8%)	<0.0001
Number of reported symptoms	3.2 (1.3)	3.3 (1.3)	4.0 (1.0)	4.0 (1.1)	<0.0001
Age of onset of rhinitis, year	24.2 (15.3)	25.4 (16.0)	21.1 (13.3)	22.0 (14.2)	<0.0001
Reported triggers of rhinitis symptoms†					
Dust mites or house dust	654 (32.4%)	246 (33.7%)	441 (39.0%)	279 (39.7%)	0.0001
Animals	222 (11.0%)	74 (10.1%)	179 (15.8%)	112 (15.9%)	<0.0001
Pollens	1,077 (53.3%)	374 (51.2%)	614 (54.3%)	419 (59.6%)	0.009
Air pollution	464 (23.0%)	203 (27.8%)	326 (28.8%)	245 (34.9%)	<0.0001
Change in weather	541 (26.8%)	151 (20.7%)	396 (35.0%)	224 (31.9%)	<0.0001
Tobacco	94 (4.7%)	52 (7.1%)	86 (7.6%)	67 (9.5%)	<0.0001
Cold air	468 (23.2%)	162 (22.2%)	306 (27.1%)	181 (25.7%)	0.03
Other	213 (10.5%)	94 (12.9%)	165 (14.6%)	109 (15.5%)	0.0007
Unknown	497 (24.6%)	238 (32.6%)	260 (23.0%)	199 (28.3%)	<0.0001
Number of reported triggers	2.1 (1.1)	2.2 (1.3)	2.5 (1.3)	2.6 (1.5)	<0.0001
Rhinitis treatment					<0.0001
Neither OAH nor INCS	873 (43.7%)	227 (31.5%)	306 (27.4%)	99 (14.3%)	
OAH only	456 (22.8%)	161 (22.4%)	266 (23.8%)	132 (19.0%)	
INCS only	211 (10.6%)	92 (12.8%)	139 (12.4%)	100 (14.4%)	
OAH and INCS	458 (22.9%)	240 (33.3%)	407 (36.4%)	363 (52.3%)	

Data are mean (SD) or n (%), BMI: Body Mass Index, INCS: Intranasal Corticosteroids, OAH: Oral Antihistamines, TNSS4: Total Symptom Score 4, †: several possible answers

Participants with persistent rhinitis reported more months of symptom occurrence than participants with intermittent rhinitis, regardless of rhinitis severity (Figure 20).

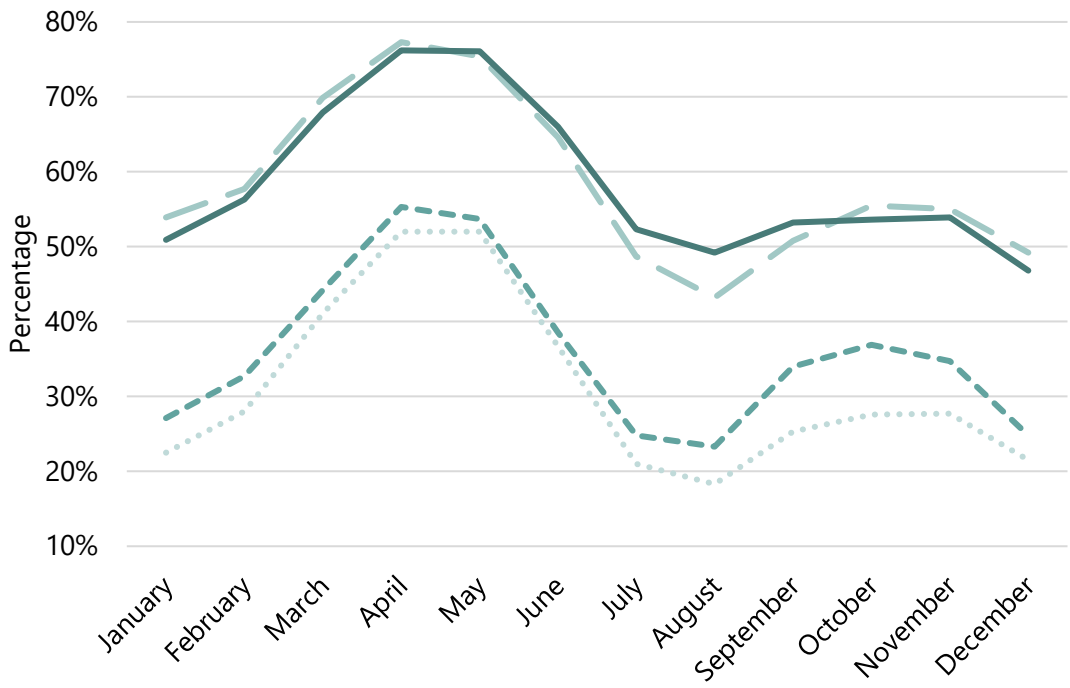


Figure 20: Percentage of participants with AR reporting symptoms by months according to ARIA classification

4.1.4.7.2. Multivariate analysis

Significant interaction coefficients were observed between severity and duration for TNSS4, rhinorrhea, pollen trigger, and symptoms reported for the months of September, October, November, December, January, February (all $p<0.05$). The results of the stratified analyses for these variables are presented in Table S3 (Appendix 6). For severity, higher ORs were observed in the intermittent stratum compared to the persistent stratum for: TNSS4, rhinorrhea and symptoms reported for the months of September, October, November, December, January, and February. In addition, the ORs for the months of symptoms were significant for the intermittent stratum but not for the persistent stratum. A significant and higher OR was observed for severity in the persistent stratum compared to the intermittent stratum. For duration, higher ORs were observed in the mild stratum compared to the moderate-severe stratum for: TNSS4, rhinorrhea and symptoms reported for the months of September, October, November, December, January, and February.

After adjusting for duration, the ORs comparing moderate-severe to mild AR were similar to those of the univariate analyses, except for the reported months of symptoms for which the ORs were lower and non-significant for the months of December, January, February, March, April, May and June (Table S4 Appendix 6).

After adjusting for duration, the ORs comparing intermittent to persistent AR were similar to those of the univariate analyses (Table S5 Appendix 6).

4.1.4.8. Influence of asthma on ARIA classification

Eight sub-classes were defined according to the ARIA classification and the ever asthma status in each subclass (Table 23), the number of participants per subclass ranging from 166 to 1,590.

When ever asthma multimorbidity was considered, differences between groups were more contrasted for most outcomes. In particular, ever conjunctivitis was higher by 10-20% in AR and ver asthma by comparison to AR alone. Age of onset of rhinitis ranged from 16.1 years (moderate-severe/intermittent AR + ever asthma) to 26.0 years (mild/intermittent AR alone). Importantly, co-medication (OAH + INCS) was reported from 18.8% (mild intermittent AR alone) to 64.1% (moderate-severe AR + ever asthma). The prevalence of reported symptoms was always higher in the AR + ever asthma group whatever the ARIA class. Reported triggers of rhinitis symptoms were far high in AR + ever asthma than AR alone for mites or house dust and animals. Moreover, significant differences in eosinophil counts were observed between classes in participants with ever asthma (range from 231 to 291 cells/mm^3) but not in the ones without asthma (range from 192 to 203 cells/mm^3).

Table 23: Characteristics of AR according to the ARIA classification and asthma status

	Mild Intermittent			Mild Persistent			Mod-Severe Intermittent			Mod-Severe Persistent		
	Never asthma (n=1,590)	Ever asthma (n=429)	p	Never asthma (n=565)	Ever asthma (n=166)	p	Never asthma (n=806)	Ever asthma (n=325)	p	Never asthma (n=463)	Ever asthma (n=240)	p
Sex			0.84			0.31			0.78			0.13
Men	736 (46.3%)	201 (46.9%)		262 (46.4%)	69 (41.6%)		310 (38.5%)	128 (39.4%)		179 (38.7%)	79 (32.9%)	
Women	854 (53.7%)	228 (53.1%)		303 (53.6%)	97 (58.4%)		496 (61.5%)	197 (60.6%)		284 (61.3%)	161 (67.1%)	
Age, years	52.6 (12.1)	49.3 (12.7)	<0.0001	52.5 (13.2)	49.2 (12.9)	0.004	48.1 (12.5)	45.7 (12.2)	0.003	49.0 (12.9)	45.5 (11.7)	0.0004
Tobacco status			0.54			0.05			0.71			0.80
Never smoker	692 (45.1%)	197 (47.9%)		268 (50.0%)	63 (39.4%)		375 (48.2%)	151 (48.1%)		205 (46.8%)	102 (44.3%)	
Ex-smoker	657 (42.8%)	164 (39.9%)		211 (39.4%)	74 (46.2%)		291 (37.4%)	112 (35.7%)		183 (41.8%)	99 (43.0%)	
Current smoker	187 (12.2%)	50 (12.2%)		57 (10.6%)	23 (14.4%)		112 (14.4%)	51 (16.2%)		50 (11.4%)	29 (12.6%)	
Educational level			0.11			0.75			0.74			0.59
Less than high school	115 (7.3%)	19 (4.5%)		40 (7.1%)	9 (5.5%)		62 (7.7%)	21 (6.5%)		36 (7.8%)	17 (7.1%)	
High school	446 (28.3%)	118 (27.9%)		156 (27.8%)	45 (27.4%)		231 (28.8%)	97 (29.9%)		124 (26.9%)	57 (23.8%)	
University	1,014 (64.4%)	286 (67.6%)		366 (65.1%)	110 (67.1%)		508 (63.4%)	206 (63.6%)		301 (65.3%)	166 (69.2%)	
BMI, kg/m^2			0.58			0.79			0.21			0.70
<18.5	25 (1.6%)	9 (2.1%)		18 (3.2%)	3 (1.8%)		20 (2.5%)	4 (1.2%)		14 (3.1%)	7 (3.0%)	
[18.5-25[	926 (59.1%)	249 (58.9%)		329 (59.3%)	98 (59.4%)		456 (58.1%)	174 (54.0%)		276 (60.9%)	131 (56.5%)	
[25-30[	457 (29.2%)	115 (27.2%)		160 (28.8%)	48 (29.1%)		230 (29.3%)	103 (32.0%)		117 (25.8%)	69 (29.7%)	
≥30	158 (10.1%)	50 (11.8%)		48 (8.6%)	16 (9.7%)		79 (10.1%)	41 (12.7%)		46 (10.2%)	25 (10.8%)	
Conjunctivitis			<0.0001			<0.0001			0.0008			<0.0001
Never conjunctivitis	771 (53.5%)	142 (35.0%)		264 (51.1%)	51 (32.7%)		340 (45.9%)	106 (34.6%)		184 (42.6%)	56 (25.0%)	
Ever conjunctivitis	670 (46.5%)	264 (65.0%)		253 (48.9%)	105 (67.3%)		401 (54.1%)	200 (65.4%)		248 (57.4%)	168 (75.0%)	
Eczema			0.0001			0.02			0.16			0.008
Never eczema	931 (64.9%)	213 (54.1%)		328 (64.3%)	85 (54.1%)		419 (57.4%)	158 (52.7%)		246 (57.3%)	99 (46.3%)	
Ever eczema	503 (35.1%)	181 (45.9%)		182 (35.7%)	72 (45.9%)		311 (42.6%)	142 (47.3%)		183 (42.7%)	115 (53.7%)	
Eosinophil count, cells/mm^3	192.4 (133.1)	231.0 (151.1)	0.00001	192.4 (121.4)	268.5 (182.5)	<0.0001	192.7 (133.3)	247.1 (157.8)	<0.0001	203.0 (155.2)	291.1 (225.0)	<0.0001
TNSS4	4.2 (2.1)	4.8 (2.1)	<0.0001	4.6 (2.2)	5.3 (2.1)	0.001	7.6 (2.2)	7.9 (2.3)	0.03	7.7 (2.5)	8.5 (2.3)	0.0002
Reported symptoms†												
Rhinorrhoea	1,045 (65.7%)	301 (70.2%)	0.08	411 (72.7%)	128 (77.1%)	0.26	667 (82.8%)	276 (84.9%)	0.38	362 (78.2%)	203 (84.6%)	0.04
Nasal congestion/obstruction	968 (60.9%)	295 (68.8%)	0.003	358 (63.4%)	129 (77.7%)	0.0006	739 (91.7%)	297 (91.4%)	0.87	428 (92.4%)	227 (94.6%)	0.29
Nasal itching	945 (59.4%)	295 (68.8%)	0.0004	332 (58.8%)	108 (65.1%)	0.14	555 (68.9%)	235 (72.3%)	0.25	324 (70.0%)	193 (80.4%)	0.003
Sneezing	1,086 (68.3%)	301 (70.2%)	0.46	392 (69.4%)	123 (74.1%)	0.24	638 (79.2%)	276 (84.9%)	0.03	359 (77.5%)	214 (89.2%)	0.0002
Associated-eye symptoms	932 (59.1%)	309 (72.5%)	<0.0001	346 (62.1%)	106 (64.6%)	0.56	570 (71.0%)	255 (79.4%)	0.004	325 (70.7%)	198 (82.8%)	0.0004

	Mild Intermittent			Mild Persistent			Mod-Severe Intermittent			Mod-Severe Persistent		
	Never asthma (n=1,590)	Ever asthma (n=429)	p	Never asthma (n=565)	Ever asthma (n=166)	p	Never asthma (n=806)	Ever asthma (n=325)	p	Never asthma (n=463)	Ever asthma (n=240)	p
Number of reported symptoms	3.1 (1.3)	3.5 (1.3)	<0.0001	3.3 (1.3)	3.6 (1.2)	0.006	3.9 (1.1)	4.1 (1.0)	0.006	3.9 (1.2)	4.3 (1.0)	<0.0001
Age of onset of rhinitis, years	26.0 (15.4)	18.6 (13.5)	<0.0001	27.5 (16.0)	18.7 (14.3)	<0.0001	23.2 (13.4)	16.1 (11.6)	<0.0001	24.4 (14.0)	17.8 (13.4)	<0.0001
Reported triggers of rhinitis symptoms†												
Dust mites or house dust	412 (25.9%)	242 (56.4%)	<0.0001	165 (29.2%)	81 (48.8%)	<0.0001	275 (34.1%)	166 (51.1%)	<0.0001	137 (29.6%)	142 (59.2%)	<0.0001
Animals	120 (7.5%)	102 (23.8%)	<0.0001	38 (6.7%)	36 (21.7%)	<0.0001	86 (10.7%)	93 (28.6%)	<0.0001	49 (10.6%)	63 (26.2%)	<0.0001
Pollens	816 (51.3%)	261 (60.8%)	0.0005	267 (47.3%)	107 (64.5%)	<0.0001	409 (50.7%)	205 (63.1%)	0.0002	249 (53.8%)	170 (70.8%)	<0.0001
Air pollution	339 (21.3%)	125 (29.1%)	0.0006	153 (27.1%)	50 (30.1%)	0.44	223 (27.7%)	103 (31.7%)	0.18	153 (33.0%)	92 (38.3%)	0.16
Change in weather	412 (25.9%)	129 (30.1%)	0.08	115 (20.4%)	36 (21.7%)	0.71	273 (33.9%)	123 (37.8%)	0.20	144 (31.1%)	80 (33.3%)	0.55
Tobacco	65 (4.1%)	29 (6.8%)	0.02	29 (5.1%)	23 (13.9%)	0.0001	46 (5.7%)	40 (12.3%)	0.0002	37 (8.0%)	30 (12.5%)	0.06
Cold air	358 (22.5%)	110 (25.6%)	0.17	130 (23.0%)	32 (19.3%)	0.31	212 (26.3%)	94 (28.9%)	0.41	111 (24.0%)	70 (29.2%)	0.13
Other	180 (11.3%)	33 (7.7%)	0.03	62 (11.0%)	32 (19.3%)	0.005	117 (14.5%)	48 (14.8%)	0.91	66 (14.3%)	43 (17.9%)	0.20
Unknown	432 (27.2%)	65 (15.2%)	<0.0001	204 (36.1%)	34 (20.5%)	0.0002	205 (25.4%)	55 (16.9%)	0.002	162 (35.0%)	37 (15.4%)	<0.0001
Number of reported triggers	2.0 (1.1)	2.6 (1.3)	<0.0001	2.1 (1.2)	2.6 (1.6)	<0.0001	2.3 (1.2)	2.9 (1.5)	<0.0001	2.4 (1.5)	3.0 (1.6)	<0.0001
Rhinitis treatment			<0.0001			<0.0001			<0.0001			0.00001
Neither OAH nor INCS	758 (48.1%)	115 (27.3%)		198 (35.6%)	29 (17.7%)		251 (31.5%)	55 (17.1%)		84 (18.4%)	15 (6.3%)	
OAH only	340 (21.6%)	116 (27.5%)		123 (22.1%)	38 (23.2%)		188 (23.6%)	78 (24.3%)		91 (19.9%)	41 (17.3%)	
INCS only	181 (11.5%)	30 (7.1%)		77 (13.8%)	15 (9.1%)		112 (14.1%)	27 (8.4%)		71 (15.5%)	29 (12.2%)	
OAH and INCS	297 (18.8%)	161 (38.2%)		158 (28.4%)	82 (50.0%)		246 (30.9%)	161 (50.2%)		211 (46.2%)	152 (64.1%)	

Data are mean (SD) or n (%), BMI: Body Mass Index, INCS: Intranasal Corticosteroids, OAH: Oral Antihistamines, TNSS4: Total Symptom Score 4, †: several possible answers

4.1.4.9. Discussion

For the first time in a population-based study in adults, AR has been described according to the four classes ARIA classification. More symptoms, conjunctivitis, and eczema were associated with moderate-severe AR. Asthma prevalence, treatments and report of rhinitis triggers were higher for participants with moderate-severe and/or persistant rhinitis. Considering asthma status gave additional information to the ARIA classification. Within each of the four ARIA classes, compared to participants with rhinitis alone, participants with rhinitis and asthma had significantly more severe symptoms, more conjunctivitis, higher eosinophil count, and more INCS and OAH co-medication.

We found that 40% of participants reported moderate to severe rhinitis, which is lower than the frequency observed in patient cohorts. Indeed, in the majority of patients cohorts, more than two-thirds of patients reported moderate to severe symptoms (105,208–210). This is not surprising as it is known that patients who consult health professional are mainly those with severe symptoms, therefore clinical studies probably underestimate mild rhinitis.
Few population-based studies have estimated the prevalence of rhinitis according to its severity. In the four studies identified (65,107–109), the prevalence of moderate to severe rhinitis ranged from 56% to 87%, which is higher than the prevalence observed in our study, but the definitions of AR were all different across studies making comparisons difficult. In the present study, participants with moderate to severe rhinitis had different characteristics from those with mild rhinitis and these characteristics are similar to those reported in the clinical practice. Participants with moderate-severe AR reported a higher TNSS4 score as compared to those with mild AR, as previously reported in the literature (106,211). Similarly to Antonicelli *et al.* (212), in our study the participants with mild rhinitis reported less treatment than those with moderate-severe rhinitis. Participants with moderate-severe rhinitis reported more asthma than participants with mild rhinitis. Actually, the relationship between the severity of rhinitis and asthma is not clearly established, some studies showed a higher prevalence of asthma in the moderate-severe rhinitis group (54,106,213–216) whereas others did not (110,214,217). The ARIA classification has been criticized for only considering the severity of rhinitis in a dichotomous way: indeed, the large prevalence of moderate-severe rhinitis found in patient cohorts suggests an important heterogeneity in this disease severity group (211). Noteworthy, in Constances the opposite was observed thus participants with mild AR constituted more than half of the population. When considering a definition of severity in four classes based on the TNSS4 the same characteristics as with the ARIA dichotomous classification were observed with a gradation between the four classes, suggesting that the severity of rhinitis follows also a continuum. In Constances, 31% of the participants had had persistent rhinitis which is very similar to the 29% reported in the population-based study conducted in Europe by Bauchau *et al.* (101). Our findings suggest that persistent AR describes a distinct

group with different characteristics from intermittent AR. Indeed as in the studies by Bauchau *et al.* (101) and Bachert *et al.* (65), participants with persistent rhinitis had more symptoms than participants with intermittent rhinitis. In contrast to these studies, we found that participants with persistent rhinitis had also more asthma and conjunctivitis. Finally, participants with persistent rhinitis also reported more moderate-severe rhinitis which is consistent with the literature (65,103). The present study is the first one to have considered the four ARIA classes to describe AR in a population-based study among adults. As expected, due to the greater number of mild rhinitis, the prevalence of the four classes was different from that found in patients' cohorts. In our analyses, the four ARIA classes had different characteristics and accounting for asthma appears to bring an additional information to the ARIA classification, in line with our previous results which seem to indicate that rhinitis alone or rhinitis without asthma are two different phenotypes. This is the first time, in the general population, that the four ARIA classes have been studied according to asthma status and further studies are needed to confirm these results. The present work showed that, in the general population, different forms of rhinitis could be considered according to the severity and persistence of rhinitis, as expected from the results of studies in patient cohorts. Our results also show that considering both severity and persistence allows us to have four different classes and the addition of asthma brings additional information to better capture the heterogeneity of rhinitis. These findings may have implications for clinical practice and reinforce the need for specific management considering asthma in the treatment of rhinitis. Furthermore, it is likely that these different classes have different aetiologies and a research perspective would be to investigate the factors influencing the risk of developing these distinct forms of rhinitis.

In conclusion, for the first time in a large population-based study in adults, the characteristics of AR according to the four ARIA classes were described. This confirms what has been observed in clinical practice and highlight the interest of using the ARIA classification to define AR in the general population. Furthermore, asthma status adds important information on the ARIA classification. This renforces the need to include asthma status in the new ARIA classification.

4.1.5. Identification of rhinitis phenotypes using an unsupervised approach

Results from this section will be published as an original article (in preparation).

4.1.5.1. Introduction

The phenotypes presented in the previous sections were based on clinical classifications with a priori knowledge (i.e. a candidate approach) allowing some subjectivity in the choice of the classes. In this context, an unsupervised approach, which does not require any a priori knowledge, allows to avoid this subjectivity and is complementary approach to the candidate one. To date, this unsupervised approach has been little used to identify rhinitis phenotypes in population-based studies.
Thus this objective aimed to identify phenotypes of rhinitis using an unsupervised approach.

4.1.5.2. Material and methods

4.1.5.2.1. Study design and definitions

Cross-sectional analyses were carried out in Constances with the data from the follow-up questionnaire of 2014. The definitions of rhinitis and the variables of interest are those presented in the overall material and methods section 3.1.2.
Only participants with current rhinitis were included in the analyses.
The main analyses were carried out in complete case, i.e. after excluding participants with missing values for the variables of interest.

4.1.5.2.2. Selection of variables of interest for the cluster analysis

The selection of variables of interest was based on knowledge of rhinitis phenotypes and on the number of missing data. Based on a priori knowledge, 27 variables covering characteristics of rhinitis, and multimorbidities, were pre-selected to be potentially included (Table 24). As eosinophil count and age of onset of rhinitis had more than 20% of missing data, they were excluded from the main analyses, leading to a total of 25 variables. A sensitivity analysis (SA1) including the 27 variables was also performed with a complete-case approach.

Table 24: Variables of interest (population: participants with current rhinitis, n = 8180)

Variables	Type	Range/Levels	n missing data (%)	Included in analysis	
				MA	SA1
Age, year	Continuous	(19.6 - 74.2)	0 (0%)	X	X
Asthma	Categorical	(Never, Ever)	164 (2%)	X	X
Conjunctivitis	Categorical	(Never, Ever)	869 (11%)	X	X
Eczema	Categorical	(Never, Ever)	911 (11%)	X	X
Nasal allergies	Categorical	(Never, Ever)	111 (1%)	X	X
Eosinophil count	Continuous	(3.6 - 1566)	1,835 (22%)		X
Age of onset of rhinitis	Continuous	(1 - 72)	2,332 (29%)		X
Dust mites or house dust trigger	Categorical	(No, Yes)	0 (0%)	X	X
Animals trigger	Categorical	(No, Yes)	0 (0%)	X	X
Air pollution trigger	Categorical	(No, Yes)	0 (0%)	X	X
Change in weather trigger	Categorical	(No, Yes)	0 (0%)	X	X
Tobacco trigger	Categorical	(No, Yes)	0 (0%)	X	X
Pollens trigger	Categorical	(No, Yes)	0 (0%)	X	X
Cold air trigger	Categorical	(No, Yes)	0 (0%)	X	X
Other trigger	Categorical	(No, Yes)	0 (0%)	X	X
Unknown trigger	Categorical	(No, Yes)	0 (0%)	X	X
Rhinorrhea symptom score	Categorical	(0, 1, 2, 3)	635 (8%)	X	X
Congestion symptom score	Categorical	(0, 1, 2, 3)	824 (10%)	X	X
Itching symptom score	Categorical	(0, 1, 2, 3)	1,029 (13%)	X	X
Sneezing symptom score	Categorical	(0, 1, 2, 3)	709 (9%)	X	X
Associated eye symptoms score	Categorical	(0, 1, 2, 3)	749 (9%)	X	X
Duration of rhinitis	Categorical	(Intermittent - Persistent)	357 (4%)	X	X
Rhinitis treatment	Categorical	(Neither OAH nor INCS, OAH only, INCS only, OAH and INCS)	296 (4%)	X	X
Symptoms in Winter	Categorical	(No, Yes)	0 (0%)	X	X
Symptoms in Spring	Categorical	(No, Yes)	0 (0%)	X	X
Symptoms in Summer	Categorical	(No, Yes)	0 (0%)	X	X
Symptoms in Autumn	Categorical	(No, Yes)	0 (0%)	X	X

Included in analysis: An "X" indicates that the variable has been included in the construction of clusters for Main Analysis (MA), Sensitivity Analysis 1 (SA1)

4.1.5.2.3. Clustering methods

4.1.5.2.3.1. Main analysis

Cluster analysis comprises several unsupervised techniques aiming to identify a partition into homogeneous clusters in a data set. The selected variables of the present analysis were mixed, i.e. the dataset included both continuous and categorical variables. Several clustering algorithms exist to process either continuous or categorical data based on appropriate metrics (218). While it is possible to combine two types of weighted metrics depending on the variable type, balancing is not always easy. To carry out our cluster analysis, we have chosen the strategy which consists in relying on data embedding performed by a suited dimensional reduction method able to deal with mixed data. Thereby, we performed a two-step analysis where the clustering is applied to the data embedding. Such an approach is referred to as a "tandem analysis" (219).

4.1.5.2.3.1.1. Step 1: dimension reduction with FAMD

The dimension reduction technique attempts to transform the data into a lower dimensional space while retaining as much information about the original data. In the case of our tandem analysis, the main objective was not to convert data into a lower dimensional space but to use this technique in order to have new continuous variables that are principal components of Factorial Analysis of Mixed Data (FAMD)[5]. In this way, we have kept all the components arising from the FAMD and we thus avoid deleting the last components which can also capture the structure in classes.

4.1.5.2.3.1.2. Step 2: cluster analysis with K-means algorithm

From the components obtained by with the FAMD, a clustering was performed by using the K-means algorithm. K-means is a reallocation method of which here are the main steps (220):

The K-means algorithm requires to choose the number of clusters beforehand. Then, the algorithm selects as many points as the number of desired clusters to create initial centers.

Each observation is then associated with the nearest center to create temporary clusters.

The gravity center of each temporary cluster is calculated and these become the new cluster center.

Each observation is reallocated to the cluster which has the closest center.

This procedure is repeated until convergence.

[5] The FAMD can be considered as a hybrid method combing principal component analysis (PCA) and multiple correspondence analysis (MCA). More specifically, FAMD acts like PCA for continuous variables and like MCA for categorical variables. Continuous and categorical variables are normalized during the analysis to balance the influence of each set of variables.

To select the number of clusters, we considered the majority rule provided by the R package NbClust (221). NbClust R package provides 30 indices for determining the number of clusters and proposes to user the best clustering scheme from the different results obtained by varying all combinations of number of clusters, distance measures, and some clustering methods including K-means.

4.1.5.2.3.2. Sensitivity and supplementary analyses

We also performed sensitivity and supplementary analyses.
To investigate whether cluster characteristics differed according to asthma status, we performed cluster analysis considering the participants with asthma and those with never asthma separately.
We also performed the cluster analysis in complete-case with 27 variables including the eosinophil count and age of onset of rhinitis (sensitivity analysis 1, see Table 24).
We performed the analyses after imputation of missing data for the 25 variables of the main analysis. The R package missMDA (222) was used with the function imputeFAMD which consists in imputing the missing values using the regularized iterative FAMD algorithm. The number of components used to predict (ncp) the missing entries were two.

Supplementary analyses were performed by changing the number of clusters initiated in the K-means: 2 and 4 clusters.

The analyses were conducted using the R statistical software (R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/). The FactoMineR package (220) was used to run the FAMD, the NbClust package (221) to select the number of clusters, and the missMDA package (222) to impute the missing data.

4.1.5.3. Results

4.1.5.3.1. Demographic characteristics of the participants

Among the 26,737 participants included in the cohort by 2013, 21,507 (80%) of them completed the follow-up questionnaire of 2014. Participants with missing data regarding the definition of rhinitis (n = 497) or with no current rhinitis (n = 12,830) were excluded from the analyses. Among participants with current rhinitis, participants with missing data in any of the 25 variables selected for the main cluster analyses (n = 2,664) were also excluded. Finally, 5,516 participants with current rhinitis were included in the clustering analysis (Figure 21).

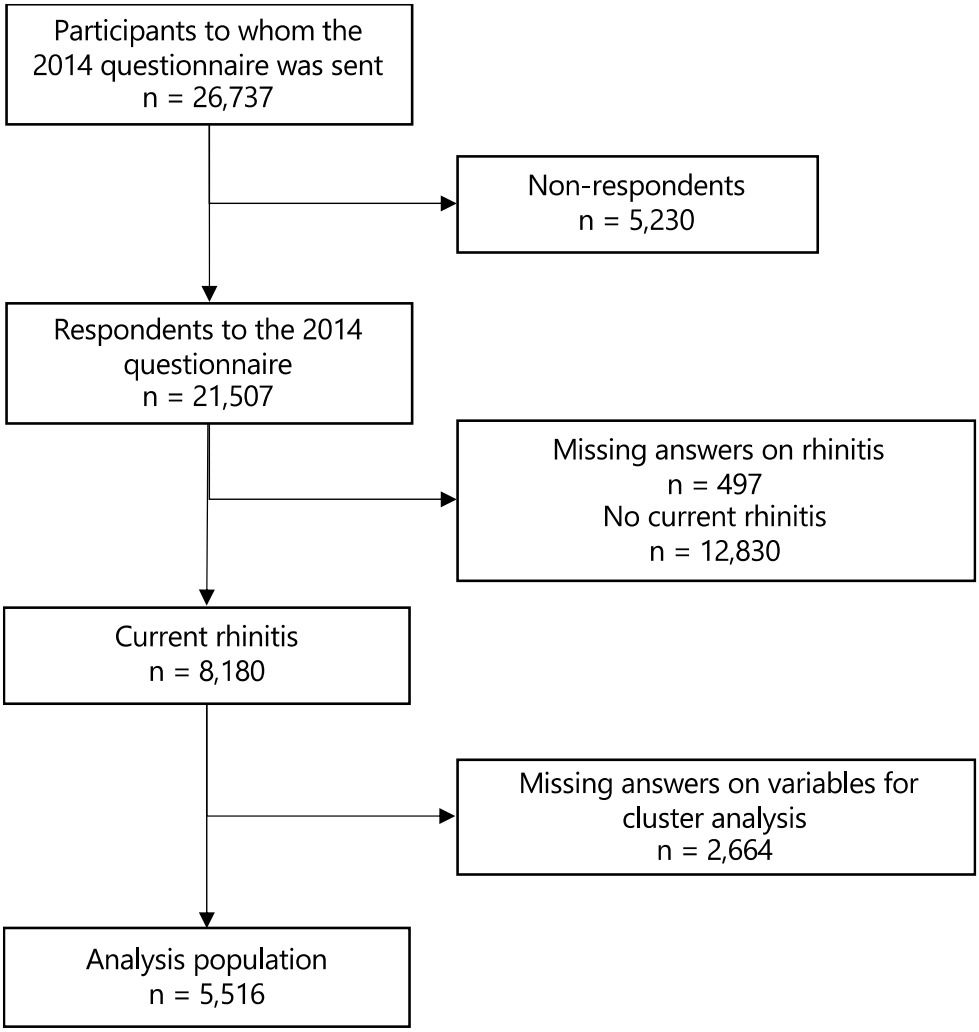


Figure 21: Flowchart of objective 1.5

Among participants included in the main analysis, 56.5% were women and the mean age was 49.6 years, 20.4% of the participants reported ever asthma and 71.6% ever nasal allergies (Table S1 Appendix 7).

4.1.5.3.2. Main analysis

The best number of clusters identified by the majority rule was three (Appendix 7).
The distribution of participants according to the three clusters was as follows: 46.9% (n = 2,586) in cluster 1, 43.1% (n = 2,379) in cluster 2 and 10.0% (n = 551) in cluster 3 (Figure 22).

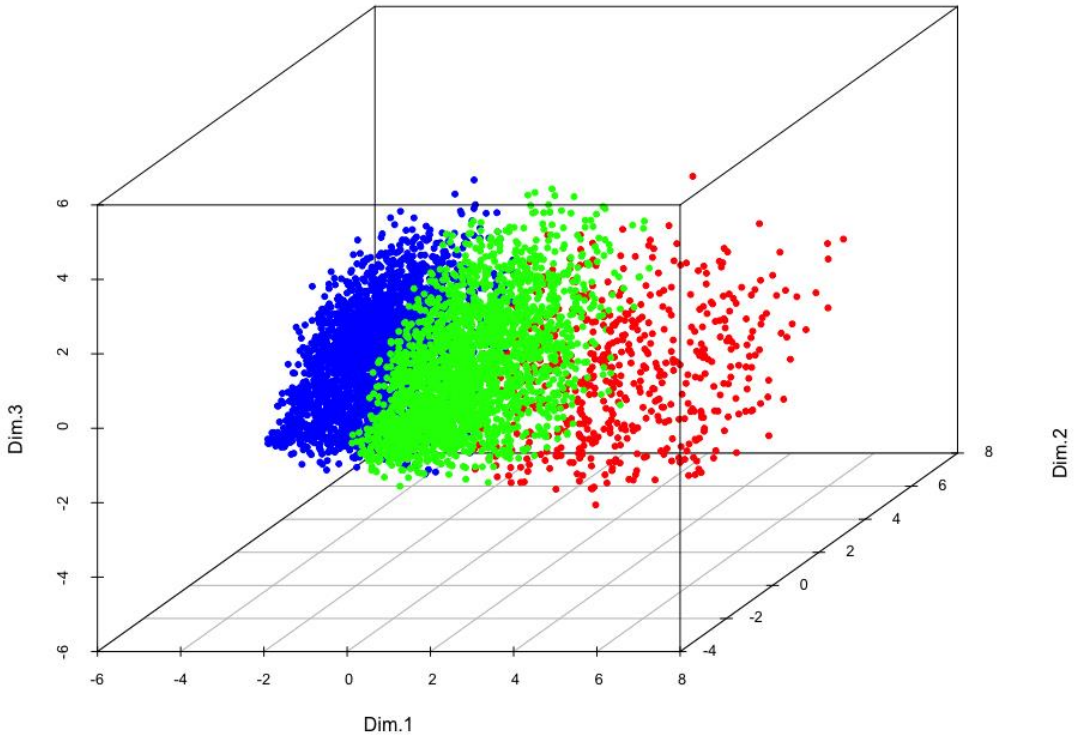


Figure 22: 3D visualization of the three clusters

The characteristics of the three clusters are shown in Table 25.
Cluster 1 was mainly characterized by rhinitis with few allergic triggers (dust mites, animals and pollens reported by less than 10% of participants), and by 53.1% of participants who did not know what triggered their symptoms. Symptoms reported were mainly congestion and rhinorrhea. Sneezing, nasal pruritus, and eye symptoms were reported by less than half of the participants. Cluster 1 was also characterized by participants with the latest age of onset of rhinitis, and who reported fewer nasal allergies and multimorbidities (ever asthma, ever conjunctivitis or ever eczema) compared to participants from clusters 2 or 3.
In clusters 2 and 3, more than 95% of participants reported ever nasal allergies and allergic triggers were more reported in cluster 2 and 3 as compared to cluster 1. All the participants from cluster 3 reported moderate-severe rhinitis. Compared to participants from cluster 2, participants from cluster 3 reported significantly more asthma, had an earlier age of symptom onset, reported more symptoms and more OAH and INCS treatments.

Table 25: Description and comparison of the three clusters identified in Constances

	Cluster 1 (n=2,586)	Cluster 2 (n=2,379)	Cluster 3 (n=551)	p	p_{C2vsC3}
Sex				<0.001	0.10
Men	1,233 (47.7%)	966 (40.6%)	202 (36.7%)		
Women	1,353 (52.3%)	1,413 (59.4%)	349 (63.3%)		
Age, years*	52.0 (13.0)	48.1 (12.6)	44.9 (12.2)	<0.001	<0.001
Tobacco status				<0.001	0.20
Never smoker	1,073 (43.2%)	1,128 (49.2%)	257 (48.6%)		
Ex-smoker	1,048 (42.2%)	896 (39.0%)	195 (36.9%)		
Current smoker	365 (14.7%)	271 (11.8%)	77 (14.6%)		
Educational level				0.01	0.41
Less than high school	170 (6.6%)	152 (6.4%)	43 (7.8%)		
High school	762 (29.7%)	603 (25.5%)	145 (26.4%)		
University	1,633 (63.7%)	1,607 (68.0%)	361 (65.8%)		
BMI, kg/m^2				0.36	0.57
<18.5	50 (2.0%)	54 (2.3%)	11 (2.0%)		
[18.5-25[	1,470 (58.0%)	1,380 (58.9%)	333 (62.0%)		
[25-30[	770 (30.4%)	666 (28.4%)	138 (25.7%)		
≥30	244 (9.6%)	244 (10.4%)	55 (10.2%)		
Asthma*				<0.001	0.003
Never asthma	2,409 (93.2%)	1,638 (68.9%)	343 (62.3%)		
Ever asthma	177 (6.8%)	741 (31.1%)	208 (37.7%)		
Conjunctivitis*				<0.001	0.86
Never conjunctivitis	2,077 (80.3%)	889 (37.4%)	203 (36.8%)		
Ever conjunctivitis	509 (19.7%)	1,490 (62.6%)	348 (63.2%)		
Eczema*				<0.001	0.19
Never eczema	2,007 (77.6%)	1,337 (56.2%)	292 (53.0%)		
Ever eczema	579 (22.4%)	1,042 (43.8%)	259 (47.0%)		
Nasal allergies*				<0.001	0.67
Never nasal allergies	1,439 (55.6%)	100 (4.2%)	26 (4.7%)		
Ever nasal allergies	1,147 (44.4%)	2,279 (95.8%)	525 (95.3%)		
Eosinophil count, $cells/mm^3$	180.6 (122.7)	208.3 (146.6)	231.0 (164.2)	<0.001	0.005
Age of onset of rhinitis	31.2 (17.3)	21.9 (13.7)	19.8 (12.7)	<0.001	0.002
Reported triggers of rhinitis symptoms†					
Dust mites or house dust*	239 (9.2%)	1,092 (45.9%)	268 (48.6%)	<0.001	0.27
Animals*	31 (1.2%)	422 (17.7%)	131 (23.8%)	<0.001	0.001
Pollens*	258 (10.0%)	1,733 (72.8%)	349 (63.3%)	<0.001	<0.001
Air pollution*	279 (10.8%)	799 (33.6%)	204 (37.0%)	<0.001	0.14
Change in weather*	680 (26.3%)	685 (28.8%)	186 (33.8%)	0.001	0.03
Tobacco*	85 (3.3%)	174 (7.3%)	61 (11.1%)	<0.001	0.005
Cold air*	677 (26.2%)	563 (23.7%)	147 (26.7%)	0.09	0.15
Other*	319 (12.3%)	269 (11.3%)	103 (18.7%)	<0.001	<0.001
Unknown*	1,372 (53.1%)	264 (11.1%)	103 (18.7%)	<0.001	<0.001
Number of reported triggers	1.5 (0.8)	2.5 (1.3)	2.8 (1.6)	<0.001	<0.001
Reported symptoms†					
Rhinorrhoea	1,503 (58.1%)	1,782 (74.9%)	487 (88.4%)	<0.001	<0.001
Nasal congestion/obstruction	1,589 (61.4%)	1,793 (75.4%)	500 (90.7%)	<0.001	<0.001
Nasal itching	941 (36.4%)	1,756 (73.8%)	467 (84.8%)	<0.001	<0.001

	Cluster 1 (n=2,586)	Cluster 2 (n=2,379)	Cluster 3 (n=551)	p	p_{C2vsC3}
Sneezing	1,281 (49.5%)	1,865 (78.4%)	520 (94.4%)	<0.001	<0.001
Associated-eye symptoms	790 (30.5%)	1,886 (79.3%)	489 (88.7%)	<0.001	<0.001
Number of symptoms	2.4 (1.2)	3.8 (1.1)	4.5 (0.8)	<0.001	<0.001
Rhinitis severity				<0.001	<0.001
Mild	1,940 (75.0%)	1,606 (67.5%)	0 (0.0%)		
Moderate-Severe	646 (25.0%)	773 (32.5%)	551 (100.0%)		
TNSS4	3.6 (2.1)	5.8 (2.2)	9.6 (2.1)	<0.001	<0.001
Rhinitis duration*				<0.001	<0.001
Intermittent	1,885 (72.9%)	1,703 (71.6%)	296 (53.7%)		
Persistent	701 (27.1%)	676 (28.4%)	255 (46.3%)		
ARIA classification				<0.001	<0.001
Mild/Intermittent	1,446 (55.9%)	1,183 (49.7%)	0 (0.0%)		
Mild/Persistent	494 (19.1%)	423 (17.8%)	0 (0.0%)		
Moderate-severe/Intermittent	439 (17.0%)	520 (21.9%)	296 (53.7%)		
Moderate-severe/Persistent	207 (8.0%)	253 (10.6%)	255 (46.3%)		
Rhinitis treatment*				<0.001	<0.001
Neither OAH nor INCS	1,786 (69.1%)	612 (25.7%)	75 (13.6%)		
OAH only	149 (5.8%)	712 (29.9%)	132 (24.0%)		
INCS only	464 (17.9%)	181 (7.6%)	37 (6.7%)		
OAH and INCS	187 (7.2%)	874 (36.7%)	307 (55.7%)		

*Data are mean (SD) or n (%), BMI: Body Mass Index, INCS: Intranasal Corticosteroids, OAH: Oral Antihistamines, TNSS4: Total Symptom Score 4, †: several possible answers, *: variables included in the construction of the clusters*

p: overall comparison p-values between the three clusters, p_{C2vsC3}: p-values of comparison between cluster 2 and cluster 3

The seasonality of symptoms differed across the clusters. In clusters 2 and 3, participants reported more symptoms during the Spring whereas participants from cluster 1 reported symptoms more symptoms during the cold months (Figure 23).

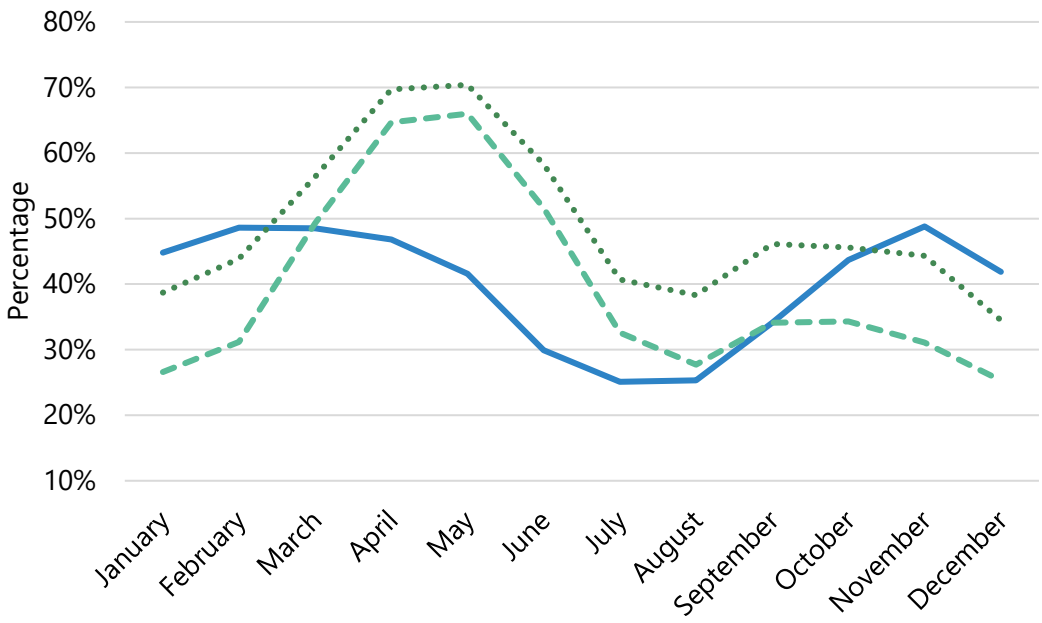


Figure 23: Percentage of participants reporting symptoms by months

4.1.5.3.3. Sensitivity and supplementary analyses

- Clustering according to asthma status

According to asthma status (4,390 participants with never asthma and 1,126 participants with ever asthma), the best number of clusters identified by the majority rule was three in both strata. The Table S2 (Appendix 7) shows the characteristics of these groups. The distribution of participants according to the three clusters was as follows: 51.3% (n = 2,250) in cluster 1, 40.0% (n = 1,755) in cluster 2 and 8.8% (n = 385) in cluster 3 in participants with never asthma; and 34.1% (n = 384) in cluster 1, 51.5% (n = 580) in cluster 2, and 14.4% (n = 162) in participants with ever asthma. Overall, the gradient in the characteristics of the clusters was the same as those of the main analysis both in the never asthma and in the ever asthma stratum, but compared to the participants with never ashtma, those with ever asthma had higher eosinophil count, more multimorbidities and more OAH and INCS treatments.

- Alternate variable selection

By adding age of onset and eosinophil count in the cluster analyses, data from 3,221 participants were analysed. The optimal number of clusters identified was also three. Overall, the gradient in the characteristics of the clusters was the same as those of the main analyses (Table S3 Appendix 7).

- Imputation of missing data

After imputation of missing values, data from 8,180 participants were analysed. Three clusters were identified, and the gradient in their characteristics was the same as those of the main analyses (Table S4 Appendix 7).

- Alternate number of clusters

Using other methods to choose the number of clusters, two and four clusters were also identified as the optimum choices (Appendix 7).

The results with two clusters are presented in Table S5 (Appendix 7). Overall, cluster 1 can be assimilated to cluster 1 highlighted in the main analyses and cluster 2 to a combination of clusters 2 and 3.

The results with four clusters are presented in Table S6 (Appendix 7). Overall, cluster 3 and cluster 4 can respectively be assimilated to cluster 2 and cluster 3 highlighted in the main analyses. Cluster 1 and 2 can be assimilated to cluster 1 of the main analyses. The difference between cluster 1 and 2 is mainly based on the reported triggers of rhinitis symptoms. In cluster 1, 80% of participants reported not knowing what triggered their symptoms while this was only 9% in cluster 2, in contrast cluster 2 was the cluster where participants reported the most triggers related to cold air or weather change.

4.1.5.4. Discussion

Performing unsupervised analyses in Constances led to the identification of three clusters. Cluster 1 (47%) can be assimilated to NAR, and clusters 2 (43%) and 3 (10%) can be assimilated to AR, cluster 3 being more severe, as all the participants from this reported moderate-severe rhinitis.

One of the strengths of this analysis is that it was conducted in a population-based study, allowing to capture mild forms of rhinitis that are not identifiable in patients' cohorts. Only three studies have been conducted in populations others than patients' cohorts: one in the Portuguese general population (112), one from the EGEA study (93), and one with 18-year-old participants from a UK birth cohort population (111). These studies were based on a relatively small number of participants, i.e. between 468 and 983. Our analyses were performed on 5,516 participants with rhinitis allowing a good stability of clusters even when considering a larger number of variables. The same clusters were found after imputation of missing data or with a different selection of variables of interest. Even if comparing our results to the literature is difficult because all the studies included different variables to construct the clusters, the following differences were consistently highlighted in the clusters: 1) allergic/non-allergic status of rhinitis (93,112) and/or 2) severity of rhinitis (111,112). In our analyses, the report of nasal allergies seems to be a discriminant variable to classify rhinitis. The severity of rhinitis was also a discriminant feature between the three groups, allowing to differentiate two allergic clusters. The cluster 3 that can be assimilated to moderate-severe AR was distinguished from cluster 2 (assimilated to AR) by the presence of more symptoms, triggers, INCS and OAH treatment and asthma. The blood eosinophil count was also the highest in the severe AR cluster.

In the supplementary analysis in which the number of clusters was two, the characteristics of the clusters were very similar to the two AR and NAR phenotypes identified with our candidate approach in Constances. In addition, to confirm the results of the candidate approach, the results of the present unsupervised approach provide an additional level of insight by showing, without *a priori* hypothesis, the importance of rhinitis severity to identify different rhinitis phenotypes.
Furthermore, it is interesting to note that when performing the unsupervised analyses accounting for asthma status, the same three clusters were found with the same gradients except that participants with ever asthma reported overall more comorbidities, more treatments, and had a higher mean count of blood eosinophils. These results are again consistent with the results of our previous candidate approach and support the hypothesis that rhinitis alone and rhinitis with asthma are two different entities.
Participants from the severe AR cluster had higher eosinophil count than participants from other groups, a difference suggesting that different pathophysiological mechanisms may be related to each cluster. Identifying rhinitis clusters based on biological and clinical variables would be of interest to identify rhinitis endotypes.

In conclusion, three clusters assimilated to NAR, AR and severe AR were identified highlighting the importance of rhinitis severity. These clusters are of great interest for the study of the aetiology of rhinitis.

4.1.6. Identification of rhinitis endotypes using an unsupervised approach

Results from this section will not be published as the findings are not innovative.

4.1.6.1. Introduction

The previous results highlighted a variability in severity that is not totally explained by the clinical features of the rhinitis. Integrating the biological markers could provide an additional and complementary level of knowledge on the pathophysiology of rhinitis. To date, the studies who have identified rhinitis endotypes with an unsupervised approach have been conducted in patients' cohorts.
Therefore, this objective aimed to identify endotypes of rhinitis using an unsupervised approach among adults.

4.1.6.2. Material and methods

4.1.6.2.1. Study design and definitions

Cross-sectional analyses were carried out with the data from the EGEA2 study.
The definitions of rhinitis and the variables of interest are those presented in the overall material and methods section 3.1.1.2.
Only participants with current rhinitis were included in the analyses.
The main analyses were carried out in complete case, i.e. after excluding participants with missing values for the variables of interest.

4.1.6.2.2. Selection of variables of interest for the cluster analysis

The selection of variables of interest was based on knowledge of rhinitis endotypes and on the number of missing data. Based on a priori knowledge, 46 variables covering characteristics of rhinitis, multimorbidities, and biology, were pre-selected to be potentially included (Table 26). We decided to exclude variables with more than 35% of missing data from the main analysis and 35 variables were included in the main cluster analysis. A sensitivity analysis (SA1) including the 46 variables was also performed with a complete-case approach.

Table 26: Variables of interest (population: participants with current rhinitis, n = 842)

Variable	Levels	missing		Included in analysis		
		n	%	MA	SA1	SA2
Dust mites or house dust trigger	No, Yes	0	0%	X	X	
Animals trigger	No, Yes	0	0%	X	X	
Other trigger	No, Yes	0	0%	X	X	
No trigger reported	No, Yes	0	0%	X	X	
Pollens trigger	No, Yes	0	0%	X	X	
Disturbance due to nasal symptoms	No, Low, Medium, High	0	0%	X	X	
Asthma*	Never, Ever	0	0%	X	X	
Age, year	Continuous	0	0%	X	X	
Duration of rhinitis	None, <1 month/year, <4 days/week, ≥4 days/week"	3	0%	X	X	
Eczema	Never, Ever	7	1%	X	X	
Nasal allergies	Never, Ever	18	2%	X	X	
Conjunctivitis	Never, Ever	27	3%	X	X	
Symptoms in Winter	No, Yes	23	3%	X	X	
Symptoms in Spring	No, Yes	24	3%	X	X	
Symptoms in Summer	No, Yes	24	3%	X	X	
Symptoms in Autumn	No, Yes	24	3%	X	X	
Age of onset of rhinitis, year	Continuous	69	8%	X	X	
Associated eye symptoms after a stimulus	No, Yes	71	8%	X	X	
Sneezing after a stimulus	No, Yes	73	9%	X	X	
Rhinorrhea after a stimulus	No, Yes	89	11%	X	X	
Allergy pathway						
IgE, IU/mL	Continuous	88	10%	X	X	X
At least one positive SPT	No, Yes	122	14%	X	X	X
IL-1RA, pg/mL	Continuous	383	45%		X	
IL-5, pg/mL	Continuous	383	45%		X	
IL-7, pg/mL	Continuous	383	45%		X	
IL-8, pg/mL	Continuous	383	45%		X	
IL-10, pg/mL	Continuous	383	45%		X	
IL-13, pg/mL	Continuous	383	45%		X	
Inflammation pathway						
Neutrophils, cells/mm^3	Continuous	87	10%	X	X	X
Eosinophils, cells/mm^3	Continuous	87	10%	X	X	X
CC-16, µg/L	Continuous	147	17%	X	X	X
HS-CRP, mg/L	Continuous	158	19%	X	X	X
TARC plasma EDTA, pg/mL	Continuous	262	31%	X	X	X
TSLP plasma EDTA, pg/mL	Continuous	262	31%	X	X	X
ECP, ng/mL	Continuous	274	33%	X	X	X

Variable	Levels	missing		Included in analysis		
		n	%	MA	SA1	SA2
EDN, ng/mL	Continuous	277	33%	X	X	X
TNFα, pg/mL	Continuous	383	45%		X	
Leptin, pg/mL	Continuous	383	45%		X	
FeNO, 50 mL/s	Continuous	440	52%		X	
Oxidative/Nitrosative pathway						
GPX, U/g	Continuous	109	13%	X	X	X
SOD, U/g	Continuous	111	13%	X	X	X
Catalase, k/g	Continuous	117	14%	X	X	X
FIOPs, RFU/mL	Continuous	133	16%	X	X	X
NO_2/NO_3 plasma, µM	Continuous	198	24%	X	X	X
NO_2/NO_3 condensate, µM	Continuous	311	37%		X	
EBC 8-iso, pg/mL	Continuous	465	55%		X	

CC-16: Clara Cell protein-16, CRP: C-Reactive Protein, EBC: Exalte Breath Condensate 8-isoprostanes, ECP: Eosinophil Cationic Protein, EDN: Eosinophil Derived Neurotoxin, FeNO: Fraction Exhaled Nitric Oxide, FlOP: Fluorescent oxidation product, GPX: Glutathione peroxidase, IgE: Immunoglobulin E, IL: Interleukin, SOD: Superoxide dismutase, SPT: Skin Prick Test, TARC: Thymus and Activation-Regulated Chemokine, TSLP: Thymic Stromal Lymphopoietin

**Asthma was not taken into account when analyses were stratified by asthma status.*

Included in analysis: An "X" indicates that the variable has been included in the construction of clusters for Main Analysis (MA), Sensitivity Analysis 1 (SA1) or Sensitivity Analysis 2 (SA2)

4.1.6.2.3. Clustering methods

Due to the design of EGEA and because the levels of biomarkers may change according to asthma, the clusters were constructed after stratification on asthma.

4.1.6.2.3.1. Main analysis

The same method as that applied in Constances (see 4.1.5.2.3.1) was carried out:

Step 1: Dimension reduction with Factorial Analysis of Mixed Data

Step 2: Cluster Analysis with K-means algorithm

4.1.6.2.3.2. Sensitivity and supplementary analyses

Sensitivity analyses were performed in complete-case by changing the variables selected to identify the clusters (see Table 26): 1) an approach including the 46 variables of interest in the selection step (SA1) and 2) an approach including only the 15 biological variables with less than 35% of missing data (SA2).

We also performed the analyses after imputation of missing data for the 35 variables of the main analysis. as done in Constances (see 4.1.5.2.3.1 Main analysis).

4.1.6.2.4. Statistical analyses

To test the differences between groups, Chi2 tests were performed for qualitative variables and ANOVA tests were performed for quantitative variables.

The analyses were conducted using the R statistical software (R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/). The FactoMineR package (220) was used to run the FAMD, the NbClust package (221) to select the number of clusters, and the missMDA package (222) to impute the missing data.

4.1.6.3. Results

4.1.6.3.1. Demographic characteristics of the participants

Among the alive cohort (n = 2,002), 92% of the participants (n = 1,845) completed a short-self-administered questionnaire, and among them 1,601 (n = 1,571 adults aged ≥16 years) had a complete examination, and 842 adults reported current rhinitis. Participants with missing data for the variables used for the main cluster analysis were excluded (n = 514). Finally, 328 participants with current rhinitis (140 with never asthma and 188 with ever asthma) were included in the analysis population (Figure 24).

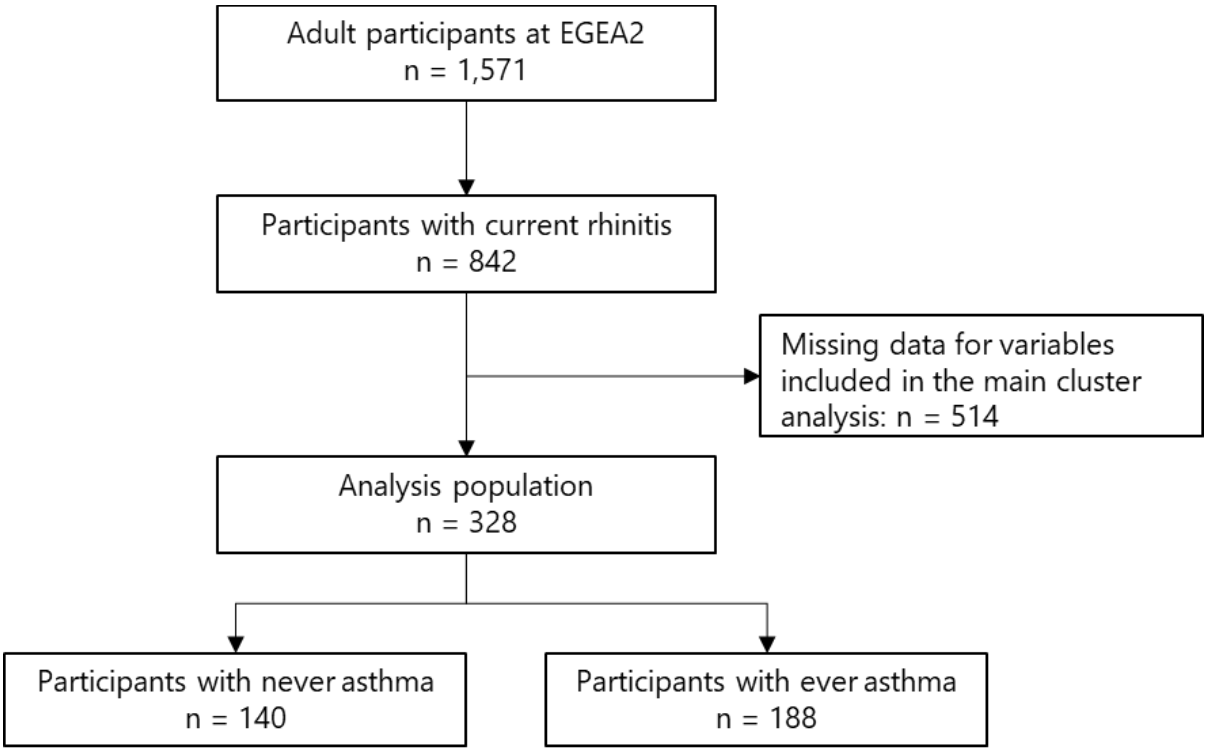


Figure 24: Flowchart of objective 1.6

The demographic characteristics of the 328 included participants are presented in Table S1 (Appendix 8), 55.5% of participants were women and the mean age was 41.3 years, 57.3% of the participants had ever asthma and 72.0% reported ever nasal allergies.
Compared to participants with never asthma, those with ever asthma had higher IgE levels and more positive SPTs, allergic triggers and disturbing symptoms.

4.1.6.3.2. Main analysis

Considering the whole population, the best number of clusters identified by the majority rule was two.
The distribution of participants according to the two clusters was as follows: 39.6% (n = 130) in cluster 1 and 60.4% (n = 198) in cluster 2 (Table 27). Cluster 1 and cluster 2 differed mainly by the allergy pathway. A large majority of cluster 2 participants had at least one positive SPT a higher average serum IgE concentration than participants in cluster 1. Cluster 2 participants also reported significantly more allergic triggers such as pollens or animals. Cluster 2 was also characterized by more participants with ever asthma than cluster 1. Levels of some biomarkers related to inflammation pathways were also on average higher in cluster 2 compared to cluster 1, in particular blood eosinophils, FeNO and EDN. The mean leptin level was higher in cluster 1 compared to cluster 2. The mean levels of biomarkers of the oxidative stress/nitrosative stress pathway were not significantly different between the two clusters.
After stratification by asthma status, the best number of clusters identified by the majority rule was also two in each one of the strata.
The distribution of participants according to the two clusters was as follows: 45.7% (n = 64) in cluster 1 and 54.3% (n = 76) in cluster 2 in participants with never asthma, and 27.7% (n = 52) in cluster 1 and 72.3% (n = 136) in cluster 2 in those with ever asthma. The Table 28 shows the characteristics of these groups. Overall, in both strata, cluster 1 and cluster 2 differed mainly by the allergy pathway, with a large majority of cluster 2 participants having at least one positive SPT and reporting allergic triggers. Interestingly, differences in the mean levels of biomarkers were greater for participants with ever asthma than for those with never asthma.

Table 27: Description and comparison of the two clusters identified in EGEA

	Cluster 1 (n=130)	Cluster 2 (n=198)	p
Sex			0.59
Men	55 (42.3%)	91 (46.0%)	
Women	75 (57.7%)	107 (54.0%)	
Age, year*	49.7 (16.6)	35.8 (14.2)	<0.001
Tobacco status			0.006
Never smoker	53 (40.8%)	102 (51.5%)	
Ex-smoker	47 (36.2%)	40 (20.2%)	
Current smoker	30 (23.1%)	56 (28.3%)	
Educational level			<0.001
Less than high school	40 (30.8%)	23 (11.7%)	
High school	25 (19.2%)	62 (31.5%)	
University	65 (50.0%)	112 (56.9%)	
Asthma*			<0.001
Never asthma	81 (62.3%)	59 (29.8%)	
Ever asthma	49 (37.7%)	139 (70.2%)	
Conjunctivitis*			<0.001
Never conjunctivitis	95 (73.1%)	80 (40.4%)	
Ever conjunctivitis	35 (26.9%)	118 (59.6%)	
Eczema*			0.15
Never eczema	81 (62.3%)	106 (53.5%)	
Ever eczema	49 (37.7%)	92 (46.5%)	
Nasal allergies*			<0.001
Never nasal allergies	79 (60.8%)	13 (6.6%)	
Ever nasal allergies	51 (39.2%)	185 (93.4%)	
Age of onset of rhinitis, year*	30.9 (18.5)	13.6 (10.7)	<0.001
Triggers of nasal symptoms†			<0.001
Dust mites or house dust*	26 (20.0%)	113 (57.1%)	<0.001
Pollens*	24 (18.5%)	163 (82.3%)	<0.001
Animals*	2 (1.5%)	84 (42.4%)	<0.001
Other*	40 (30.8%)	1 (0.5%)	<0.001
No trigger reported*	44 (33.8%)	0 (0.0%)	<0.001
Symptoms after a stimulus†			
Rhinorrhea*	67 (51.5%)	167 (84.3%)	<0.001
Sneezing*	86 (66.2%)	178 (89.9%)	<0.001
Eye symptoms*	75 (57.7%)	169 (85.4%)	<0.001
Disturbance due to nasal symptoms*			<0.001
No	86 (66.2%)	78 (39.4%)	
Low	27 (20.8%)	80 (40.4%)	
Medium	13 (10.0%)	28 (14.1%)	
High	4 (3.1%)	12 (6.1%)	
Duration of rhinitis*			0.08
<1 month/year	60 (46.2%)	67 (33.8%)	
<4 days/week	31 (23.8%)	56 (28.3%)	
≥4 days/week	39 (30.0%)	75 (37.9%)	
Allergy pathway			
At least one positive SPT*	44 (33.8%)	188 (94.9%)	<0.001
IgE, IU/mL*	190.8 (496.8)	352.2 (535.7)	0.006
IL-1RA, pg/mL	0.5 (1.2)	0.3 (0.4)	0.05
IL-5, pg/mL	0.4 (0.3)	0.4 (0.4)	0.96
IL-7, pg/mL	0.6 (0.4)	0.6 (0.5)	0.38

	Cluster 1 (n=130)	Cluster 2 (n=198)	p
IL-8, pg/mL	0.4 (0.3)	0.4 (0.4)	0.56
IL-10, pg/mL	0.6 (1.2)	0.4 (0.5)	0.04
IL-13, pg/mL	0.5 (0.4)	0.5 (0.3)	0.43
Inflammation pathway			
Eosinophils, cells/mm^3*	179.2 (150.0)	262.4 (198.5)	<0.001
Neutrophils, cells/mm^3*	4152.2 (1464.2)	3928.4 (1334.3)	0.15
FeNO, 50 mL/s	16.9 (10.6)	22.6 (13.5)	0.002
EDN, ng/mL*	23.9 (11.7)	32.5 (17.0)	<0.001
ECP, ng/mL*	4.4 (2.7)	7.2 (19.8)	0.11
HS-CRP, mg/L*	2.1 (2.9)	2.8 (5.4)	0.16
CC-16, µg/L*	14.9 (1.0)	15.1 (0.9)	0.14
TNFα, pg/mL	0.4 (0.3)	0.4 (0.4)	0.55
Leptin, pg/mL	1.1 (0.7)	0.7 (0.6)	<0.001
TARC plasma EDTA, pg/mL*	92.0 (86.2)	107.0 (229.6)	0.48
TSLP plasma EDTA, pg/mL*	0.7 (0.4)	0.7 (0.5)	0.49
Oxidative/Nitrosative pathway			
NO_2/NO_3 plasma, µM*	45.3 (28.6)	40.6 (24.8)	0.12
NO_2/NO_3 condensate, µM	4.1 (5.9)	4.8 (8.5)	0.51
FIOPs, RFU/mL*	97.1 (25.2)	94.7 (22.7)	0.38
EBC 8-iso, pg/mL	7.9 (18.3)	8.0 (26.1)	0.99
SOD, U/g*	1285.4 (300.2)	1263.0 (266.4)	0.48
GPX, U/g*	41.2 (8.7)	39.5 (8.8)	0.08
Catalase, k/g*	163.4 (44.3)	166.4 (39.2)	0.53

*Data are n (%) or mean (SD), AR: Allergic Rhinitis, CC-16: Clara Cell protein-16, CRP: C-Reactive Protein, EBC 8-iso: Exalate Breath Condensate 8-isoprostanes, ECP: Eosinophil Cationic Protein, EDN: Eosinophil Derived Neurotoxin, FeNO: Fraction Exhaled Nitric Oxide, FlOP: Fluorescent oxidation product, GPX: Glutathione peroxidase, IgE: Immunoglobulin E, IL: Interleukin, SOD: Superoxide dismutase, SPT: Skin Prick Test, TARC: Thymus and Activation-Regulated Chemokine, TNF: Tumor Necrosis Factor, TSLP: Thymic Stromal Lymphopoietin, †: several possible answers, *: variables included in the construction of the clusters*

Table 28: Description of the two clusters identified in participants with never asthma and ever asthma in EGEA

	Never asthma			Ever asthma		
	Cluster 1 (n=64)	Cluster 2 (n=76)	p	Cluster 1 (n=52)	Cluster 2 (n=136)	p
Sex			0.73			0.55
Men	28 (43.8%)	30 (39.5%)		22 (42.3%)	66 (48.5%)	
Women	36 (56.2%)	46 (60.5%)		30 (57.7%)	70 (51.5%)	
Age, year*	51.9 (15.8)	38.9 (14.6)	<0.001	48.2 (17.9)	35.0 (14.1)	<0.001
Tobacco status			0.09			0.02
Never smoker	25 (39.1%)	36 (47.4%)		21 (40.4%)	73 (53.7%)	
Ex-smoker	26 (40.6%)	18 (23.7%)		19 (36.5%)	24 (17.6%)	
Current smoker	13 (20.3%)	22 (28.9%)		12 (23.1%)	39 (28.7%)	
Educational level			0.004			0.004
Less than high school	21 (32.8%)	8 (10.5%)		17 (32.7%)	17 (12.6%)	
High school	11 (17.2%)	21 (27.6%)		10 (19.2%)	45 (33.3%)	
University	32 (50.0%)	47 (61.8%)		25 (48.1%)	73 (54.1%)	
Conjunctivitis*			0.001			<0.001
Never conjunctivitis	49 (76.6%)	37 (48.7%)		36 (69.2%)	53 (39.0%)	
Ever conjunctivitis	15 (23.4%)	39 (51.3%)		16 (30.8%)	83 (61.0%)	
Eczema*			0.44			0.65
Never eczema	38 (59.4%)	51 (67.1%)		29 (55.8%)	69 (50.7%)	
Ever eczema	26 (40.6%)	25 (32.9%)		23 (44.2%)	67 (49.3%)	
Nasal allergies*			<0.001			<0.001
Never nasal allergies	43 (67.2%)	16 (21.1%)		27 (51.9%)	6 (4.4%)	
Ever nasal allergies	21 (32.8%)	60 (78.9%)		25 (48.1%)	130 (95.6%)	
Age of onset of rhinitis, year*	35.4 (18.8)	20.5 (12.2)	<0.001	25.7 (18.6)	11.5 (9.6)	<0.001
Triggers of nasal symptoms†						
Dust mites or house dust*	6 (9.4%)	29 (38.2%)	<0.001	15 (28.8%)	89 (65.4%)	<0.001
Pollens*	4 (6.2%)	64 (84.2%)	<0.001	8 (15.4%)	111 (81.6%)	<0.001
Animals*	0 (0.0%)	17 (22.4%)	<0.001	1 (1.9%)	68 (50.0%)	<0.001
Other*	28 (43.8%)	0 (0.0%)	<0.001	13 (25.0%)	0 (0.0%)	<0.001
No trigger reported*	26 (40.6%)	0 (0.0%)	<0.001	18 (34.6%)	0 (0.0%)	<0.001
Symptoms after a stimulus†						
Rhinorrhea*	29 (45.3%)	59 (77.6%)	<0.001	30 (57.7%)	116 (85.3%)	<0.001
Sneezing*	38 (59.4%)	70 (92.1%)	<0.001	35 (67.3%)	121 (89.0%)	0.001
Eye symptoms*	36 (56.2%)	66 (86.8%)	<0.001	29 (55.8%)	113 (83.1%)	<0.001
Disturbance due to nasal symptoms*			0.16			0.009
No	44 (68.8%)	39 (51.3%)		31 (59.6%)	50 (36.8%)	
Low	17 (26.6%)	29 (38.2%)		8 (15.4%)	53 (39.0%)	
Medium	2 (3.1%)	7 (9.2%)		10 (19.2%)	22 (16.2%)	
High	1 (1.6%)	1 (1.3%)		3 (5.8%)	11 (8.1%)	
Duration of rhinitis*			0.70			0.61
<1 month/year	29 (45.3%)	39 (51.3%)		19 (36.5%)	40 (29.4%)	
<4 days/week	17 (26.6%)	16 (21.1%)		13 (25.0%)	41 (30.1%)	
≥4 days/week	18 (28.1%)	21 (27.6%)		20 (38.5%)	55 (40.4%)	
Allergy pathway						
At least one positive SPT*	12 (18.8%)	65 (85.5%)	<0.001	25 (48.1%)	130 (95.6%)	<0.001
IgE, IU/mL*	175.0 (534.9)	211.1 (306.1)	0.62	204.2 (477.8)	416.8 (607.6)	0.02
IL-1RA, pg/mL	0.4 (0.5)	0.4 (0.6)	0.85	0.6 (1.5)	0.3 (0.4)	0.04
IL-5, pg/mL	0.4 (0.3)	0.5 (0.6)	0.40	0.4 (0.3)	0.4 (0.3)	0.96

	Never asthma			Ever asthma		
	Cluster 1 (n=64)	Cluster 2 (n=76)	p	Cluster 1 (n=52)	Cluster 2 (n=136)	p
IL-7, pg/mL	0.6 (0.4)	0.7 (0.6)	0.72	0.6 (0.4)	0.6 (0.4)	0.84
IL-8, pg/mL	0.4 (0.3)	0.5 (0.5)	0.36	0.4 (0.3)	0.4 (0.3)	0.68
IL-10, pg/mL	0.6 (0.9)	0.4 (0.6)	0.42	0.6 (1.5)	0.4 (0.4)	0.10
IL-13, pg/mL	0.5 (0.3)	0.5 (0.2)	0.85	0.5 (0.4)	0.5 (0.4)	0.72
Inflammation pathway						
Eosinophils, cells/mm^3*	171.4 (172.7)	204.1 (105.3)	0.17	196.9 (164.8)	283.3 (217.7)	0.01
Neutrophils, cells/mm^3*	3970.0 (1321.9)	3907.1 (1419.1)	0.79	4343.7 (1413.3)	3975.9 (1391.4)	0.11
FeNO, 50 mL/s	15.9 (8.2)	20.7 (12.6)	0.05	21.7 (18.4)	21.7 (11.7)	0.99
EDN, ng/mL*	22.9 (11.3)	26.5 (13.0)	0.09	26.4 (12.8)	34.5 (18.1)	0.003
ECP, ng/mL*	4.4 (3.1)	4.7 (2.8)	0.57	4.7 (2.3)	8.2 (23.7)	0.29
HS-CRP, mg/L*	2.2 (3.7)	2.2 (3.5)	0.94	2.0 (1.7)	3.1 (6.0)	0.19
CC-16, µg/L*	14.8 (1.1)	15.2 (0.9)	0.06	15.0 (1.0)	15.1 (1.0)	0.92
TNFα, pg/mL	0.4 (0.3)	0.4 (0.6)	0.63	0.4 (0.4)	0.3 (0.3)	0.49
Leptin, pg/mL	1.0 (0.6)	0.8 (0.6)	0.10	1.1 (0.7)	0.7 (0.7)	0.008
TARC plasma EDTA, pg/mL*	103.1 (101.6)	95.2 (86.6)	0.62	78.5 (55.7)	112.0 (271.4)	0.38
TSLP plasma EDTA, pg/mL*	0.7 (0.4)	0.6 (0.3)	0.20	0.7 (0.3)	0.7 (0.6)	0.69
Oxidative/Nitrosative pathway						
NO_2/NO_3 plasma, µM*	48.1 (32.8)	41.3 (29.3)	0.20	41.4 (20.0)	40.8 (23.3)	0.85
NO_2/NO_3 condensate, µM	4.8 (7.7)	3.5 (3.7)	0.24	3.9 (3.9)	5.2 (10.0)	0.41
FIOPs, RFU/mL*	96.5 (18.2)	97.8 (27.4)	0.74	94.2 (24.0)	94.6 (23.7)	0.91
EBC 8-iso, pg/mL	5.5 (12.4)	9.1 (20.8)	0.34	4.8 (5.4)	10.0 (32.4)	0.41
SOD, U/g*	1275.5 (331.3)	1272.1 (261.3)	0.95	1291.8 (262.7)	1262.4 (273.0)	0.51
GPX, U/g*	41.9 (10.0)	39.4 (7.5)	0.09	40.9 (7.6)	39.5 (9.2)	0.34
Catalase, k/g*	167.8 (39.6)	166.9 (40.6)	0.90	155.7 (47.0)	166.7 (40.0)	0.11

*Data are n (%) or mean (SD), AR: Allergic Rhinitis, CC-16: Clara Cell protein-16, CRP: C-Reactive Protein, EBC 8-iso: Exalate Breath Condensate 8-isoprostanes, ECP: Eosinophil Cationic Protein, EDN: Eosinophil Derived Neurotoxin, FeNO: Fraction Exhaled Nitric Oxide, FlOP: Fluorescent oxidation product, GPX: Glutathione peroxidase, IgE: Immunoglobulin E, IL: Interleukin, SOD: Superoxide dismutase, SPT: Skin Prick Test, TARC: Thymus and Activation-Regulated Chemokine, TNF: Tumor Necrosis Factor, TSLP: Thymic Stromal Lymphopoietin, †: several possible answers, *: variables included in the construction of the clusters*

4.1.6.3.3. Sensitivity and supplementary analyses

- Alternate variable selection

By considering all the variables of interest (SA1), data from 77 participants were analysed (Table S2 Appendix 8). The optimal number of clusters identified was three. Cluster 1 assimilated to NAR and cluster 2 and 3 to AR. Due to the small number of participants, analyses could not be performed according to asthma status.
By considering only biological variables (SA2), data from 437 participants were analysed (Table S3 Appendix 8). The optimal number of clusters identified was two. Overall, cluster 1 and cluster 2 had similar characteristics to those 1 and 2 found in the main analyses. After stratification on asthma status, similar results were observed as those obtained in the main analysis (Table S4 Appendix 8).

- Imputations

After imputation of the missing values, data from 842 participants (365 with never asthma and 477 with ever asthma) were analysed (Table S5 and Table S6 Appendix 8). Two clusters were identified with the same characteristics as those of the main analysis.

4.1.6.4. Discussion

The unsupervised analysis performed in EGEA led to the identification of two clusters assimilated to two endotypes mainly discriminated by allergy pathways: NAR and AR.

For the first time in population that is not based on patients consulting for their rhinitis, an unsupervised approach considering both the clinical features of rhinitis and biomarkers was performed. A wide variety of biomarkers were measured at EGEA2, giving a very good characterisation of the participants for three main pathways: allergy, inflammation, and nitrosative/oxidative stress. Two clusters assimilated to AR and NAR were identified and these clusters remained consistent across the analyses. Our results are in line with the endotypes previously identified in the literature reviews (15,26,27). In these reviews, only non-IgE-mediated and IgE-mediated endotypes have been identified from analyses including blood biomarkers. Overall, according to the literature and our results, the allergy pathway seems to be the most important one to identify rhinitis endotypes.
Previously, Burte *et al.* identified rhinitis phenotypes using an unsupervised approach in EGEA based only on clinical variables and the presence or absence of at least one positive SPT (93). Interestingly, the present clusters analyses adding the biological variables have given almost identical clusters to those of Burte *et al.* (93). This may indicate that clinical features probably carry more weight than biology in identifying different rhinitis clusters. In link with this hypothesis, by performing a sensitivity analysis considering only biological variables, we also identified two clusters well discriminated and related to AR and NAR but their characteristics were less differentiated than in the analyses with both clinical characteristics and biological variables.

The results also showed that asthma status has a greater influence on the biomarkers levels than rhinitis status. While the endotypes identified in the ever asthma and never asthma groups were similar, it is interesting to note that the mean levels of eosinophils, EDN, ECP, TARC, and serum IgE were highest in the ever asthma and "AR" cluster compared to clusters. This result reinforces the hypotheses that asthma combined with AR could lead to a phenotype/endotype of rhinitis with its own characteristics, in particular a more marked severity and higher levels of biomarkers involved in allergy or inflammation pathways.

As the allergy pathway is predominant, it would be interesting to study rhinitis endotypes in the AR and NAR groups considered separately. Due to the design of EGEA and because biomarkers levels may vary according to asthma, clusters should also be indentified in participants with ever asthma and never asthma considered separately. Unfortunately, although the EGEA study has a relatively high number of participants with available biomarkers compared to studies conducted in patient cohorts, the number of participants is still too small to stratify on both allergic and asthmatic status. To further identify other endotypes, other measures are also probably needed: measurements of markers in nasal fluids for local AR, nasal challenge tests for neurogenic endotypes or medical examination for structural abnormalities (6). Thus, new population-based presenting both a larger number of participants and of biological variables are necessary to study in depth the endotypes of rhinitis. Research on rhinitis endotypes is only at its beginning and very few studies currently exist, pursuing them would make it possible to identify new biological pathways of interest for more targeted treatments.

In conclusion, this unsupervised analysis identified two endotypes assimilated to AR and NAR and highlighted the importance of the allergy pathways which is well known and evident in clinical practice. Thus, due to the lack of new findings, we have decided not to publish the results of this work. However, this approach has allowed us to plan new research perspectives and to recognize the methodological limitations of endotypes identification.

To sumarise this first objective, we first showed in EGEA that a questionnaire definition could be a good proxy for identifying AR and NAR. Then, based on these questionnaire definitions, we estimated the prevalences of rhinitis, AR and NAR based on data from the population-based cohort Constances. We described the characteristics of rhinitis, AR and NAR and explored phenotypic differences between rhinitis alone and including asthma and/or conjunctivitis. We also described AR according to its severity and duration defined by the ARIA classification with a specific focus on asthma multimorbidity. In Constances, the unsupervised approach identified three phenotypes assimilated to AR, severe AR and NAR. In EGEA, the unsupervised approach highlighted the importance of the allergy pathways. All these results provide recent, population-based data on rhinitis phenotypes and their characteristics. Consistently across all analyses, including asthma allows to identify new phenotypes of rhinitis with specific characteristics. These phenotypes provide research perspectives for a better understanding of rhinitis and its etiology, which will lead to better management of rhinitis and better knowledge of its risk factors.

4.2. OBJECTIVE 2: LONG-TERM EXPOSURE TO AIR POLLUTION AND RHINITIS IN CONSTANCES

The literature review that we conducted has highlighted an increase in the rhinitis prevalence worldwide over the last few decades. One of the environmental factors that could partly explain this increase is air pollution. However, there are few epidemiological studies on the link between long-term exposure to air pollution and rhinitis, especially in adults. The second objective of this thesis was therefore to investigate the associations between long-term exposure to air pollution and rhinitis phenotypes in Constances.

Objective 2 is divided into three specific objectives:

1) First, to investigate cross-sectional associations at inclusion between air pollution and current rhinitis prevalence.
2) Then, to investigate these associations by considering the multimorbidity of rhinitis and asthma.
3) Finally, to study the effects of air pollution on incident rhinitis in longitudinal analyses.

4.2.1. Effect of long-term exposure to air pollution on prevalence of current rhinitis

Results from this section were published as an original article in Environment International (158)*, see Appendix 9 for full text.*

4.2.1.1. Introduction

In adults, the association between long-term exposure to air pollution and rhinitis has been poorly investigated in population-based studies. Additionally the results from available studies are inconsistent: exposure to traffic or specific pollutants such as fractions of PM, NO_2 or NO_x were significantly associated with an increased risk of current AR in some studies (70,155,159), while others found null or non-significant positive results (151,153,161). Although there is a growing body of literature showing the harmful effect of BC on health (223), only one study had examined the association between BC exposure and the prevalence of current AR (155). Furthermore, most of the previous studies did not study the effets of air pollution exposure on NAR.
The aim of the present study was to assess the associations between long-term exposures to $PM_{2.5}$, BC and NO_2 and the prevalence of current rhinitis.

4.2.1.2. Material and methods

4.2.1.2.1. Study design and definitions

Cross-sectional analyses were carried out in Constances with the data from the inclusion. The definitions of rhinitis and the variables of interest are those presented in the overall material and methods section 3.1.2.

In the present analysis, participants with current rhinitis were compared to those of the reference group, defined as participants with never or non-current rhinitis.

4.2.1.2.2. Air pollution exposure assessment

Modelled exposures were assigned at the participants' residential address at inclusion. We used annual averages for each pollutant from year 2010 models at the address of inclusion as a proxy for participants' long-term exposure to air pollution.

4.2.1.2.3. Statistical analyses

The main analyses were complete case analyses, i.e. after excluding participants with missing data for rhinitis, air pollution or adjustment variables.
The general characteristics of participants who reported current rhinitis in the last 12 months were compared to those of the reference group, defined as participants with never or non-current rhinitis, using standard statistical tests: Chi2 for categorical

variables and Student tests for continuous variables. Spearman correlation coefficients were performed to study the correlations between the different pollutants.

4.2.1.2.3.1. Main analyses

The cross-sectional associations between long-term exposure to air pollutants and current rhinitis were studied using logistic regression models. Estimates were calculated considering each pollutant separately for an increase of their interquartile range (IQR), i.e. 4.85 µg/m^3 for $PM_{2.5}$, 0.88 10^{-5} m^{-1} for BC and 17.3 µg/m^3 for NO_2.
As recruited participants lived in departments where HSC are located, analyses were carried out using marginal models with generalized estimating equations (224) to take into account potential clustering, i.e. that participants living in the same department were likely more similar than those living in other departments.
Associations between each air pollutant and current rhinitis were assessed with single-pollutant models. Univariate analyses were first performed (model M0). A first level of adjustments for age, sex and smoking status (never smoker, ex-smoker, current smoker) was made on the basis of *a priori* hypotheses based on the literature (model M1). Further adjustment was made for educational level (no diploma/grade school, high school, university) as a proxy for SES at the individual level (model M2). Finally, as taking both individual and contextual SES into account is of importance in studies on the health effects of air pollution (225,226), a model with an additional adjustment on FDep was conducted (model M3 = main model).

4.2.1.2.3.2. Supplementary analyses

All supplementary analyses were performed with the main M3 model.
As BC is a component of $PM_{2.5}$, and as BC and $PM_{2.5}$ are highly correlated, using a two-pollutant model mutually adjusting one pollutant for the other is precluded. As an alternative to isolate the effect of BC from that of total $PM_{2.5}$, we used the residuals method described by Mostofsky *et al.* (227). Following this approach, we regressed BC as response variable on $PM_{2.5}$. These residuals were decorrelated from $PM_{2.5}$ and an increase in these residuals corresponds to an increase in BC holding total $PM_{2.5}$ constant. We used these residuals as a new exposure variable in a single pollutant model.
The analyses were also carried out for current AR (reference group: never rhinitis and non-current AR) and current NAR (reference group: never rhinitis and non-current NAR) separately.
As air pollution could lead to different responses between men and women, stratification according to sex was performed. As air pollution and tobacco may share similar underlying biological mechanisms, stratification according to smoking was also performed. Heterogeneity between strata were tested using interaction tests.
As an alternative of the marginal model, models were also performed with HSC as an adjustment variable, in a meta-analysis on HSC or without considering the HSC.

As the main analyses were complete case analyses, additional analyses were also carried out after multiple imputations (n = 10) for missing data on smoking status and diploma using the SAS procedures MI and MIANALYZE.
Analyses were also performed by changing the reference group i.e. by comparing current rhinitis to never rhinitis and current rhinitis to non-current rhinitis separately.

All analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC).

4.2.1.3. Results

Data from participants included in the cohort between 2012 and 2017 (n = 150,231) were analysed. Participants with missing data regarding the definitions of rhinitis (n = 6,344), the presence of nasal allergies (n = 1,945), air pollution (n = 681), diploma (n = 1,728) or tobacco status (n = 4,816) were excluded from the main analyses. Participants who answered yes to "*Have you ever had any nasal allergies including hay fever?*" and no 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?*" were considered as inconsistent and were also excluded from the analyses (n = 7,609). The flowchart is presented in Figure 25.

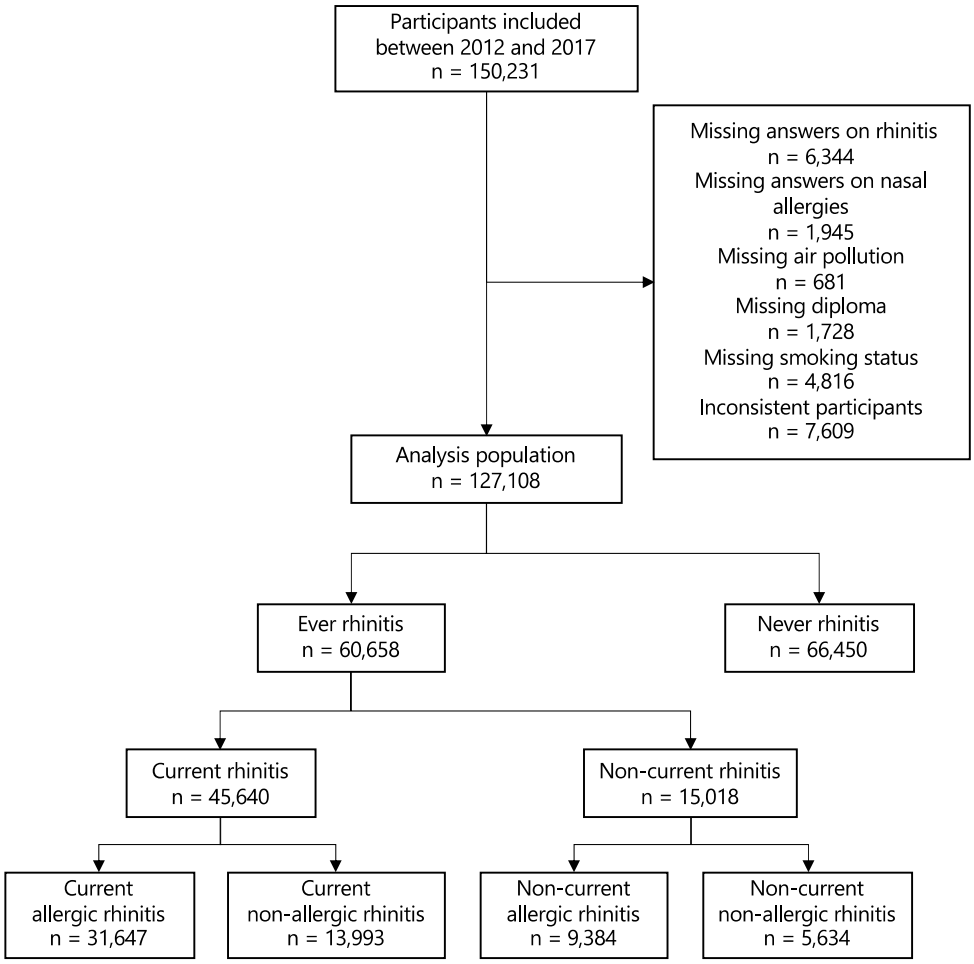


Figure 25: Flowchart of objective 2.1

A total of 127,108 adults were included in the main analyses. The differences regarding the main characteristics between participants included and those not included were small, although statistically significant due to the large number of participants (Table S1 Appendix 9B).

Characteristics of the participants included in the analyses are presented in Table 29. They were on average 47 years old and 53.8% were women. The prevalence of ever rhinitis and current rhinitis were 47.7% and 35.9% respectively. The prevalence of current AR and current NAR were 24.9% and 11.0% respectively. Compared to the reference group, the current rhinitis group comprised more women, a lower average age, higher education level and reported more ever asthma. More details about the participants characteristics according to their rhinitis status are given in Table S2 (Appendix 9B).

Table 29: Characteristics of participants of objective 2.1

	All (n=127,108)	**Reference population[a] (n=81,468)**	**Current rhinitis (n=45,640)**	**p**
Women	68,354 (53.8%)	42,883 (52.6%)	25,471 (55.8%)	<.0001
Age, year, mean (SD)	47.1 (13.6)	47.9 (13.5)	45.7 (13.8)	<.0001
BMI, kg/m^2				<.0001
<18.5	3,350 (2.8%)	2,010 (2.6%)	1,340 (3.1%)	
[18.5–25[	66,309 (54.5%)	41,561 (53.3%)	24,748 (56.5%)	
[25–30[	37,164 (30.5%)	24,464 (31.4%)	12,700 (29.0%)	
≥30	14,936 (12.3%)	9,911 (12.7%)	5,025 (11.5%)	
Smoking status				<.0001
Never	59,922 (47.1%)	38,888 (47.7%)	21,034 (46.1%)	
Ex-smoker	42,943 (33.8%)	27,437 (33.7%)	15,506 (34.0%)	
Current	24,243 (19.1%)	15,143 (18.6%)	9,100 (19.9%)	
Educational level				<.0001
Less than high school	11,355 (8.9%)	7,723 (9.5%)	3,632 (8.0%)	
High school	43,290 (34.1%)	28,888 (35.5%)	14,402 (31.6%)	
University	72,463 (57.0%)	44,857 (55.1%)	27,606 (60.5%)	
Ever asthma	17,148 (13.6%)	7,014 (8.7%)	10,134 (22.4%)	<.0001
Ever rhinitis	60,658 (47.7%)	15,018 (18.4%)	45,640 (100%)	<.0001
Current rhinitis	45,640 (35.9%)	-	45,640 (100%)	
Current AR	31,647 (24.9%)	-	31,647 (69.3%)	
Current NAR	13,993 (11.0%)	-	13,993 (30.7%)	
$PM_{2.5}$, µg/m^3, mean (SD)	17.1 (3.35)	17.0 (3.31)	17.3 (3.40)	<.0001
BC, 10^{-5} m^{-1}, mean (SD)	1.82 (0.59)	1.79 (0.58)	1.87 (0.59)	<.0001
NO_2, µg/m^3, mean (SD)	26.5 (12.3)	25.9 (12.2)	27.4 (12.5)	<.0001

Data are mean (SD) or n (%)

AR: Allergic Rhinitis, BC: Black Carbon; BMI: Body Mass Index, NAR: Non-Allergic Rhinitis, NO_2: Nitrogen Dioxide, $PM_{2.5}$ Particulate Matter ≤2.5 µm, SD: standard deviation

a: reference population = never rhinitis + non-current rhinitis

Pollutant levels differed across HSC and within HSC (Figure S2 Appendix 9B). Table S3 (Appendix 9B) shows the distribution of pollutants and their correlation coefficients. The annual mean concentration of $PM_{2.5}$ was 17.1 µg/m^3 which is above the 2021 WHO guideline of 5 µg/m^3, and the annual mean concentration of NO_2 was 26.5 µg/m^3 which is above the 2021 WHO guideline of 10 µg/m^3. The annual average concentration of BC was 1.82 10^{-5} m^{-1}. Correlations between the three pollutants were high (0.80 between $PM_{2.5}$ and BC, 0.87 between $PM_{2.5}$ and NO_2, and 0.93 between BC and NO_2).

Table 30 shows the associations between $PM_{2.5}$, BC and NO_2 and current rhinitis. In all models, thus is whatever the adjustment, an increase of $PM_{2.5}$, BC, or NO_2 was significantly associated with an increased risk of current rhinitis. Adjusted ORs for the main model M3 were 1.13 (95% CI: 1.08, 1.17) per IQR increase in $PM_{2.5}$, 1.12 (95% CI: 1.07, 1.17) per IQR increase in BC and 1.11 (95% CI: 1.06, 1.17) per IQR increase in NO_2. BC residuals regressed on $PM_{2.5}$ were also significantly associated with an increase of current rhinitis (OR: 1.05, 95% CI: 1.02, 1.07 for an IQR increase of BC residuals).

Table 30: ORs (95% CI) of the associations between $PM_{2.5}$, BC and NO_2 and current rhinitis

	$PM_{2.5}$	**BC**	**NO_2**
M0	1.16 (1.11-1.22)	1.17 (1.10-1.23)	1.15 (1.08-1.22)
M1	1.13 (1.09-1.19)	1.13 (1.08-1.19)	1.12 (1.07-1.18)
M2	1.12 (1.07-1.17)	1.12 (1.06-1.17)	1.11 (1.05-1.17)
M3 = main model	1.13 (1.08-1.17)	1.12 (1.07-1.17)	1.11 (1.06-1.17)

BC: Black Carbon, CI: Confidence Interval, NO_2: Nitrogen Dioxide, OR: Odds Ratio, $PM_{2.5}$: Particulate Matter ≤2.5 µm

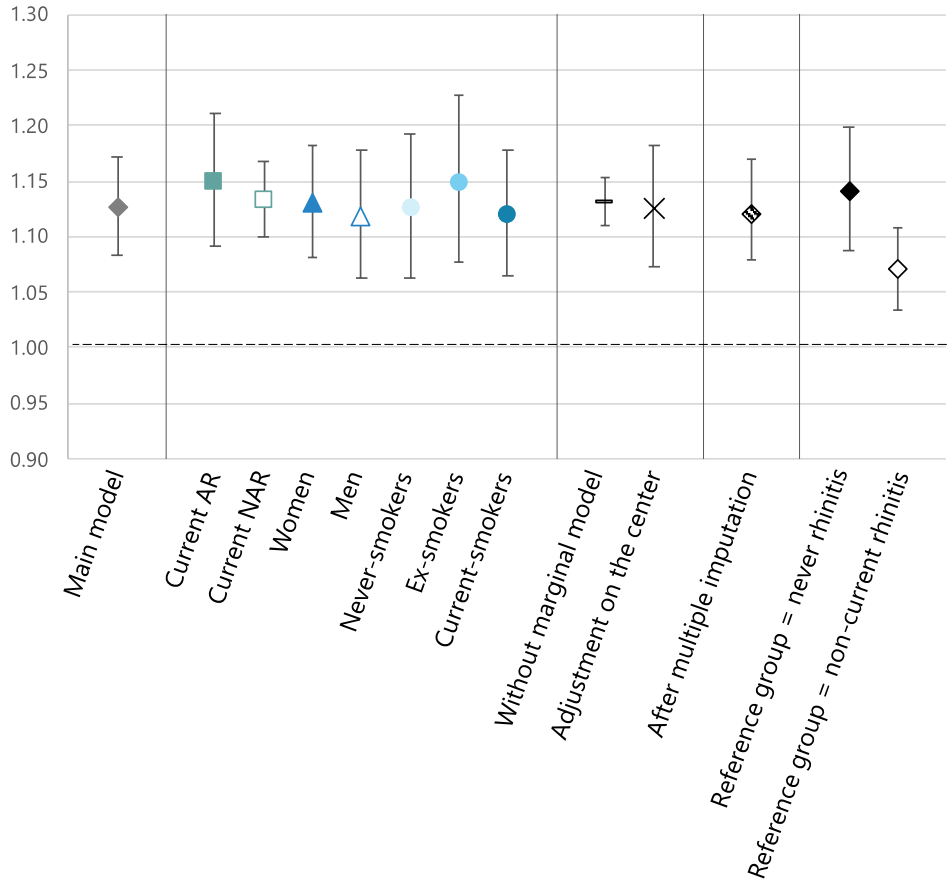
All estimates were from logistic regression models, ORs (95% CI) were calculated for an increase of an interquartile range (4.85 µg/m^3 for $PM_{2.5}$, 0.88 10^{-5} m^{-1} for BC and 17.3 µg/m^3 for NO_2). The health screening center was taken into account by marginal models with generalized estimating equations Current rhinitis was compared to never rhinitis + non-current rhinitis.

M0: univariate analysis, M1: adjusted for age, sex, and smoking status, M2: adjusted for age, sex, smoking status, and educational level, M3: adjusted for age, sex, smoking status, educational level, and French Deprivation index. All p-values were < 10^{-4}

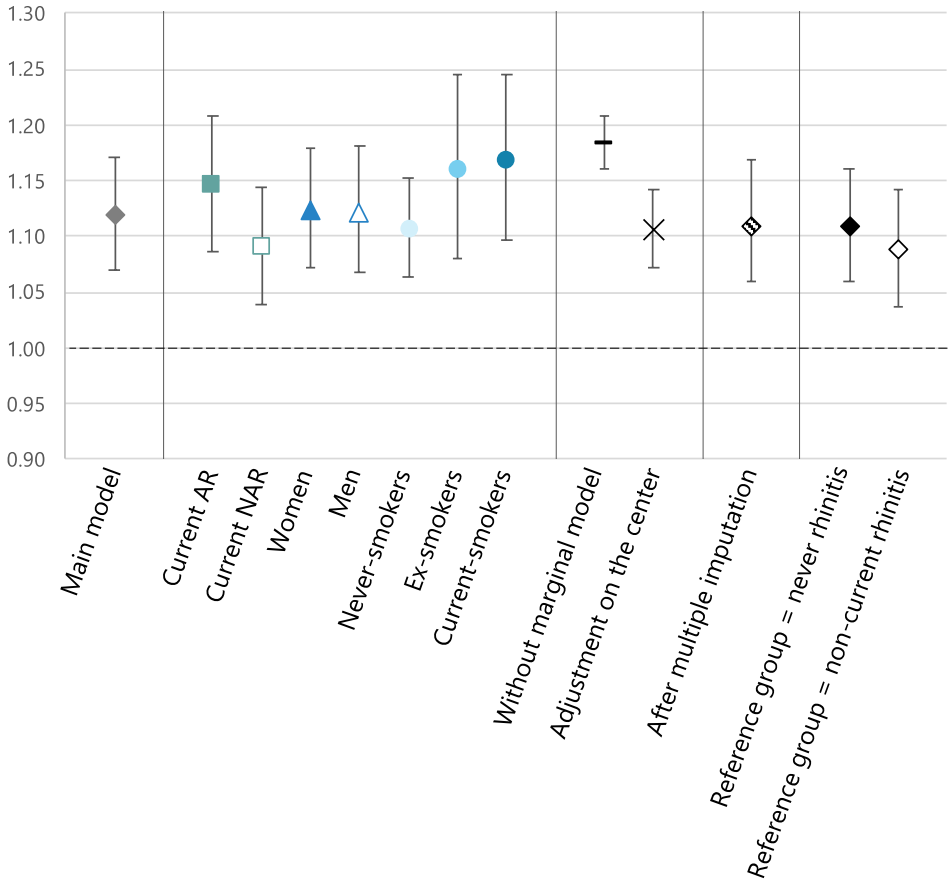
The results of the supplementary analyses are shown in Figure 26, Table S4, and Figure S3 (Appendix 9B). Significant and positive associations were also found for both AR and NAR with similar effect estimates between AR and NAR for $PM_{2.5}$ and NO_2. For BC, the adjusted OR was slightly higher in AR compared to NAR (ORs: 1.15 *vs* 1.09 respectively). The ORs were similar between men and women and there were no significant interactions between each pollutant and sex. Stratification by smoking status yielded similar results for each stratum and there were no significant interactions between each pollutant and smoking status.

Similar results were obtained for $PM_{2.5}$ when not considering the HSC in the model, and the ORs were slightly higher for BC and NO_2. Adjusting on the HSC gave similar results to those of the marginal model for all pollutants. Similarly, the meta-analyses gave similar results to those of the main model for $PM_{2.5}$, BC and NO_2, for both fixed and random effects: the heterogeneity was not significant (I^2 = 0%, p = 0.58) for $PM_{2.5}$, and was significant for BC and NO_2 (I^2 = 48%, p = 0.01 and I^2 = 44%, p = 0.02 respectively). Multiple imputations yielded significant and similar results as those of the main model. Taking as a reference group only participants who never had rhinitis, the ORs were similar to those reported in the main model. In contrast, when only participants with non-current rhinitis were included as a reference group, ORs were still significant but lower than those obtained with the main model.

A.


1.30
1.25
1.20
1.15
1.10
1.05
1.00
0.95
0.90
Main model
Current AR
Current NAR
Women
Men
Never-smokers
Ex-smokers
Current-smokers
Without marginal model
Adjustment on the center
After multiple imputation
Reference group = never rhinitis
Reference group = non-current rhinitis

B.


1.30
1.25
1.20
1.15
1.10
1.05
1.00
0.95
0.90
Main model
Current AR
Current NAR
Women
Men
Never-smokers
Ex-smokers
Current-smokers
Without marginal model
Adjustment on the center
After multiple imputation
Reference group = never rhinitis
Reference group = non-current rhinitis

C.

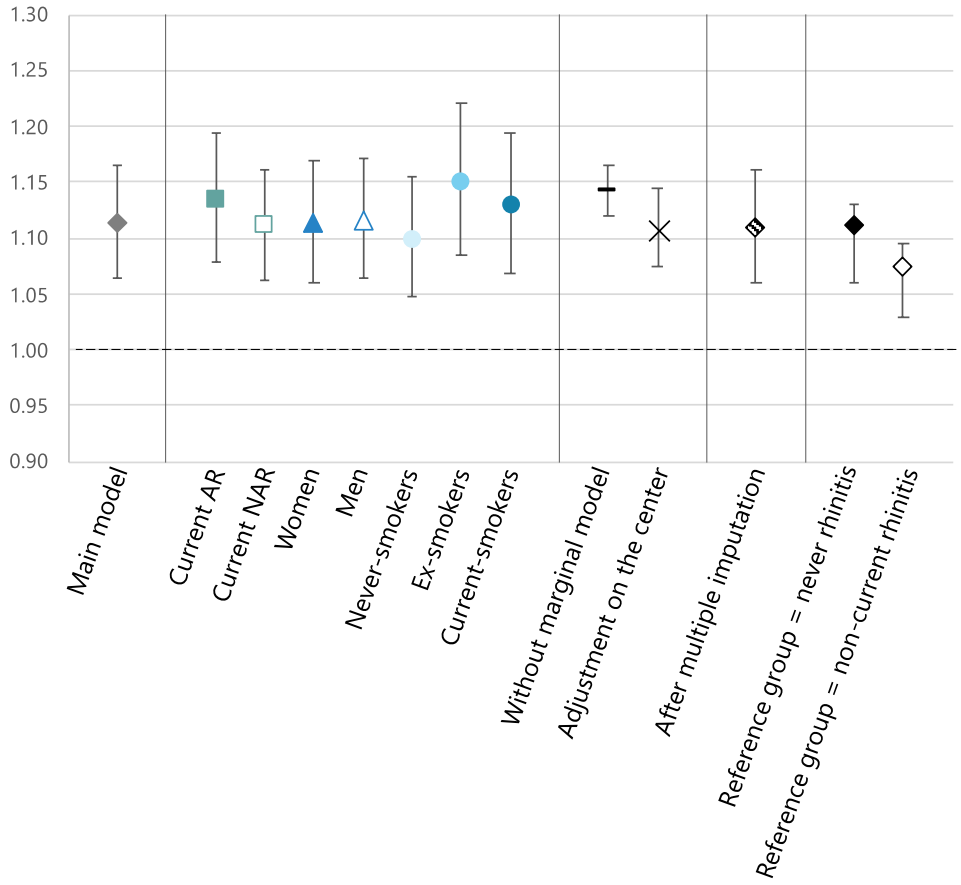


Figure 26: Associations between exposure to air pollution and current rhinitis

OR (95% CI) were calculated:

A. For an increase of an IQR of $PM_{2.5}$ (4.85 µg/m³)

B. For an increase of an IQR of BC (0.88 $10^{-5}m^{-1}$)

C. For an increase of an IQR of NO_2 (17.3 µg/m³)

◆■□–X◆◇: adjusted ORs for age, sex, smoking status, educational level, and FDep

▲△: adjusted ORs for age, smoking status, educational level, and FDep

●●●: adjusted ORs for age, sex, educational level, and FDep

AR: Allergic Rhinitis, BC: Black Carbon; CI: confidence interval, FDep: French Deprivation index, NAR: Non-Allergic Rhinitis, NO_2: Nitrogen Dioxide, OR: Odds Ratio; $PM_{2.5}$ Particulate Matter ≤2.5 µm

The health screening centre was considered by marginal models with generalized estimating equations (except in the model adjusted on the centre and in the model without marginal model)

All p-values were < 10^{-4}

4.2.1.4. Discussion

In this cross-sectional analysis, an increase of modelled annual average residential exposure to $PM_{2.5}$, BC, and NO_2 was significantly associated with an increased risk of current rhinitis in adults from a large population-based study which yielded very high statistical power. These results were consistent regardless of the adjustment, the stratification and the sensitivity analyses.

In this study, long-term exposure to air pollutants was estimated at the participants' residential address at inclusion using validated European LUR models that provide a fine-scale (100 x 100 m) estimate of exposure (192). We considered outdoor pollution at the residential address, and as participants are not always at home, this can lead to exposure misclassification. The analyses were performed in a cross-sectional setting, so temporality is not defined, and causality cannot be drawn. The measurements performed in 2010 at the inclusion address was hypothesised to reflect the long-term air pollution exposure of the participants. It has been shown that the pollution levels from one year to another for the same geographical area are very similar (228). We assume that the annual mean of the pollutants reflects a long-term exposure, which is probably true for those who did not move for several years prior to outcome assessment. The limitations presented above may lead to a non-differential measurement error suggesting that the actual effect of long-term exposure to air pollution on rhinitis may be higher than the one identified. Although we adjusted for the main confounders associated with both rhinitis and air pollution, a residual confound could remain. In Constances, each participant is assigned to an HSC. The estimation of air pollution was based on the same LUR model and rhinitis was assessed by questionnaire, which is the same for all participants, independently of the HSC. In the present study, there is no center effect as classically defined in epidemiology, i.e. meaning that exposure or/and the outcome of interest are differentially assessed across centers. However, it is possible that participants living near the same HSC are more similar e.g. in terms of lifestyle or pollen exposure than participants from different HSC. That is why the HSC was considered in a marginal model with generalized equations. The results were similar when considering the HSC in an adjusted model or in meta-analyses. However, for the meta-analyses the coefficient of heterogeneity was significant for BC and NO_2. This heterogeneity is mainly due to the results for Paris HSC. The results for Paris could be explained by the fact that Parisian participants show less variability in air pollution exposure. Not considering the HSC gave similar results to those of the marginal model for $PM_{2.5}$ and slightly higher ORs for BC and NO_2. Overall, the analyses yielded significant results and the sensitivity analyses performed support the robustness of the results.

The existing literature is ambiguous as to which group current rhinitis is compared to, and previous studies have not consistently defined whether or not non-current rhinitis was included in the reference group. Participants who have non-current rhinitis may be

considered as a "special group" as they used to have rhinitis that is no longer active. Thus, conducting an extra analysis excluding participants with non-current rhinitis, yielded results nearly identical to those of the main analysis. An analysis comparing current rhinitis to non-current rhinitis was also performed. The research question behind the latter analysis was to determine if long-term exposure to air pollution could affect symptom activation among participants with a history of rhinitis. The present study is the first to report this comparison. The results were significant and can be added to the growing literature on the association of air pollution with the severity and exacerbation of rhinitis (181,207,229). In addition, the present analyses comparing current rhinitis to non-current rhinitis yielded lower ORs than analyses comparing current rhinitis to never rhinitis. This difference in the strength of the associations could be partly explained by the study population: indeed, the comparison between current rhinitis and non-current rhinitis was conducted in a more homogenous population of participants with a rhinitis during their lifetime. These results need to be explored further but they could suggest that air pollution may be associated not only with the presence of rhinitis symptoms but also with the activation of rhinitis symptoms in participants who previously have had rhinitis.

The main results of this study are difficult to compare with those in the literature as there are only few studies on the association between long-term exposure to air pollution and the prevalence of current rhinitis in adults in population-based cohorts. Three studies in Europe (70,155,159) have shown that exposure to NO_2 was associated with an increase in the prevalence of current AR in adults. In these studies, as in the present result, associations were observed even at relatively of air pollution suporting the report of the 2021 WHO air quality guidelines. Only one study (155) has examined the effects of $PM_{2.5}$ and BC on current AR in adults. In the study by Nordeide Kuiper *et al.*, Swedish and Norwegian adults were included and the long-term exposures to $PM_{2.5}$, BC and NO_2 were estimated with the same European LUR as the one used in the present study (192). Similarly to the present study, long-term exposure to $PM_{2.5}$, BC or NO_2 in the year prior to the report of current AR was significantly associated with an increased risk of current AR (155). Long-term exposures over the lifetime, the period of adolescence, or in childhood, of participants were not significantly associated with current AR in adults (155). This may suggest that recent exposure to air pollution may be more important in the occurrence of current rhinitis. Only one study (70) has considered both AR and NAR. The authors found that road traffic exposure in an adult population was associated with a higher prevalence of AR but not NAR, suggesting that rhinitis should be considered as an heteregenous disease (70). In the present study, significant associations between each of the three pollutants and both AR and NAR were observed. The results were very similar between AR and NAR for $PM_{2.5}$ and NO_2, but interestingly for BC the OR was slightly higher for AR compared to NAR. AR and NAR present distinct physiopathological mechanisms, and it is therefore possible that the effect of pollutants is different according to the phenotypes of rhinitis. Given the

limited literature that has considered AR and NAR, these hypotheses need to be further explored.

As air pollution could lead to different responses between men and women, we performed analyses stratifying by sex (230). The interactions were non-significant between the different pollutants and sex, and the results were similar for women and men. As tobacco and air pollutants may share similar underlying biological mechanisms on the onset of respiratory disease (231), We have also stratified according to smoking status. No interaction between smoking status and the pollutants were observed, and the results were very similar according to the different strata suggesting that the effect of air pollution on rhinitis would be independent of smoking status.

Due to the high correlation between the three pollutants, We could not perform a tri-pollutant model by adjusting for the other pollutants (232). As BC is a component of PMs, We used the residual method proposed by Mostofsky *et al.* to take into account the confounding induced by $PM_{2.5}$ (227). The present results with BC residuals were very similar to those of BC, suggesting that BC and closely-linked components are associated with rhinitis independently of total $PM_{2.5}$. These results reinforce the hypothesis that BC is one of the most harmful components of PMs (223) even if further studies between exposure to BC and rhinitis are needed to confirm these findings.

We did not adjust for the different distribution of pollen species in France. However, the marginal model allowed us to consider indirectly, among other things, the differences in the distribution of pollens between the different HSC. The associations between long-term exposure to air pollution, greenspace and rhinitis is understudied. In the recent study by Nordeide Kuiper *et al.*, no significant association was observed between greenspace and rhinitis (155). However, in the study by Markevych *et al.*, early life residence in places with many allergenic trees increased the prevalence of allergic rhinitis later in life. Exposure to greenspace could promote rhinitis by increasing exposure to pollens (233). There is no previous study on the interaction between long-term exposure to air pollution, greenspace and rhinitis in adults. In their study in 2020, Nordeide Kuiper *et al.* simultaneously adjusted on greenspace and air pollution in their analyses, but potential interactions were not tested. Considering the relationships between greenspace, air pollution and rhinitis is an interesting research perspective, especially given climate change and its connection with air pollution and respiratory health (234).

In conclusion, long-term exposure to air pollution was associated with current rhinitis in adults in a large French population-based study. The results suggest that among air pollutants, BC may be of special interest. In view of the high prevalence of rhinitis, these findings have an important public health impact and reinforce the need to reduce the population's exposure to air pollution.

4.2.2. Effect of long-term exposure to air pollution on rhinitis and asthma multimorbidity

Results from this section will be published as an original article (in preparation).

4.2.2.1. Introduction

We have previously observed that the presence of asthma impacted the characteristics of rhinitis (objective 1) and that exposure to air pollution was significantly associated with rhinitis. However, to our knowledge no study as investigated the association between air pollution and rhinitis and asthma multimorbidity. We therefore decided to study the association between air pollution and rhinitis accounting for asthma status.

4.2.2.2. Material and methods

4.2.2.2.1. Study design and definitions

Cross-sectional analyses were carried out in Constances with the data from the inclusion. The definitions of rhinitis and the variables of interest are those presented in the overall material and methods section 3.1.2.
By combining asthma and rhinitis, four groups were investigated: 1) neither current rhinitis nor current asthma (reference group) 2) current rhinitis alone 3) current asthma alone 4) current rhinitis and current asthma.

4.2.2.2.2. Air pollution exposure assessment

Modelled exposures were assigned at the participants' residential address at inclusion. We used annual averages for each pollutant from year 2010 models at the address of inclusion as a proxy for participants' long-term exposure to air pollution.

4.2.2.2.3. Statistical analyses

The main analyses were complete case analyses, i.e. after excluding participants with missing data for rhinitis, asthma, air pollution or adjustment variables. The general characteristics between the four groups were compared with standard statistical tests: Chi2 for categorical variables and Anova tests for continuous variables. Spearman correlation coefficients were performed to study the correlations between pollutants.

4.2.2.2.3.1. Main analyses

The cross-sectional associations between long-term exposure to air pollutants and current rhinitis and current asthma multimorbidity were studied using multinomial logistic regression models with neither current rhinitis no current asthma as the reference group. Estimates were calculated considering each pollutant separately for

an increase of their interquartile range (IQR), i.e. 4.66 µg/m^3 for $PM_{2.5}$, 0.87 10^{-5} m^{-1} for BC and 16.7 µg/m^3 for NO_2.
Associations between each air pollutant and current rhinitis and current asthma multimorbidity were assessed with several single-pollutant models. Firstly, univariate analyses were performed (model M0). A first level of adjustments for age, sex and smoking status (never smoker, ex-smoker, current smoker) was made (model M1). Further adjustment was made for educational level (no diploma/grade school, high school, university) as a proxy for SES at the individual level (model M2). Finally, to take both individual and contextual SES into account as previously recommended (225,226), a model with an additional adjustment on FDep was used (model M3 = main model).
As BC is a component of $PM_{2.5}$, and as they are highly correlated, using a two-pollutant model mutually adjusting one pollutant for the other is precluded. As an alternative to isolate the effect of BC from that of total $PM_{2.5}$, we used the residuals method described by Mostofsky *et al.* (227). Following this approach, we regressed BC as response variable on $PM_{2.5}$. These residuals were decorrelated from $PM_{2.5}$ and an increase in these residuals correspond to an increase in BC holding total $PM_{2.5}$ constant. We used these residuals as a new exposure variable in a single-pollutant model.

4.2.2.2.3.2. Supplementary analyses

All supplementary analyses were performed with the main M3 model.

As the effects of air pollution could be different according to the AR/NAR phenotypes of rhinitis, the analyses were carried out separately after exclusion of NAR or AR.
As air pollution could lead to different responses between men and women, stratification according to sex was performed. As air pollution and tobacco may share similar underlying biological mechanisms, stratification according to smoking was also performed. Heterogeneity between strata were tested using interaction tests.
As recruited participants lived in departments where HSC are located, analyses were carried out using marginal models with generalized estimating equations (224) to take into account potential clustering, i.e. that participants living in the same department were likely more similar than those living in other departments.
As the main analyses were complete case analyses, additional analyses were also carried out after multiple imputations (n = 5) for missing data on smoking status and diploma using the SAS procedures MI and MIANALYZE.
We also performed analyses by changing the reference group i.e. by excluding participants with non-current rhinitis or non-current asthma.
All analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC).

4.2.2.3. Results

Data from participants included in the cohort between 2012 and 2019 (n = 202,767) were analyzed. Participants with missing data regarding the definition of current rhinitis (n = 9,052), nasal allergies (n = 2,505), the definition of current asthma (n = 1,983), the geocode for air pollution exposure assignment (n = 2,401), diploma (n = 2,413), tobacco status (n = 6,381) or FDep (n = 2) were excluded from the main analyses. The flow chart is presented in Figure 27.

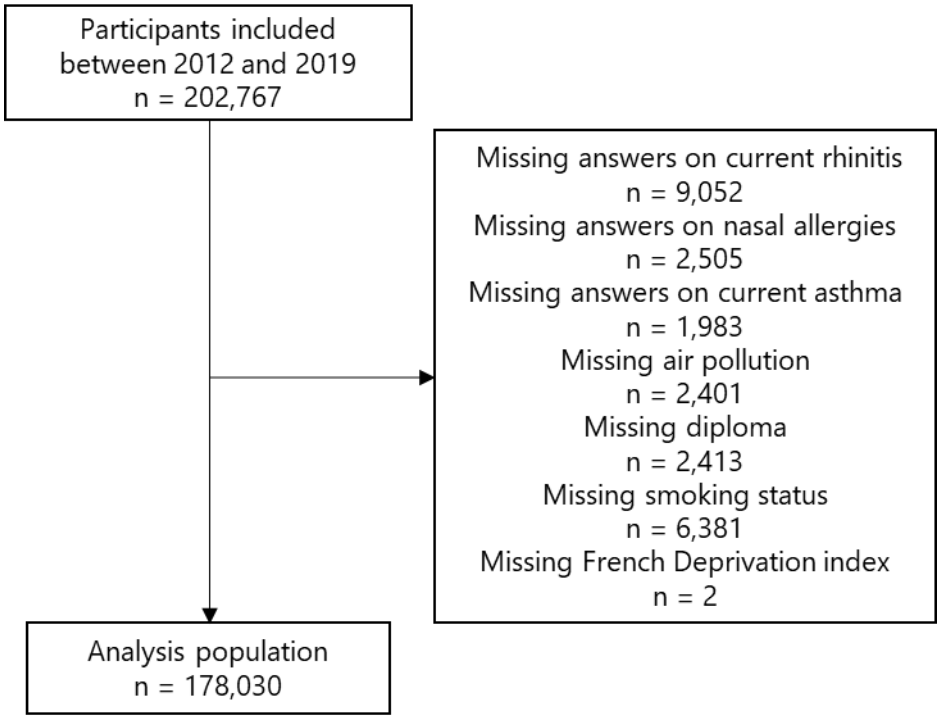


Figure 27: Flowchart of objective 2.2

A total of 178,030 adults were included in the main analyses. The main characteristics between participants included and those not included were similar, although very small differences were still statistically significant due to the large number of participants (Table S1 Appendix 10).

Characteristics of the participants included in the analyses are presented in Table 31. They were on average 47 years old and 53.5% were women, 111,142 (62.4%) were classified as neither current rhinitis nor current asthma, 49,992 (28.1%) current rhinitis alone, 6,436 (3.6%) current asthma alone, and 10,460 (5.9%) current rhinitis and current asthma. The current rhinitis and current asthma group was the group with the highest number of women, the lowest average age, and the highest education level. The median concentration of $PM_{2.5}$ was 16.2 µg/m^3 which is above the 2021 WHO guideline of 5 µg/m^3, and the median concentration of NO_2 was 23.3 µg/m^3 which is above the WHO guideline of 10 µg/m^3. The median concentration of BC was 1.64 10^{-5} m^{-1}.

Correlations between the three pollutants were high: 0.79 between $PM_{2.5}$ and BC, 0.86 between $PM_{2.5}$ and NO_2, and 0.92 between BC and NO_2 (Table S2 Appendix 10).

Table 31: Characteristics of the participants of objective 2.2

	All (n=178,030)	No-CR no-CA (n=111,142)	CR alone (n=49,992)	CA alone (n=6,436)	CR and CA (n=10,460)	p
Sex						<.0001
Men	82,718 (46.5%)	52,928 (47.6%)	22,383 (44.8%)	3,042 (47.3%)	4,365 (41.7%)	
Women	95,312 (53.5%)	58,214 (52.4%)	27,609 (55.2%)	3,394 (52.7%)	6,095 (58.3%)	
Age, years, mean (SD)	46.8 (15.0)	47.6 (13.3)	45.9 (13.5)	45.5 (13.9)	42.8 (13.3)	<.0001
Tobacco status						<.0001
Never-smoker	84,999 (47.7%)	53,970 (48.6%)	23,517 (47.0%)	2,716 (42.2%)	4,796 (45.9%)	
Ex-smoker	60,002 (33.7%)	37,399 (33.7%)	17,166 (34.3%)	2,105 (32.7%)	3,332 (31.9%)	
Current smoker	33,029 (18.6%)	19,773 (17.8%)	9,309 (18.6%)	1,615 (25.1%)	2,332 (22.3%)	
BMI, kg/m^2						<.0001
<18.5	4,905 (2.8%)	2,909 (2.7%)	1,540 (3.1%)	154 (2.4%)	302 (2.9%)	
[18.5-25[	95,649 (54.6%)	58,975 (54.0%)	28,381 (57.7%)	2,875 (45.6%)	5,418 (52.6%)	
[25-30[	53,146 (30.4%)	34,031 (31.1%)	13,974 (28.4%)	2,077 (32.9%)	3,064 (29.8%)	
≥30	21,388 (12.2%)	13,366 (12.2%)	5,311 (10.8%)	1,199 (19.0%)	1,512 (14.7%)	
Educational level						<.0001
Less than high school	14,537 (8.2%)	9,511 (8.6%)	3,626 (7.3%)	640 (9.9%)	760 (7.3%)	
High school	57,505 (32.3%)	37,268 (33.5%)	14,944 (29.9%)	2,242 (34.8%)	3,051 (29.2%)	
University	105,988 (59.5%)	64,363 (57.9%)	31,422 (62.9%)	3,554 (55.2%)	6,649 (63.6%)	
Air pollutants, med (IQR)						
$PM_{2.5}$, $\mu g/m^3$	16.2 (4.7)	16.1 (4.3)	16.4 (5.1)	16.2 (4.4)	16.3 (4.9)	<.0001
BC, 10^{-5} m^{-1}	1.6 (0.9)	1.6 (0.8)	1.7 (0.9)	1.6 (0.9)	1.7 (0.9)	<.0001
NO_2, $\mu g/m^3$	23.3 (16.7)	22.9 (15.7)	24.3 (18.8)	23.3 (16.6)	24.1 (18.1)	<.0001

Data are n (%) or mean (SD) or med (IQR)
BC: Black Carbon, BMI: Body Mass index, CA: Current Asthma, CR: Current Rhinitis, IQR: Interquartile Range, Med: Median, NO_2: Nitrogen Dioxide, $PM_{2.5}$ Particulate Matter ≤2.5 µm, SD: Standard Deviation

The results of the main analyses are presented in Table 32. Using participants without current rhinitis nor current asthma as reference, the main model M3 shows that an increase of an IQR of $PM_{2.5}$ was significantly associated with current rhinitis alone (OR: 1.13 ($CI_{95\%}$: 1.12-1.16)), current asthma alone (1.07 (1.03-1.12)), and current rhinitis combined with current asthma (1.06 (1.02-1.09)). An increase of an IQR of BC was significantly associated with current rhinitis alone (1.18 (1.16-1.20)), current asthma alone (1.10 (1.05-1.15)), and current rhinitis combined with current asthma (1.12 (1.08-1.16)). An increase of an IQR of NO_2 was significantly associated with current rhinitis alone (1.14 (1.12-1.16)), current asthma alone (1.07 (1.03-1.11)), and current rhinitis combined with current asthma (1.07 (1.04-1.11)). An increase of an IQR of BC residuals regressed on $PM_{2.5}$ was also significantly associated with current rhinitis alone (1.05 (1.04-1.07)), current asthma alone (1.04 (1.01-1.07)), and current rhinitis combined with current asthma (1.07 (1.04-1.09)).

Table 32: OR (95% CI) of the associations between $PM_{2.5}$, BC and NO_2 and current rhinitis and current asthma

	$PM_{2.5}$		**BC**		**NO_2**	
	OR ($CI_{95\%}$)	p	OR ($CI_{95\%}$)	p	OR ($CI_{95\%}$)	p
M0						
Neither CR nor CA (ref)	.	.	.	.	.	.
CR alone	1.16 (1.15-1.18)	<.0001	1.20 (1.18-1.22)	<.0001	1.17 (1.15-1.19)	<.0001
CA alone	1.04 (1.01-1.08)	0.02	1.07 (1.03-1.11)	0.0007	1.05 (1.01-1.08)	0.01
CR and CA	1.11 (1.08-1.14)	<.0001	1.17 (1.13-1.20)	<.0001	1.12 (1.09-1.15)	<.0001
M1						
Neither CR nor CA (ref)	.	.	.	.	.	.
CR alone	1.15 (1.13-1.16)	<.0001	1.18 (1.16-1.20)	<.0001	1.15 (1.13-1.17)	<.0001
CA alone	1.02 (0.98-1.05)	0.37	1.03 (0.99-1.07)	0.12	1.01 (0.98-1.05)	0.43
CR and CA	1.05 (1.02-1.08)	0.0003	1.10 (1.07-1.13)	<.0001	1.06 (1.04-1.09)	<.0001
M2						
Neither CR nor CA (ref)	.	.	.	.	.	.
CR alone	1.13 (1.11-1.15)	<.0001	1.16 (1.14-1.18)	<.0001	1.13 (1.11-1.15)	<.0001
CA alone	1.04 (1.00-1.07)	0.06	1.06 (1.02-1.10)	0.006	1.04 (1.00-1.07)	0.06
CR and CA	1.04 (1.01-1.07)	0.009	1.08 (1.05-1.12)	<.0001	1.05 (1.02-1.08)	0.0008
M3 = main model						
Neither CR nor CA (ref)	.	.	.	.	.	.
CR alone	1.13 (1.12-1.16)	<.0001	1.18 (1.16-1.20)	<.0001	1.14 (1.12-1.16)	<.0001
CA alone	1.07 (1.03-1.12)	0.002	1.10 (1.05-1.15)	<.0001	1.07 (1.03-1.11)	0.002
CR and CA	1.06 (1.02-1.09)	0.001	1.12 (1.08-1.16)	<.0001	1.07 (1.04-1.11)	<.0001

BC: Black Carbon, CA: Current Asthma, CI: Confidence Interval, CR: Current Rhinitis, NO_2: Nitrogen Dioxide, OR: Odds Ratio, $PM_{2.5}$: Particulate Matter ≤2.5 µm

All estimates were from multinomial logistic regression models, ORs (95% CI) were calculated for an increase of an interquartile range (4.66 µg/m^3 for $PM_{2.5}$, 0.87 10^{-5} m^{-1} for BC and 16.7 µg/m^3 for NO_2). M0: univariate analysis, M1: adjusted for age, sex, and smoking, M2: adjusted for age, sex, smoking, and educational level, M3: adjusted for age, sex, smoking, educational level, and French Deprivation index

The results of the supplementary analyses are shown in Table 33. Results were similar when excluding NAR or AR. Compared to men, slightly higher ORs for women were observed although the confidence intervals overlap and there were no significant interactions between each pollutant and sex. Stratification by smoking status yielded similar results for each stratum and there were no significant interactions between each pollutant and smoking status.

Similar results of those of the main model were obtained for $PM_{2.5}$ when considering the HSC in a marginal model. Multiple imputations yielded same results as those of the main model.

After exclusion of non-CR and non-CA, the ORs were similar to those reported in the main model.

Table 33: Associations between exposure to air pollution and current rhinitis and current asthma, supplementary analyses

		$PM_{2.5}$		BC		NO_2	
	n	OR ($CI_{95\%}$)	p	OR ($CI_{95\%}$)	p	OR ($CI_{95\%}$)	p
Main model (M3)							
Neither CR nor CA (ref)	111,142	.	.	.	.	.	.
CR alone	49,992	1.13 (1.12-1.16)	<.0001	1.18 (1.16-1.20)	<.0001	1.14 (1.12-1.16)	<.0001
CA alone	6,436	1.07 (1.03-1.12)	0.002	1.10 (1.05-1.15)	<.0001	1.07 (1.03-1.11)	0.002
CR and CA	10,460	1.06 (1.02-1.09)	0.001	1.12 (1.08-1.16)	<.0001	1.07 (1.04-1.11)	<.0001
AR and NAR							
Exclusion of current NAR							
Neither CR nor CA (ref)	104,400	.	.	.	.	.	.
CR alone	32,742	1.14 (1.12-1.16)	<.0001	1.22 (1.19-1.25)	<.0001	1.16 (1.14-1.19)	<.0001
CA alone	5,829	1.07 (1.03-1.12)	0.002	1.11 (1.06-1.16)	<.0001	1.07 (1.01-1.13)	0.02
CR and CA	9,164	1.05 (1.02-1.09)	0.006	1.13 (1.09-1.18)	<.0001	1.08 (1.04-1.12)	<.0001
Exclusion of current AR							
Neither CR nor CA (ref)	100,659	.	.	.	.	.	.
CR alone	17,250	1.14 (1.11-1.17)	<.0001	1.13 (1.09-1.16)	<.0001	1.13 (1.10-1.16)	<.0001
CA alone	4,371	1.07 (1.02-1.13)	0.01	1.09 (1.03-1.15)	0.002	1.06 (1.01-1.12)	0.02
CR and CA	1,296	1.14 (1.04-1.25)	0.006	1.09 (0.99-1.20)	0.10	1.11 (1.02-1.21)	0.02
Stratification by sex							
Men							
Neither CR nor CA (ref)	52,928	.	.	.	.	.	.
CR alone	22,383	1.11 (1.08-1.14)	<.0001	1.15 (1.12-1.18)	<.0001	1.13 (1.10-1.15)	<.0001
CA alone	3,042	1.03 (0.97-1.09)	0.37	1.06 (0.99-1.13)	0.09	1.02 (0.96-1.09)	0.44
CR and CA	4,365	1.03 (0.98-1.08)	0.31	1.06 (1.00-1.12)	0.04	1.04 (0.99-1.09)	0.14
Women							
Neither CR nor CA (ref)	58,214	.	.	.	.	.	.
CR alone	27,609	1.16 (1.13-1.18)	<.0001	1.20 (1.17-1.23)	<.0001	1.15 (1.13-1.18)	<.0001
CA alone	3,394	1.11 (1.04-1.17)	0.0008	1.14 (1.07-1.21)	<.0001	1.11 (1.05-1.17)	<.0001
CR and CA	6,095	1.08 (1.03-1.13)	0.0009	1.16 (1.11-1.22)	<.0001	1.09 (1.05-1.14)	0.0005
Stratification by tobacco status							
Never smokers							
Neither CR nor CA (ref)	53,970	.	.	.	.	.	.
CR alone	23,517	1.13 (1.10-1.16)	<.0001	1.17 (1.14-1.20)	<.0001	1.13 (1.10-1.16)	<.0001
CA alone	2,716	1.08 (1.01-1.15)	0.03	1.10 (1.03-1.18)	0.006	1.07 (1.01-1.14)	0.03
CR and CA	4,796	1.07 (1.01-1.12)	0.01	1.12 (1.06-1.18)	<.0001	1.08 (1.02-1.13)	0.003
Ex-smokers							
Neither CR nor CA (ref)	37,399	.	.	.	.	.	.
CR alone	17,166	1.15 (1.11-1.18)	<.0001	1.19 (1.15-1.23)	<.0001	1.16 (1.12-1.19)	<.0001
CA alone	2,105	1.06 (0.98-1.14)	0.14	1.10 (1.02-1.19)	0.02	1.06 (0.99-1.14)	0.10
CR and CA	3,332	1.10 (1.03-1.17)	0.002	1.17 (1.09-1.24)	<.0001	1.12 (1.06-1.19)	0.0001
Current smokers							
Neither CR nor CA (ref)	19,773	.	.	.	.	.	.
CR alone	9,309	1.13 (1.09-1.18)	<.0001	1.18 (1.13-1.24)	<.0001	1.14 (1.10-1.19)	<.0001
CA alone	1,615	1.08 (0.99-1.17)	0.09	1.11 (1.01-1.21)	0.03	1.07 (0.99-1.17)	0.09
CR and CA	2,332	0.99 (0.93-1.07)	0.84	1.07 (0.99-1.15)	0.09	1.00 (0.94-1.08)	0.90
Marginal model							
Neither CR nor CA (ref)	111,142	.	.	.	.	.	.
CR alone	49,992	1.13 (1.08-1.19)	<.0001	1.18 (1.13-1.22)	<.0001	1.14 (1.10-1.19)	<.0001
CA alone	6,436	1.07 (1.01-1.13)	0.0151	1.10 (1.05-1.15)	<.0001	1.07 (1.02-1.12)	0.008

		$PM_{2.5}$		BC		NO_2	
	n	OR ($CI_{95\%}$)	p	OR ($CI_{95\%}$)	p	OR ($CI_{95\%}$)	p
CR and CA	10,460	1.06 (0.99-1.13)	0.1049	1.12 (1.07-1.17)	<.0001	1.07 (1.01-1.14)	0.02
Multiple imputations							
Neither CR nor CA (ref)	116,873	.	.	.	.	.	.
CR alone	52,274	1.13 (1.11-1.15)	<.0001	1.17 (1.15-1.19)	<.0001	1.14 (1.12-1.16)	<.0001
CA alone	6,761	1.06 (1.02-1.10)	0.007	1.09 (1.04-1.14)	0.0001	1.06 (1.02-1.10)	0.006
CR and CA	10,918	1.06 (1.03-1.10)	0.0005	1.12 (1.08-1.16)	<.0001	1.07 (1.04-1.11)	<.0001
Exclusion of non-CR and non-CA							
Neither CR nor CA (ref)	91,182	.	.	.	.	.	.
CR alone	46,955	1.15 (1.13-1.18)	<.0001	1.20 (1.18-1.23)	<.0001	1.16 (1.14-1.18)	<.0001
CA alone	3,764	1.07 (1.01-1.13)	0.02	1.10 (1.03-1.16)	0.003	1.07 (1.01-1.13)	0.02
CR and CA	10,460	1.06 (1.03-1.10)	0.0005	1.13 (1.09-1.18)	<.0001	1.08 (1.05-1.12)	<.0001

BC: Black Carbon, BMI: Body Mass Index, CA: Current Asthma, CI: Confidence Interval, CR: Current Rhinitis, NO_2: Nitrogen Dioxide, OR: Odds Ratio, $PM_{2.5}$ Particulate Matter ≤2.5 µm
All estimates were from multinomial logistic regression models, ORs (95% CI) were calculated for an increase of an interquartile range (4.66 µg/m³ for $PM_{2.5}$, 0.87 10^{-5} m^{-1} for BC and 16.7 µg/m³ for NO_2)
a: adjusted for age, sex, smoking status, educational level, and French Deprivation index
b: adjusted for age, sex, smoking status, educational level, and French Deprivation index and BMI
c: adjusted for age, smoking status, educational level, and French Deprivation index
d: adjusted for age, sex, educational level, and French Deprivation index

4.2.2.4. Discussion

For the first time, we investigated the effect of long-term exposure to air pollution considering rhinitis and asthma multimorbidity. An increase of modelled annual average residential exposure to $PM_{2.5}$, BC, and NO_2 was significantly associated with an increased risk of current rhinitis and/or current asthma in a large population-based study. Whatever the pollutant, associations were higher for current rhinitis alone than for the other groups. These results were consistent regardless of the adjustment, the stratification, and the sensitivity analysis.

The cross-sectional setting of the analyses, the representativeness of Constances, the definitions used, and the estimation of exposure to air pollution have already been discussed (see 4.2.1.4 Discussion).

These main results are difficult to compare with those in the literature as there is no study on the association between long-term exposure to air pollution and rhinitis and asthma multimorbidity in adults from population-based cohorts. However, our results are consistent with the literature that has studied rhinitis and asthma separately and suggest that air pollution is associated both with asthma (235) and rhinitis (see 1.2.2 Air pollution and rhinitis).
Although air pollution was associated with current rhinitis alone, current asthma alone and current rhinitis combined with current asthma, the group with current rhinitis alone had the highest association. This is an innovative result for two main reasons. Firstly, in the air pollution and asthma analyses, if rhinitis is not considered, participants with rhinitis without asthma are in the reference group. Thus, the effects of air pollution on

asthma could be masked by the presence of participants with rhinitis in the reference group, especially since rhinitis is a very prevalent disease. Secondly, these results suggest that rhinitis alone or rhinitis combined with asthma are two distinct phenotypes with potentially different risk factors. Results from objective 1 of this thesis shows that rhinitis alone has different clinical and biological characteristics from rhinitis with asthma. The results of the present study reinforce these results and suggest that rhinitis-alone phenotype would be the most sensitive phenotype to the effects of pollution. One explanation is that the phenotypes rhinitis alone and rhinitis and asthma have distinct biological mechanisms. Another hypothesis is that since the symptoms of asthma combined with rhinitis are more severe than those of rhinitis alone, participants with asthma are more likely to seek to avoid air pollution, which could explain the weaker associations we observed for the asthma groups. Further studies considering rhinitis and asthma multimorbidity are needed to confirm our results.

In conclusion, these results strengthen the evidence that air pollution is associated with rhinitis and that rhinitis alone and rhinitis combined asthma are different diseases with possible different aetiology.

4.2.3. Effect of long-term exposure to air pollution on rhinitis incidence

These results are exploratory and will not published as they are.

4.2.3.1. Introduction

As showed in the introduction, only two studies -Burte *et al.* in 2018 and Fasola *et al.* in 2020- have investigated the effects of air pollution on the rhinitis incidence in adults. However, it is especially interesting to study the risk factors for incident rhinitis in adults as the risk factors of late onset rhinitis are probably different from those related to early onset rhinitis (19).
Thus, we aimed to study the associations between long-term exposure to NO_2, $PM_{2.5}$ and BC and incident rhinitis among adults.

4.2.3.2. Material and methods

4.2.3.2.1. Study design and definitions

A longitudinal study was carried out in Constances with the data from the inclusion and from the follow-up questionnaire of 2014.

Two definitions of the rhinitis incidence were used:
1) "**General incidence**": when the participant reported never rhinitis at inclusion and reported ever rhinitis at follow-up
2) "**Strict incidence**": "general incidence" and in addition the age of onset of rhinitis reported at follow-up was equal or higher than the age at inclusion.

The main analyses considered the strict incidence definition and excluded participants with missing data on age of onset of rhinitis and those with an age of onset lower than the age at inclusion. The present longitudinal analysis was performed on a subsample of 6,914 participants, included between 2012 et 2013 who reported never rhinitis at inclusion and with available data on rhinitis in 2014 and air pollution.

4.2.3.2.2. Air pollution exposure assessment

Modelled exposures were assigned at the participants' residential address at inclusion. Annual averages for each pollutant from year 2010 models at the address of inclusion as a proxy for participants' long-term exposure to air pollution were used.

4.2.3.2.3. Statistical analyses

The main analyses were complete case analyses, i.e. after excluding participants with missing data for rhinitis, air pollution or adjustment variables.

4.2.3.2.3.1. Main analyses

The longitudinal associations between long-term exposure to air pollutants and incident rhinitis were studied using Poisson regression models with time between inclusion and follow-up as an offset (156). Incidence Risk Ratios (IRR) were calculated considering each pollutant separately for an increase of their IQR, i.e. 3.17 µg/m^3 for $PM_{2.5}$, 0.77 10^{-5} m^{-1} for BC and 13.8 µg/m^3 for NO_2.
Associations between each air pollutant and rhinitis incidence were assessed with several single-pollutant models with the same adjustments as in the inclusion analyses (see 4.2.1.2.3 Statistical analyses and 4.2.2.2.3 Statistical analyses).

4.2.3.2.3.2. Supplementary analyses

All supplementary analyses were performed with the main M3 model.

As the effects of pollution could be different according to the AR/NAR phenotypes of rhinitis, the analyses were carried out after exclusion of NAR or AR.
As air pollution could lead to different responses between men and women, stratification according to sex was performed. As air pollution and tobacco may share similar underlying biological mechanisms, stratification according to smoking was also performed. Heterogeneity between strata were tested using interaction tests.
As recruited participants lived in departments where HSC are located, analyses were carried out using marginal models with generalized estimating equations (224) to take into account potential clustering, i.e. that participants living in the same department were likely more similar than those living in other departments.
As the main analyses were complete case analyses, additional analyses were also carried out after multiple imputations (n = 10) for missing data on smoking status and diploma using the SAS procedures MI and MIANALYZE.
The analyses were also performed after excluding participants who had changed their address between inclusion and the 2014 follow-up.
The analyses were performed by changing the statistical model used: logistic regression model with results expressed as OR or Cox model with results expressed as Hazard Ratios (HR).
We also conducted a sensitivity analysis by considering the associations between air pollution and general incidence.

All analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC).

4.2.3.3. Results

Data from participants included in the cohort between 2012 and 2013 (n = 26,737) were analyzed. Non-respondents at the follow-up questionnaire of 2014 (n = 5,230), participants with missing data regarding ever rhinitis (n = 485) or nasal allergies (n = 325) at inclusion, or at the follow-up questionnaire of 2014 (n = 179 and n = 224), length of follow-up (n = 1), geocode for air pollution exposure assignment (n = 4), diploma (n = 192) or tobacco status (n = 803) were excluded. Among participants without missing data, prevalent cases of ever rhinitis (n = 8,634) at inclusion were excluded from the main analyses. Participants who answered yes to "*Have you ever had any nasal allergies including hay fever?*" and no 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?*" at inclusion (n = 998) or at follow-up (n = 436) were considered inconsistent and were also excluded from the analyses. We also excluded participants with general incident rhinitis who did not have strict incident rhinitis because of a missing age of onset of rhinitis (n = 1,037) or an age of onset of rhinitis lower than the age at inclusion (n = 1,275). A total of 6,914 adults were included in the main analyses. The flowchart is presented Figure 28.
The differences regarding the main characteristics between participants included and those not included were small, although statistically significant due to the large number of participants (Appendix 11 Table S1).

Characteristics of the participants included in the analyses are presented in Table 34. They were on average 51.0 years old and 56.4% were women. The average time from inclusion to follow-up in 2014 was 1.55 years. There were 138 cases of incident rhinitis according to the strict definition, giving a crude incidence rate of 19 per 1,000 person-year. Among incident cases, the mean age of onset of rhinitis was 49.3 year and 65.2% were NAR. Compared to the never rhinitis group, the incident cases comprised more women and had a lower mean age.

Table S2 (Appendix 11) shows the distribution of pollutants and the correlation coefficients between them. The annual mean concentration of $PM_{2.5}$, BC and NO_2 were 16.2 µg/m^3, 1.75 10^{-5} m^{-1} and 24.8 µg/m^3, respectively. Correlation coefficients between the three pollutants were 0.78 between $PM_{2.5}$ and BC, 0.86 between $PM_{2.5}$ and NO_2, and 0.91 between BC and NO_2.

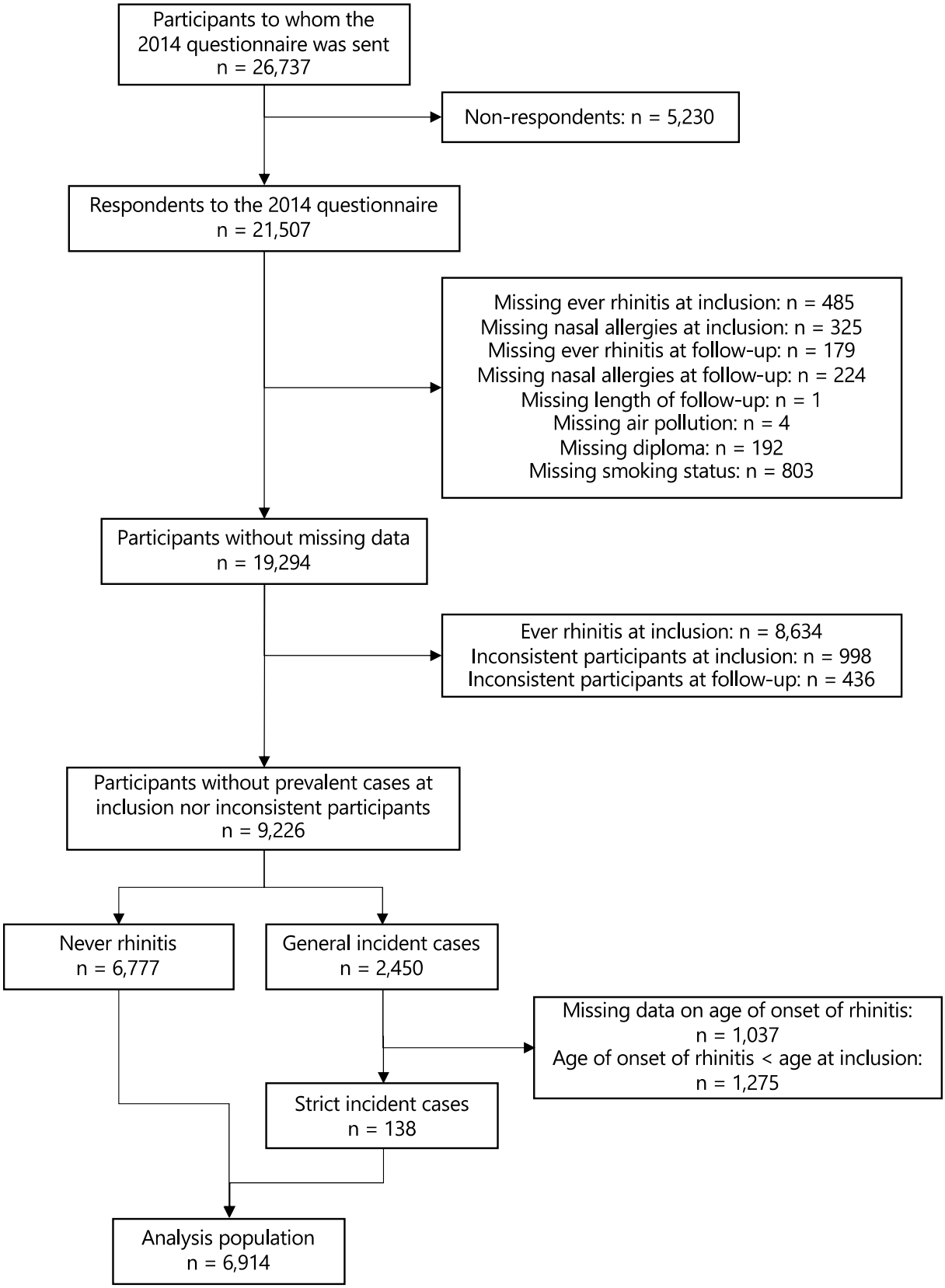


Figure 28: Flowchart of objective 2.3

Table 34: Characteristics of the participants of objective 2.3

	All (n=6,914)	Never rhinitis (n=6,776)	Strict incident rhinitis (n=138)	p
Sex				0.001
Men	3,016 (43.6%)	2,975 (43.9%)	41 (29.7%)	
Women	3,898 (56.4%)	3,801 (56.1%)	97 (70.3%)	
Age, years (mean SD)	51.0 (12.3)	51.0 (12.3)	48.7 (14.4)	0.06
Tobacco status				0.48
Never smoker	3,380 (48.9%)	3,310 (48.9%)	70 (50.7%)	
Ex-smoker	2,460 (35.6%)	2,417 (35.7%)	43 (31.2%)	
Current smoker	1,074 (15.5%)	1,049 (15.5%)	25 (18.1%)	
BMI, kg/m^2				0.68
<18.5	160 (2.4%)	156 (2.3%)	4 (2.9%)	
[18.5-25[	3,782 (55.5%)	3,703 (55.4%)	79 (57.7%)	
[25-30[	2,141 (31.4%)	2,104 (31.5%)	37 (27.0%)	
≥30	734 (10.8%)	717 (10.7%)	17 (12.4%)	
Educational level				0.32
Less than high school	657 (9.5%)	649 (9.6%)	8 (5.8%)	
High school	2,366 (34.2%)	2,316 (34.2%)	50 (36.2%)	
University	3,891 (56.3%)	3,811 (56.2%)	80 (58.0%)	
Asthma				0.30
Never asthma	6,595 (95.9%)	6,467 (95.9%)	128 (94.1%)	
Ever asthma	284 (4.1%)	276 (4.1%)	8 (5.9%)	
Incident rhinitis				
NAR			90 (65.2%)	
AR			48 (34.8%)	
Air pollutants (Med IQR)				
PM2.5, $\mu g/m^3$	15.9 (3.2)	16 (3.2)	16.0 (4.8)	0.22
BC, $10^{-5}\ m^{-1}$	1.6 (0.8)	1.6 (0.8)	1.6 (0.8)	0.22
NO2, $\mu g/m^3$	21.9 (13.8)	21.9 (13.8)	23.6 (15.7)	0.27

Data are n (%) or mean (SD) or Med (IQR).

AR: Allergic Rhinitis, BC: Black Carbon, BMI: Body Mass Index, IQR: Interquartile Range, Med: Median, NAR: Non-Allergic Rhinitis, NO_2: Nitrogen Dioxide, $PM_{2.5}$: Particulate Matter ≤2.5 µm, SD: Standard Deviation

Table 35 shows the associations between $PM_{2.5}$, BC and NO_2 and incident rhinitis. Adjusted IRRs for the main model M3 were 1.20 ($CI_{95\%}$: 1.00-1.45) per IQR increase in $PM_{2.5}$, 1.28 (0.99-1.66) per IQR increase in BC and 1.22 (0.98-1.52) per IQR increase in NO_2. BC residuals regressed on $PM_{2.5}$ were not significantly associated with an increase of incident rhinitis (1.10 (0.64-1.91) for an IQR increase of BC residuals).

Table 35: IRRs ($CI_{95\%}$) of the associations between $PM_{2.5}$, BC and NO_2 and incident rhinitis

	$PM_{2.5}$		**BC**		**NO_2**	
	IRR ($CI_{95\%}$)	p	IRR ($CI_{95\%}$)	p	IRR ($CI_{95\%}$)	p
M0	1.12 (0.96-1.31)	0.15	1.16 (0.93-1.44)	0.19	1.13 (0.94-1.36)	0.21
M1	1.11 (0.95-1.31)	0.18	1.15 (0.92-1.43)	0.21	1.12 (0.93-1.35)	0.25
M2	1.12 (0.95-1.32)	0.17	1.16 (0.93-1.46)	0.20	1.13 (0.93-1.37)	0.23
M3 = main model	1.20 (1.00-1.45)	0.05	1.28 (0.99-1.66)	0.06	1.22 (0.98-1.52)	0.08

BC: Black Carbon, CI: Confidence Interval, NO_2: Nitrogen Dioxide, IRR: Incidence Rate Ratio, $PM_{2.5}$ Particulate Matter ≤2.5 µm

All estimates were from Poisson logistic regression models, IRR (95% CI) were calculated for an increase of an interquartile range (3.17 µg/m^3 for $PM_{2.5}$, 0.77 10^{-5} m^{-1} for BC and 13.8 µg/m^3 for NO_2)

M0: univariate analysis, M1: adjusted for age, sex, and smoking status, M2: adjusted for age, sex, smoking status, and educational level, M3: adjusted for age, sex, smoking status, educational level, and French Deprivation index

The results of the supplementary analyses are shown in Table 36. Although the confidence intervals overlapped, IRRs were higher for NAR compared to AR, with significant IRR for BC and NAR (1.38 (1.01-1.89)). Similarly, IRRs were higher for women compared to men, and significant associations were found in women strata for BC (1.43 (1.06-1.93)) and NO_2 (1.31 (1.01-1.69)). Regarding smoking status, significant associations for each of the three pollutants were observed only among never smokers. The IRRs were very similar to those of the main model after considering the HSC in a marginal model, multiple imputations, logistic model, or the Cox model. In the case of multiple imputations and the Cox model significant associations were observed. After excluding participants who changed their address between inclusion and the follow-up questionnaire of 2014, the associations were slightly higher and significant for all pollutants.

Finally, when considering the general definition of incident rhinitis, 2,450 incident cases were considered giving a crude incident rate of 171 per 1,000 person-year. Although the associations were all statistically significant, lower IRRs than those considering the strict definition were observed.

Table 36: Associations between exposure to air pollution and incident rhinitis, supplementary analyses

	n			$PM_{2.5}$		BC		NO_2	
	Total	Ref.	Incid.	IRR ($CI_{95\%}$)	p	IRR ($CI_{95\%}$)	p	IRR ($CI_{95\%}$)	p
M3 = main analysis[a]	6,914	6,776	138	1.20 (1.00-1.45)	0.05	1.28 (0.99-1.66)	0.06	1.22 (0.98-1.52)	0.08
AR and NAR[a]									
AR	6,824	6,776	48	1.18 (0.84-1.67)	0.34	1.12 (0.69-1.84)	0.64	1.18 (0.78-1.77)	0.43
NAR	6,866	6,776	90	1.21 (0.96-1.52)	0.10	1.38 (1.01-1.89)	0.04	1.24 (0.95-1.63)	0.11
Stratification by sex[b]									
Men	3,016	2,975	41	1.25 (0.89-1.75)	0.20	0.96 (0.58-1.58)	0.87	1.01 (0.67-1.54)	0.95
Women	3,898	3,801	97	1.17 (0.94-1.47)	0.15	1.43 (1.06-1.93)	0.02	1.31 (1.01-1.69)	0.04
Stratification by tobacco status[c]									
Never smokers	3,380	3,310	70	1.37 (1.06-1.78)	0.02	1.61 (1.12-2.31)	0.01	1.54 (1.14-2.09)	0.01
Ex-smokers	2,460	2,417	43	1.07 (0.76-1.52)	0.69	1.06 (0.66-1.72)	0.81	0.96 (0.63-1.46)	0.85
Current smokers	1,074	1,049	25	0.96 (0.62-1.47)	0.85	0.90 (0.48-1.66)	0.73	0.91 (0.54-1.53)	0.73
Marginal model[d]	6,914	6,776	138	1.21 (0.89-1.66)	0.22	1.28 (0.94-1.74)	0.11	1.22 (0.94-1.59)	0.13
Multiple imputations[a]	7,243	7,095	148	1.20 (1.00-1.43)	0.04	1.31 (1.03-1.68)	0.03	1.23 (1.00-1.52)	0.05
Logistic model[e]	6,914	6,776	138	1.19 (0.98-1.43)	0.08	1.29 (0.99-1.67)	0.06	1.21 (0.97-1.52)	0.09
Cox model[f]	6,914	6,776	138	1.24 (1.03-1.49)	0.02	1.28 (1.00-1.65)	0.05	1.23 (0.99-1.53)	0.06
Exclusion of participants who have moved	5,218	5,121	97	1.31 (1.05-1.63)	0.02	1.39 (1.02-1.89)	0.03	1.29 (0.99-1.68)	0.06
General incident rhinitis[a]	9,226	6,776	2,450	1.06 (1.01-1.10)	0.01	1.08 (1.02-1.15)	0.01	1.07 (1.02-1.12)	0.01

BC: Black Carbon, CI: Confidence Interval, Incid: number of incident cases, IRR: Incident Rate Ratio, NO_2: Nitrogen Dioxide, $PM_{2.5}$ Particulate Matter ≤2.5 µm, Ref: number of references cases

Associations (95% CI) were calculated for an increase of an interquartile range (3.17 µg/m^3 for $PM_{2.5}$, 0.77 10^{-5} m^{-1} for BC and 13.8 µg/m^3 for NO_2)

a: Poisson logistic regression model adjusted for age, sex, smoking status, educational level, and French Deprivation index

b: Poisson logistic regression model adjusted for adjusted for age, smoking status, educational level, and French Deprivation index

c: Poisson logistic regression model adjusted for adjusted for age, sex, educational level, and French Deprivation index

d: Poisson marginal model adjusted for age, sex, smoking status, educational level, and French Deprivation index

e: Logistic regression model adjusted for age, sex, smoking status, educational level, and French Deprivation index, results expressed as Odds Ratios

f: Cox model adjusted for age, sex, smoking status, educational level, and French Deprivation index, results expressed as Hazard Ratios

4.2.3.4. Discussion

In this longitudinal analysis, close to significant associations were observed between $PM_{2.5}$, BC, and NO_2 and strict incident rhinitis. Significant associations were observed in sensibility or stratified analyses, namely among never smokers for all pollutants, in women for BC and NO_2, and with incident NAR for BC.

These results raise the methodological issue to define the rhinitis incidence. Classically in epidemiology, the incidence of a disease is defined as ever having a disease at follow-up among those who did never have had the disease at inclusion. In the present study, the "general incidence" of rhinitis is defined according to this criterion. With this definition, that we only used for sensitivity analyses, we observed a crude incidence rate of 171 per 1,000 person-year. By considering a second, definition of incidence that restricted the incident cases to participants who reported an age of onset of rhinitis greater than or equal to their age at inclusion, the incident rate was 13 per 1,000 person-year. Such a difference in the incidence rates could be explained by the fact that since rhinitis is a relatively benign and a very common disease, it is quite possible for a participant to forget having had rhinitis in his or her lifetime and to remember it at follow-up. Using the "general" definition would possibly mean studying the effects of air pollution on the lifetime prevalence of rhinitis rather than the incidence. In the present analysis, we found that the strength of association was higher with the "strict" definition than with the "general" definition, suggesting less classification error with the "strict" definition. The "strict" definition has, however, the limitation that it is based on self-reported age of onset, a variable missing for many participants in the present analyses. We could assume that participants with missing variable for age of onset have an age of onset long ago likely before baseline which is only one year and a half before the follow-up meaning that they are probably not true incidence cases.
Only two previous studies have investigated the effects of long-term exposure to air pollution on the rhinitis incidence in adults (156,157). The first study did not find any significant associations between exposure to NO_2, PM_{10} or $PM_{2.5}$ and rhinitis incidence (156) and the second showed a significant association with $PM_{2.5}$ but not PM_{10} (157). In these two studies, a definition of incidence similar to our "general" definition was used. Thus, the lack of significant results could possibly be explained by a misclassification of incident cases.

In the present study, with the main model, associations at the borderline significance were observed for $PM_{2.5}$, BC, and NO_2 with incident rhinitis. The IRRs were very stable regardless of the statistical model used: marginal model, multiple imputations, logistic model, Cox model. We can supppose that the associations in the main model are non-significant due to power issue and that with a larger number of participants and/or a longer follow-up the results would be potentially significant. This hypothesis is supported by the fact that in the sensitivity analysis with multiple imputations, the analyses could be performed on a slightly larger number of participants and the results

were significant for each of the three pollutants. Otherwise, by restricting the analysis population to participants who had not updated their address between inclusion and the 2014 follow-up, the IRRs were higher and significant for $PM_{2.5}$ and BC. This further supports the potential association between air pollution and the rhinitis incidence.
We also found significant associations with incident NAR for BC, in women for BC and NO_2, and in the never smoker group for all three pollutants. These results should be taken with caution given the small number of participants in the strata and the fact that the confidence intervals overlap, but they are linked to interesting mechanistic hypotheses. It is possible that the effects are different between AR and NAR as the mechanisms and pathways involved may be different. Women could be more sensitive to the effects of air pollution due to hormonal factors, smaller lung volume or due to gender-related factors such as differential accuracy in residence-based exposure assignment (230). Finally, as tobacco could have similar pathological pathways to pollution (231), it is possible that smokers/ex-smokers are less sensitive to the effects of air pollution than never smokers due to a saturation effect.

The major limitation of our study is that we have a short follow-up. There is no clear recommendation on the minimum follow-up time needed in epidemiological cohorts and the only requirement is that the follow-up time should be sufficient for a sufficient number of events to occur. In the case of large cohorts such as Constances, the sufficient number of cases is very quickly reached which gives the possibility for early prospective analyses (236). For example, in 1.5 years of follow-up we had 138 incident cases (2,450 if we considered the general incidence), whereas in 10 years of follow-up Fasola *et al.* had only 90 general incident cases (157). In a study looking at the impact of the follow-up time on the association between physical activity and mortality outcomes in UK Biobank, Strain *et al.* found that analyses with longer follow-up times showed weaker associations (236). Strain *et al*. studied another exposure and outcome that may be subject to reverse causality bias (e.g. people who are ill and therefore at greater risk of dying will engage in less physical activity) (236), for which we are not concerned with. However, the results of the study by Strain *et al.* raise questions about the interpretation and validity of our results. Moreover, as we discussed earlier, we suppose that the associations in the main model are non-significant due to power issue. With a longer follow-up time, the number of new cases of rhinitis would be higher, which would provide more statistical power. Furthermore, the development process of rhinitis is long, so with a short follow-up time we cannot be sure that the incidence is due to air pollution exposure at inclusion. For all these reasons, we consider the results of the present study as preliminary, and we decided to not publish them as such. These preliminary results, although debatable, are nevertheless very promising and offer interesting research prospects. Our objective is to reproduce these analyses in Constances but with a longer follow-up time.

In conclusion, air pollution may increase the risk of incident rhinitis in adults from the general population and the results suggest that women and never smokers may be more sensitive to the effects of air pollution. This study also highlights the methodological importance of an accurate definition of rhinitis incidence. Due to the short duration of the follow-up, we consider the results of this study as preliminary and longer follow-up is needed to validate them.

5. DISCUSSION AND PUBLIC HEALTH IMPLICATIONS

In this section, I will discuss the interrelatedness of the results, their potential impact on public health and the resulting research perspectives.

5.1. CHARACTERISATION OF RHINITIS

During my thesis, I have studied the heterogeneity of rhinitis in two complementary French studies. The EGEA study has the strength of having a large biobank which allows a wide range of biomarkers to be studied. However, this study is limited by the number of participants and its asthma case-control design. On the other hand, Constances currently lacks SPTs and specific IgE but it is a population-based study with a very large number of participants.

5.1.1. Public health impacts of the results

5.1.1.1. Defining rhinitis in epidemiology

Our literature review on the definitions and prevalences of rhinitis highlighted that there were no consensual definitions of rhinitis, AR and NAR. Thus, my first objective was to define rhinitis. In EGEA2, I was able to compare a questionnaire and a SPT definition of AR and NAR and I showed that a questionnaire definition could be a good proxy for AR and NAR. I have subsequently used this definition in Constances and observed the classic clinically known characteristics of AR and NAR, which reinforces the validity of this proxy. This work on the definitions of rhinitis by questionnaire has a direct impact and use in epidemiology. Indeed, the definitions used to distinguish AR and NAR are very simple and can therefore be easily used in large population-based epidemiological studies. Using this definition would allow harmonisation between studies and thus allow comparison of results. In addition, it would allow to study NAR for which there is currently scarce data in general population.
I also pointed out a methodological issue in defining rhinitis incidence. Incident rhinitis may be biased with a definition -called “general incident rhinitis” in the analyses- that only considers the absence of ever rhinitis at time t and the presence of ever rhinitis at a later follow-up. Combining “general incident rhinitis” with other variables to "validate" incident cases, namely age of onset of rhinitis would be less biased. The strength of the associations between air pollution and incident rhinitis were weaker with “general” definition compared to the definition based on age of onset. Using a more accurate definition of rhinitis would potentially highlight risk factors that would not be significant with the “general definition”.

5.1.1.2. Prevalences of rhinitis

I was able to estimate prevalences of rhinitis, AR and NAR in the general adult population and to show that the prevalence of rhinitis in France is high. In addition, I was able to provide data on the severity, duration and multimorbidities of rhinitis. These figures could eventually be used in burden studies and health economics. Indeed, in order to establish estimates of the cost of rhinitis, prevalence data are needed and knowing the proportion of severe/persistent cases is also useful as the cost of rhinitis differs according to its severity and duration (60). This will have public health impacts as health economics studies allow to quantify the cost of rhinitis and to target cost-effective intervention. These studies also allow to see the positive impact that rhinitis treatments and diagnostics could have on health care expenditure and to no longer consider them as costs but rather as investments (237).

5.1.1.3. Rhinitis characterisation and importance of asthma

Beyond the prevalences of rhinitis, I was able to study their characteristics according to its phenotypes and multimorbidities. The characteristics of AR and NAR classically known by the physician were observed and there was a much higher proportion of cases of mild rhinitis in general population than in patient's cohorts. This result was expected as patients with severe rhinitis are more prone to consult health professionals (54), but it was never been reported in a the literature. The unsupervised approach confirmed the results of the candidate approach and highlighted the importance of rhinitis severity.

I was also able consider asthma as a multimorbidity of rhinitis, and for the first time in a population-based study, the characteristics of rhinitis according to asthma were investigated in depth. Consistently in the analyses, both in EGEA and Constances, rhinitis without asthma and rhinitis with asthma had different characteristics in terms of severity, biology and multimorbidities. Furthermore, I showed that the ARIA classification varied according to asthma status. These results are paradigm changing and challenge the ARIA classification which should systematically consider asthma status of patients. Overall, the results from this thesis would have an impact on clinical practice and on the management of rhinitis by reinforcing the need to treat rhinitis not on its own but in the context of all its multimorbidities, and by opening a whole field of research to find new treatments targeting both asthma and rhinitis pathways.

5.1.2. Research perspectives

5.1.2.1. Other phenotypes of rhinitis

The main phenotypes considered in this thesis are AR, NAR and the severity and duration of rhinitis. There are other phenotypes of interest that have not been studied in this thesis e.g. mixed rhinitis and local AR. These two phenotypes are difficult to identify even in clinical practice and require specific tests for local AR and a thorough

examination of patients' triggers for mixed rhinitis, which makes their identification in large epidemiological studies difficult. On another hand, this thesis has considered NAR as a single entity but there are many different sub-phenotypes, e.g. rhinitis of the elderly, hormonal rhinitis, occupational rhinitis, that may be of interest to study as they may differ greatly in characteristics, mechanisms, and risk factors. Thus, further studies focusing on these other phenotypes are needed.

5.1.2.2. Other endotypes of rhinitis

Beyond the phenotypes, the underlying biological pathways of rhinitis are of interest and can be the target of specific management. This thesis identified endotypes of rhinitis with an unsupervised approach in EGEA and highlighted the importance of allergy pathways. Due to the small number of participants, the high weight of the allergy pathway and the study design, it was not possible to identify endotypes related to other biological pathways in EGEA. One perspective would be to study endotypes for allergic and non-allergic rhinitis separately and new analyses with more participants are needed. In addition, it might be interesting to consider non-biological markers, such as tests involving neurogenic pathways or anatomical examination of the nose, to identify new endotypes of rhinitis.

5.1.2.3. Results in other cohorts outside France

The results of this thesis are based on two French cohorts which gave very consistent results. As there are differences in genetic components and lifestyles between countries, replicating the analyses of this thesis in other cohorts outside France could validate the phenotypes/endotypes identified to other countries and/or bring new knowledge on rhinitis.

5.1.2.4. Evolution of rhinitis over time

In this thesis the characteristics of the phenotypes and endotypes of rhinitis were investigated based on cross-sectional approaches. A research perspective is to study the evolution of rhinitis over time and which factors impact its severity evolution and its duration or remission. The adult population is of particular interest regarding the age-related variations, such as menopause, or immunosenescent (238), which could have a direct impact on the evolution of the disease. However, this research topic has never been properly investigated in population-based studies.

5.1.2.5. Aetiology of rhinitis

From the findings of this thesis, another research question that emerges is: what is the aetiology of the different phenotypes/endotypes of rhinitis? So far, the majority of studies have focused on risk factors for AR. There are few studies on the risk factors of other phenotypes, even though these may be very different from AR. Environmental

factors are particularly interesting to study because they could explain the rapid increase in the rhinitis prevalence and can be the target of prevention measures. Beyond this question, genetics should not be forgotten. Genetics is one of the major risk factors for AR and play a larger role than environmental factors (239), it could also explain the appearance of some phenotypes/endotypes through the activation of specific biological pathways. On the other hand, environmental factors can also affect gene expression. Thus, a research perspective would be to study epigenetic mechanisms and gene/environment interactions involved in the aetiology of rhinitis.

5.2. LONG-TERM EXPOSURE TO AIR POLLUTION AND RHINITIS

Among the environmental factors that could be linked to rhinitis, I focused on the long-term exposure to $PM_{2.5}$, BC and NO_2 in Constances.

5.2.1. Public health impacts of the results

This thesis studied, in a cross-sectional analysis, the long-term effects of air pollution on the presence of rhinitis symptoms during the last 12 months, i.e. current rhinitis. I found that an increase of modelled annual average residential exposure to $PM_{2.5}$, BC, and NO_2 was significantly associated with an increased risk of current rhinitis. Starting from theses associations and from the differences in the characteristics between rhinitis alone and rhinitis with asthma, this thesis further studied the effects of long-term exposure to air pollution on rhinitis and asthma multimorbidity. An increase of modelled annual average residential exposure to $PM_{2.5}$, BC, and NO_2 was significantly associated with an increased risk of current rhinitis and/or current asthma whatever the pollutant, associations were higher for current rhinitis without current asthma than for the other phenotypes. These results reinforce the hypothesis that rhinitis alone and rhinitis with asthma are two distinct diseases. They also suggest that these phenotypes may have different risk and susceptibility factors, a hypothesis that opens a whole field of epidemiological investigation in the risk factors and determinants of these phenotypes. Finally, longitudinal analyses between inclusion and the follow-up questionnaire of 2014 were conducted. Close to significant associations were observed between $PM_{2.5}$, BC, and NO_2 and "strict incident" rhinitis, based on a coherent age of onset. The associations between air pollution and incident rhinitis were stronger in women and never smokers and this could suggest that some populations are more vulnerable to the effects of air pollution in terms of the development of new cases of rhinitis in adults. However, these longitudinal results should be viewed with great caution given the very short follow-up time, and further studies with longer follow-up are needed.

5.2.2. Research perspectives

5.2.2.1. Need for a systematic review and meta-analysis

A proper literature review and meta-analysis is now needed to allow an assessment of the health risks of air pollution on rhinitis. A meta-analysis on the subject combined with toxicological studies would provide 1) elements to determine the causal relationship between air pollution and rhinitis and 2) risk estimates, that would allow to quantify the economic and health burden of air pollution on rhinitis, giving figures for health policies.

5.2.2.2. Effects of long-term exposure to air pollution on other rhinitis phenotypes/endotypes and biological pathways

It may be also of interest to investigate in Constances whether air pollution is associated with other phenotypes of rhinitis, such as the severity of rhinitis as suggested in EGEA and ECRHS (207). Studying the associations between air pollution and endotypes could also provide a better understanding of the aetiology of rhinitis. One objective of this thesis was to study the association between air pollution and the rhinitis endotypes identified in EGEA. However, the identification of endotypes did not lead to the identification of other forms of rhinitis than AR and NAR, and the relationship between air pollution and these phenotypes was previously studied in EGEA (156). For this reason, I did not conduct analyses between long-term exposure to air pollution and rhinitis endotypes in EGEA but this is a research perspective of interest with larger cohorts.
Another perspective would be to look at the association between air pollution and rhinitis in terms of the underlying biological mechanisms by considering biological markers of interest as mediators of the observed relationship. This research would bridge the gap with the results of toxicology studies and provide a better understanding of the mechanisms of air pollution on the pathophysiology of rhinitis.

5.2.2.3. Air pollution exposure measurement error

In this thesis, air pollution exposure was assessed only at the residential address of participants in the inclusion year with estimates obtained via a LUR model developed from 2010 data. It is undeniable that this leads to measurement errors in particular time-activity error and model misspecification (240). These measurement errors are either classical non-differential measurement errors or Berkson type errors (241). They imply little bias and/or a bias towards an underestimation of the association (240). These measurement errors are very common in environmental epidemiology and few studies have attempted to quantify and correct them (241). However, having a more accurate estimate of exposure is still a main issue and a goal to achieve as they could provide a more accurate estimate of the health effects of air pollution. Correction methods have been proposed to reduce the measurement errors, but studies on the

transferability of these correction factors to other epidemiological studies are currently lacking (241).
Furthermore, in the present thesis, annual average of air pollution exposure at inclusion address was considered as a reflection of the participant's long-term exposures. This assumption is less accurate for participants who moved just prior to inclusion. It would be more accurate to consider a long-term average air pollution exposure weighted by the participant's residential history. Residential history data were not available in Constances for this thesis, but the complete residential history is now available for 80,000 Constances participants, and new analyses could now be performed taking this history into account.

5.2.2.4. Multi-pollutant model

I have studied the effects of $PM_{2.5}$, BC and NO_2 separately. However, we breathe a cocktail of pollutants that interact with each other and are not limited to these three pollutants. A research perspective would be to study the effects of air pollution in a multi-pollutant model. In the case of air pollution there are methodological issue that prevent the use of "classical" statistical regression models (such as fitting one pollutant to another or using an interaction term). First, air pollutants are very often highly correlated with each other, which makes regression models highly unstable and results impossible to interpret (232). Finally, some pollutants belong to subcategories of other pollutants, e.g. BC belongs to the $PM_{2.5}$ which itself belongs to the PM_{10} (232). Several statistical approaches have been proposed to overcome these problems, including: 1) methods for dimension reduction, 2) methods for variable selection, 3) or methods for grouping of observations (242). These methods differ in their approach and address different research questions and objectives. Ideally, these methods should be applied based on knowledge of the biological mechanisms of air pollutants on health outcomes, as some pollutants are probably related to similar biological pathways (232). A transdisciplinary approach including epidemiologists, biostatisticians and toxicologists is necessary. As I had only studied three pollutants including BC which belonged to $PM_{2.5}$, a multi-pollutant model would have had little interest. However, I used the residual method proposed by Mostofsky *et al.* to study the potential effect of BC independently of $PM_{2.5}$ (227). I showed an effect of BC independent of $PM_{2.5}$, which strengthens the level of evidence regarding the adverse effects of BC and reinforces the need for routine measurement and regulation of BC.

5.2.2.5. Toward a transdisciplinary exposome approach

Beyond air pollution, we are exposed to other environmental exposures that could be of interest in the study of risk or protective factors related to rhinitis such as occupational exposures to chemicals (243), exposure to green spaces (244), or pollens (245). In this context, an exposome approach is of particular interest. The concept of exposome was proposed in 2005 by Wild and refers to the wide environmental (non-genetic) exposures from conception onwards (246). Currently, as more and more

measurements of environmental exposures are collected and as statistical methods evolve, part of the exposome can be captured and a growing number of epidemiological studies are beginning to look at associations between the exposome and health outcomes (247). The study of the exposome remains a real challenge both conceptually -there is still a need to define what the exposome really is- and methodologically -how to obtain all the data relating to the exposome and how to process them statistically?- (242,247). Furthermore, the essential role of social sciences in the exposome approach should not be overlooked, as economic, social, and cultural capital will have a huge impact on environmental and behavioural exposures (248). Overall, the study of the exposome can only be done through a profoundly multi- and trans-disciplinary approach involving epidemiology, biology, toxicology, statistics, high-dimensional modelling data sciences, and human and social sciences, which makes it both a methodological challenge and a very interesting research perspective.

5.2.2.6. Climate change

To add another level of complexity to the issue of environmental exposures, we must not forget that we may be entering in a new era called Anthropocene in which climate change is also a major concern. Climate change can affect respiratory health through several ways (235,249), the main ones related to rhinitis are: 1) more intense and longer pollen seasons (250–252), 2) changes in the ecological niches of plants and colonization of new areas by particularly allergic species, e.g. ragweed in Europe (253,254), 3) more allergenic pollens (252,255), or 4) more rain and flooding leading to mould proliferation (256). Moreover, because air pollution and climate change share common sources, they are linked and may also interact with each other (235). Air pollution could increase the allergenicity of pollens and acts as an adjuvant and stimulates the allergic response (235). By the increase of extreme climatic events such as thunderstorm, wildfire, or dust storm, climate change could indirectly modify the composition of PM and increase its toxicity (235). Although there are many reviews on the potential environmental and health effects of climate change, there are few epidemiological studies that have looked at this issue. Studying the effects of climate change is therefore a hot topic and could provide strong arguments for environmental health policies.

6. OVERALL CONCLUSION

The overall aim of this thesis was to study, in adults, the characteristics of rhinitis and its phenotypes and their associations with long-term exposure to air pollution.
The literature review conducted on the definitions and prevalences of rhinitis around the world highlighted the urgent need for a consensus on standardised definitions for rhinitis to be used in epidemiological studies. From the knowledge of the literature, we were able to establish recommendations on good definitions of rhinitis, AR and NAR and we showed, using the EGEA data, that a questionnaire-based definition of AR and NAR can be used as an appropriate proxy in the absence of biological measures. This definition was used in Constances and could be used in any epidemiological study due to its simplicity. From this definition by questionnaire, prevalence data in the general adult population have been established, which is very important for quantifying the burden of the disease and could be used notably in health economics studies. Analyses in Constances on rhinitis phenotypes provided recent, population-based data on rhinitis and could be used in pharmaco-epidemiological and/or health economics studies. Beyond these results, throughout this thesis, asthma status has been shown to add important information on rhinitis phenotypes. This is paradigm changing and asthma status should be included for furture classifications of rhinitis. Overall, the results of this thesis contribute to a better understanding of rhinitis and add knowledge for a better management and a decrease of its economic and social burden. These results will have a major impact as the prevalence of rhinitis continues to increase.
This thesis focused on the long-term effects of air pollution on rhinitis and contributed to the evidence that air pollution has an adverse effect on health, even at low levels of exposure. Reducing exposure to air pollution is now a public health priority and a real challenge for health policies. The European Commission has just issued at the end of October 2022 proposals for new air quality standards with annual limit values of 10 $\mu g/m^3$ for $PM_{2.5}$ and 20 $\mu g/m^3$ for NO_2 (136). The purpose of this proposed revision is to "*set interim 2030 EU air quality standards, aligned more closely with World Health Organization guidelines, while putting the EU on a trajectory to achieve zero pollution for air at the latest by 2050*" (257). Although these air quality standards are more restrictive than the current ones, they are not fully aligned with the WHO recommendations. As pointed out by the first-line joint response from the European Respiratory Society and the International Society of Environmental Epidemiology (258), these European limit values are still too high, and it is imperative to continue to reduce air pollution exposure. Given the harmful effects of air pollution on health and the environment, there is no doubt that air pollution reduction will have strong positive impacts on the whole society.

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Appendix 1: Worldwide prevalence of rhinitis in adults: A review of definitions and temporal evolution

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REVIEW ARTICLE

Worldwide prevalence of rhinitis in adults: A review of definitions and temporal evolution

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Abstract

Introduction: Although rhinitis is among the most common diseases worldwide, rhinitis prevalence in the general adult population is unclear and definitions differ widely.

Objective: To summarize the literature on rhinitis prevalence in the general adult population and to assess: (1) the prevalence according to different rhinitis definitions overall and in different regions of the world, and (2) the evolution of rhinitis prevalence over time.

Methods: We conducted an extensive literature review of publications including rhinitis prevalence using Pubmed and Scopus databases up to October 2020. We classified the definitions into three categories: unspecified rhinitis, allergic rhinitis (AR), and nonallergic rhinitis (NAR).

Results: Among 5878 articles screened, 184 articles were included, presenting 156 different definitions of rhinitis. Rhinitis prevalence ranged from 1% to 63%. The overall median prevalences of unspecified rhinitis, AR and NAR were 29.4%, 18.1% and 12.0%, and they varied according to the geographical location. Rhinitis prevalence tended to increase over time.

Conclusions: This review highlights the great heterogeneity of the definitions. The majority of studies had focused on AR, while only a few epidemiological data exist

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on NAR. We found geographical variability in rhinitis prevalence. Most of studies reported an increase of rhinitis prevalence over the last decades.

KEYWORDS
allergic rhinitis, epidemiology, non-allergic rhinitis, prevalence, rhinitis

MOTS-CLÉS
épidémiologie, prévalence, rhinite, rhinite allergique, rhinite non-allergique

SCHLÜSSELWÖRTER
Allergische Rhinitis, Epidemiologie, Nicht-allergische Rhinitis, Prevalenz, Rhinitis

PALABRAS CLAVE
rinitis alérgica, epidemiología, rinitis no alérgica, prevalencia, rinitis

1 | INTRODUCTION

Rhinitis is among the most common chronic diseases in the world.[1] Rhinitis is a generic term describing nasal symptoms resulting from inflammation and/or dysfunction of the nasal mucosa.[2] In this study, we will not consider acute infectious rhinitis that is often due to common cold or flu. The two other main phenotypes of rhinitis are allergic rhinitis (AR) and nonallergic rhinitis (NAR): AR refers to nasal symptoms that are triggered by Immunoglobulin E (IgE)-mediated response to exposure to allergens, while NAR refers to a heterogeneous group of nasal symptoms without allergic sensitization.[3]

Several definitions of rhinitis have been used in epidemiological studies, some of them defining rhinitis as a unified entity, while others define AR and NAR separately. To date, literature reviews on rhinitis prevalence have focused solely on AR.[4–7] To our knowledge, the last extensive review of the literature on the prevalence of AR worldwide was conducted by the AR and its Impact on Asthma (ARIA) in 2008, and at that time the identified studies were mainly conducted in Europe or in the United States.[4] In 2012, a literature review was conducted on the prevalence of AR outside North America and Europe[5] and two recent literature reviews reported prevalence of AR only in China.[6,7] Therefore, there is no recent literature review on rhinitis prevalence worldwide.

Regarding the worldwide prevalence of rhinitis among children, the International Study of Asthma and Allergies in Childhood (ISAAC), which is considered as the landmark study in this field, reported in 2004 a prevalence of self-reported current nasal symptoms of 31.7% (ranging from 11.9% to 80.6%) based on data from 97 countries.[8] Among adult populations, the largest international multicenter study is the European Community Respiratory Heath Survey (ECRHS), and it estimated a median prevalence of self-reported nasal allergies of 20.9% (ranging from 9.5% to 40.9%) in 1995.[9] That study did not estimate the overall prevalence of rhinitis nor that of NAR, and even though it included altogether 20 countries, they were mainly from the same geographical area, that is from the Western Europe. It is commonly proposed in the literature that rhinitis prevalence has increased in recent decades,[4] but there is no literature review on this topic.

In summary, many different definitions of rhinitis have been applied, and the majority of the studies have focused on AR, with only a few studies focusing on NAR. Moreover, the estimates of rhinitis prevalence in adults in different parts of the world are still poorly known.

The objective of the present study was to conduct an extensive literature review on rhinitis prevalence in general adult population around the world. This review describes rhinitis prevalence according to different definitions and worldwide. It also aims to describe the temporal evolution of rhinitis prevalence.

2 | METHODS

The present literature review on rhinitis prevalence was performed according to the four-phase flow diagram presented in the PRISMA statement as follows: identification, screening, defining eligibility, and inclusion (Figure 1).

2.1 | Information sources, search strategy, selection process and eligibility criteria

The literature search used the computerized bibliographic databases PubMed and Scopus and included all the existing literature up to October 13, 2020.

We searched for the terms “rhinitis” or “hay fever” combined with “epidemio*" or “preval*” in the title or abstract. The only limitation we applied was that the studies had to be written in English, French, or Spanish language. Additional records from the references of the literature reviews and of the eligible publications identified in the search were included. The articles were first screened based on their title and abstract, and then articles of interest were read entirely to assess their eligibility.

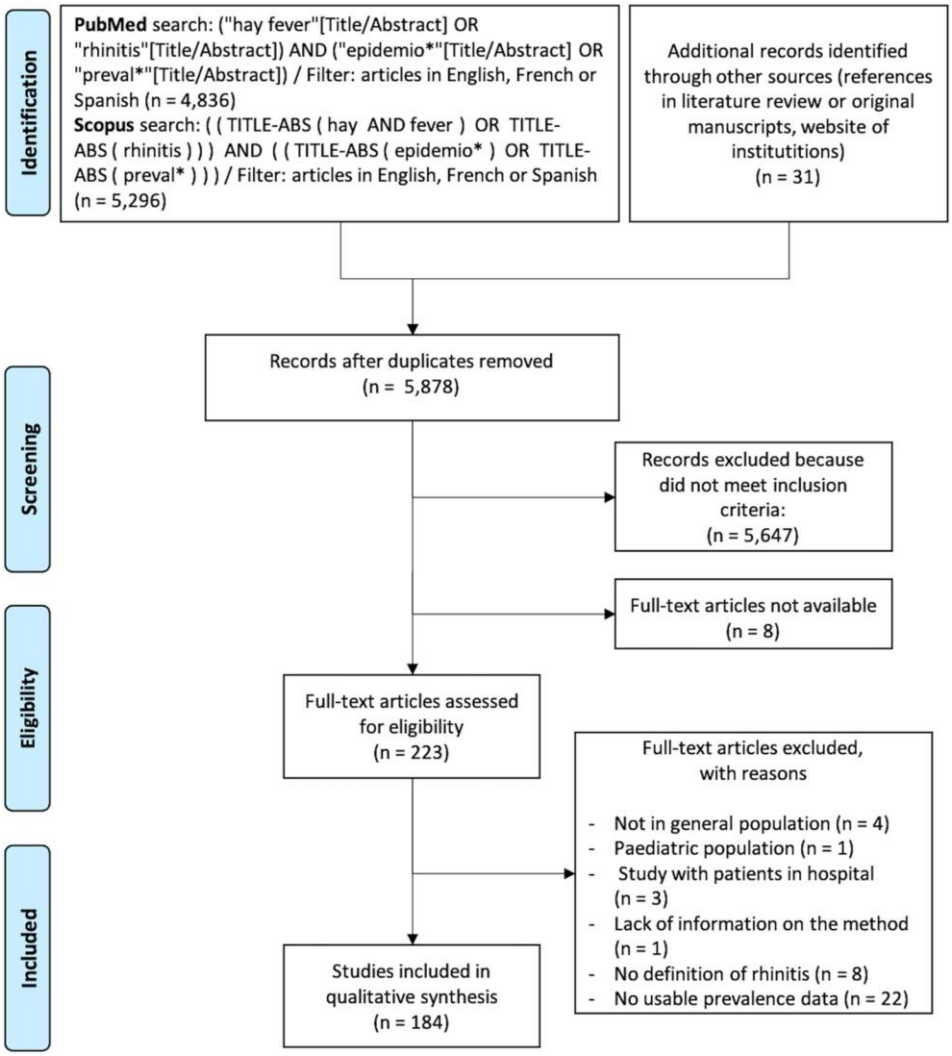

FIGURE 1 Flow diagram showing selection of articles reviewed

Articles were selected according to the following criteria: the articles were required to (1) be an original epidemiological study, (2) include prevalence data on rhinitis, AR and/or NAR, (3) be based on a general adult population or a population including all ages. As this study focuses on rhinitis prevalence in general population, we excluded studies focusing only on specific subpopulations such as children, students, farmers, exclusively in men, or women. We also excluded studies that were conducted in specific health centers or allergy clinics and studies that did not contain any information on the definition of rhinitis, or that did not provide any calculable rhinitis prevalence in the general population.

2.2 | Data items

The following data were collected: (1) the year of publication, (2) the country where the study was conducted, (3) the period during which the study was conducted, (4) the size and age range of the studied population, (5) the study design, including cross-sectional and/or longitudinal, (6) the method applied to assess the prevalence, including interview or self-report, and (7) the definition applied for rhinitis.

When not directly reported in the article, the prevalence was calculated based on the available data, applying the following formula: the number of participants with rhinitis divided by the total number of participants. We reported the prevalence in adults only if available, otherwise we reported the prevalence of the population including adults and children.

2.2.1 | Classification of the data

We have categorized the different definitions of rhinitis into three categories as follows: “unspecified rhinitis” refers to a definition of rhinitis that did not specify whether it was allergic or nonallergic; AR refers to a definition that included the term “AR” and/or “hay fever”

and/or included exposures known to induce an allergic inflammation of the airways, such as pollen, furry animals, or house dust mites; and/or assessment of allergic sensitization by skin tests and/or serum specific IgE; NAR refers to a definition that excluded AR and/or referred to triggers known to induce NAR, such as cold and dry air, temperature change, airborne chemical irritants, spicy food, alcoholic beverages, exercise, use of tobacco, anti-inflammatory drugs, stress, and/or printer ink. In addition, we have further subcategorized unspecified rhinitis, AR and NAR according to the method on which the definition was based: "symptoms-based definition" which refers to a definition that is based on a question asking from the participant himself/herself about the presence of rhinitis or nasal symptoms; while "doctor diagnosis-based definition" of rhinitis was based on asking a question referring to a previous self-reported medical diagnosis of rhinitis or on a diagnosis made by a physician for the study. Finally, "IgE/SPT-based definition" refers to a definition based on either of the two previously mentioned definitions in combination with the assessment of the IgE-mediated sensitization with measurements of specific IgE and/or skin prick tests (SPTs). Participants with positive SPTs and/or positive specific IgE were defined as AR IgE/SPT-based definition, those with negative IgE/SPT results were defined as NAR IgE/SPT-based definition. Finally, we subcategorized unspecified rhinitis, AR and NAR into (1) "ever rhinitis" that refers to the presence of rhinitis ever in the study participant's lifetime (i.e., lifetime prevalence), and (2) "current rhinitis" that refers to the presence of rhinitis at the time of the study or in the last few months (i.e., point or months/1-year period prevalence). The details of the definitions and their categorization are presented in Appendix 2 in Supporting Information S2.

2.3 | Statistical methods

Mean prevalences were calculated for the unspecified rhinitis, AR, and NAR applying Microsoft Excel®. For each definition, we calculated the crude mean, median and confidence intervals based on binomial distribution with R 4.3. To compare rhinitis prevalence according to different regions of the world, prevalences were first grouped by country and then the countries were stratified by continent.

To study the evolution of rhinitis prevalence over time, we selected studies that had repeated measures of the prevalence using the same definition and comparable populations over time.

As a complementary analysis, we calculated the rhinitis prevalences based solely on the ISAAC and ECRHS questions that are from the two largest international studies on rhinitis and that were used in several studies included in the present literature review.

We also conducted sensitivity analyses with more restrictive definitions and populations to obtain less biased prevalences of unspecified rhinitis, AR and NAR in the general adult populations. We conducted sensitivity analyses based on the following two criteria:

(1) To include only more "reliable" definitions of rhinitis, we excluded those studies in which the definition was/had been based on: (a) questions that did not exclude explicitly common cold or flu; (b) questions that included other allergic diseases in the same item, such as conjunctivitis or eczema; (c) questions that were limited to the time of the survey; (d) questions that did not specify when rhinitis was or had been present, and (e) questions that focused solely on specific sub-phenotypes of rhinitis such as rhinoconjunctivitis, seasonal AR, or peri-annual rhinitis.
(2) To have a more homogeneous adult population, we excluded studies that reported prevalences based on populations: (a) that combined adults and children (i.e., under the age of 16 years), and (b) that included the elderly only (i.e., above the age of 60 years).

3 | RESULTS

After excluding duplicates, a total of 5878 records were identified. Altogether 184 articles were included in the present review (Figure 1, Appendix 1 in Supporting Information S1) with 426 reported prevalences of unspecified rhinitis, AR or NAR.

3.1 | Rhinitis definitions and estimates for prevalence

A total of 156 different definitions of rhinitis were identified: 58 for unspecified rhinitis, 86 for AR, and 12 for NAR (see Appendix 2 in Supporting Information S2). Table 1 describes the rhinitis prevalences for these three main categories and their subcategories. The median rhinitis prevalences were: 29.4% (ranging from 1.1% to 63.3% based on 103 reported prevalences) for unspecified rhinitis, 18.1% (ranging from 1.0% to 54.5% based on 310 reported prevalences) for AR, and 12.0% (ranging from 4.0% to 31.4% based on 13 reported prevalences) for NAR. The median prevalence of current AR was 21.6% based on symptoms-based definition and 16.4% based on IgE/SPT-based definition. For NAR, the median prevalence was 16.4% based on symptoms-based definition and 31.4% based on IgE/SPT-based definition. In adults of all ages, NAR was reported in 24.4%–67.1% of participants with rhinitis.[10–20]

Using the ECRHS definition, the median current AR prevalence was 22.7% (ranging from 7.0% to 47.5% based on 87 reported prevalences). Using the ISAAC definitions, the median prevalence was 32.7% (ranging from 11.4% to 38.0% based on 6 reported prevalences) for ever rhinitis, and 30.8% (ranging from 10.4% to 38.3% based on 15 reported prevalences) for current rhinitis.

Sensitivity analyses were based on 63 "reliable" definitions of rhinitis, while 333 prevalences were excluded: 284 due to the definition criteria, 49 due to the age range studied. A total of 93 reported prevalences were included, the median prevalences being 32.4% (ranging from 10.4% to 54.1% based on 27 reported prevalences) for unspecified rhinitis, 17.1% (ranging from 1.0% to 44.2% based on 63 reported prevalences) for AR, and 16.4% (ranging from 6.5% to 23.5% based on 3 reported prevalences) for NAR (Table S1 in Supporting Information S3).

TABLE 1 Rhinitis prevalences according to the different definitions

	n	Mean (%)	Med (%)	SD (%)	$CI_{95\%}$	Min. (%)	Max. (%)
All definitions							
Unspecified rhinitis	103	27.0	29.4	14.0	(24.3, 29.7)	1.1	63.3
AR	311	19.1	18.1	10.2	(18.0, 20.3)	1.0	54.5
NAR	13	14.6	12.0	8.3	(9.6, 19.6)	4.0	31.4
Symptoms-based definitions							
Unspecified rhinitis							
Ever	20	28.1	30.4	12.8	(22.1, 34.0)	10.8	50.2
Current	68	30.8	32.3	12.5	(27.8, 33.8)	4.1	63.3
AR							
Ever	42	21.4	20.7	10.9	(18.0, 24.8)	4.2	52.0
Current	145	23.5	21.6	9.7	(21.9, 25.1)	3.6	54.5
NAR							
Ever	1	7.9					
Current	6	10.0	16.4	4.4	(5.4, 14.6)	4.0	16.4
Doctor diagnosis-based definitions							
Unspecified rhinitis							
Ever	14	9.0	9.1	3.3	(7.2, 10.9)	2.5	14.0
Current	1	1.1					
AR							
Ever	53	12.8	13.0	6.9	(10.9, 14.7)	1.0	30.9
Current	28	7.9	7.9	1.4	(7.4, 8.5)	3.9	11.4
IgE/SPT-based definitions							
AR							
Ever	3	15.5	28.5	11.3		8.9	28.5
Current	39	17.4	16.4	7.3	(15.1, 19.8)	3.7	44.2
NAR							
Ever	0						
Current	6	20.4	31.4	8.5	(11.5, 29.3)	5.5	31.4

Abbreviations: AR, allergic rhinitis; CI, confidence interval; Current, combination of point and period prevalences; Ever, Lifetime prevalences; Max, highest reported prevalence; Med, Median; Min, lowest reported prevalence; *n*: number of reported prevalences; NAR, non-allergic rhinitis; SD, standard deviation.

3.2 | Rhinitis prevalences worldwide

World maps showing the average prevalences for the unspecified rhinitis, AR and NAR are presented in Figure 2. There was a wide variation in the reported prevalences even within the same continent for all categories of rhinitis. Details of the reported prevalences by country are presented in Table S2 in Supporting Information S3. Prevalence of unspecified rhinitis ranged from 10.4% to 37.8% for Africa, from 14.0% to 63.3% for America, from 1.1% to 50.2% for Asia, from 4.1% to 56.6% for Europe, and 13.2% for Oceania (based on a single study[21]). Prevalence of AR ranged from 3.6% to 22.8% for Africa, from 3.5% to 54.5% for America, from 1.0% to 47.9% for Asia, from 1.0% to 43.9% for Europe, and from 19.2% to 47.5% for Oceania. Only a few prevalences of NAR have been reported, and no data was found from America, Africa or Oceania; for Asia, six reported prevalences were found ranging from 4.0% to 31.4%, and for Europe, six prevalences were found ranging from 5.5% to 23.5%.

3.3 | Evolution in the rhinitis prevalence over time

The evolution over time of rhinitis prevalence within the same population or similar populations and applying the same definition in the same geographical region are presented in Figure 3. Table S3 in

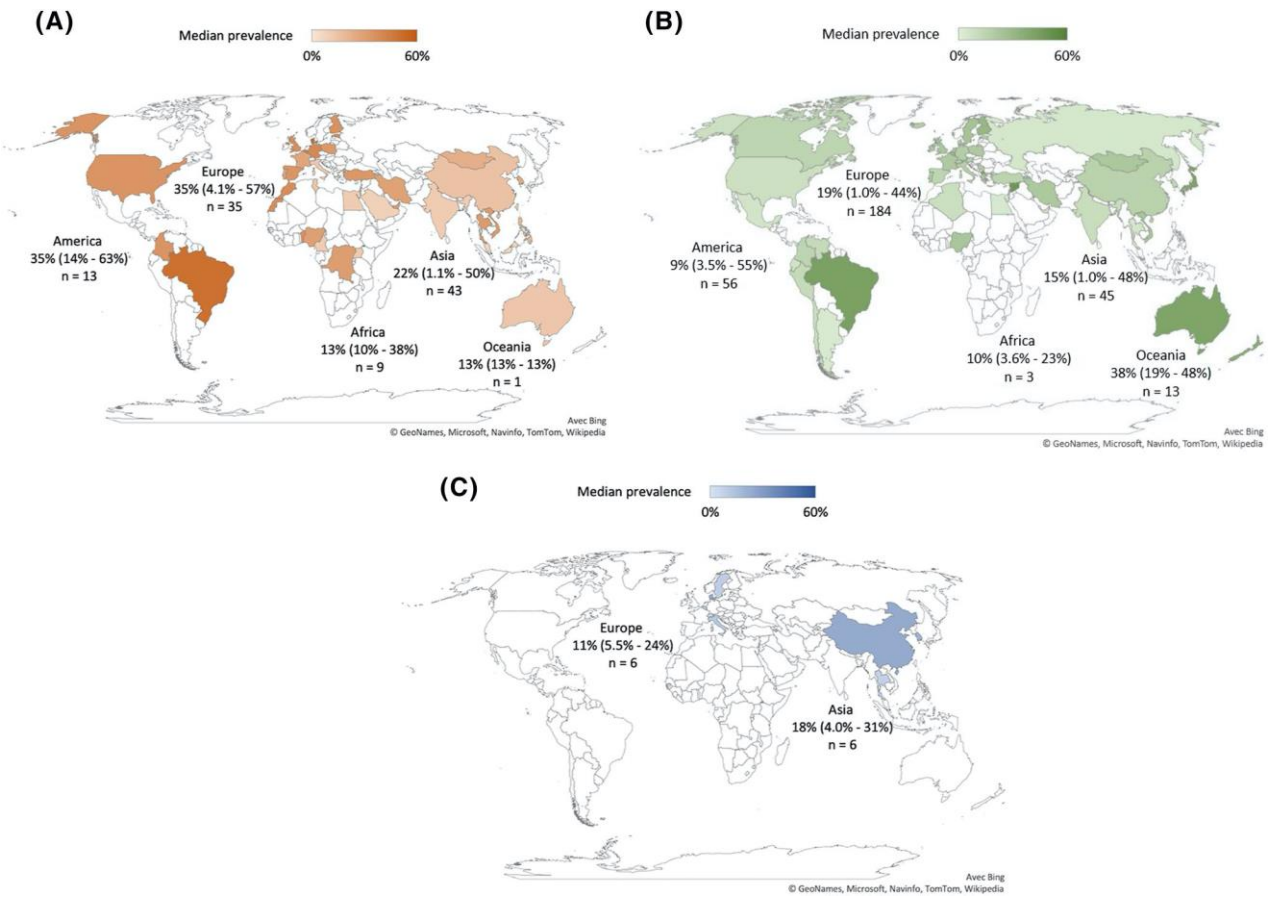

FIGURE 2 Rhinitis prevalences in different regions of the world. (A) Unspecified rhinitis; (B) allergic rhinitis; (C) non-allergic rhinitis. The data for continents are presented as follows: median (minimum reported–maximum reported), *n* = number of reported prevalences. Colored countries are those for which data are available. The darkest countries are those for which the median prevalence is the highest

Supporting Information S3 provides details of the prevalences by country.

In the America, in Brazil a 10% decrease in the rhinitis prevalence was reported between 2011 and 2018.[22] In the United States, the National Health and Nutrition Examination Survey (NHANES) reported that episodes of hay fever in the past 12 months increased from 11.8% to 13.6% between 2007 and 2012. In the National Health Interview Survey (NHIS), the prevalence of AR decreased from 9.3% in 1997 to 7.3% in 2018.

In Asia, the Korean National Health and Nutrition Examination Survey reported that the prevalence of AR increased between 1998 and 2017 from 1.0% to 17.1%.[23,24]

In Europe, studies from Denmark,[25,26] Finland,[27,28] France,[29,30] Germany,[31] Italy,[32] Russia,[27] Scotland,[33] and Sweden[34–36] reported an increase in the prevalence of rhinitis. In Poland, the results varied depending on the definition used: between 2003 and 2012 a slight decrease was observed for rhinitis based on "Problem with sneezing or a runny or blocked nose or itchy eyes in April, May, June, or July" and "In last 12 months, have you had a problem with sneezing or a runny or blocked nose or itchy eyes when you (your child) did not have a cold or flu?".[37] In the same study, an increase from 4.8% to 7.7% was observed in rhinitis defined by "Has a physician ever told you that you have hay fever?".[37]

For Oceania, one study in Australia showed that between 1981 and 1990 the hay fever prevalence increased from 21.9% to 46.7%.[38] No studies were found on the evolution of rhinitis prevalence over time from the African continent.

4 | DISCUSSION

In this study, we identified a total of 184 articles that included data on the rhinitis prevalence among adults, contributing altogether 156 different definitions of rhinitis. Depending on the definition used and the geographical area studied, rhinitis prevalence ranged from 1% to over 60%. The median worldwide prevalences of unspecified rhinitis, AR and NAR were 29.4%, 18.1%, and 12.0%. A geographical variability was observed in the prevalences of subtypes of rhinitis. Irrespective of the definition used, most of the studies reported an increase in the rhinitis prevalence over the last decades.

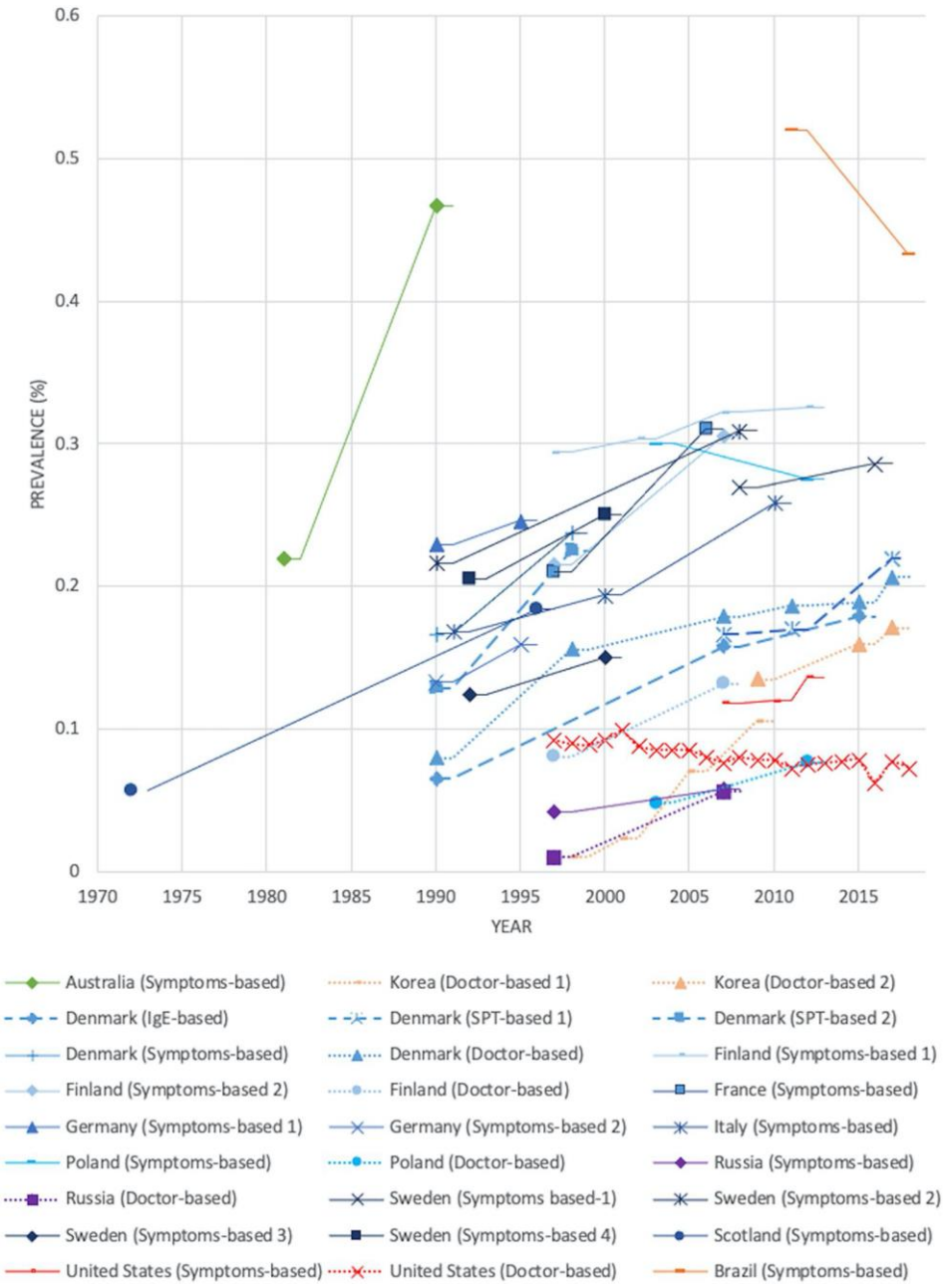

FIGURE 3 Evolution of allergic rhinitis prevalence worldwide over time

We conducted an extensive literature search using the most commonly used keywords for rhinitis and AR, namely "rhinitis" and "hay fever". In an additional search, we also considered to use keywords "nose symptoms" or "nasal symptoms" as synonyms for rhinitis, but the results of these searches only provided additional articles that referred to differential diagnoses of rhinitis, such as COVID-19 or nasal polyps. Therefore, these terms were not included in the main search. As we have limited this review to articles published in English, French and Spanish, it is possible that we may have omitted some prevalence data from articles published in other languages.

We found a total of 156 rhinitis definitions in the present literature review, so we decided to classify them into three distinct categories: unspecified rhinitis, AR and NAR. To our knowledge, this is the first time that such categorization of rhinitis has been applied within an extensive literature review, usually all definitions of rhinitis being considered together within one term. We focused on a classification of rhinitis as an entity or according to its two main phenotypes: AR or NAR. Prevalences of other sub-phenotypes of rhinitis, such as rhino-conjunctivitis, are also of interest per se and should be assessed in more specific reviews.

Overall, we found a median prevalence of 29% for unspecified rhinitis, which is close to the prevalence of 31.7% reported for children aged 13–14 years in the ISAAC phase 3 study.[8] However, a large variability was observed between the studies of rhinitis prevalence. This variability is probably partly explained by heterogeneity in the definitions used in the studies. Indeed, within the same population the prevalence was found to vary greatly depending on the definition used: for example, in the study by Bauchau et al. rhinitis prevalence in Belgium varied by more than 30% depending on whether rhinitis was defined based on doctor diagnosis or on reported symptoms.[39] Considering all the studies, we found that the average prevalence of doctor diagnosis-based definitions was lower compared to the other definitions. This could be partly explained by the fact that rhinitis prevalence is often underestimated when based on the doctor diagnosis. Indeed, it is recognized that patients with rhinitis often tend to self-diagnose their rhinitis and treat themselves,[40] and those who consult a doctor are likely to have more often moderate to severe rhinitis.[41] In addition, access to health professionals may be heterogeneous according to the geographic location, healthcare system, or socio-economic status of the patient. Large variabilities in reported prevalences were also observed for AR and NAR. The median prevalence of AR obtained in this literature review based on all definitions was 18%, with a higher average prevalence being detected with the symptoms-based definitions compared to the IgE/SPT-based definitions. We obtained a median prevalence of NAR of 12%, which is lower than the prevalence obtained for AR. Nevertheless, based on our literature review, compared to AR, NAR could represent 20%–80% of rhinitis cases in adults. As only 13 studies had evaluated the prevalence of NAR, it is rather difficult to make conclusions on the "true" prevalence of NAR.

The wide variability in definitions of rhinitis detected in this extensive review makes it recommendable to try to achieve a consensus on which definitions should be used in epidemiological studies. However, to date, no such consensus has been reached. In our opinion, it would be best to define unspecified rhinitis in epidemiological studies applying a question that is easily understandable by all participants, that refers to the main symptoms of rhinitis, and that does not include specific medical terms. The AR and Its Impact on Asthma (ARIA) recommended to use a question including symptoms of "sneezing, runny nose and/or blocked nose when the patient does not have a cold".[3] The definitions of current and ever rhinitis should not include any ambiguous terms, such as "often," "several," or "most of the time." Instead, it would be better to refer to clear time periods, for example, "in the last 12 months" or "during your lifetime." The two questions in the ISAAC study[42] comply with these recommendations, and, in our opinion, are accurate questions to define current and ever unspecified rhinitis. In clinical practice, to define AR and NAR, the measurement of specific IgE or SPTs combined with a medical history by the doctor is "the gold standard." However, as these diagnostic tools are not always easily available in large epidemiological studies, it could be useful to have a proxy for AR and NAR defined based on questionnaire. We have recently shown that a combination of the ISAAC and ECRHS definitions could be a suitable proxy.[43] Another way to define AR and NAR in the absence of IgE/SPT measurements would be to use questions referring to the main triggers of nasal symptoms. Specific allergens triggering rhinitis symptoms, such as pollen or animal exposure, or the presence of eye symptoms in combination with rhinitis symptoms have been shown to have a moderately high positive predictive value for AR in participants with SPT positivity to common aeroallergens.[44] These triggers as well as associated eye symptoms emerged as important discriminative variables in a clustering analysis that was performed without any a priori hypothesis to identify AR and NAR.[45] However, an expert consensus and/or methodological research comparing different definitions with a clinical diagnosis of rhinitis is needed to establish the best definitions for rhinitis, AR and NAR, to be used in epidemiological studies.

In this study, we carried out a sensitivity analysis including only definitions that were judged as "reliable" based on our proposed criteria for unspecified rhinitis, AR and NAR. Nevertheless, even in this sensitivity analysis a great heterogeneity was observed between the different prevalences. Moreover, using identical definitions, for example, ISAAC or ECRHS definitions, rhinitis prevalence still varies between different countries of the world.

This geographical variability in rhinitis prevalence could be partly explained by different environmental exposures, such as different species of pollen, different lifestyle factors, including dietary habits and keeping of pets indoors, or different host risk factors.[5] As in this study, we have reported rhinitis prevalences without considering these risk factors, these hypotheses need to be tested in future studies. It should be noted that these factors were rarely considered and/or investigated in the studies that were identified by this literature review.

Rhinitis appears to be a common disease in the European and American countries, which is consistent with some previous reports.[4,5] In other parts of the world, far fewer studies have been reported on the prevalence of different types of rhinitis, which makes it more difficult to calculate reliable estimates and make firm conclusions. It is noteworthy that the global distribution of rhinitis prevalence was found to be similar to that of global distribution of asthma prevalence, for which there is more studies.[46] Further studies that apply standardized definitions of rhinitis in different parts of the world would throw more light on potential "true" differences in rhinitis prevalence and on potential causes underlying such differences.

Our extensive review showed that most studies reported an increase in rhinitis prevalence over time. One explanation could be that the awareness of rhinitis has improved in parallel in different populations around the world due to advertising of over-the-counter medicines for rhinitis, and with the development of the Internet making it easier to get information on rhinitis. In addition, medical examinations may have become better accessible and thus, the rhinitis diagnosis may also be more easily accessible. In any case, rhinitis prevalence seems to have increased in many parts of the world, whatever the definition of rhinitis. Concerning the trend of increasing prevalence of different types of rhinitis, potential impact of risk factors, including global warming, changes in seasonal patterns, and air pollution, have been proposed.[47] However, only few studies have investigated potential impact of such factors on rhinitis prevalence over time.

In conclusion, our review highlights the lack of consensus on which questions the phenotypes of rhinitis should be based. This review also found a geographical variability of rhinitis prevalences, and pointed out the scarcity or even inexistence of data from some parts of the world. While these points could appear as not being novel, there is no recent literature review on this topic that would summarize these facts. The present extensive review underlines the urgent need for a consensus on standardized definitions for rhinitis to be used in epidemiological studies. Finally, for the first time in a literature review, this study shows that rhinitis prevalence in adults is increasing.

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CONFLICT OF INTERESTS

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this study.

AUTHOR CONTRIBUTIONS

Marine Savouré: Conceptualization; Lead, Data curation; Lead, Formal analysis; Lead, Funding acquisition; Lead, Investigation; Lead, Methodology; Lead, Visualization; Lead, Writing – original draft; Lead, Writing – review & editing; Lead, **Jean Bousquet:** Conceptualization; Supporting, Methodology; Supporting, Visualization; Supporting, Writing – original draft; Supporting, Writing – review & editing; Equal, **Jouni J.K. Jaakkola:** Conceptualization; Supporting, Methodology; Supporting, Visualization; Supporting, Writing – original draft; Supporting, Writing – review & editing; Equal, **Maritta Jaakkola:** Conceptualization; Supporting, Methodology; Supporting, Visualization; Supporting, Writing – original draft; Supporting, Writing – review & editing; Equal, **Benedicte Jacquemin:** Conceptualization; Equal, Methodology; Equal, Supervision; Equal, Validation; Equal, Visualization; Equal, Writing – original draft; Equal, Writing – review & editing; Equal, **Rachel Nadif:** Conceptualization; Equal, Methodology; Equal, Resources; Lead, Supervision; Equal, Validation; Equal, Visualization; Equal, Writing – original draft; Equal, Writing – review & editing; Equal.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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1.B – Supplementary material

Appendix:

Appendix 1: Details of the selected studies (excel file, available at **https://onlinelibrary.wiley.com/doi/10.1002/clt2.12130**)

Appendix 2: Details of the definitions (excel file, available at **https://onlinelibrary.wiley.com/doi/10.1002/clt2.12130**)

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Tables

Table S1: Prevalences of rhinitis according to the different definitions (sensitivity analysis)

	n	Mean	Med	Sd	$CI_{95\%}$		Min	Max
All definitions								
Unspecified rhinitis	27	31.5%	32.4%	12.4%	26.6%,	36.4%	10.4%	54.1%
AR	63	19.1%	17.1%	9.6%	16.7%,	21.5%	1.00%	44.2%
NAR	3	15.5%	16.4%	8.54%			6.49%	23.5%
Symptoms-based definitions								
Unspecified rhinitis								
Ever	9	30.4%	31.3%	13.3%	20.1%,	40.6%	11.4%	50.2%
Current	17	33.1%	34.6%	11.8%	27.0%,	39.2%	10.40%	54.1%
AR								
Ever	8	25.1%	24.7%	8.6%	17.9%,	32.4%	14.5%	41.6%
Current	18	22.9%	25.5%	10.7%	17.6%,	28.2%	3.6%	37.7%
NAR								
Ever	0							
Current	2	11.45%		7.01%			6.49%	16.40%
Doctor diagnosis-based definitions								
Unspecified rhinitis								
Ever	1	14.0%						
Current	0							
AR								
Ever	24	14.6%	13.4%	7.00%	11.6%,	17.5%	1.00%	30.6%
Current	1	11.4%						
IgE/SPT-based definitions								
AR								
Ever	0							
Current	12	18.9%	17.7%	9.53%	12.9%,	25.0%	6.50%	44.2%
NAR								
Ever	0							
Current	1	23.5%						

AR: Allergic Rhinitis; CI: Confidence Interval; Current: combination of point and period prevalences; Ever: Lifetime prevalences; Max: highest reported prevalence; Med: Median; Min: lowest reported prevalence; n: number of reported prevalences; NAR: Non-Allergic Rhinitis; sd: standard deviation.

Analyses after exclusion of: 1) definitions based on: a) questions that did not explicitly exclude common cold or the flu; b) questions that included other allergic diseases such as conjunctivitis or eczema; c) questions that were limited to the time of the survey; d) questions that were not specific of a timeframe and e) questions that focused solely on specific sub-phenotypes of rhinitis, such as rhino-conjunctivitis, seasonal AR, or peri-annual rhinitis (as prevalences of those sub-phenotypes reflect only a part of the prevalence of AR, NAR or unspecified rhinitis),

2) prevalences calculated on populations: a) that mixed adults and children (i.e. under the age of 16), and b) including only elder (i.e. above the age of 60).

Table S2: Prevalences of rhinitis in different countries

	Unspecified rhinitis					AR					NAR				
Country	**n**	**Med**	**Mean**	**Min**	**Max**	**n**	**Med**	**Mean**	**Min**	**Max**	**n**	**Med**	**Mean**	**Min**	**Max**
Africa	**9**	**13.4%**	**21.3%**	**10.4%**	**37.8%**	**3**	**9.5%**	**12.0%**	**3.6%**	**22.8%**					
Algeria						1	9.5%	9.5%	9.5%	9.5%					
Benin	1	35.7%	35.7%	35.7%	35.7%										
Cameroon	2	10.9%	10.9%	10.4%	11.4%										
Congo	1	30.8%	30.8%	30.8%	30.8%										
Egypt	1	11.0%	11.0%	11.0%	11.0%	1	3.6%	3.6%	3.6%	3.6%					
Morocco	1	37.8%	37.8%	37.8%	37.8%										
Nigeria	1	29.6%	29.6%	29.6%	29.6%	1	22.8%	22.8%	22.8%	22.8%					
Tunisia	1	13.4%	13.4%	13.4%	13.4%										
Uganda	1	11.9%	11.9%	11.9%	11.9%										
America	**13**	**35.4%**	**36.9%**	**14.0%**	**63.3%**	**56**	**8.9%**	**14.1%**	**3.5%**	**54.5%**					
Argentina						1	3.5%	3.5%	3.5%	3.5%					
Brazil	3	50.5%	46.6%	26.0%	63.3%	3	43.3%	34.7%	8.8%	52.0%					
Canada						4	14.7%	13.0%	5.7%	17.0%					
Chile						1	9.8%	9.8%	9.8%	9.8%					
Colombia	2	35.0%	35.0%	32.0%	38.0%	2	14.8%	14.8%	7.0%	22.6%					
Ecuador						1	6.4%	6.4%	6.4%	6.4%					
Mexico						1	6.3%	6.3%	6.3%	6.3%					
Peru						1	11.6%	11.6%	11.6%	11.6%					
United States	8	34.8%	33.8%	14.0%	46.2%	41	8.6%	13.5%	3.9%	54.5%					
Venezuela						1	11.4%	11.4%	11.4%	11.4%					
Asia	**43**	**21.7%**	**20.8%**	**1.1%**	**50.2%**	**45**	**15.4%**	**16.8%**	**1.0%**	**47.9%**	**6**	**17.60%**	**16.7%**	**4.0%**	**31.4%**
China	7	15.5%	22.2%	6.2%	46.8%	4	16.6%	14.6%	6.7%	18.5%	2	23.90%	23.9%	16.4%	31.4%
Gulf cluster*						1	6.4%	6.4%	6.4%	6.4%					
India	1	11.0%	11.0%	11.0%	11.0%	1	10.1%	10.1%	10.1%	10.1%					
Iran	1	29.1%	29.1%	29.1%	29.1%	4	21.4%	21.6%	15.4%	28.3%					
Israel	1	14.0%	14.0%	14.0%	14.0%										

	Unspecified rhinitis					AR					NAR				
Country	**n**	**Med**	**Mean**	**Min**	**Max**	**n**	**Med**	**Mean**	**Min**	**Max**	**n**	**Med**	**Mean**	**Min**	**Max**
Japan						2	41.0%	41.0%	37.7%	44.2%					
Lebanon	1	8.0%	8.0%	8.0%	8.0%										
Malaysia	1	7.1%	7.1%	7.1%	7.1%										
Mongolia	1	23.6%	23.6%	23.6%	23.6%	4	21.8%	24.2%	14.6%	36.3%					
Philippines	3	20.0%	15.4%	2.5%	23.8%										
Saudi Arabia	1	9.0%	9.0%	9.0%	9.0%										
Singapore	6	12.0%	15.9%	4.9%	32.5%	1	4.5%	4.5%	4.5%	4.5%	1	4.00%	4.0%	4.0%	4.0%
South Korea	9	25.6%	23.0%	1.1%	29.4%	17	13.4%	12.7%	1.0%	29.0%	2	20.30%	20.3%	18.8%	21.8%
Syria						1	47.9%	47.9%	47.9%	47.9%					
Taïwan	2	10.5%	10.5%	9.6%	11.3%										
Thailand	3	32.1%	27.7%	13.2%	37.7%	1	5.2%	5.2%	5.2%	5.2%	1	7.93%	7.9%	7.9%	7.9%
Turkey	2	33.2%	33.2%	31.3%	35.1%	8	15.5%	16.9%	6.4%	29.6%					
United Arab Emirates	3	32.0%	25.6%	9.0%	35.9%	1	7.0%	7.0%	7.0%	7.0%					
Vietnam	2	31.3%	31.3%	12.3%	50.2%	1	22.4%	22.4%	22.4%	22.4%					
Europe	**35**	**34.6%**	**32.6%**	**4.1%**	**56.6%**	**184**	**18.8%**	**20.1%**	**1.0%**	**43.9%**	**6**	**10.60%**	**11.4%**	**5.5%**	**23.5%**
Austria						1	16.4%	16.4%	16.4%	16.4%					
Belgium	2	46.0%	46.0%	39.3%	52.7%	8	24.7%	23.5%	13.9%	30.9%	1	9.60%	9.6%	9.6%	9.6%
Denmark	3	54.1%	47.4%	31.6%	56.6%	22	17.9%	17.4%	6.5%	26.1%	1	23.50%	23.5%	23.5%	23.5%
Estonia	1	39.1%	39.1%	39.1%	39.1%	4	18.0%	16.5%	9.1%	21.1%					
Finland	1	35.7%	35.7%	35.7%	35.7%	14	30.4%	28.5%	8.1%	42.3%					
France	4	27.4%	25.4%	4.1%	42.7%	11	21.0%	23.9%	8.9%	43.9%					
Germany	1	39.6%	39.6%	39.6%	39.6%	13	18.1%	16.9%	8.3%	25.0%					
Greece						2	21.6%	21.6%	18.4%	24.7%					
Iceland						3	17.8%	17.5%	11.2%	23.6%					
Ireland						3	20.0%	19.3%	14.3%	23.6%					
Italy	5	12.9%	19.8%	5.6%	36.1%	21	18.3%	19.2%	11.1%	37.7%	1	11.60%	11.6%	11.6%	11.6%
Macedonia						1	41.3%	41.3%	41.3%	41.3%					
Netherlands						6	22.2%	22.6%	14.4%	29.5%					

	Unspecified rhinitis					AR					NAR				
Country	**n**	**Med**	**Mean**	**Min**	**Max**	**n**	**Med**	**Mean**	**Min**	**Max**	**n**	**Med**	**Mean**	**Min**	**Max**
Norway						6	14.2%	16.1%	10.0%	28.4%					
Poland	5	32.6%	32.3%	27.5%	36.0%	6	20.9%	20.2%	4.8%	36.1%					
Portugal	2	28.0%	28.0%	26.1%	29.8%	4	20.0%	20.6%	9.4%	32.9%					
Russia						6	4.9%	7.4%	1.0%	26.1%					
Scotland						3	18.2%	14.1%	5.7%	18.4%					
Serbia						1	19.4%	19.4%	19.4%	19.4%					
Spain	1	34.6%	34.6%	34.6%	34.6%	6	14.4%	13.6%	8.3%	18.1%					
Sweden	7		35.0%	19.3%	51.0%	22	24.5%	23.3%	7.7%	30.9%	2	9.20%	9.2%	6.5%	12.0%
Switzerland						12	16.6%	17.6%	11.2%	25.7%	1	5.50%	5.5%	5.5%	5.5%
United Kingdom	3	37.0%	31.6%	13.7%	44.0%	9	21.8%	23.6%	13.2%	33.2%					
Oceania	**1**	**13.2%**	**13.2%**	**13.2%**	**13.2%**	**13**	**38.2%**	**36.5%**	**19.2%**	**47.5%**					
Australia	1	13.2%	13.2%	13.2%	13.2%	10	41.0%	37.4%	19.2%	47.5%					
New Zealand						3	36.4%	33.5%	25.8%	38.2%					

AR: Allergic Rhinitis; Max: highest reported prevalence; Med: Median; Min: lowest reported prevalence; n: number of reported prevalences; NAR: Non-Allergic Rhinitis.
**Gulf cluster: Kuwait, Saudi Arabia, United Arab Emirates*

Table S3: Evolution of rhinitis prevalence over time

Country	Reference	Definition	Year: prevalence	
Americas				
Brazil	Oliveira *et al.* 2020	*"Have you ever had sneezing and runny nose in the past 12 months?"*	2011: 63.3% 2018: 50.5%	↓
	Oliveira *et al.* 2020	"*Have you ever had or have hay fever?*"	2011: 52% 2018: 43.3%	↓
United States	NHANES	Episode of hay fever in the past 12 months	2007-2008: 11.8% 2009-2010: 12.0% 2011-2012: 13.6%	↑
	Blackwell *et al.* 2002 Pleis *et al.* 2002 Pleis *et al.* 2003 Pleis *et al.* 2003 Lucas *et al.* 2004 Lethbridge-Çejku *et al.* 2004 Lethbridge-Çejku *et al.* 2005 Lethbridge-Çejku *et al.* 2006 Pleis *et al.* 2006 Pleis *et al.* 2007 Pleis *et al.* 2009 Pleis *et al.* 2009 Pleis *et al.* 2010 Schiller *et al.* 2012 Schiller *et al.* 2012 Blackwell *et al.* 2014 NHIS	"*During the past 12 months, have you been told by a doctor or other health professional that you had hay fever?*"	1997: 9.3% 1998: 9.0% 1999: 8.9% 2000: 9.3% 2001: 10.0% 2002: 8.8% 2003: 8.6% 2004: 8.6% 2005: 8.6% 2006: 8.0% 2007: 7.6% 2008: 8.0% 2009: 7.8% 2010: 7.8% 2011: 7.3% 2012: 7.5% 2013: 7.6% 2014: 7.7% 2015: 7.9% 2016: 6.2% 2017: 7.7% 2018: 7.3%	↓

Country	Reference	Definition	Year: prevalence	
Asia				
Korea	Myong *et al.* 2012	"*Have you ever been diagnosed with allergic rhinitis by a doctor?*"	1998: 1.0% 2001: 2.3% 2005: 7.0% 2007-2009: 10.6%	↑
	Ha *et al.* 2020	"*Have you ever been diagnosed with allergic rhinitis by a doctor?*"	2008-2009: 13.5% 2013-2015: 16.0% 2016-2017: 17.1%	↑
Europe				
Denmark	Leth-Møller *et al.* 2019	a) Itchy or stuffy nose or sneezing when near grass, trees, or flowers within the last 12 months OR b) Itchy or stuffy nose or sneezing when near furry animals within the last 12 months OR c) Itchy or stuffy nose or sneezing when cleaning rooms or making beds, or when in bed within the last 12 months AND sIgE sensitisation	1990-1991: 6.5% 2006-2008: 15.8% 2012-2015: 17.9%	↑
	Leth-Møller *et al.* 2019	a) Itchy or stuffy nose or sneezing when near grass, trees, or flowers within the last 12 months OR b) Itchy or stuffy nose or sneezing when near furry animals within the last 12 months OR c) Itchy or stuffy nose or sneezing when cleaning rooms or making beds, or when in bed within the last 12 months AND SPT sensitisation	2006-2008: 16.7% 2010-2011: 17.0% 2016-2017: 22.0%	↑
	Linneberg *et al.* 2000	Itchy or stuffy nose or sneezing during summer months or when near grass, trees, or flowers or when near furry animals + SPT positive	1990: 12.9% 1998: 22.5%	↑
	Linneberg *et al.* 2000	Self-reported hay fever	1990: 16.7% 1998: 23.7%	↑

Country	Reference	Definition	Year: prevalence	
	Linneberg *et al.* 2000 Leth-Møller *et al.* 2019	"*Has a physician ever told you that you have hay fever?*"	1990-1991: 8.0% 1998: 15.6% 2006-2008: 17.9% 2010-2011: 18.7% 2012-2015:18.9% 2016-2017: 20.7%	↑
Finland	Jousilahti *et al.* 2016	"*Have you ever had hay fever or other allergic nasal symptoms?*" "*Yes in the past 12 months*"	1997: 29.4% 2002: 30.3% 2007: 32.2% 2012: 32.6%	↑
	Laatikainen *et al.* 2011	Hay fever ever occurred, self-reported symptoms/disease	1997: 21.9% 2007: 30.5%	↑
	Laatikainen *et al.* 2011	"*Has a physician ever told you that you have hay fever?*"	1997: 8.1% 2007: 13.2%	↑
France	Annesi-Maesano *et al.* 2002 Klossek *et al.* 2009	Score for Allergic Rhinitis ≥ 7	1997: 21.0% 2007: 31.0%	↑
Germany	Heinrich *et al.* 1998	"*Do you have any nasal allergies including hay fever?*"	1990-1992: - 13.3% Est Germany -22.9% West Germany 1994-1995: - 15.9% Est Germany - 24.6% West Germany	↑
Italy	Marco *et al.* 2011	"*Do you have any nasal allergies including hay fever?*"	1991-1993: 16.8% 1998-2000: 19.4% 2007-2010: 25.8%	↑

Country	Reference	Definition	Year: prevalence	
Poland	Sozańska *et al.* 2014	"*Problem with sneezing or a runny or blocked nose or itchy eyes in April, May, June, or July*"	2003: 30.0% 2012: 27.5%	↓
	Sozańska *et al.* 2014	"*In last 12 mo, have you had a problem with sneezing or a runny or blocked nose or itchy eyes when you (your child) did not have a cold or flu?*"	2003: 35.2% 2012: 32.6%	↓
	Sozańska *et al.* 2014	"*Has a physician ever told you that you have hay fever?*"	2003: 4.8% 2012: 7.7%	↑
Russia	Laatikainen *et al.* 2011	Ever hay fever	1997-1998: 4.2% 2007: 5.8%	↑
	Laatikainen *et al.* 2011	"*Has a physician ever told you that you have hay fever?*"	1997-1998: 1.0% 2007: 5.6%	↑
Scotland	Upton *et al.* 2000	*"Do you suffer from, or have you ever suffered from, hay fever?"*	1972-1976: 5.73% 1996: 18.4%	↑
Sweden	Nihlén *et al.* 2006	"*Do you have or do you have had hay fever?*" and "*Do you have nasal symptoms either permanently or recurrently?"* Moreover, a report was required that at least one of the following four environmental factors provoked nasal symptoms: tree-, grass pollen, furred animals, or house dust.	1992: 12.4% 2000: 15%	↑
	Nihlén *et al.* 2006	*"Do you have or do you have had hay fever?"*	1992: 20.5% 2000: 25.0%	↑
	Bjerg *et al.* 2011	*"Do you have any nasal allergies including hay fever?''*	1990: 21.6% 2008: 30.9%	↑
	Borna *et al.* 2019	*"Have you now, or have you ever had allergic rhinitis (hay-fever)?"*	2008: 26.9% 2016: 28.6%	↑
Oceania				
Australia	Peat *et al.* 1992	Hay fever in the previous 12 months	1981: 21.9% 1990: 46.7%	↑

Appendix 2: English translation of the rhinitis part of the 2014 annual follow-up questionnaire

Available in French at: https://www.constances.fr/S2014

Q.22: "*During your lifetime, have you ever had any nasal allergies including hay fever?*" Yes/No

Q.23: "*During your lifetime, 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?*" Yes/No
If yes:

- Q23.A: "*Did your eyes itch or cry when you had these nose problems?*" Yes/No
- Q23.B: "*How old were you the first time?*" …. Years
- Q23.C: "*Have you had these nose problems in the last 12 months?*" Yes/No

Questions 24 to 29 ask about nose problems you have had in the last 12 months.

Q.24: "*In which month did you have these nose problems? (several answers possible)*" January, February, March, April, May, June, July, August, September, October, November, December

Q.25: "*What factor triggered or increased these nose problems? (several answers possible)*" Dust mites or house dust, Animals, Air pollution, Change in weather, Tobacco, Pollens, Cold air, Other, Unknown

Q.26: "*Have you had these nose problems for more than 4 days in a week?*" Yes/No
If yes

- Q.26.A: "*Did these problems last more than 4 consecutive weeks?*" Yes/No

Q27: "*For each of the following problems, indicate whether you have had it in the last 12 months and whether it has been bothersome. If you have not been affected by any of them, indicate this in the first column of the table.*"

	I didn't have this problem	I had this problem but:		
		It didn't bother me	It bothered me without affecting my daily activities or my sleep	It has bothered me and affected my daily activities or sleep
The nose that flows like water				
Blocked nose (feeling like you can't breathe through your nose)				
Itchy nose				
Sneezing that is particularly violent and occurs in attacks				
Eyes that cry, red, itchy				

Q.28: "*Have you used nasal corticosteroid sprays to treat these nose problems? (Nasacort, Nasonex, Avamys, Rhinocort, Beconase, Beclometasone...)"* Yes/No

Q.29: "*Have you used any oral antihistamines/anti-allergic treatments to treat these nose problems? (Aerius, Xyzall, Clarityne, Kestin, Virlix, Zyrtec, Cetirizine, Loratadine, Desloratadine...)"* Yes/No

Appendix 3: Questionnaire as an alternative of skin prick tests to differentiate allergic from non-allergic rhinitis in epidemiological studies

This is the accepted version of the following article: Savouré M, Bousquet J, Burte E, Just J, Pin I, Siroux V, Orsi L, Jacquemin B, Nadif R. Questionnaire as an alternative of skin prick tests to differentiate allergic from non-allergic rhinitis in epidemiological studies. Allergy 2021; 76: 2291–2294., which has been published in final form at https://doi.org/10.1111/all.14812

3.A – Main text

Title: Questionnaire as an alternative of skin prick tests to differentiate allergic from non-allergic rhinitis in epidemiological studies
Short running title: rhinitis: questionnaire versus Skin Prick Test

To the Editor,
Defining allergic rhinitis (AR) and non-allergic rhinitis (NAR) in epidemiological studies is complex. Skin prick tests (SPTs) or serum specific immunoglobulin E (IgE) are the gold-standard to differentiate AR from NAR (1), but they are not often available in large cohorts.

We therefore compared questionnaire-based versus SPT-based definition for AR and for NAR in adults from the first follow-up of the French Epidemiological case-control and family study on the Genetics and Environment of Asthma (EGEA) (https://egeanet.vjf.inserm.fr/index.php/en/; see Online Supplementary 1 for details). Current rhinitis was defined by a positive response to: "*Have you had problems with sneezing, runny nose or stuffy nose when you didn't have a cold or flu in the last 12 months?*". Among the participants with current rhinitis, two definitions of AR and NAR were used: one based on SPTs and one on questionnaire. Participants who had at least one positive SPT were classified as SPT-based AR (AR-SPT), otherwise as SPT-based NAR (NAR-SPT). Participants who responded positively to "*Have you ever had allergic rhinitis?*" or "*Have you ever had hay fever?*" were classified as questionnaire-based AR (AR-Q), otherwise as questionnaire-based NAR (NAR-Q). Due to the EGEA design, analyses were separately conducted among never asthmatics and ever asthmatics. Characteristics of AR or NAR were compared between SPTs and questionnaire definitions using a marginal logistic model to account for matched pair data.

Among the 696 participants included in the analyses (mean 42 years), 53.6% were women, 51.4% non-smokers, and 57.5% ever-asthmatics. Agreement measures between SPTs and questionnaire definitions were satisfactory for never asthmatics. For ever asthmatics, sensitivity and Positive Predictive Value were high but specificity, Negative Predictive Value, Youden's index and Cohen's Kappa coefficient were rather low (Table 1). Among never-asthmatics, differences in participants' characteristics

between questionnaire and SPTs were observed for age for both AR and NAR, and for age of onset and one trigger for AR (Table 2). Among ever-asthmatics, differences were observed for age, sex, smoking and IgE level for both AR and NAR; for age of onset and one trigger for AR, and for ever-allergic conjunctivitis, associated eye-symptoms and two triggers for NAR. AR-Q participants reported more symptoms during the spring than AR-SPT participants and this being even significant for ever-asthmatic participants, conversely to what is observed for NAR (Online Supplementary 2).

In epidemiological studies, when allergy tests are lacking, a simple and easily available definition of AR and NAR is needed. We acknowledge that the best possible diagnosis of AR and NAR is achieved with a specific clinical diagnosis: anamnesis and SPTs/specific IgE, by a specialized health professional. As we did not have anamnesis, our definition of current rhinitis is based on the ISAAC definition (2) as suggested by the ARIA (3). To distinguish AR from NAR by questionnaire, we used an adaptation of the ECRHS definition (4). Although SPTs are the gold-standard for distinguishing AR from NAR, SPT positivity is not systematically associated with nasal symptoms (5). Indeed, among EGEA participants with never rhinitis, 29% of those with never-asthma and 67% of those with ever-asthma had at least one positive SPT (6). Also, SPT negativity does not systematically reflect NAR, as observed for local allergic rhinitis (7). The questionnaire approach has the advantage of relying on what participants directly identify as nasal allergies, and could therefore consider the forms of local allergic rhinitis that the SPTs approach does not. This could partly explain the higher reports of pollen trigger, associated eye-symptoms and symptoms in spring we observed in the NAR group with the SPT-based definition compared to the questionnaire-based definition. Based on this, the moderate agreement we observed between SPTs and questionnaire would not necessarily reflect a false classification of AR/NAR by questionnaire.
In conclusion, our results suggest that a simple definition of AR and NAR based on a validated and standardized questionnaire could be a suitable proxy for AR and NAR in the absence of biological measures.

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Conflict of Interest Statement:
J. Bousquet reports personal fees from Chiesi, Cipla, Hikma, Menarini, Mundipharma, Mylan, Novartis, Purina, Sanofi-Aventis, Takeda, Teva, Uriach, other from KYomed-Innov, outside the submitted work.
J. Just reports personal fees from Novartis, Sanofi-Aventis, ALK-Abello, other from GSK outside the submitted work.
I. Pin reports personal fees from AGIRàdom, other from SANOFI, other from GSK, outside the submitted work.
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Tables

Table 1: Number of participants classified as allergic rhinitis (AR) or non-allergic rhinitis (NAR) according to SPT-based and questionnaire-based (Q) definitions

	Never-asthmatics participants			**Ever-asthmatics participants**		
	AR-SPT	**NAR-SPT**	**Total**	**AR-SPT**	**NAR-SPT**	**Total**
AR-Q	**109**	45	154	**282**	53	335
NAR-Q	32	**110**	142	38	**27**	65
Total	141	155	296	320	80	400
	Estimation ($CI_{95\%}$)			**Estimation ($CI_{95\%}$)**		
Sensitivity	0.77 (0.70 – 0.84)			0.88 (0.85 – 0.92)		
Specificity	0.71 (0.64 – 0.78)			0.34 (0.23 – 0.44)		
PPV	0.71 (0.64 – 0.78)			0.84 (0.80 – 0.88)		
NPV	0.77 (0.71 – 0.84)			0.42 (0.30 – 0.54)		
Youden Index	0.48			0.22		
Cohen's Kappa	0.48 (0.38 – 0.58)			0.24 (0.12 – 0.35)		

PPV: Positive Predictive Value; CI: Confidence Interval; NPV: Negative Predictive Value.

Table 2: Comparison of characteristics between SPT-based and questionnaire-based (Q) definition for allergic rhinitis (AR) and for non-allergic rhinitis (NAR). A: In never-asthmatics; B: In ever-asthmatics.

A. In never-asthmatics	**AR-SPT**	**AR-Q**	**Pval†**	**NAR-SPT**	**NAR-Q**	**Pval‡**
	n = 141	**n = 154**		**n = 155**	**n = 142**	
Age (year), mean ± sd	40.6 ± 14.3	44.2 ± 15.0	<.0001	51.3 ± 14.8	48.4 ± 15.8	0.002
Sex, women %	57.5	58.4	0.76	63.9	63.4	0.93
Tobacco status, %			0.18			0.25
Non-smoker	51.1	50.0		50.3	51.4	
Ex-smoker	24.1	28.6		31.6	27.5	
Smoker	24.8	21.4		18.1	21.1	
Ever allergic conjunctivitis, %	44.9	46.4	0.67	28.1	25.0	0.27
At least one positive SPT, %	100	70.8		0.00	22.5	
Serum IgE, GM (Q1-Q3)	95.8 (46.7–209)	83.5 (36.3–201)	0.08	40.5 (15.4–91.3)	43.6 (15.4–105)	0.39
Age of onset of rhinitis, mean ± sd	21.7 ± 13.1	24.5 ± 15.3	0.007	36.1 ± 18.2	34.3 ± 18.5	0.17
Associated eye symptoms, %	78.7	77.9	0.67	36.8	33.8	0.29
Trigger(s) of symptoms§, %						
Dust mites or house dust	37.6	31.8	0.03	20.7	25.4	0.10
Pollens	68.1	69.5	0.91	27.1	21.8	0.07
Animals	18.4	16.9	0.36	2.58	2.82	1.00
Other	9.22	13.0	0.16	31.6	29.6	0.46
No trigger reported	4.96	5.84	0.60	29.0	30.3	0.47

†: P-values for the comparison of the characteristics of AR between SPTs and questionnaire definitions; ‡: P-values for the comparison of the characteristics of NAR between SPTs and questionnaire definitions; §: Several possible answers; sd: standard deviation; IgE: immunoglobulin E; GM: geometric mean; Q1–Q3: quartile 1–quartile 3; P-values in bold are < 0.05.

B. In ever-asthmatics	AR-SPT	AR-Q	Pval†	NAR-SPT	NAR-Q	Pval‡
	n = 320	n = 335		n = 80	n = 65	
Age (year), mean ± sd	35.9 ± 15.1	38.4 ± 15.9	<.0001	47.9 ± 16.7	37.9 ± 17.7	<.0001
Sex, women %	45.3	49.3	0.007	60.0	43.1	0.02
Tobacco status, %			0.04			0.03
Non-smoker	53.4	51.0		46.3	56.9	
Ex-smoker	19.1	22.4		28.8	13.9	
Smoker	27.5	26.6		25.0	29.2	
Ever allergic conjunctivitis, %	54.8	56.8	0.20	40.3	25.8	0.02
At least one positive SPT, %	100.0	84.2		0.0	58.5	
Serum IgE, GM (Q1-Q3)	197 (86.1–451)	160 (68.7–373)	<.0001	49.8 (16.7–138)	112 (28.4–338)	0.01
Age of onset of rhinitis, mean ± sd	13.3 ± 11.9	14.4 ± 12.5	0.01	24.3 ± 16.6	22.0 ± 17.9	0.95
Associated eye symptoms, %	79.1	81.5	0.16	61.3	44.6	0.009
Trigger(s) of symptoms§, %						
Dust mites or house dust	56.9	54.9	0.18	30.0	33.9	0.60
Pollens	65.0	66.3	0.55	31.3	16.9	0.02
Animals	38.8	34.9	0.002	3.75	15.4	0.05
Other	7.81	8.36	0.61	21.3	21.5	0.93
No trigger reported	5.31	5.97	0.55	27.5	29.2	0.49

†: P-values for the comparison of the characteristics of AR between SPTs and questionnaire definitions; ‡: P-values for the comparison of the characteristics of NAR between SPTs and questionnaire definitions; §: Several possible answers; sd: standard deviation; IgE: immunoglobulin E; GM: geometric mean; Q1 – Q3: quartile 1 – quartile 3; P-values in bold are < 0.05.

3.B – Supplementary material

Online Supplementary 1: Supplement on the method

EGEA

The EGEA is a cohort study based on an initial group of asthma cases recruited in chest clinics from five French cities (1991-1995) along with their first-degree relatives, and a group of controls. Briefly, 2,047 children (<16 years) and adult participants were enrolled at baseline, including 348 participants with current asthma from chest clinics, their 1,244 first-degree relatives, and 415 population-based controls. The protocol and descriptive characteristics of the EGEA study have been previously published (1,2).

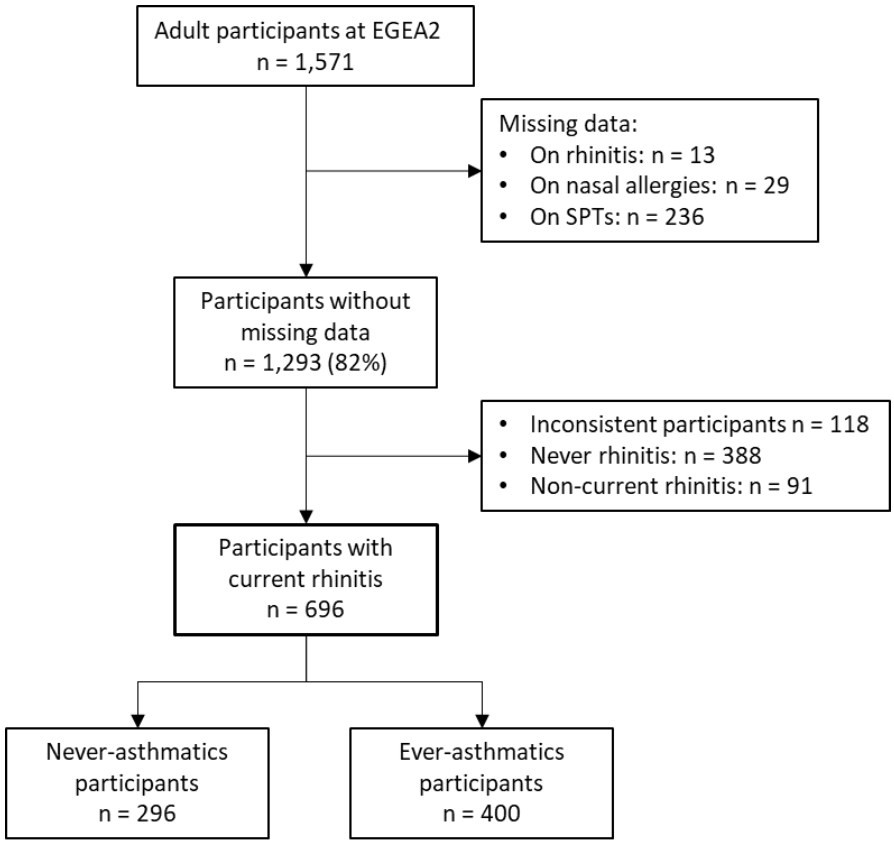
A 12-year follow-up of the initial cohort was conducted between 2003 and 2007 (EGEA2). Among the alive cohort (n=2,002), 92% (n=1,845) completed a short self-administered questionnaire, and among them 1,601 (n=1,571 adults aged ≥16 years) had a complete examination. As a follow-up study of EGEA2, the third survey (EGEA3, 2011-2013, n=1558) was conducted using self-completed questionnaire only.

The EGEA collection was certified ISO 9001 from 2006 to 2018 (3). Ethical approval was obtained from the relevant institutional review board committees (Cochin Port-Royal Hospital and Necker-Enfants Malades Hospital, Paris). All participants signed a written informed consent.

Analysis population of the present letter

The analyses of the present paper were performed at EGEA2. Among the 1,571 adults, those with missing data regarding the definitions of rhinitis (n = 13), the presence of nasal allergies (n = 29) and participants who did not have SPTs (n = 236) were excluded from the analyses. Participants who answered yes to "*Have you ever had allergic rhinitis?*" or "*Have you ever had hay fever?*" and no 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?*" were considered inconsistent and were also excluded from the analyses (n = 118). A total of 696 participants reported current rhinitis and were included in the analyses (Figure S1).

Figure S1: Flow chart



Variables of interest

Participants with ever-asthma were defined by a positive answer to: "*Have you ever had attacks of breathlessness at rest with wheezing?"* or "*Have you ever had asthma attacks?*" or if they were recruited as asthmatic cases at the first survey (2).

The absence of rhinitis in a lifetime (never rhinitis) was defined by a negative answer to: "*Have you ever had problems with sneezing, runny nose or stuffy nose when you didn't have a cold and the flu?*". Ever allergic conjunctivitis: positive answer to "*Have you ever had allergic conjunctivitis?*". Age of onset: answer to "*At what age did you first experience these nose problems?*". Associated eye symptoms: positive answer to "*did your eyes sting or cry when you had these nose problems?*". Triggers of the symptoms: answer to "*In the last 12 months, what factors have triggered or increased these nose problems? a. dust mites or house dust b. pollens c. animals d. other*". Several responses were possible, participants who did not provide any of the possible answers were categorized as "no trigger reported". Seasonality: answer to "*During which of the last 12 months have you had these nose problems?*"

SPTs to 12 aeroallergens ((indoor: cat, *Dermatophagoides pteronyssinus*, *Blattela germanica*; outdoor: olive, birch, *Parieteria judaica*, timothy grass, and ragweed pollen; moulds: *Aspergillus*, *Cladosporium herbarum*, *Alternaria tenuis*, Cupressus) were performed.

All analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC).

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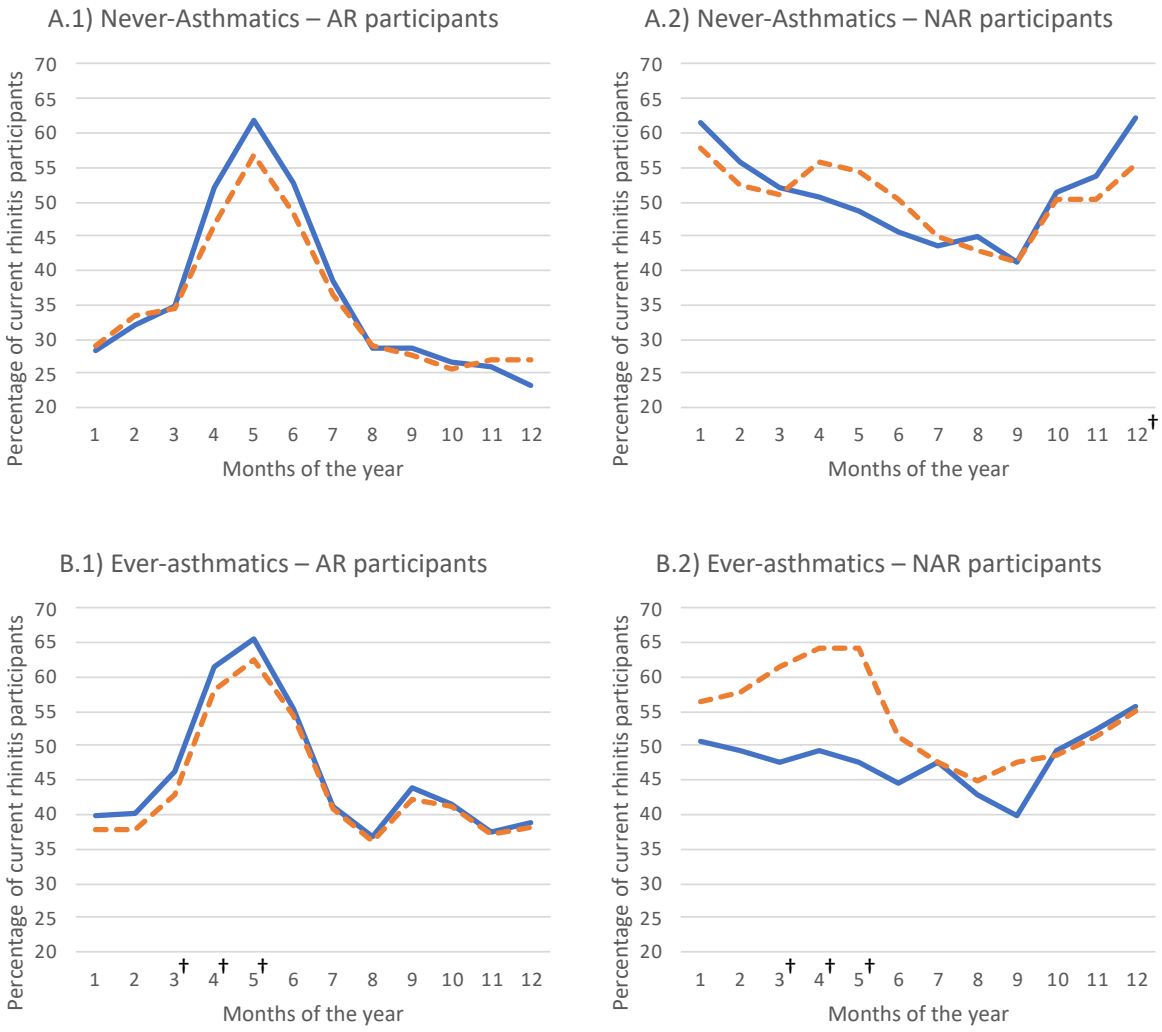
Online Supplementary 2: Comparison of seasonality between SPT-based and questionnaire-based definition for allergic rhinitis (AR) and for non-allergic rhinitis (NAR)



A: In never-asthmatics; B: In ever-asthmatics. 1: AR participants; 2: NAR participants.
- - - SPT-based definition; — Questionnaire-based definition.
†: P-values of comparison between SPTs and questionnaire definitions < 0.05.

Online Supplementary 3: Number of participants classified as allergic rhinitis (AR) or non-allergic rhinitis (NAR) according to clustering approach and questionnaire-based (Q) definition

In the same EGEA study, rhinitis clusters have previously been described (4). This was a mixture model approach without a priori and 21 variables were selected for analysis: report of nasal symptoms, current/ever symptoms, persistence and disturbance of these symptoms, seasonal pattern, sensitivity to seven triggers, report of allergic rhinitis, hay fever, conjunctivitis, sinusitis and eczema, report of diagnostic of allergy by a physician, SPT, report of spray, report of drug except spray, and allergic immunotherapy since the last survey. We also compared the number of participants classified as allergic rhinitis (AR) or non-allergic rhinitis (NAR) according to this clustering approach and questionnaire-based (Q) definition.

	Never-asthmatics participants			**Ever-asthmatics participants**		
	AR-cluster	**NAR-cluster**	**Total**	**AR-cluster**	**NAR-cluster**	**Total**
AR-Q	**108**	19	127	**169**	87	256
NAR-Q	7	**108**	115	1	**55**	56
Total	115	127	242	170	142	312
	Estimation ($CI_{95\%}$)			**Estimation ($CI_{95\%}$)**		
Sensitivity	0.94 (0.90 – 0.98)			0.99 (0.98 – 1.0)		
Specificity	0.85 (0.79 – 0.91)			0.39 (0.31 – 0.47)		
PPV	0.85 (0.79 – 0.91)			0.66 (0.60 – 0.72)		
NPV	0.94 (0.90 – 0.98)			0.98 (0.95 – 1.0)		
Youden Index	0.79			0.38		
Cohen's Kappa	0.79 (0.71 – 0.86)			0.40 (0.32 – 0.49)		

Noteworthy, we observed a higher agreement between the clustering approach and questionnaire (Online supplementary 3) than between SPTs and questionnaire (Table 1).

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Appendix 4: Prevalences of rhinitis in Constances – Supplementary material

Table S1: Description of the analysis population by invitation year

	2013 (n=13,556)	2014 (n=1,8535)	2015 (n=23,531)	2016 (n=21,625)	2017 (n=25,521)
Age, years					
<30	1,183 (16.6%)	2,257 (17.5%)	2,714 (14.6%)	2,796 (15.5%)	3,030 (17.6%)
[30 - 45[	3,915 (33.2%)	5,874 (34.3%)	7,841 (33.7%)	7,812 (32.1%)	9,011 (33.0%)
[45-60[	5,077 (31.4%)	6,525 (30.9%)	7,975 (31.7%)	6,641 (29.0%)	8,162 (30.4%)
≥60	3,381 (18.8%)	3,879 (17.3%)	5,001 (20.0%)	4,376 (23.5%)	5,318 (19.0%)
Sex					
Men	6,455 (49.3%)	8,809 (48.9%)	11,587 (48.5%)	10,001 (48.1%)	11,577 (48.1%)
Women	7,101 (50.7%)	9,726 (51.1%)	11,944 (51.5%)	11,624 (51.9%)	13,944 (51.9%)
Tobacco status					
Never smoker	5,808 (44.6%)	8,129 (44.9%)	10,585 (44.9%)	9,850 (45.9%)	11,794 (46.4%)
Ex-smoker	4,642 (31.3%)	5,991 (30.5%)	7,714 (32.2%)	6,980 (32.9%)	8,445 (32.1%)
Current smoker	2,530 (24.1%)	3,639 (24.6%)	4,321 (22.9%)	4,058 (21.1%)	4,528 (21.5%)
Body-mass index, kg/m^2					
<18.5	310 (3.0%)	447 (2.8%)	572 (2.3%)	583 (2.6%)	736 (3.3%)
[18.5 - 25[	7,235 (53.4%)	9,786 (52.7%)	12,571 (51.8%)	11,626 (51.4%)	13,439 (50.5%)
[25 - 30[	4,103 (29.9%)	5,641 (30.0%)	7,317 (31.6%)	6,394 (31.2%)	7,653 (30.7%)
≥30	1,596 (13.8%)	2,393 (14.5%)	2,819 (14.3%)	2,635 (14.9%)	3,242 (15.5%)
Educational level					
<High school	1,218 (11.6%)	1,783 (11.3%)	1,774 (11.1%)	1,745 (10.7%)	1,965 (10.6%)
High school	4,171 (37.4%)	6,809 (38.3%)	7,666 (37.0%)	6,736 (35.6%)	8,114 (38.4%)
University	7,975 (51.0%)	9,710 (50.5%)	13,762 (51.8%)	12,882 (53.7%)	15,122 (51.1%)
Level of urbanity					
Rural	2,081 (13.5%)	3,243 (13.5%)	3,960 (14.0%)	4234 (15.5%)	5,591 (20.6%)
Urban	11,475 (86.5%)	15,292 (86.5%)	19,571 (86.0%)	17,391 (84.5%)	19,930 (79.4%)
Rhinitis					
Never rhinitis	7,601 (55.0%)	10,252 (53.5%)	12,952 (54.8%)	11,792 (54.0%)	13,981 (54.8%)
Non-current rhinitis	1,490 (11.0%)	2,145 (11.8%)	2,601 (10.8%)	2,390 (11.3%)	2,868 (11.2%)
Current rhinitis	4,465 (34.0%)	6,138 (34.7%)	7,978 (34.5%)	7,443 (34.7%)	8,672 (34.0%)
Current NAR	1,351 (11.0%)	1,959 (11.4%)	2,345 (10.2%)	2,266 (10.8%)	2,618 (10.7%)
Current AR	3,114 (23.0%)	4,179 (23.3%)	5,633 (24.2%)	5,177 (24.0%)	6,054 (23.0%)
Department					
Bouches-du-Rhône	669 (11.4%)	864 (11.2%)	1,130 (11.1%)	1,159 (10.6%)	1,020 (7.2%)
Calvados	0 (0.0%)	0 (0.0%)	0 (0.0%)	1,203 (3.7%)	905 (2.9%)
Charente	520 (2.0%)	654 (1.8%)	949 (1.7%)	954 (1.7%)	789 (2.6%)
Côtes-d'Armor	1,090 (3.3%)	1,305 (3.1%)	1,251 (3.1%)	1,389 (3.0%)	1,359 (5.3%)
Gard	448 (4.1%)	436 (3.8%)	873 (4.0%)	696 (3.6%)	823 (2.8%)
Gironde	593 (7.8%)	1,524 (8.0%)	1,022 (6.9%)	1,294 (7.1%)	2,151 (5.8%)
Haute-Garonne	995 (7.5%)	1,347 (7.4%)	1,426 (8.0%)	999 (7.3%)	1,353 (4.9%)
Haut-Rhin	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1,747 (3.6%)
Ille-et-Vilaine	784 (5.7%)	1,118 (5.6%)	1,288 (5.6%)	1,046 (5.2%)	936 (3.7%)
Indre-et-Loire	1,433 (3.6%)	1,723 (3.5%)	1,302 (3.5%)	640 (3.1%)	1,042 (5.5%)
Loire-Atlantique	397 (7.8%)	513 (7.2%)	698 (8.2%)	603 (7.9%)	913 (5.1%)

	2013 (n=13,556)	2014 (n=1,8535)	2015 (n=23,531)	2016 (n=21,625)	2017 (n=25,521)
Loiret	271 (3.8%)	986 (3.7%)	971 (3.9%)	903 (3.6%)	631 (4.3%)
Meurthe-et-Moselle	714 (4.4%)	821 (4.1%)	2,032 (4.2%)	1,547 (3.7%)	1,608 (6.4%)
Nord	932 (9.9%)	1,422 (10.4%)	1,636 (9.5%)	1,171 (8.8%)	1,295 (6.4%)
Paris	3,052 (14.4%)	2,347 (13.6%)	4,790 (14.3%)	3,888 (13.0%)	3,041 (9.9%)
Pyrénées-Atlantiques	788 (2.2%)	1,075 (3.7%)	1,273 (2.6%)	640 (2.8%)	812 (3.3%)
Rhône	541 (9.9%)	1,796 (10.9%)	1,808 (11.0%)	1,317 (10.0%)	1,453 (7.0%)
Sarthe	0 (0.0%)	0 (0.0%)	0 (0.0%)	1,297 (3.3%)	1,412 (8.4%)
Vienne	329 (2.1%)	604 (2.2%)	1,082 (2.2%)	879 (1.9%)	878 (3.6%)
Yonne	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1,353 (1.5%)

Data are n (% weighted prevalence), AR: Allergic Rhinitis; NAR: Non-Allergic Rhinitis

Table S2: Weighted prevalences of current rhinitis according to the year of invitation and to the department

	2013			2014			2015			2016			2017		
Department	Current rhinitis	Current NAR	Current AR	Current rhinitis	Current NAR	Current AR	Current rhinitis	Current NAR	Current AR	Current rhinitis	Current NAR	Current AR	Current rhinitis	Current NAR	Current AR
Bouches-du-Rhône	37.0	9.3	27.8	38.5	11.3	27.2	42.1	11.6	30.5	39.6	10.8	28.8	35.2	8.3	27.0
Calvados	-	-	-	-	-	-	-	-	-	32.7	10.1	22.6	32.3	10.1	22.2
Charente	30.1	8.1	22.0	31.9	12.2	19.7	28.9	10.7	18.2	31.9	9.7	22.2	35.1	8.8	26.4
Côtes-d'Armor	27.9	8.1	19.8	29.6	11.8	17.8	27.3	10.5	16.8	30.1	11.3	18.7	27.7	8.6	19.1
Gard	34.3	9.5	24.8	37.1	12.1	25.0	38.7	8.6	30.1	36.7	12.5	24.3	34.7	9.5	25.1
Gironde	34.3	12.6	21.7	35.7	9.8	26.0	32.4	10.0	22.4	35.3	11.1	24.2	38.0	10.0	28.0
Haut-Rhin	-	-	-	-	-	-	-	-	-	-	-	-	33.2	12.4	20.8
Haute-Garonne	34.4	9.1	25.3	35.4	9.2	26.2	35.8	9.6	26.1	36.7	11.4	25.3	35.2	10.9	24.3
Ille-et-Vilaine	30.4	9.7	20.7	29.1	11.4	17.7	31.0	10.7	20.3	29.8	8.6	21.1	31.5	11.6	19.9
Indre-et-Loire	30.6	9.3	21.3	29.2	10.6	18.6	31.1	10.1	21.0	36.2	13.0	23.2	28.2	10.3	17.9
Loire-Atlantique	30.7	11.9	18.9	31.0	9.7	21.3	28.4	7.0	21.4	30.2	8.8	21.4	35.4	13.8	21.6
Loiret	31.6	12.2	19.4	27.6	7.3	20.2	34.9	10.3	24.6	34.9	13.3	21.6	33.4	7.4	26.0
Meurthe-et-Moselle	32.5	11.1	21.5	33.4	11.7	21.7	29.8	9.6	20.2	32.2	13.6	18.6	33.9	13.4	20.6
Nord	36.8	15.1	21.7	33.3	12.4	21.0	36.6	13.0	23.6	31.5	10.2	21.3	34.2	12.7	21.5
Paris	37.8	12.6	25.2	37.7	13.5	24.2	34.8	11.0	23.9	38.6	10.4	28.2	37.8	12.1	25.8
Pyrénées-Atlantiques	32.1	10.7	21.4	32.3	10.1	22.2	33.1	10.6	22.5	35.5	9.6	25.9	32.2	10.4	21.8
Rhône	32.4	9.5	22.8	39.5	13.1	26.3	36.4	9.1	27.3	36.1	10.8	25.3	35.9	11.0	24.9
Sarthe	-	-	-	-	-	-	-	-	-	29.1	10.4	18.7	30.4	10.2	20.2
Vienne	32.7	8.9	23.8	31.3	12.1	19.2	30.0	8.7	21.3	32.9	11.5	21.4	31.4	8.5	22.9
Yonne	-	-	-	-	-	-	-	-	-	-	-	-	31.3	10.0	21.2

AR: Allergic rhinitis, NAR: Non-Allergic Rhinitis

Appendix 5: Rhinitis phenotypes and multimorbidities in the general population Constances cohort

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5.A – Main text

Title: Rhinitis phenotypes and multimorbidities in the general population Constances cohort

Short title: Rhinitis phenotypes and multimorbidities

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Take home message: For the first time in a general adult population, we showed novel rhinitis phenotypes based on AR and NAR multimorbidities, and that participants with asthma and conjunctivitis had more severe rhinitis.

Abstract

Background: Scarce epidemiological studies have characterized allergic rhinitis (AR) and non-allergic rhinitis (NAR) in adults.
Aims: In a population-based cohort, to (1) describe rhinitis, AR and NAR, and (2) explore how asthma and conjunctivitis may lead to the identification of novel rhinitis phenotypes.
Methods: In this cross-sectional analysis, current rhinitis was defined in the last 12 months using questionnaire from the French Constances cohort. Participants with current rhinitis reporting nasal allergies were considered as AR, otherwise as NAR. We described AR and NAR phenotypes, and their phenotypes including co-occurrence with ever-asthma and ever-conjunctivitis.
Results: Among the 20772 participants included in this analysis (55.2% women, mean age: 53±13 years), crude prevalences of AR and NAR were 28.0% and 10.9%. AR participants reported more frequently persistent rhinitis (31.6% *versus* 25.1%), and moderate-severe rhinitis (40.1% *versus* 24.2%) than NAR participants. Among AR or NAR participants, those with ever-asthma reported more moderate-severe rhinitis. Participants with AR, ever-asthma, and ever-conjunctivitis had an earlier age of rhinitis onset, more severe rhinitis, and higher eosinophil count than participants in other groups. Results were replicated in another cohort.
Conclusions: In this large population-based cohort, 40% reported current rhinitis, with a lower prevalence of moderate-severe rhinitis than in clinical practice. For the first time in a general adult population, we showed that AR and NAR alone or in combination with asthma or in combination with asthma and conjunctivitis are different phenotypes. These results provide new insights on how best to manage rhinitis and its multimorbidities.

Key words: allergic-rhinitis, asthma, conjunctivitis, non-allergic rhinitis, rhinitis

1. Introduction

Rhinitis describes nasal symptoms resulting from inflammation and/or dysfunction of the nasal mucosa.(1) It is one of the most common chronic conditions, and is a global health problem causing major burden and disability worldwide.(2,3)

Behind the apparent simplicity of its clinical definition, rhinitis is a complex and heterogeneous disease characterized by several phenotypes. After excluding acute infectious rhinitis, rhinitis can be divided into two major phenotypes: allergic rhinitis (AR) and non-allergic rhinitis (NAR). AR is caused by immunoglobulin E (IgE)-mediated reactions to inhaled allergens, and NAR is a heterogeneous group of nasal conditions.(4) However allergic and non-allergic mechanisms are often intertwined. Actually AR and NAR even share some common symptoms (nasal congestion and rhinorrhea), but they have different clinical features and treatments.(5) AR usually starts in childhood, whereas NAR often appears later. Many patients with AR have a seasonal exacerbation of symptoms, mainly due to aeroallergen exposure, and AR is characterized by the presence of the full spectrum of nasal symptoms, which are frequently associated with eye symptoms.(5) Most NAR patients have symptoms triggered by non-allergenic exposures, and ocular symptoms appear to be uncommon.(5) However, most of this knowledge on rhinitis is derived from clinical practice, and there are few epidemiological studies in general population in adults that have assessed the prevalence and characteristics of phenotypes of rhinitis. Furthermore, few of them have assessed NAR.(3,6,7)

Asthma is a major multimorbidity of both AR and NAR, over 80% of patients with asthma have rhinitis and 10-40% of patients with rhinitis have asthma.(1) Surprisingly, although many studies have described the characteristics of asthma in relation to the presence or absence of rhinitis, few population-based epidemiological studies have described rhinitis in relation to asthma multimorbidity.(8) In particular, the association between asthma and severity of rhinitis is unclear.(1,9) Conjunctivitis is also an important multimorbidity of AR (3), and provides additional information when studying allergic multimorbidities.(10) This suggests that there may be different AR phenotypes depending on the presence or absence of asthma and conjunctivitis. However, to our knowledge, no population-based study in adults has investigated the characteristics of AR in relation to asthma and conjunctivitis.

Our objective was to describe the characteristics of rhinitis, considering separately AR and NAR in adults from the French population-based cohort Constances, and to explore phenotypic differences between rhinitis alone and rhinitis associated with asthma and/or conjunctivitis. Finally, we externally validated our results in the French case-control epidemiological study on asthma (EGEA).

2. Methods

2.1. Study design

A cross-sectional study was carried out with the data from the follow-up questionnaire of 2014 of Constances.

Constances is a population-based cohort of almost 220,000 adults aged 18 to 69 at inclusion, randomly selected from social security affiliates in France (https://www.constances.fr). The participants were enrolled from 2012 to 2020 in 20 administrative districts (see Figure S1). At inclusion, participants completed standardized questionnaires and had a complete medical examination.(11–13) An annual follow-up is done by questionnaire.

All participants who were included until the end of 2013 received the 2014 questionnaire which included two pages of detailed, validated, and standardized questions on rhinitis (online supplements).

All confidentiality, safety and security procedures were approved by the French legal authorities (online supplements). All participants signed a written informed consent.

2.2. Definitions

Rhinitis: we defined current and ever-rhinitis using the standardized questions proposed in the International Study of Asthma and Allergies in Childhood (ISAAC) (14), as recommended by the Allergic Rhinitis and its Impact on Asthma (ARIA).(15) Participants were considered as having ever-rhinitis if they answered yes to "*During your lifetime, 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?*", otherwise as never having rhinitis. Among those with ever-rhinitis, participants were classified as having current rhinitis if they answered yes to "*Have you had these problems in the last 12 months?*", otherwise as having non-current rhinitis.

To distinguish AR from NAR, we used an adaptation of the ECRHS question to define nasal allergies (16) that was recently shown to be a suitable proxy in epidemiologic studies.(17) Participants with rhinitis who answered yes to "*Have you ever had nasal allergies in your lifetime, including hay fever?*" were classified as AR, otherwise participants who answered no were classified as NAR.

Definitions of nasal allergies, rhinitis duration, rhinitis severity, and reported symptoms are described in the online supplements.

Asthma: participants were considered as having ever-asthma if they answered yes at inclusion to "*Have you ever had asthma?*" or answer "asthma" at the follow-up questionnaire of 2014 to: "*Here is a list of health problems. Indicate here the ones you have suffered from in the last 12 months (whether or not there was a work interruption, whether or not there is a treatment).*".

Conjunctivitis: participants were considered as having ever-conjunctivitis if they answered yes at the 2014 annual follow-up questionnaire to *"During your lifetime, have you ever had allergic conjunctivitis?*".

2.3. Statistical methods

Analyses were carried out in complete cases i.e. participants with missing data were excluded and no imputation was performed.

Pearson Chi-2 tests for categorical variables, and Student' t test (when comparing two groups) or ANOVA comparison of variances (when comparing more than two groups) for continuous variables were used. We also conducted sensitivity analyses using alternate definitions to distinguish AR from NAR: one based on the triggers of nasal symptoms and one based on the classification tree obtained by Burte *et al*. with an unsupervised approach to identify AR and NAR (18) (online supplements).

As asthma is a major multimorbidity of AR and NAR, we described AR or NAR according to whether or not participants had reported ever-asthma. Subsequently, we described phenotypes of AR including ever-conjunctivitis: participants who reported only AR, those who reported AR + ever-conjunctivitis only, those who reported AR + ever-asthma only, and those who reported AR + ever-conjunctivitis + ever-asthma. This step could only be done for AR as there is not enough participants with NAR reporting both ever-asthma and ever-conjunctivitis.

All analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC).

2.4. Replication study

To validate our findings, we replicated some analyses in the case control EGEA study. We used a rhinitis definition based on very similar questions and participants in EGEA also had biomarkers and test of allergic sensitization (total IgE and SPTs to 12 allergens). (online supplements).

3. Results

3.1. Demographic characteristics of the participants

The follow-up questionnaire of 2014 was sent to 26737 participants included by 2013 and was completed by 21507 (80%) of them. Participants with missing data regarding the definitions of rhinitis (n=497) or nasal allergies (n=238) were excluded from the analyses (Figure S2). Non-included participants were on average more often male, younger, smoker, with a lower level of education and a higher body mass index (BMI) and reported more ever-asthma than included participants (Table S1).

There were 20772 participants included in the main analyses with a mean age of 52.6 ± 12.6 years and 55.2% were women. Among them, 13.5% were current smokers, 12.7% reported ever-asthma and 29.2% ever-conjunctivitis (Table 1).

3.2. AR and NAR

The crude prevalences of ever-rhinitis, ever AR and ever NAR were 53.4% (Confidence Interval $(CI)_{95\%}$: 52.8%-54.1%), 36.5% (35.9%-37.2%) and 16.9% (16.4%-17.4%). The crude prevalences of current rhinitis, current AR and current NAR were 38.9% (38.2%-39.5%), 28.0% (27.3%-28.6%) and 10.9% (10.5%-11.3%).

The description of the participants according to their rhinitis status (never, non-current or current) is presented in Table 1. Participants with current rhinitis were more often women, younger, with a higher education level, had higher eosinophil count, and had more ever-asthma, ever-conjunctivitis, and ever-eczema than participants with never rhinitis or with non-current rhinitis.

Participants with current AR reported significantly more often ever-asthma, ever-conjunctivitis, and ever-eczema than those with NAR (Table 2). The age of rhinitis onset was on average 10 years earlier for AR compared to NAR. AR participants reported more nasal symptoms than NAR participants, the highest differences between the two groups were observed for associated-eye symptoms (68.8% *vs* 35.3%) and nasal itching (67.0% *vs* 39.7%). AR participants reported more persistent symptoms (31.6% *vs* 25.1%) and more moderate-severe rhinitis (40.1% vs 24.2%) than NAR ones. Triggers of rhinitis symptoms differed between AR and NAR: the largest differences were observed for pollens (52.3% *vs* 10.2%), dust mites/house dust (33.4% *vs* 10.4%), and unknown triggers (27.1% *vs* 48.6%). Treatment by oral antihistamines and intra-nasal corticosteroids were reported by 32.0% of AR participants, and 6.0% of NAR participants.

The seasonality of symptoms differed between AR and NAR, AR participants reported symptoms mainly during the Spring whereas NAR participants reported symptoms mainly during the Winter (Figure 1).

Using alternate definitions of rhinitis, the crude prevalence of current AR varied from 20.3% to 28.4% and that of current NAR varied from 10.0% to 18.6% (Table S2). The kappa concordance coefficient between the main definition and the alternate definitions was the highest for the alternate definition based on the classification tree adaptation (kappa=0.96) and the lowest for the alternate definition based on the

symptom triggers (kappa=0.37). Similar differences between AR and NAR were found with the main and alternate definitions in terms of multimorbidities, reported symptoms, triggers, seasonality, and treatments (Table S3, Figure S3, Figure S4).

3.3. Rhinitis phenotypes including ever-asthma and ever-conjunctivitis status

Among AR participants, 1383 reported ever asthma (24.3%). Among NAR participants, 166 reported ever asthma (7.5%) (Table 3). Both among AR and NAR participants, those who reported ever-asthma had higher eosinophil counts, an earlier age of rhinitis onset and more moderate-severe rhinitis than those with never asthma. Participants with AR and ever-asthma also reported more ever-conjunctivitis and ever-eczema than those with AR only. These differences were not significant for participants with NAR, even if the tendency was the same.

For replication analyses in EGEA, 842 participants with current rhinitis were included 174 with AR and never asthma, 380 with AR and ever-asthma, 176 with NAR and never asthma, and 83 with NAR and ever-asthma. Similar results were observed (Table S4). Furthermore, participants who reported ever-asthma had higher serum IgE levels and allergen sensitization assessed by SPT. Participants with ever-asthma had on average a higher mean number of positive SPTs than those with never asthma for both AR (2.6 *vs* 1.9) and NAR (1.6 *vs* 0.4). When using the SPT definition instead of the questionnaire definition the results were almost identical (Table S5).

In Constances, accounting for ever asthma and ever conjunctivitis, the characteristics of 1,855 participants with AR only, 1,958with AR + ever conjunctivitis, 418 with AR + ever asthma, and 848 with AR + ever conjunctivitis + ever asthma are shown in in Table 4. Statistically significant differences were observed for almost all the characteristics. In particular, participants with AR + ever-conjunctivitis + ever-asthma, had an earlier age of rhinitis onset, more moderate-severe rhinitis, reported more comedication (intranasal corticosteroids and antihistamines), and higher blood eosinophil count than participants from the other groups.

The results observed in the EGEA study were almost identical (Table S6, Figure S5). In addition, we observed that participants with AR + ever-conjunctivitis + ever-asthma had the highest mean number of positive SPTs. When using the SPT definition the results were also almost identical (Table S7).

4. Discussion

In a large population-based study, four out of ten adults reported current rhinitis, and 30% of them reported moderate-severe rhinitis. We observed the well-known characteristics of AR and NAR with questionnaire-based definitions. We showed that AR and NAR alone or with asthma or with asthma and conjunctivitis are different phenotypes.

4.1. Strengths and limitations

Constances is the largest French population-based epidemiological study in adults. Constances is however not fully representative of the French adult population as 1) participants were randomly selected from the beneficiaries of the National Health Insurance Fund ("Caisse nationale d'assurance maladie", CNAM) that covered around 85% of the French population, and 2) some geographical areas of France were not included. This may lead of a misestimation of the actual rhinitis prevalence. Furthermore, the 2014 population is even more selected mainly regarding age with few participants under 30 years old. This may have slightly impacted the characterization and identification of our phenotypes. Recall bias is possible, likely more for ever asthma than for current rhinitis as the questions on current rhinitis characteristics covered the last 12 months, limiting memory issues.

We acknowledge the lack of SPTs and/or serum specific IgE measurement is a limitation. However, we have defined AR and NAR using validated and standardized questions (16) that were shown to be a good alternative to differentiate AR from NAR in epidemiologic studies (17) even if classification errors cannot be excluded. We observed that a few participants classified as NAR reported allergic triggers and we could not exclude that they could have AR without knowing it. By using alternate definitions of AR and NAR, the prevalence and characteristics of AR and NAR were very similar regardless of the definitions used, showing the robustness of our results. Considering asthma status, we observed that, even among NAR, participants with ever asthma reported more allergic triggers of rhinitis symptoms, compared to those with never asthma. It is possible that among those with ever asthma, some participants with AR were misclassified as NAR. Even if misclassifications exist, it could not explain by itself the contrasted results observed between the four groups.The present study did not distinguish local AR and mixed rhinitis from other forms of AR. We also acknowledge that the rhinitis definition based on symptoms did not distinguish rhinitis from chronic rhinosinusitis which share some symptoms including nasal congestion.

We defined ever-asthma based on a validated and standardized question used in ECRHS (16), and recently published in Constances.(19,20)

4.2. Interpretation of results

The prevalence of current rhinitis in our population was 40%. This result is difficult to compare with the literature as the definition of rhinitis varies greatly between studies and ranges from less than 10% to more than 50%.(1) According to the ARIA 2008 (1),

the prevalence of AR was estimated to be around 25% of the general European population, which is consistent with our findings. Three studies conducted in Belgium, Sweden and Italy found very similar prevalence of NAR, between 9.6% and 12.0% (21–23). Recently, a study in the Netherlands found a prevalence of NAR of 26% (7). The actual prevalences of rhinitis may be underestimated because most studies had only considered AR. Studies considering both AR and NAR are needed to obtain an overall prevalence of rhinitis and to confirm our results.

Most of the current knowledge about AR and NAR is derived from clinical knowledge. Few population-based studies have described the rhinitis characteristics. We confirmed the main differences observed in clinical practice (24): AR participants reported on average more allergic multimorbidities, an earlier age of onset, more allergic triggers than NAR participants.

We observed that the seasonal pattern of AR and NAR are different. Indeed, NAR showed a peak of declarations during the cold months in France and fewer declarations during the summer months. For AR there was a major peak during the spring season which is when the main pollens are released. It is interesting to note that there is also a second, smaller peak for AR in autumn, which corresponds to the season when ragweed pollens (notably *Ambrosia artemisiifolia*) are released in France. About half of AR participants reported anti-histamine treatments. The majority of NAR participants did not report anti-histamine or corticosteroid treatments, consistent with the lack of effective treatments for NAR.(25) The seasonality, triggers and treatments we observed for AR or NAR are consistent with the literature and clinical settings, suggesting that the questionnaire-based definition used is a good proxy to identify AR and NAR.

We observed that the age of AR onset was on average lower than that of NAR, even if it is often reported that AR starts in childhood whereas in our study the average age of AR onset was 24 years. We cannot exclude the possibility that a memory bias exists for age of onset, as some participants with childhood rhinitis may not remember it. Regarding the symptoms, we also found well-known differences: AR participants reported more sneezing, nasal itching and eye symptoms than NAR ones. Itching and eye symptoms are commonly described as rare in NAR.(24) In our study, over 30% of participants with NAR reported these symptoms. Similar results were found in many studies that have considered definitions of AR and NAR based on medical diagnosis or biological tests.(26,27) There are still many gaps in knowledge about NAR, but it is possible that some of its forms present symptoms usually considered as allergic. Another explanation could be that AR and NAR are not necessarily mutually exclusive, as up to 50% of rhinitis patients may have mixed rhinitis combining AR and NAR.(28)

There are few epidemiological studies in adults that estimate the proportion of persistent and severe rhinitis in general population, especially for NAR. In the present study, the prevalence of persistent rhinitis represents 31% of AR and 25% of NAR. Moderate-severe rhinitis was found in 40% for AR and 24% for NAR. These figures are lower than those found in clinical practice as most patients who consult a physician have severe rhinitis.(29) This shows that studies in the general population are needed to reflect the actual situation of rhinitis.

For the first time in adults from a population-based study, we described phenotypes of AR and NAR accounting for ever-asthma status. We observed contrasted characteristics across the groups. Our results showed that by comparison with AR participants without ever-asthma, those with ever-asthma reported (i) earlier onset of the disease, (ii) more frequent moderate-severe rhinitis, (iii) more conjunctivitis and eczema multimorbidities, (iv) a higher level of blood eosinophils and (v) more comedication. This latter finding suggests a more severe AR.(30) We validated these results by finding similar characteristics for all groups in the EGEA study. Moreover, allergen sensitization is available in EGEA and there was an increased number of sensitizations in AR with asthma.(10) It therefore appears that rhinitis alone and rhinitis and asthma represent two different diseases as found in real-life (31,32) and genetic studies, rhinitis alone being associated with Toll-like receptors and rhinitis and asthma multimorbidity with IL-5 (associated with eosinophilia) and IL-33.(33) However, biological pathways that are involved in rhinitis alone versus rhinitis with asthma are only partly understood, and further studies are needed to understand the underlying biological mechanisms involved in the aetiology of these phenotypes.

We further described the AR characteristics including ever-asthma and ever-conjunctivitis status. There was an extreme rhinitis phenotype in terms of rhinitis severity (symptoms and treatment) and eosinophil counts with the three multimorbidities associated. It is possible that the natural history of rhinitis alone or in multimorbidity differs. Based on our results, another potential explanation is that the intensity of allergic sensitization increases the risk of having more than one condition or conversely. It is of paramount importance that these newly described phenotypes can be observed in this large population-based study.

4.3. Implications of all the available evidence

The high rhinitis prevalence is an issue for health policy, especially as more than a third of the participants reported having symptoms that interfered with their daily activities or sleep in the past 12 months. In this context, it is important to study the risk factors that could explain the increase in the rhinitis prevalence. These factors are not all clearly identified at present, in particular environmental factors. Further studies on the rhinitis etiology are needed.

We showed that AR and NAR alone, or with asthma, or with asthma and conjunctivitis had different characteristics, and thus may have different etiologies. This raises the question of how best to manage rhinitis and its multimorbidities in terms of natural history, impact on ageing processes or management. Furthermore, studying the evolution of these rhinitis phenotypes over time is an essential research perspective, especially in adults for whom data are scarce. How does rhinitis evolve with advanced age? How does the rhinitis severity evolve over time? Does rhinitis lead to multimorbidities or vice versa? Do other morbidities appear over time? There is an unmet need to answer these questions.

4.4. Conclusion

In a large population-based cohort among adults we found a high prevalence of self-reported rhinitis, with, as expected but never shown before, a lower prevalence of moderate-severe rhinitis than in clinical practice. We showed that AR and NAR alone or with asthma or with asthma and conjunctivitis are different phenotypes. These results were replicated in the EGEA study. These rhinitis phenotypes will have major implications in terms of clinical practice.

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Tables

Table 1: Description of the participants according to their rhinitis status

	All (n=20772)	Never rhinitis (n=9674)	Non-current rhinitis (n=3029)	Current rhinitis (n=8069)	p value
Sex					<0.0001
Men	9297 (44.8%)	4358 (45.0%)	1459 (48.2%)	3480 (43.1%)	
Women	11475 (55.2%)	5316 (55.0%)	1570 (51.8%)	4589 (56.9%)	
Age, years					<.0001
<30	1057 (5.1%)	470 (4.9%)	123 (4.1%)	464 (5.8%)	
[30-45[	4924 (44.1%)	2181 (22.5%)	645 (21.3%)	2098 (26.0%)	
[45-60[	7648 (36.8%)	3659 (37.8%)	1184 (39.1%)	2805 (34.8%)	
≥60	7143 (34.4%)	3364 (34.8%)	1077 (35.6%)	2702 (33.5%)	
Tobacco status					0.063
Never-smoker	9164 (46.4%)	4353 (47.3%)	1323 (46.0%)	3488 (45.5%)	
Ex-smoker	7904 (40.0%)	3588 (39.0%)	1157 (40.2%)	3159 (41.2%)	
Current smoker	2675 (13.5%)	1259 (13.7%)	398 (13.8%)	1018 (13.3%)	
Educational level					<0.0001
Less than high school	1938 (9.4%)	927 (9.7%)	316 (10.6%)	695 (8.7%)	
High school	6755 (32.9%)	3321 (34.7%)	1036 (34.8%)	2398 (30.1%)	
University	11825 (57.6%)	5316 (55.6%)	1625 (54.6%)	4884 (61.2%)	
Body-mass index, kg/m^2					0.019
<18.5	460 (2.3%)	222 (2.3%)	66 (2.2%)	172 (2.2%)	
[18.5 - 25[	11510 (56.5%)	5327 (56.2%)	1610 (54.1%)	4573 (57.9%)	
[25 - 30[	6283 (30.9%)	2970 (31.3%)	966 (32.5%)	2347 (29.7%)	
≥ 30	2104 (10.3%)	968 (10.2%)	332 (11.2%)	804 (10.2%)	
Asthma					<0.0001
Never asthma	17793 (87.3%)	8948 (94.2%)	2485 (83.8%)	6360 (80.4%)	
Ever asthma	2579 (12.7%)	549 (5.8%)	481 (16.2%)	1549 (19.6%)	
Conjunctivitis					<0.0001
Never conjunctivitis	13354 (70.8%)	7582 (85.3%)	1803 (65.9%)	3969 (54.8%)	
Ever conjunctivitis	5509 (29.2%)	1308 (14.7%)	931 (34.1%)	3270 (45.2%)	
Eczema					<0.0001
Never eczema	13631 (71.9%)	7166 (79.4%)	1883 (68.7%)	4582 (63.7%)	
Ever eczema	5337 (28.1%)	1863 (20.6%)	858 (31.3%)	2616 (36.3%)	
Blood eosinophil count, cells/mm^3	185.5 (126.2)	172.0 (112.2)	189.7 (125.5)	199.8 (139.7)	<0.0001
Age of onset of rhinitis, year	26.3 (16.1)	NA	25.2 (15.1)	26.7 (16.5)	0.0002

Data are mean (SD) or n (%), NA: Not Applicable

Table 2: Characteristics of participants with current rhinitis, current Allergic Rhinitis (AR) or current Non-Allergic Rhinitis (NAR)

	All current rhinitis (n=8069)	AR (n=5806)	NAR (n=2263)	p value
Sex				0.072
Men	3480 (43.1%)	2468 (42.5%)	1012 (44.7%)	
Women	4589 (56.9%)	3338 (57.5%)	1251 (55.3%)	
Age, years	51.9 (12.9)	51.7 (12.8)	52.4 (13.3)	0.036
Tobacco status				0.0044
Never-smoker	3488 (45.5%)	2534 (46.0%)	954 (44.3%)	
Ex-smoker	3159 (41.2%)	2289 (41.5%)	870 (40.4%)	
Current smoker	1018 (13.3%)	688 (12.5%)	330 (15.3%)	
Educational level				0.77
Less than high school	695 (8.7%)	495 (8.6%)	200 (8.9%)	
High school	2398 (30.1%)	1717 (29.9%)	681 (30.4%)	
University	4884 (61.2%)	3528 (61.5%)	1356 (60.6%)	
Body-mass index, kg/m^2				0.34
<18.5	172 (2.2%)	124 (2.2%)	48 (2.2%)	
[18.5 – 25[	4573 (57.9%)	3264 (57.5%)	1309 (59.0%)	
[25 – 30[	2347 (29.7%)	1690 (29.8%)	657 (29.6%)	
≥ 30	804 (10.2%)	599 (10.6%)	205 (9.2%)	
Asthma				<0.0001
Never asthma	6360 (80.4%)	4304 (75.7%)	2056 (92.5%)	
Ever asthma	1549 (19.6%)	1383 (24.3%)	166 (7.5%)	
Conjunctivitis				<0.0001
Never conjunctivitis	3969 (54.8%)	2317 (44.7%)	1652 (80.4%)	
Ever conjunctivitis	3270 (45.2%)	2868 (55.3%)	402 (19.6%)	
Eczema				<0.0001
Never eczema	4582 (63.7%)	3021 (59.2%)	1561 (74.5%)	
Ever eczema	2616 (36.3%)	2081 (40.8%)	535 (25.5%)	
Blood eosinophil count, cells/mm^3	199.8 (139.7)	208.6 (146.4)	177.3 (117.9)	<0.0001
Age of onset of rhinitis, year	26.7 (16.5)	24.3 (15.3)	34.6 (17.5)	<0.0001
Reported triggers of rhinitis symptoms†				
Dust mites or house dust	2172 (26.9%)	1937 (33.4%)	235 (10.4%)	<0.0001
Animals	732 (9.1%)	677 (11.7%)	55 (2.4%)	<0.0001
Air pollution	1847 (22.9%)	1560 (26.9%)	287 (12.7%)	<0.0001
Change in weather	2278 (28.2%)	1677 (28.9%)	601 (26.6%)	0.037
Tobacco	452 (5.6%)	359 (6.2%)	93 (4.1%)	0.0003
Pollens	3266 (40.5%)	3035 (52.3%)	231 (10.2%)	<0.0001
Cold air	2050 (25.4%)	1423 (24.5%)	627 (27.7%)	0.0030
Other	1017 (12.6%)	735 (12.7%)	282 (12.5%)	0.81
Unknown	2673 (33.1%)	1573 (27.1%)	1100 (48.6%)	<0.0001
Reported symptoms†				
Rhinorrhoea	5266 (70.7%)	4051 (75.1%)	1215 (59.0%)	<0.0001
Nasal congestion/obstruction	5257 (72.4%)	4000 (76.3%)	1257 (62.1%)	<0.0001
Nasal itching	4212 (59.5%)	3445 (67.0%)	767 (39.7%)	<0.0001
Sneezing	5128 (69.4%)	4073 (75.9%)	1055 (52.2%)	<0.0001
Associated-eye symptoms	4391 (59.8%)	3693 (68.8%)	698 (35.3%)	<0.0001
Number of reported symptoms	3.2 (1.4)	3.6 (1.3)	2.3 (1.3)	<0.0001
Rhinitis severity				<0.0001
Mild	4253 (64.3%)	2862 (59.9%)	1391 (75.8%)	
Moderate/severe	2358 (35.7%)	1913 (40.1%)	445 (24.2%)	
Rhinitis duration				<0.0001
Intermittent	5422 (70.2%)	3798 (68.4%)	1624 (74.9%)	
Persistent	2302 (29.8%)	1758 (31.6%)	544 (25.1%)	

	All current rhinitis (n=8069)	AR (n=5806)	NAR (n=2263)	p value
Rhinitis treatment				<0.0001
Neither OAH nor INCS	3507 (45.1%)	1911 (34.1%)	1596 (73.5%)	
OAH only	1322 (17.0%)	1204 (21.5%)	118 (5.4%)	
INCS only	1025 (13.2%)	700 (12.5%)	325 (15.0%)	
OAH and INCS	1925 (24.7%)	1794 (32.0%)	131 (6.0%)	

Data are mean (SD) or n (%), †: several possible answers, OAH: Oral Antihistamines, INCS: Intranasal Corticosteroids

Table 3: Characteristics of participants with current Allergic Rhinitis (AR) or current Non-Allergic Rhinitis (NAR) including ever-asthma status

	AR			NAR		
	Never asthma (n=4304)	Ever-asthma (n=1383)	p value	Never asthma (n=2056)	Ever-asthma (n=166)	p value
Sex			0.090			0.25
Men	1851 (43.0%)	559 (40.4%)		925 (45.0%)	67 (40.4%)	
Women	2453 (57.0%)	824 (59.6%)		1131 (55.0%)	99 (59.6%)	
Age, years	52.5 (12.6)	48.9 (12.7)	<0.0001	52.7 (13.3)	48.6 (13.8)	0.0001
Tobacco status			0.65			0.18
Never-smoker	1883 (46.1%)	613 (46.4%)		879 (44.8%)	59 (37.8%)	
Ex-smoker	1702 (41.7%)	536 (40.6%)		786 (40.1%)	67 (42.9%)	
Current smoker	498 (12.2%)	172 (13.0%)		297 (15.1%)	30 (19.2%)	
Educational level			0.17			0.70
Less than high school	380 (8.9%)	104 (7.6%)		177 (8.7%)	17 (10.5%)	
High school	1285 (30.1%)	396 (28.9%)		619 (30.4%)	50 (30.9%)	
University	2604 (61.0%)	868 (63.5%)		1242 (60.9%)	95 (58.6%)	
Body-mass index, kg/m^2			0.13			0.0098
<18.5	95 (2.3%)	26 (1.9%)		42 (2.1%)	5 (3.1%)	
[18.5 - 25[	2446 (58.1%)	760 (56.0%)		1200 (59.6%)	83 (50.9%)	
[25 - 30[	1244 (29.6%)	407 (30.0%)		599 (29.7%)	49 (30.1%)	
≥ 30	423 (10.1%)	165 (12.2%)		174 (8.6%)	26 (16.0%)	
Conjunctivitis			<0.0001			0.19
Never conjunctivitis	1855 (48.6%)	418 (33.0%)		1511 (80.8%)	113 (76.4%)	
Ever conjunctivitis	1958 (51.4%)	848 (67.0%)		360 (19.2%)	35 (23.6%)	
Eczema			<0.0001			0.36
Never eczema	2329 (62.0%)	639 (51.3%)		1426 (74.8%)	110 (71.4%)	
Ever eczema	1426 (38.0%)	607 (48.7%)		481 (25.2%)	44 (28.6%)	
Blood eosinophil count, cells/mm^3	194.6 (133.7)	252.1 (175.1)	<0.0001	173.8 (114.1)	224.2 (150.9)	<0.0001
Age of onset of rhinitis, year	26.4 (15.4)	18.3 (13.4)	<0.0001	35.2 (17.6)	28.8 (16.2)	0.0004
Reported triggers of rhinitis symptoms†						
Dust mites or house dust	1167 (27.1%)	729 (52.7%)	<0.0001	194 (9.4%)	38 (22.9%)	<0.0001
Animals	338 (7.9%)	331 (23.9%)	<0.0001	39 (1.9%)	14 (8.4%)	<0.0001
Air pollution	1083 (25.2%)	443 (32.0%)	<0.0001	257 (12.5%)	27 (16.3%)	0.16
Change in weather	1189 (27.6%)	442 (32.0%)	0.0019	549 (26.7%)	46 (27.7%)	0.78
Tobacco	210 (4.9%)	142 (10.3%)	<0.0001	83 (4.0%)	9 (5.4%)	0.39
Pollens	2119 (49.2%)	861 (62.3%)	<0.0001	199 (9.7%)	26 (15.7%)	0.014
Cold air	1026 (23.8%)	359 (26.0%)	0.11	565 (27.5%)	48 (28.9%)	0.69
Other	534 (12.4%)	186 (13.4%)	0.31	254 (12.4%)	20 (12.0%)	0.91
Unknown	1301 (30.2%)	240 (17.4%)	<0.0001	1019 (49.6%)	63 (38.0%)	0.0040
Reported symptoms†						
Rhinorrhoea	2951 (74.1%)	1022 (78.3%)	0.0022	1096 (58.5%)	90 (62.1%)	0.39
Nasal congestion/obstruction	2861 (74.3%)	1056 (82.2%)	<0.0001	1131 (61.3%)	103 (70.5%)	0.027
Nasal itching	2456 (65.0%)	918 (72.7%)	<0.0001	683 (38.9%)	69 (49.3%)	0.015
Sneezing	2945 (74.4%)	1039 (79.6%)	0.0002	951 (51.8%)	80 (54.4%)	0.54
Associated-eye symptoms	2621 (66.1%)	990 (76.3%)	<0.0001	615 (34.1%)	71 (49.3%)	0.0002
Number of reported symptoms	3.4 (1.3)	3.8 (1.2)	<0.0001	2.3 (1.3)	2.7 (1.4)	0.0004
Rhinitis severity			<0.0001			0.0042
Mild	2198 (62.8%)	609 (51.5%)		1285 (76.6%)	83 (65.4%)	
Moderate/severe	1301 (37.2%)	574 (48.5%)		392 (23.4%)	44 (34.6%)	
Rhinitis duration			0.0025			0.74
Intermittent	2853 (69.5%)	870 (65.1%)		1481 (75.1%)	116 (73.9%)	
Persistent	1252 (30.5%)	467 (34.9%)		492 (24.9%)	41 (26.1%)	
Rhinitis treatment			<0.0001			<0.0001
Neither OAH nor INCS	1618 (39.0%)	259 (19.3%)		1475 (74.6%)	94 (60.3%)	
OAH only	869 (20.9%)	307 (22.8%)		102 (5.2%)	15 (9.6%)	
INCS only	552 (13.3%)	132 (9.8%)		293 (14.8%)	23 (14.7%)	
OAH and INCS	1113 (26.8%)	646 (48.1%)		106 (5.4%)	24 (15.4%)	

Data are mean (SD) or n (%), †: several possible answers, OAH: Oral Antihistamines, INCS: Intranasal Corticosteroids

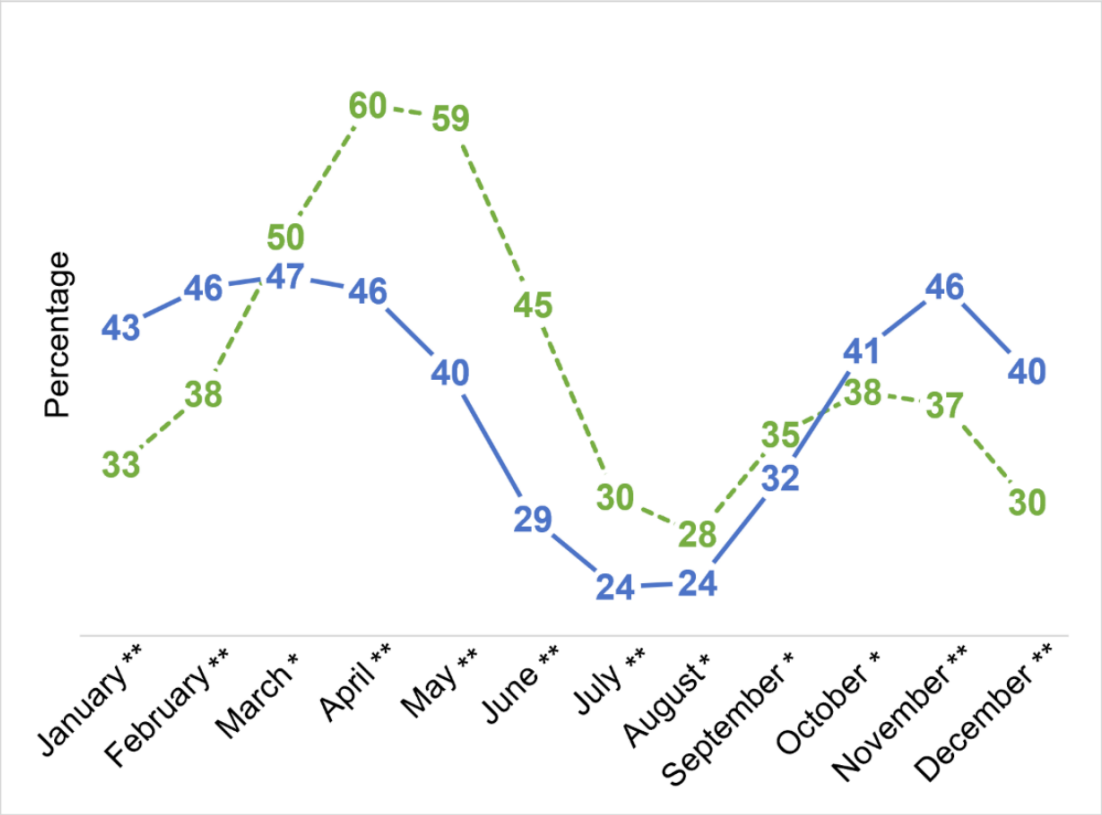
Table 4: Characteristics of participants with current Allergic Rhinitis (AR) including ever-asthma (A) and ever-conjunctivitis (C) status

	AR alone (n=1855)	AR + C (n=1958)	AR + A (n=418)	AR + C + A (n=848)	p value
Sex					<0.0001
Men	941 (50.7%)	671 (34.3%)	196 (46.9%)	308 (36.3%)	
Women	914 (49.3%)	1287 (65.7%)	222 (53.1%)	540 (63.7%)	
Age, years	51.9 (12.9)	51.6 (12.5)	48.7 (12.7)	48.1 (12.6)	<0.0001
Tobacco status					0.0030
Never-smoker	775 (43.9%)	920 (49.4%)	167 (42.0%)	397 (48.7%)	
Ex-smoker	756 (42.8%)	740 (39.7%)	169 (42.5%)	321 (39.4%)	
Current smoker	236 (13.4%)	202 (10.8%)	62 (15.6%)	97 (11.9%)	
Educational level					0.033
Less than high school	148 (8.0%)	154 (7.9%)	34 (8.2%)	54 (6.4%)	
High school	573 (31.1%)	519 (26.7%)	123 (29.8%)	229 (27.3%)	
University	1120 (60.8%)	1270 (65.4%)	256 (62.0%)	556 (66.3%)	
Body-mass index, kg/m^2					0.086
<18.5	32 (1.8%)	50 (2.6%)	6 (1.5%)	18 (2.2%)	
[18.5 – 25[	1041 (57.6%)	1151 (59.9%)	249 (60.6%)	455 (54.4%)	
[25 – 30[	548 (30.3%)	530 (27.6%)	109 (26.5%)	265 (31.7%)	
≥ 30	187 (10.3%)	189 (9.8%)	47 (11.4%)	98 (11.7%)	
Eczema					<0.0001
Never eczema	1398 (75.6%)	915 (52.6%)	301 (72.7%)	334 (43.2%)	
Ever eczema	450 (24.4%)	823 (47.4%)	113 (27.3%)	440 (56.8%)	
Blood eosinophil count, cells/mm^3	196.8 (134.0)	191.6 (134.2)	260.9 (183.3)	247.4 (169.1)	<0.0001
Age of onset of rhinitis, year	27.3 (15.7%)	24.7 (14.4%)	21.4 (14.6%)	16.4 (12.1%)	<0.0001
Reported triggers of rhinitis symptoms†					
Dust mites or house dust	441 (23.8%)	620 (31.7%)	210 (50.2%)	470 (55.4%)	<0.0001
Animals	118 (6.4%)	200 (10.2%)	91 (21.8%)	224 (26.4%)	<0.0001
Air pollution	412 (22.2%)	571 (29.2%)	114 (27.3%)	292 (34.4%)	<0.0001
Change in weather	474 (25.6%)	568 (29.0%)	135 (32.3%)	271 (32.0%)	0.0011
Tobacco	78 (4.2%)	107 (5.5%)	42 (10.0%)	88 (10.4%)	<0.0001
Pollens	789 (42.5%)	1149 (58.7%)	217 (51.9%)	591 (69.7%)	<0.0001
Cold air	445 (24.0%)	459 (23.4%)	111 (26.6%)	220 (25.9%)	0.35
Other	225 (12.1%)	247 (12.6%)	49 (11.7%)	126 (14.9%)	0.22
Unknown	617 (33.3%)	492 (25.1%)	87 (20.8%)	114 (13.4%)	<0.0001
Reported symptoms†					
Rhinorrhoea	1230 (70.3%)	1394 (76.5%)	291 (74.2%)	651 (80.0%)	<0.0001
Nasal congestion/obstruction	1198 (71.0%)	1364 (76.9%)	308 (79.8%)	656 (82.1%)	<0.0001
Nasal itching	982 (58.7%)	1235 (71.0%)	251 (65.2%)	614 (77.2%)	<0.0001
Sneezing	1231 (71.1%)	1395 (77.0%)	297 (74.6%)	669 (82.2%)	<0.0001
Associated-eye symptoms	912 (53.1%)	1488 (80.3%)	245 (62.0%)	689 (84.7%)	<0.0001
Number of reported symptoms	3.2 (1.3)	3.7 (1.2)	3.5 (1.3)	4.0 (1.1)	<0.0001
Rhinitis severity					<0.0001
Mild	1047 (66.1%)	947 (58.8%)	196 (54.4%)	377 (50.1%)	
Moderate/severe	537 (33.9%)	664 (41.2%)	164 (45.6%)	375 (49.9%)	
Rhinitis duration					0.0016
Intermittent	1268 (70.9%)	1275 (68.4%)	284 (70.1%)	521 (63.4%)	
Persistent	520 (29.1%)	590 (31.6%)	121 (29.9%)	301 (36.6%)	
Rhinitis treatment					<0.0001
Neither OAH nor INCS	819 (45.5%)	603 (31.9%)	114 (28.2%)	120 (14.5%)	
OAH only	329 (18.3%)	472 (24.9%)	91 (22.5%)	207 (25.0%)	
INCS only	272 (15.1%)	200 (10.6%)	44 (10.9%)	60 (7.2%)	
OAH and INCS	380 (21.1%)	617 (32.6%)	155 (38.4%)	442 (53.3%)	

Data are mean (SD) or n (%), †: several possible answers, OAH: Oral Antihistamines, INCS: Intranasal Corticosteroids

Figures

Figure 1: Percentage of participants with AR or NAR reporting symptoms by months
- - -: Current Allergic Rhinitis
—: Current Non-Allergic Rhinitis
* p-value <0.05, ** p-value <0.0001



5.B – Supplementary material

Supplement on the method - CONSTANCES

Assets

Constances is a "general purpose" population-based epidemiological cohort. It is a nationally representative sample of 220,000 adults aged between 18 and 69 years at inclusion.

Due to its population size, the quality and diversity of data, and its monitoring methods, Constances is a unique epidemiological research tool. Constances, is a research platform broadly accessible to the scientific community that can be compared to the largest international cohorts.

Constances is also a public health tool, designed to support the public health objectives of the French National Health Insurance Fund for Employees (CNAMTS) and of the national government, owing to the collection of highly diverse data from multiple sources on a representative sample.

Constances is an epidemiological surveillance tool, implemented through a partnership with the French institute for public health surveillance. Its data covers multiple domains, such as the epidemiological surveillance of occupational hazards.

The Constances project, managed through the participation of French local health insurance funds and health clinics, is a partnership between INSERM, Versailles Saint Quentin University (UVSQ), the French national health insurance fund (CNAMTS), the French national retirement pension fund (Cnav) and the support of the French Ministry of health (Directorate general for health). Constances has received French government funding for an 8-year period (Investment for the Future Program).

Protocol

The goal of the Constances project is to implement a large epidemiological cohort aimed at contributing to the development of epidemiological research and to provide public health information. The purpose of this cohort, created in the context of a partnership between the French national health insurance fund (CNAM) and the French national Old-Age insurance fund (Cnav), is to constitute an infrastructure open to the research community. Constances is labelled National Biology and Health Research Infrastructure by the French government's Commissariat-General for Investment.

Constances is a "general purpose" research infrastructure designed to help analysing a broad range of scientific problems. Constances was also designed as a public health and surveillance tool, thanks to the particularly exhaustive nature of the system for collecting and monitoring a great variety of data from a large representative sample of the adult population covered by the General Social Security scheme.

Random sampling: subjects considered as eligible due to their age and place of residence are drawn randomly by stratified sampling with unequal probabilities, over-representing individuals with a higher probability of non-volunteering according to age, gender and SES. Random sampling is performed by the Cnav from the French national

inter-scheme registry of health insurance beneficiaries (RNIAM), linked to the National careers management system (SNGC).
Data flow: the Constances cohort constitutes a complex database with characteristics rendering it highly sensitive under the terms of the French data protection act, in particular due to the collection of personal data. Moreover, some data collected at the individual level come from linkage to national databases: National inter-scheme health insurance information system (SNIIRAM), causes of death information system (CépiDc-INSERM) and the Cnav (Annual Social Security declarations, Named quarterly data, absenteeism due to illness, Active solidarity income, maternity). Very strict data collection, organisation, and management constraints are required. The procedures in place conform to legislative and regulatory texts intended to preserve high-level personal data confidentiality and security.

Confidentiality, safety and security approvals
All confidentiality, safety and security procedures were approved by the French legal authorities (online supplement 1). Approvals were obtained from the National Data Protection Authority on March 3, 2011 (Commission Nationale de l'Informatique et des Libertés—CNIL, French National Data Protection Authority (authorisation no. 910486)), the National Council for Statistical Information (Conseil National de l'Information Statistique—CNIS), the National Medical Council (Conseil National de l'Ordre des Médecins—CNOM), and the Institutional Review Board of the National Institute for Medical Research-INSERM (authorisation no. 01-011). All participants signed a written informed consent.

Health check and questionnaires
The invitation to participate to Constances implies to undergo a health examination in a health clinic. The randomly drawn individuals first receive at home an invitation letter presenting the project, along with a mail-back coupon enabling them to give their consent.
The persons having consented to participate in Constances are invited by letter to come to a health screening center (HSC), specifying the date and location of the examination. They also receive two self-questionnaires to be filled in at home: a health and lifestyle questionnaire, and a professional calendar tracing their full job history.
In addition to the self-questionnaire completed at home, subjects undergo a health examination used to collect health-related data: clinical examination, blood analysis, blood pressure, weight, height and waist-to-hip ratio, electrocardiogram and spirometry, sight and hearing examination. This examination is standardised by means of Standard Operating Procedures (SOPs) and permanent quality control is ensured in collaboration with the ClinSearch company and the Asqualab and Eurocell associations. Additional questionnaires, to be completed on-site (whole-life occupational exposures, women's health), are collected at the health clinic. The informed consent signature validates the collection of these data and authorises their use for research purposes.
Participants aged 45 years and over are invited to undergo a cognitive and functional check-up. This examination is performed by a neuropsychologist and includes a series

of tests. The documents pertaining to this check-up (protocol, data collection form), along with related videos, are available on request.
A yearly postal or Web-based self-questionnaire is used for active follow-up at the subjects' homes, and an invitation to come to an HSC once every 4 years is scheduled for all cohort participants.
Moreover, health and socio-professional data, along with causes of death, are regularly retrieved from the national health insurance, retirement pension fund and mortality databases.

More information on the full Constances' protocol is available here:
https://www.constances.fr/_assets/_pdf/Scientific-protocol-01-2015.pdf

For further information see the Constances website: https://www.constances.fr/index_EN.php

Definitions of nasal allergies, rhinitis duration, rhinitis severity and reported symptoms

Nasal allergies: based on the answer to the Q.22 "*During your lifetime, have you ever had any nasal allergies including hay fever?*".

Rhinitis duration and severity were defined according to the Allergic Rhinitis and its Impact on Asthma (ARIA) recommendations.(1) Rhinitis was considered to be persistent if symptoms occur more than four days per week and more than four consecutive weeks (Q.26). Otherwise, the symptoms were considered intermittent. Rhinitis was considered to be moderate/severe if at least one of the symptoms of rhinitis (rhinorrhea, nasal congestion, nasal pruritus, sneezing) has been reported as a disturbing problem affecting daily activities and sleep (Q.27). Otherwise, rhinitis was considered to be mild if none of the symptoms have been reported as a disturbing problem affecting daily activities and sleep.

Reported symptoms (rhinorrhea, nasal congestion, nasal pruritus, sneezing, associated-eye symptoms): if in Q.27 participants reported having this problem.

Alternate definitions of rhinitis

Alternate definition of ever-rhinitis: yes to: "*During your lifetime, 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?*" or yes to: "*During your lifetime, have you ever had any nasal allergies including hay fever?*".

Alternate definition of ever AR = definition based on adaptation of the ECRHS question on nasal allergies (2): yes to: "*During your lifetime, have you ever had any nasal allergies including hay fever?*".

Alternate definition 1 of current AR and NAR = Triggers-based:

- Current AR: Yes to: "*Have you had these nose problems in the last 12 months?*" and answer *pollens* or *dust mites or house dust*, or *animal* to: "*what factor triggered or increased these nose problems? (several answers possible)*".
- Current NAR: Yes to: "*Have you had these nose problems in the last 12 months?*" and no answer *pollens* or *dust mites or house dust*, or *animal* to: "*What factor triggered or increased these nose problems? (several answers possible)*".

Alternate definition 2 of current AR = Classification tree-based: this definition was adapted from the classification tree obtained by Burte *et al.* with an unsupervised approach to identify rhinitis.(3)

- Current AR: Yes to: "*Have you had these nose problems in the last 12 months?*" and yes to: "*During your lifetime, have you ever had any nasal allergies including hay fever?*" or answer *pollens* to: "*What factor triggered or increased these nose problems? (several answers possible)*" and Yes to: "*Did your eyes itch or cry when you had these nose problems?*".
- Current NAR: Yes to: "*Have you had these nose problems in the last 12 months?*" and no to: "*During your lifetime, have you ever had any nasal allergies including hay fever?*" and no answer *pollens* to: "*What factor triggered or increased these nose problems? (several answers possible)*" or no to: "*During your lifetime, have you ever had any nasal allergies including*

hay fever?" and answer pollens to: "*What factor triggered or increased these nose problems? (several answers possible)"* and no to: "*Did your eyes itch or cry when you had these nose problems?*".

References:

1. Bousquet J, Khaltaev N, Cruz AA, *et al.* Allergic Rhinitis and its Impact on Asthma (ARIA) 2008*. *Allergy* 2008; 63: 8–160.

2. ECRHS. Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey (ECRHS). *European Respiratory Journal* 1996; 9: 687–95.

3. Burte E, Bousquet J, Varraso R, *et al.* Characterization of Rhinitis According to the Asthma Status in Adults Using an Unsupervised Approach in the EGEA Study. *PLoS ONE* 2015; 10: e0136191.

Supplement on the method – EGEA

EGEA is a cohort study based on an initial group of asthma cases recruited in chest clinics from five French cities (1991-1995) along with their first-degree relatives, and a group of controls. Briefly, 2047 children (<16 years) and adult participants were enrolled at baseline, including 348 participants with current asthma from chest clinics, their 1244 first-degree relatives, and 415 population-based controls. The protocol and descriptive characteristics of the EGEA study have been previously published.(1,2)

A 12-year follow-up of the initial cohort was conducted between 2003 and 2007 (EGEA2). Among the alive cohort (n=2002), 92% (n=1845) completed a short self-administered questionnaire, and among them 1602 (n=1571 adults aged ≥16 years) had a complete examination. As a follow-up study of EGEA2, the third survey (EGEA3, 2011-2013, n=1558) was conducted using self-completed questionnaire only.

The EGEA collection was certified ISO 9001 from 2006 to 2018.(3) Ethical approval was obtained from the relevant institutional review board committees (Cochin Port-Royal Hospital and Necker-Enfants Malades Hospital, Paris). All participants signed a written informed consent.

Analysis population of the present paper

The analyses of the present paper were performed at EGEA2. Among the 1571 adults, those with missing data regarding the definitions of rhinitis (n=13), or the presence of nasal allergies (n=29) were excluded from the analyses.

A total of 842 participants reported current rhinitis and were included in the analyses.

Variables of interest

Current rhinitis was defined by a positive response to: "*Have you had problems with sneezing, runny nose or stuffy nose when you didn't have a cold or flu in the last 12 months?*". Among the participants with current rhinitis, participants who responded positively to "*Have you ever had allergic rhinitis?*" or "*Have you ever had hay fever?*" were classified as AR otherwise as NAR.

Participants with ever-asthma were defined by a positive answer to: *"Have you ever had attacks of breathlessness at rest with wheezing?"* or *"Have you ever had asthma attacks?"* or if they were recruited as asthmatic cases at the first survey.[2]

Ever-conjunctivitis: positive answer to "*Have you ever had allergic conjunctivitis?"*. Age of onset: answer to "*At what age did you first experience these nose problems?"*.

Reported triggers of the symptoms of rhinitis: answer to "*In the last 12 months, what factors have triggered or increased these nose problems? a. dust mites or house dust b. pollens c. animals d. other*". Several responses were possible, participants who did not provide any of the possible answers were categorized as "no trigger reported".

SPTs to 12 aeroallergens ((indoor: cat, *Dermatophagoides pteronyssinus*, *Blattela germanica*; outdoor: olive, birch, *Parieteria judaica*, timothy grass, ragweed pollen and *Cupressus*; moulds: *Aspergillus*, *Cladosporium herbarum*, *Alternaria tenuis*) were performed.

Alternate definition of AR and NAR

We performed the description of allergic and non-allergic rhinitis defined by SPT in EGEA2. Current rhinitis was defined by a positive response to: "*Have you had problems with sneezing, runny nose or stuffy nose when you didn't have a cold or flu in the last 12 months?*". Among the participants with current rhinitis, those who had at least one positive SPT were classified as SPT-based AR (AR-SPT), otherwise as SPT-based NAR (NAR-SPT).

EGEA cooperative group:

Coordination: V Siroux (epidemiology, PI since 2013); F Demenais (genetics); I Pin (clinical aspects); R Nadif (biology); F Kauffmann (PI 1992-2012). Respiratory epidemiology: *Inserm ex-U 700, Paris:* M Korobaeff (Egea1), F Neukirch (Egea1); *Inserm ex-U 707, Paris:* I Annesi-Maesano (Egea1-2); *Inserm U 1018, Villejuif:* O Dumas, F Kauffmann, N Le Moual, R Nadif, MP Oryszczyn (Egea1-2), R Varraso; *Inserm U 1209 Grenoble:* J Lepeule, V Siroux. Genetics: *Inserm ex-U 393, Paris*: J Feingold; *Inserm UMR 1124, Paris:* E Bouzigon, MH Dizier, F Demenais; *CNG, Evry:* I Gut (now CNAG, Barcelona, Spain), M Lathrop (now Univ McGill, Montreal, Canada). Clinical centres: *Grenoble:* I Pin, C Pison; *Lyon:* D Ecochard (Egea1), F Gormand, Y Pacheco;*Marseille:* D Charpin (Egea1), D Vervloet (Egea1-2); *Montpellier:* J Bousquet; *Paris Cochin:* A Lockhart (Egea1), R Matran (now in Lille); *Paris Necker:* E Paty (Egea1-2), P Scheinmann (Egea1-2); *Paris-Trousseau:* A Grimfeld (Egea1-2), J Just. Data management and quality: *Inserm ex-U155, Paris:* J Hochez (Egea1); *Inserm U 1018, Villejuif:* N Le Moual, L Orsi; *Inserm ex-U780, Villejuif:* C Ravault (Egea1-2); *Inserm ex-U794, Evry:* N Chateigner (Egea1-2); *Inserm UMR 1124, Paris:* H Mohamdi; *Inserm U1209, Grenoble:* A Boudier, J Quentin (Egea1-2).

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Table S1: Comparison between participants included and non-included in the analysis

	Non-included (n=5965)	Included (n=20772)	p value
Sex			0.0001
Men	2836 (47.5%)	9297 (44.8%)	
Women	3129 (52.5%)	11475 (55.2%)	
Age at inclusion, years	48.4 (13.6)	51.0 (12.6)	<0.0001
Tobacco status at inclusion			<0.0001
Never-smoker	2326 (41.7%)	9395 (47.2%)	
Ex-smoker	1736 (31.1%)	7366 (37.0%)	
Current smoker	1521 (27.2%)	3126 (15.7%)	
Educational level at inclusion			<0.0001
Less than high school	974 (16.7%)	1938 (9.4%)	
High school	2283 (39.2%)	6755 (32.9%)	
University	2566 (44.1%)	11825 (57.6%)	
Body-mass index at inclusion, kg/m^2			<0.0001
<18.5	162 (2.8%)	449 (2.2%)	
[18.5 - 25[	2879 (49.5%)	11164 (54.7%)	
[25 - 30[	1855 (31.9%)	6492 (31.8%)	
≥ 30	918 (15.8%)	2308 (11.3%)	
Asthma at inclusion			<0.0001
Never asthma	4955 (86.0%)	17911 (88.0%)	
Ever asthma	805 (14.0%)	2440 (12.0%)	
Ever rhinitis at inclusion			<0.0001
Never rhinitis	2982 (52.0%)	11202 (55.1%)	
Ever rhinitis	2748 (48.0%)	9130 (44.9%)	

Data are mean (SD) or n (%)

Table S2: Prevalence of rhinitis according to different definitions

	Definition	n/N	Crude Prevalence [CI 95%]
Ever-rhinitis			
Main definition	Yes to: "*During your lifetime, 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?*"	11098/20772	53.4% [52.8% – 54.1%]
Alternate definition	- Yes to: "*During your lifetime, 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?*" or - Yes to: "*During your lifetime, have you ever had any nasal allergies including hay fever?*"	12207/20772	58.8% [58.1% – 59.4%]
Ever AR			
Main definition	- Yes to: "*During your lifetime, 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?*" and - Yes to: "*During your lifetime, have you ever had any nasal allergies including hay fever?*"	7589/20772	36.5% [35.9% – 37.2%]
Alternate definition	Yes to: "*During your lifetime, have you ever had any nasal allergies including hay fever?*"	8698/20772	41.9% [41.2% - 42.5%]
Ever NAR			
Main definition	- Yes to: "*During your lifetime, 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?*" and - No to: "*During your lifetime, have you ever had any nasal allergies including hay fever?*"	3509/20772	16.9% [16.4% – 17.4%]
Current rhinitis			
Main definition	Yes to: "*Have you had these nose problems in the last 12 months?*"	8069/20772	38.9% [38.2% – 39.5%]
Current AR			
Main definition	- Yes to: "*Have you had these nose problems in the last 12 months?*" and - Yes to: "*During your lifetime, have you ever had any nasal allergies including hay fever?*"	5806/20772	28.0% [27.3% – 28.6%]
Alternate definition 1	- Yes to: "*Have you had these nose problems in the last 12 months?*" and - Answer pollens or dust mites or house dust or animal to: "*What factor triggered or increased these nose problems? (several answers possible)*"	4208/20772	20.3% [19.7% – 20.8%]
Alternate definition 2	- Yes to: "*Have you had these nose problems in the last 12 months?*" and - Yes to: "*During your lifetime, have you ever had any nasal allergies including hay fever?*" or - Answer pollens to: "*What factor triggered or increased these nose problems? (several answers possible)*" and Yes to: "*Did your eyes itch or cry when you had these nose problems?*"	5858/20627	28.4% [27.8% – 29.0%]
Current NAR			
Main definition	- Yes to: "*Have you had these nose problems in the last 12 months?*" and - No to: "*During your lifetime, have you ever had any nasal allergies including hay fever?*"	2263/20772	10.9% [10.5% – 11.3%]
Alternate definition 1 = Triggers-based	- Yes to: "*Have you had these nose problems in the last 12 months?*" and - No answer pollens or dust mites or house dust or animal to: "*What factor triggered or increased these nose problems? (several answers possible)*"	3861/20772	18.6% [18.1% - 19.1%]
Alternate definition 2 = Classification tree-based	- Yes to: "*Have you had these nose problems in the last 12 months?*" and - No to: "*During your lifetime, have you ever had any nasal allergies including hay fever?*" and no answer pollens to: "*What factor triggered or increased these nose problems? (several answers possible)*" or - No to: "*During your lifetime, have you ever had any nasal allergies including hay fever?*" and answer pollens to: "*What factor triggered or increased these nose problems? (several answers possible)*" and no to: "*Did your eyes itch or cry when you had these nose problems?*"	2066/20627	10.0% [9.6% - 10.4%]

n/N: number of cases/Total number of participants, CI 95%: Confidence Interval 95%

Table S3: Comparison of participants with current Allergic Rhinitis (AR) and current Non-Allergic Rhinitis (NAR) according to alternate definitions

	Main definition			Alternate definition 1: Triggers-based			Alternate definition 2: Classification tree-based		
	AR (n=5806)	NAR (n=2263)	p value	AR (n=4208)	NAR (n=3861)	p value	AR (n=5858)	NAR (n=2066)	p value
Sex			0.072			0.14			0.0056
Men	2468 (42.5%)	1012 (44.7%)		1782 (42.3%)	1698 (44.0%)		2471 (42.2%)	944 (45.7%)	
Women	3338 (57.5%)	1251 (55.3%)		2426 (57.7%)	2163 (56.0%)		3387 (57.8%)	1122 (54.3%)	
Age, years	51.7 (12.8)	52.4 (13.3)	0.032	49.5 (12.9)	54.5 (12.5)	<0.0001	51.5 (12.8)	52.5 (13.3)	0.0029
Tobacco status			0.0044			<0.0001			0.0059
Never-smoker	2534 (46.0%)	954 (44.3%)		1942 (48.5%)	1546 (42.2%)		2568 (46.2%)	870 (44.3%)	
Ex-smoker	2289 (41.5%)	870 (40.4%)		1580 (39.5%)	1579 (43.1%)		2299 (41.3%)	794 (40.4%)	
Current smoker	688 (12.5%)	330 (15.3%)		483 (12.1%)	535 (14.6%)		697 (12.5%)	302 (15.4%)	
Educational level			0.77			<0.0001			0.53
Less than high school	495 (8.6%)	200 (8.9%)		321 (7.7%)	374 (9.8%)		502 (8.7%)	183 (9.0%)	
High school	1717 (29.9%)	681 (30.4%)		1164 (28.0%)	1234 (32.3%)		1721 (29.7%)	630 (30.8%)	
University	3528 (61.5%)	1356 (60.6%)		2675 (64.3%)	2209 (57.9%)		3570 (61.6%)	1231 (60.2%)	
Body-mass index, kg/m^2			0.34			0.094			0.089
<18.5	124 (2.2%)	48 (2.2%)		99 (2.4%)	73 (1.9%)		122 (2.1%)	43 (2.1%)	
[18.5 - 25[	3264 (57.5%)	1309 (59.0%)		2429 (58.9%)	2144 (56.9%)		3284 (57.3%)	1214 (60.0%)	
[25 - 30[	1690 (29.8%)	657 (29.6%)		1194 (28.9%)	1153 (30.6%)		1713 (29.9%)	585 (28.9%)	
≥ 30	599 (10.6%)	205 (9.2%)		404 (9.8%)	400 (10.6%)		612 (10.7%)	182 (9.0%)	
Asthma			<0.0001			<0.0001			<0.0001
Never asthma	4304 (75.7%)	2056 (92.5%)		2959 (71.8%)	3401 (89.9%)		4347 (75.8%)	1889 (93.1%)	
Ever asthma	1383 (24.3%)	166 (7.5%)		1165 (28.2%)	384 (10.1%)		1388 (24.2%)	141 (6.9%)	
Conjunctivitis			<0.0001			<0.0001			<0.0001
Never conjunctivitis	2317 (44.7%)	1652 (80.4%)		1628 (42.1%)	2341 (69.4%)		2369 (45.1%)	1532 (81.8%)	
Ever conjunctivitis	2868 (55.3%)	402 (19.6%)		2236 (57.9%)	1034 (30.6%)		2885 (54.9%)	342 (18.2%)	
Eczema			<0.0001			<0.0001			<0.0001
Never eczema	3021 (59.2%)	1561 (74.5%)		2202 (58.4%)	2380 (69.5%)		3078 (59.6%)	1436 (74.9%)	
Ever eczema	2081 (40.8%)	535 (25.5%)		1571 (41.6%)	1045 (30.5%)		2088 (40.4%)	481 (25.1%)	
Nasal allergies			<0.0001			<0.0001			<0.0001
Never nasal allergies	0 (0.0%)	2263 (100.0%)		439 (10.4%)	1824 (47.2%)		139 (2.4%)	2066 (100.0%)	
Ever nasal allergies	5806 (100.0%)	0 (0.0%)		3769 (89.6%)	2037 (52.8%)		5719 (97.6%)	0 (0.0%)	
Eosinophils count, cells/mm^3	208.6 (146.4)	177.3 (117.9)	<0.0001	212.1 (147.6)	186.3 (129.0)	<0.0001	207.9 (146.1)	176.2 (116.4)	<0.0001
Age of onset of rhinitis, year	24.3 (15.3)	34.6 (17.5)	<0.0001	23.1 (14.7)	31.9 (17.5)	<0.0001	24.5 (15.4)	34.5 (17.7)	<0.0001
Reported triggers of rhinitis symptoms[†]									
Dust mites or house dust	1937 (33.4%)	235 (10.4%)	<0.0001	2172 (51.6%)	0 (0.0%)	<0.0001	1946 (33.2%)	198 (9.6%)	<0.0001
Animals	677 (11.7%)	55 (2.4%)	<0.0001	732 (17.4%)	0 (0.0%)	<0.0001	675 (11.5%)	48 (2.3%)	<0.0001
Air pollution	1560 (26.9%)	287 (12.7%)	<0.0001	1361 (32.3%)	486 (12.6%)	<0.0001	1590 (27.1%)	235 (11.4%)	<0.0001

	Main definition			Alternate definition 1: Triggers-based			Alternate definition 2: Classification tree-based		
	AR (n=5806)	NAR (n=2263)	p value	AR (n=4208)	NAR (n=3861)	p value	AR (n=5858)	NAR (n=2066)	p value
Change in weather	1677 (28.9%)	601 (26.6%)	0.037	1240 (29.5%)	1038 (26.9%)	0.010	1689 (28.8%)	546 (26.4%)	0.037
Tobacco	359 (6.2%)	93 (4.1%)	0.0003	315 (7.5%)	137 (3.5%)	<0.0001	356 (6.1%)	86 (4.2%)	0.0011
Pollens	3035 (52.3%)	231 (10.2%)	<0.0001	3266 (77.6%)	0 (0.0%)	<0.0001	3144 (53.7%)	88 (4.3%)	<0.0001
Cold air	1423 (24.5%)	627 (27.7%)	0.0030	1055 (25.1%)	995 (25.8%)	0.47	1433 (24.5%)	585 (28.3%)	0.0005
Other	735 (12.7%)	282 (12.5%)	0.81	478 (11.4%)	539 (14.0%)	0.0004	733 (12.5%)	267 (12.9%)	0.63
Unknown	1573 (27.1%)	1100 (48.6%)	<0.0001	410 (9.7%)	2263 (58.6%)	<0.0001	1562 (26.7%)	1051 (50.9%)	<0.0001
Reported symptoms†									
Rhinorrhoea	4051 (75.1%)	1215 (59.0%)	<0.0001	2969 (74.9%)	2297 (65.9%)	<0.0001	4084 (74.9%)	1111 (59.0%)	<0.0001
Nasal congestion/obstruction	4000 (76.3%)	1257 (62.1%)	<0.0001	2886 (75.0%)	2371 (69.3%)	<0.0001	4019 (75.9%)	1148 (61.9%)	<0.0001
Nasal itching	3445 (67.0%)	767 (39.7%)	<0.0001	2696 (70.4%)	1516 (46.7%)	<0.0001	3476 (66.9%)	670 (37.9%)	<0.0001
Sneezing	4073 (75.9%)	1055 (52.2%)	<0.0001	3098 (78.1%)	2030 (59.3%)	<0.0001	4104 (75.6%)	958 (51.7%)	<0.0001
Associated-eye symptoms	3693 (68.8%)	698 (35.3%)	<0.0001	2943 (73.9%)	1448 (43.0%)	<0.0001	3768 (69.4%)	574 (31.7%)	<0.0001
Number of reported symptoms	3.6 (1.3)	2.3 (1.3)	<0.0001	3.7 (1.2)	2.7 (1.4)	<0.0001	3.5 (1.3)	2.3 (1.3)	<0.0001
Rhinitis severity			<0.0001			<0.0001			<0.0001
Mild	2862 (59.9%)	1391 (75.8%)		2132 (59.7%)	2121 (69.8%)		2902 (60.0%)	1286 (76.3%)	
Moderate/severe	1913 (40.1%)	445 (24.2%)		1441 (40.3%)	917 (30.2%)		1938 (40.0%)	399 (23.7%)	
Rhinitis duration			<0.0001			0.11			<0.0001
Intermittent	3798 (68.4%)	1624 (74.9%)		2884 (71.0%)	2538 (69.3%)		3863 (68.8%)	1465 (73.9%)	
Persistent	1758 (31.6%)	544 (25.1%)		1179 (29.0%)	1123 (30.7%)		1750 (31.2%)	518 (26.1%)	
Rhinitis treatment			<0.0001			<0.0001			<0.0001
Neither oral antihistamines nor intranasal corticoids	1911 (34.1%)	1596 (73.5%)		1255 (30.7%)	2252 (61.1%)		1954 (34.5%)	1484 (74.7%)	
Oral antihistamines only	1204 (21.5%)	118 (5.4%)		1022 (25.0%)	300 (8.1%)		1204 (21.3%)	95 (4.8%)	
Intranasal corticoids only	700 (12.5%)	325 (15.0%)		376 (9.2%)	649 (17.6%)		705 (12.4%)	304 (15.3%)	
Oral antihistamines and intranasal corticoids	1794 (32.0%)	131 (6.0%)		1439 (35.2%)	486 (13.2%)		1802 (31.8%)	104 (5.2%)	

Data are mean (SD) or n (%), †: several possible answers

Current rhinitis: Yes to Q.23 "During your lifetime, 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?"

AR Main definition: current rhinitis and Yes to Q.22: "During your lifetime, have you ever had any nasal allergies including hay fever?"

NAR Main definition: current rhinitis and No to Q.22: "During your lifetime, have you ever had any nasal allergies including hay fever?"

AR Alternate Definition 1: current rhinitis and answer pollens or dust mites or house dust or animal to Q.25: "What factor triggered or increased these nose problems? (several answers possible)"

NAR Alternate Definition 1: current rhinitis and no answer pollens and dust mites and house dust and animal to Q.25: "What factor triggered or increased these nose problems? (several answers possible)"

AR Alternate Definition 2: current rhinitis and Yes to Q.22: "During your lifetime, have you ever had any nasal allergies including hay fever?" or Answer pollens to Q.25: "What factor triggered or increased these nose problems? (several answers possible)" and Yes to Q.23.A "Did your eyes itch or cry when you had these nose problems?"

NAR Alternate Definition 2: current rhinitis and No to Q.22: "During your lifetime, have you ever had any nasal allergies including hay fever?" and no answer pollens to Q.25: "What factor triggered or increased these nose problems? (several answers possible)" or no to Q.23.A "Did your eyes itch or cry when you had these nose problems?"

Kappa concordance coefficient between the main definition and the alternate definition 1 = 0.37

Kappa concordance coefficient between the main definition and the alternate definition 2 = 0.96

Table S4: Characteristics of participants with current Allergic Rhinitis (AR) or current Non-Allergic Rhinitis (NAR) including ever-asthma status in EGEA

	AR			NAR		
	Never asthma (n=174)	Ever asthma (n=380)	p-value	Never asthma (n=176)	Ever asthma (n=83)	p-value
Sex			0.49			0.01
Men	81 (46.6%)	189 (49.7%)		68 (38.6%)	46 (55.4%)	
Women	93 (53.5%)	191 (50.3%)		108 (61.4%)	37 (44.6%)	
Age, years	44.7 (15.4)	38.4 (15.8)	<0.0001	48.3 (15.2)	37.2 (17.3)	<0.0001
Tobacco status			0.23			0.01
Never-smoker	85 (48.9%)	189 (49.9%)		90 (51.1%)	51 (61.5%)	
Ex-smoker	50 (28.7%)	86 (22.7%)		51 (29.0%)	10 (12.1%)	
Current smoker	39 (22.4%)	104 (27.4%)		35 (19.9%)	22 (26.5%)	
Educational level			0.12			0.25
Less than high school	35 (21.0%)	62 (17.3%)		51 (30.2%)	19 (23.2%)	
High school	43 (25.8%)	124 (34.5%)		44 (26.0%)	18 (22.0%)	
University	89 (53.3%)	173 (48.2%)		74 (43.8%)	45 (54.9%)	
Conjunctivitis			0.04			0.80
Never conjunctivitis	92 (53.8%)	166 (44.2%)		134 (77.0%)	62 (78.5%)	
Ever conjunctivitis	79 (46.2%)	210 (55.9%)		40 (23.0%)	17 (21.5%)	
Eczema			0.0003			0.02
Never eczema	110 (64.0%)	178 (47.2%)		130 (74.3%)	49 (59.8%)	
Ever eczema	62 (36.1%)	199 (52.8%)		45 (25.7%)	33 (40.2%)	
All SPTs			0.0006			<.0001
No positive SPT	45 (29.2%)	53 (15.8%)		110 (77.5%)	27 (41.5%)	
At least one positive SPT	109 (70.8%)	282 (84.2%)		32 (22.5%)	38 (58.5%)	
Indoor SPTs			<.0001			<.0001
No positive SPT	80 (52.0%)	108 (32.2%)		119 (83.8%)	31 (47.7%)	
At least one positive SPT	74 (48.1%)	227 (67.8%)		23 (16.2%)	34 (52.3%)	
Mould SPTs			0.19			0.01
No positive SPT	130 (84.4%)	266 (79.4%)		136 (95.8%)	56 (86.2%)	
At least one positive SPT	24 (15.6%)	69 (20.6%)		6 (4.2%)	9 (13.9%)	
Outdoor SPTs			0.03			<.0001
No positive SPT	69 (44.8%)	115 (34.3%)		125 (88.0%)	36 (55.4%)	
At least one positive SPT	85 (55.2%)	220 (65.7%)		17 (12.0%)	29 (44.6%)	
Number of positive SPTs	1.9 (1.8)	2.6 (1.9)	<0.0001	0.4 (0.9)	1.6 (1.6)	<0.0001
Immunoglobulin E, IU/mL	82.3 (34.5-201.0)	160.2 (68.7-385.0)	<0.0001	43.4 (15.4-105.0)	119.4 (32.1-350.0)	<.0001
Blood eosinophils count, cells/mm^3	191.6 (125.5)	260.1 (200.6)	<0.0001	170.7 (143.9)	262.0 (208.6)	0.001
Age of onset of rhinitis, year	24.9 (15.8)	14.3 (12.3)	<0.0001	34.4 (17.9)	20.9 (18.4)	<.0001
Reported triggers of rhinitis symptoms†						
Dust mites or house dust	57 (32.8%)	206 (54.2%)	<.0001	40 (22.7%)	29 (34.9%)	0.04
Animals	29 (16.7%)	133 (35.0%)	<.0001	5 (2.8%)	12 (14.5%)	0.0004
Pollens	121 (69.5%)	250 (65.8%)	0.38	37 (21.0%)	13 (15.7%)	0.31
Other	20 (11.5%)	33 (8.7%)	0.30	55 (31.3%)	19 (22.9%)	0.16
No trigger reported	12 (6.9%)	25 (6.6%)	0.89	54 (30.7%)	23 (27.7%)	0.63
Reported symptoms†				0 (0.0%)		
Rhinorrhoea	114 (72.2%)	288 (81.4%)	0.02	67 (46.5%)	39 (52.0%)	0.44
Sneezing	141 (87.0%)	315 (88.0%)	0.76	104 (68.4%)	48 (63.2%)	0.43
Associated-eye symptoms	135 (86.0%)	289 (80.5%)	0.13	92 (60.1%)	47 (59.5%)	0.93
Impairment in daily activities			0.01			0.002
None	86 (49.4%)	155 (40.8%)		139 (79.0%)	48 (57.8%)	
A little	61 (35.1%)	123 (32.4%)		27 (15.3%)	21 (25.3%)	
Moderate	22 (12.6%)	68 (17.9%)		8 (4.6%)	9 (10.8%)	
A lot	5 (2.9%)	34 (9.0%)		2 (1.1%)	5 (6.0%)	

	AR			NAR		
	Never asthma (n=174)	Ever asthma (n=380)	p-value	Never asthma (n=176)	Ever asthma (n=83)	p-value
Duration			0.10			0.45
<1 month/year	70 (40.5%)	116 (30.6%)		87 (49.7%)	38 (45.8%)	
>1 month/year and <4 days/week	47 (27.2%)	117 (30.9%)		30 (17.1%)	17 (20.5%)	
>1 month/year and >4 days/week	56 (32.4%)	143 (37.7%)		58 (33.1%)	27 (32.5%)	

Data are mean (SD) or geometric mean (quartile 1 – quartile 3) or n (%), +: several possible answers, all SPTs: skin prick tests to 12 aeroallergens: indoor: cat, Dermatophagoides pteronyssinus, Blattela germanica; outdoor: olive, birch, Parieteria judaica, timothy grass, ragweed pollen and Cupressus; moulds: Aspergillus, Cladosporium herbarum, Alternaria tenuis

Table S5: Characteristics of participants with current allergic rhinitis (AR) or current non-allergic rhinitis (NAR) defined by SPTs and including ever-asthma status in EGEA

	AR-SPT			NAR-SPT		
	Never asthma (n=141)	Ever asthma (n=320)	p-value	Never asthma (n=155)	Ever asthma (n=80)	p-value
Sex			0.02			0.56
Men	60 (42.6%)	175 (54.7%)		56 (36.1%)	32 (40.0%)	
Women	81 (57.5%)	145 (45.3%)		99 (63.9%)	48 (60.0%)	
Age, years	40.6 (14.3)	35.9 (15.1)	0.002	51.3 (14.8)	47.9 (16.7)	0.11
Tobacco status			0.45			0.46
Never-smoker	72 (51.1%)	171 (53.4%)		78 (50.3%)	37 (46.3%)	
Ex-smoker	34 (24.1%)	61 (19.1%)		49 (31.6%)	23 (28.8%)	
Current smoker	35 (24.8%)	88 (27.5%)		28 (18.1%)	20 (25.0%)	
Educational level			0.11			0.98
Less than high school	21 (14.9%)	46 (14.5%)		50 (32.3%)	25 (31.3%)	
High school	34 (24.1%)	107 (33.8%)		41 (26.5%)	21 (26.3%)	
University	86 (61.0%)	164 (51.7%)		64 (41.3%)	34 (42.5%)	
Conjunctivitis			0.05			0.06
Never conjunctivitis	76 (55.1%)	143 (45.3%)		110 (71.9%)	46 (59.7%)	
Ever conjunctivitis	62 (44.9%)	173 (54.8%)		43 (28.1%)	31 (40.3%)	
Eczema			<.0001			0.99
Never eczema	98 (70.0%)	143 (45.0%)		100 (64.9%)	52 (65.0%)	
Ever eczema	42 (30.0%)	175 (55.0%)		54 (35.1%)	28 (35.0%)	
Indoor SPTs			0.002			-
No positive SPT	44 (31.2%)	59 (18.4%)		-	-	
At least one positive SPT	97 (68.8%)	261 (81.6%)		-	-	
Mould SPTs			0.47			-
No positive SPT	111 (78.7%)	242 (75.6%)		-	-	
At least one positive SPT	30 (21.3%)	78 (24.4%)		-	-	
Outdoor SPTs			0.20			-
No positive SPT	39 (27.7%)	71 (22.2%)		-	-	
At least one positive SPT	102 (72.3%)	249 (77.8%)		-	-	
Number of positive SPTs	2.4 (1.6)	3.0 (1.6)	0.0004	-	-	-
Immunoglobulin E, IU/mL	95.8 (46.7-209.0)	197.1 (86.1-451.0)	<.0001	40.5 (15.4-91.3)	49.8 (16.7-138.0)	0.32
Blood eosinophils count, cell/mm^3	198.0 (130.5)	259.6 (191.9)	0.0006	170.1 (140.1)	229.9 (212.3)	0.03
Age of onset of rhinitis, year	21.7 (13.1)	13.3 (11.9)	<.0001	36.1 (18.3)	24.3 (16.6)	<.0001
Reported triggers of rhinitis symptoms†						
Dust mites or house dust	53 (37.6%)	182 (56.9%)	0.0001	32 (20.7%)	24 (30.0%)	0.11
Animals	26 (18.4%)	124 (38.8%)	<.0001	4 (2.6%)	3 (3.8%)	0.62
Pollens	96 (68.1%)	208 (65.0%)	0.52	42 (27.1%)	25 (31.3%)	0.50
Other	13 (9.2%)	25 (7.8%)	0.61	49 (31.6%)	17 (21.3%)	0.09
No trigger reported	7 (5.0%)	17 (5.3%)	0.88	45 (29.0%)	22 (27.5%)	0.81
Reported symptoms†						
Rhinorrhoea	95 (70.4%)	241 (78.8%)	0.06	66 (50.4%)	47 (67.1%)	0.02
Sneezing	123 (88.5%)	264 (85.4%)	0.38	98 (70.0%)	50 (71.4%)	0.83
Associated-eye symptoms	112 (83.6%)	248 (80.5%)	0.45	88 (63.3%)	49 (65.3%)	0.77
Impairment in daily activities			0.009			0.001
None	75 (53.2%)	141 (44.1%)		113 (72.9%)	38 (47.5%)	
A little	47 (33.3%)	98 (30.6%)		27 (17.4%)	23 (28.8%)	
Moderate	17 (12.1%)	52 (16.3%)		11 (7.1%)	13 (16.3%)	
A lot	2 (1.4%)	29 (9.1%)		4 (2.6%)	6 (7.5%)	
Duration			0.05			0.25
<1 month/year	64 (45.7%)	108 (33.8%)		72 (46.8%)	28 (35.4%)	
>1 month/year and <4 days/week	32 (22.9%)	91 (28.4%)		35 (22.7%)	23 (29.1%)	
>1 month/year and >4 days/week	44 (31.4%)	121 (37.8%)		47 (30.5%)	28 (35.4%)	

Data are mean (SD) or geometric mean (quartile 1 – quartile 3) or n (%), † : several possible answers, all SPTs : skin prick tests to 12 aeroallergens : indoor : cat, Dermatophagoides pteronyssinus, Blattela germanica ; outdoor : olive, birch, Parieteria judaica, timothy grass, ragweed pollen and Cupressus ; moulds : Aspergillus, Cladosporium herbarum, Alternaria tenuis

Table S6: Characteristics of participants with current Allergic Rhinitis (AR) including ever-asthma (A) and ever-conjunctivitis (C) status in EGEA

	AR alone (n=92)	AR and C (n=79)	AR and A (n=166)	AR and C and A (n=210)	p-value
Sex					0.39
Men	48 (52.2%)	32 (40.5%)	85 (51.2%)	102 (48.6%)	
Women	44 (47.8%)	47 (59.5%)	81 (48.8%)	108 (51.4%)	
Age, years	43.9 (16.2)	45.5 (14.8)	36.4 (15.4)	40.1 (16.0)	<0.0001
Tobacco status					0.37
Never-smoker	40 (43.5%)	44 (55.7%)	78 (47.0%)	111 (53.1%)	
Ex-smoker	29 (31.5%)	19 (24.1%)	40 (24.1%)	44 (21.1%)	
Current smoker	23 (25.0%)	16 (20.3%)	48 (28.9%)	54 (25.8%)	
Educational level					0.07
Less than high school	20 (23.0%)	15 (19.5%)	33 (21.4%)	28 (13.9%)	
High school	24 (27.6%)	18 (23.4%)	58 (37.7%)	66 (32.8%)	
University	43 (49.4%)	44 (57.1%)	63 (40.9%)	107 (53.2%)	
Eczema					0.001
Never eczema	58 (64.4%)	49 (62.0%)	87 (53.4%)	90 (42.9%)	
Ever eczema	32 (35.6%)	30 (38.0%)	76 (46.6%)	120 (57.1%)	
All SPTs					0.003
No positive SPT	25 (30.9%)	20 (28.6%)	26 (18.2%)	26 (13.8%)	
At least one positive SPT	56 (69.1%)	50 (71.4%)	117 (81.8%)	162 (86.2%)	
Indoor SPTs					<.0001
No positive SPT	46 (56.8%)	34 (48.6%)	41 (28.7%)	65 (34.6%)	
At least one positive SPT	35 (43.2%)	36 (51.4%)	102 (71.3%)	123 (65.4%)	
Mould SPTs					0.63
No positive SPT	69 (85.2%)	59 (84.3%)	114 (79.7%)	150 (79.8%)	
At least one positive SPT	12 (14.8%)	11 (15.7%)	29 (20.3%)	38 (20.2%)	
Outdoor SPTs					0.01
No positive SPT	35 (43.2%)	32 (45.7%)	60 (42.0%)	52 (27.7%)	
At least one positive SPT	46 (56.8%)	38 (54.3%)	83 (58.0%)	136 (72.3%)	
Number of positive SPTs	1.6 (1.6)	2.1 (2.1)	2.4 (1.9)	2.7 (1.8)	0.0002
Immunoglobulin E, IU/ml	79.2 (30.9-196.0)	86.9 (36.3-209.0)	162.9 (67.8-394.0)	157.5 (68.9-351.3)	<.0001
Blood eosinophils count, cell/mm^3	179.6 (128.3)	206.7 (122.0)	260.2 (184.4)	259.9 (213.7)	0.001
Age of onset of rhinitis, year	23.1 (15.5)	27.2 (15.9)	14.9 (12.8)	13.6 (11.9)	<.0001
Reported triggers of rhinitis symptoms†					
Dust mites or house dust	28 (30.4%)	27 (34.2%)	95 (57.2%)	111 (52.9%)	<.0001
Animals	14 (15.2%)	15 (19.0%)	48 (28.9%)	84 (40.0%)	<.0001
Pollens	67 (72.8%)	53 (67.1%)	93 (56.0%)	155 (73.8%)	0.002
Other	8 (8.7%)	11 (13.9%)	18 (10.8%)	15 (7.1%)	0.31
No trigger reported	6 (6.5%)	6 (7.6%)	12 (7.2%)	12 (5.7%)	0.92
Reported symptoms†					
Rhinorrhoea	62 (73.8%)	50 (70.4%)	121 (77.1%)	163 (84.5%)	0.04
Sneezing	76 (88.4%)	63 (86.3%)	138 (87.3%)	173 (88.3%)	0.97
Associated-eye symptoms	69 (83.1%)	63 (88.7%)	112 (71.8%)	173 (86.9%)	0.001
Impairment in daily activities					0.005
None	53 (57.6%)	32 (40.5%)	80 (48.2%)	75 (35.7%)	
A little	25 (27.2%)	35 (44.3%)	47 (28.3%)	73 (34.8%)	
Moderate	12 (13.0%)	9 (11.4%)	27 (16.3%)	40 (19.1%)	
A lot	2 (2.2%)	3 (3.8%)	12 (7.2%)	22 (10.5%)	
Duration					0.01
<1 month/year	43 (47.3%)	27 (34.2%)	61 (37.0%)	55 (26.2%)	
>1 month/year and <4 days/week	26 (28.6%)	19 (24.1%)	49 (29.7%)	67 (31.9%)	
>1 month/year and >4 days/week	22 (24.2%)	33 (41.8%)	55 (33.3%)	85 (40.5%)	

Data are mean (SD) or n (%), †: several possible answers, all SPTs: skin prick tests to 12 aeroallergens: indoor: cat, Dermatophagoides pteronyssinus, Blattela germanica; outdoor: olive, birch, Parieteria judaica, timothy grass, ragweed pollen and Cupressus; moulds: Aspergillus, Cladosporium herbarum, Alternaria tenuis

Table S7: Characteristics of participants with current Allergic Rhinitis (AR) defined by SPTs including ever-asthma (A) and ever-conjunctivitis (C) status in EGEA

	AR-SPT alone (n=76)	AR-SPT and C (n=62)	AR-SPT and A (n=143)	AR-SPT and C and A (n=173)	p-value
Sex					0.06
Men	35 (46.1%)	24 (38.7%)	83 (58.0%)	89 (51.5%)	
Women	41 (54.0%)	38 (61.3%)	60 (42.0%)	84 (48.6%)	
Age, years	38.6 (14.1)	42.8 (14.6)	33.9 (14.9)	37.8 (15.2)	0.001
Tobacco status					0.86
Never-smoker	36 (47.4%)	35 (56.5%)	77 (53.9%)	93 (53.8%)	
Ex-smoker	20 (26.3%)	12 (19.4%)	28 (19.6%)	32 (18.5%)	
Current smoker	20 (26.3%)	15 (24.2%)	38 (26.6%)	48 (27.8%)	
Educational level					0.15
Less than high school	14 (18.4%)	7 (11.3%)	26 (18.4%)	20 (11.6%)	
High school	18 (23.7%)	15 (24.2%)	48 (34.0%)	59 (34.3%)	
University	44 (57.9%)	40 (64.5%)	67 (47.5%)	93 (54.1%)	
Eczema					<.0001
Never eczema	53 (70.7%)	42 (67.7%)	71 (50.4%)	70 (40.5%)	
Ever eczema	22 (29.3%)	20 (32.3%)	70 (49.7%)	103 (59.5%)	
Indoor SPTs					0.001
No positive SPT	26 (34.2%)	18 (29.0%)	18 (12.6%)	40 (23.1%)	
At least one positive SPT	50 (65.8%)	44 (71.0%)	125 (87.4%)	133 (76.9%)	
Mould SPTs					0.89
No positive SPT	61 (80.3%)	48 (77.4%)	108 (75.5%)	133 (76.9%)	
At least one positive SPT	15 (19.7%)	14 (22.6%)	35 (24.5%)	40 (23.1%)	
Outdoor SPTs					0.11
No positive SPT	22 (29.0%)	15 (24.2%)	39 (27.3%)	30 (17.3%)	
At least one positive SPT	54 (71.1%)	47 (75.8%)	104 (72.7%)	143 (82.7%)	
Number of positive SPTs	2.2 (1.3)	2.8 (1.9)	2.9 (1.7)	3.1 (1.6)	0.0006
Immunoglobulin E, IU/mL	92.4 (46.4-197.0)	102.3 (48.0-209.0)	212.2 (90.0-495.0)	184.4 (84.1-385.0)	<.0001
Blood eosinophils count, cells/mm^3	182.3 (136.6)	219.3 (121.5)	271.3 (198.4)	249.4 (187.5)	0.004
Age of onset of rhinitis, year	20.7 (12.9)	23.0 (13.3)	14.3 (13.1)	12.5 (10.9)	<.0001
Reported triggers of rhinitis symptoms†					
Dust mites or house dust	26 (34.2%)	25 (40.3%)	83 (58.0%)	99 (57.2%)	0.0007
Animals	13 (17.1%)	13 (21.0%)	44 (30.8%)	79 (45.7%)	<.0001
Pollens	50 (65.8%)	45 (72.6%)	77 (53.9%)	130 (75.1%)	0.001
Other	9 (11.8%)	3 (4.8%)	15 (10.5%)	9 (5.2%)	0.14
No trigger reported	4 (5.3%)	3 (4.8%)	11 (7.7%)	5 (2.9%)	0.29
Reported symptoms†					
Rhinorrhoea	52 (71.2%)	41 (69.5%)	102 (74.5%)	135 (81.8%)	0.14
Sneezing	66 (88.0%)	55 (90.2%)	116 (84.7%)	144 (85.7%)	0.73
Associated-eye symptoms	56 (77.8%)	53 (89.8%)	98 (72.1%)	146 (86.9%)	0.002
Impairment in daily activities					0.004
None	46 (60.5%)	28 (45.2%)	76 (53.2%)	64 (37.0%)	
A little	21 (27.6%)	25 (40.3%)	34 (23.8%)	62 (35.8%)	
Moderate	8 (10.5%)	8 (12.9%)	21 (14.7%)	30 (17.3%)	
A lot	1 (1.3%)	1 (1.6%)	12 (8.4%)	17 (9.8%)	
Duration					0.02
<1 month/year	38 (50.7%)	26 (41.9%)	57 (39.9%)	50 (28.9%)	
>1 month/year and <4 days/week	19 (25.3%)	11 (17.7%)	37 (25.9%)	53 (30.6%)	
>1 month/year and >4 days/week	18 (24.0%)	25 (40.3%)	49 (34.3%)	70 (40.5%)	

Data are mean (SD) or geometric mean (quartile 1 – quartile 3) or n (%), †: several possible answers, all SPTs: skin prick tests to 12 aeroallergens: indoor: cat, *Dermatophagoides pteronyssinus*, *Blattela germanica*; outdoor: olive, birch, *Parieteria judaica*, timothy grass, ragweed pollen and *Cupressus*; moulds: *Aspergillus*, *Cladosporium herbarum*, *Alternaria tenuis*

Figure S1: Location of the participating Health Prevention Centers in France
Three health prevention centers were located in Paris.

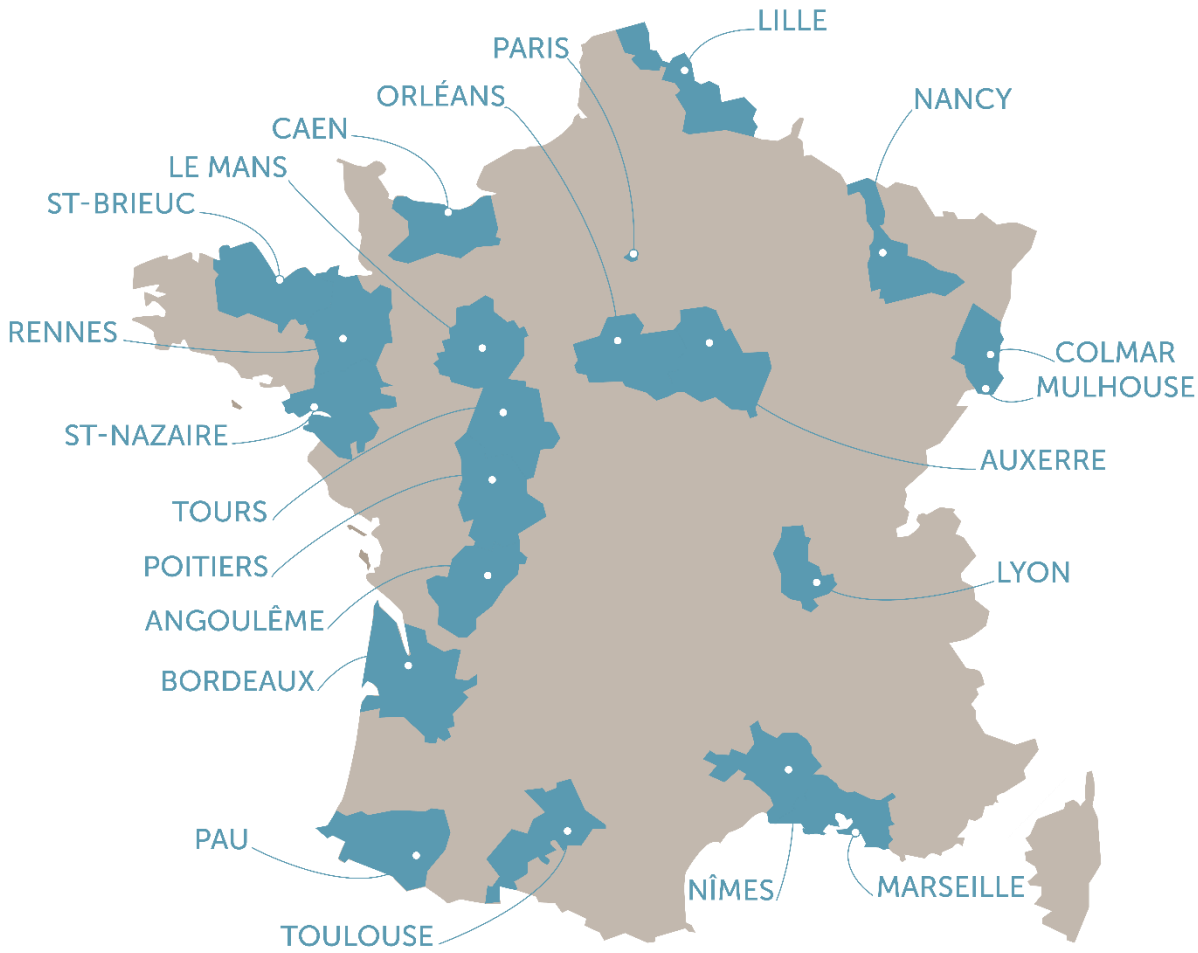


Figure S2: Flowchart

AR: Allergic Rhinitis

NAR: Non-Allergic Rhinitis

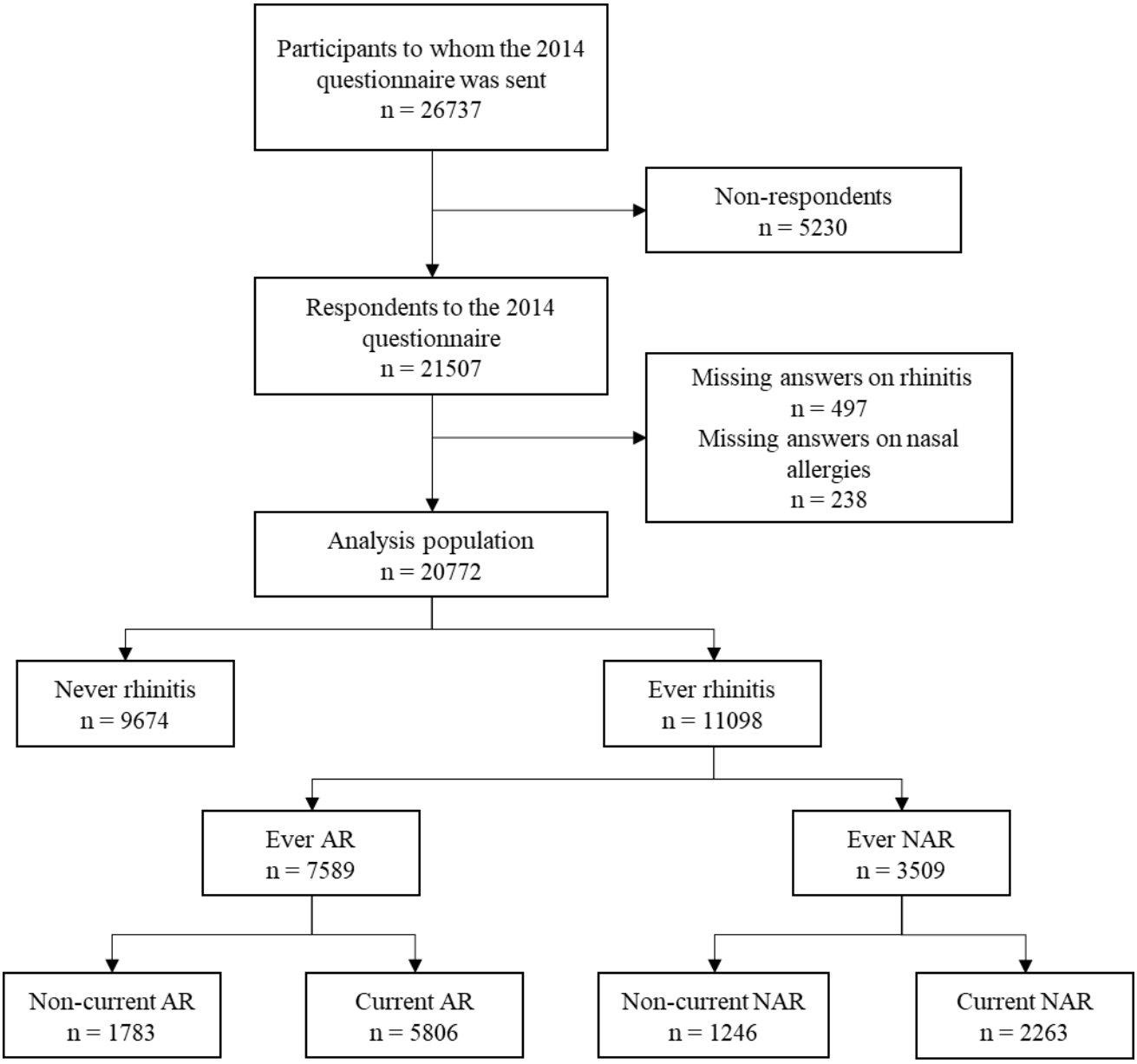


Figure S3: Percentage of participants reporting symptoms by months

A: Current Allergic Rhinitis

Current rhinitis: Yes to Q.23 "During your lifetime, 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?"

.... *AR Main definition: current rhinitis and Yes to Q.22: "During your lifetime, have you ever had any nasal allergies including hay fever?"*

- - *AR Alternate Definition 1: current rhinitis and answer pollens or dust mites or house dust or animal to Q.25: "What factor triggered or increased these nose problems? (several answers possible)"*

—— *AR Alternate Definition 2: current rhinitis and Yes to Q.22: "During your lifetime, have you ever had any nasal allergies including hay fever?" or Answer pollens to Q.25: "What factor triggered or increased these nose problems? (several answers possible)" and Yes to Q.23.A "Did your eyes itch or cry when you had these nose problems?"*

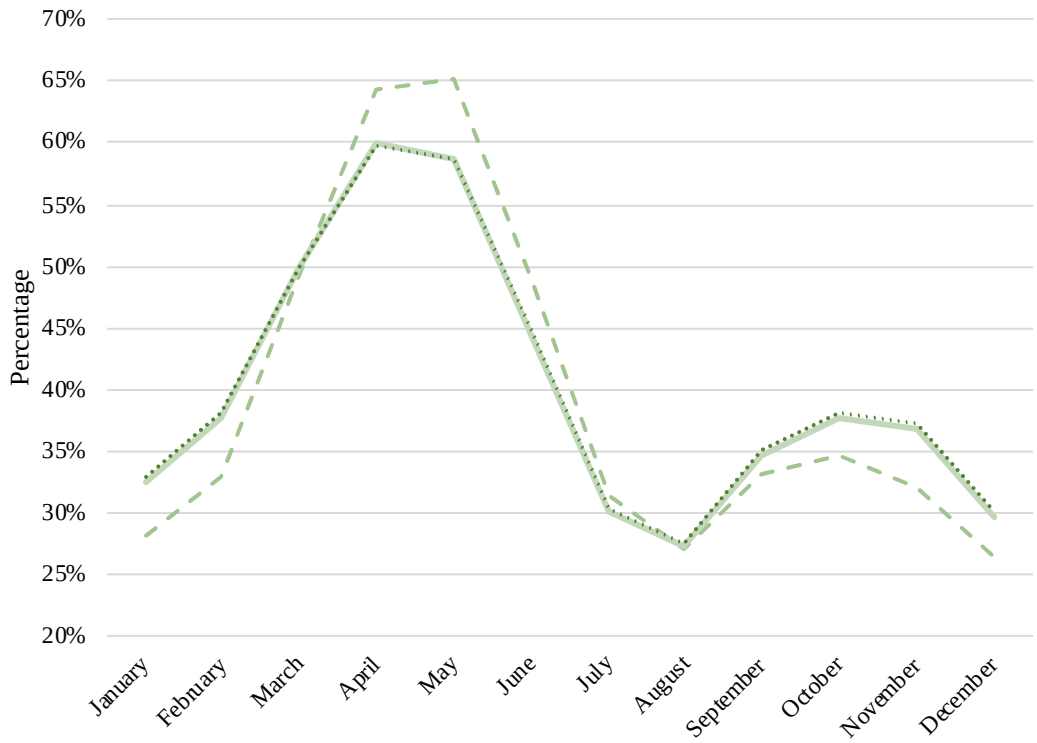
B: Current Non-Allergic Rhinitis

.... *NAR Main definition: current rhinitis and No to Q.22: "During your lifetime, have you ever had any nasal allergies including hay fever?"*

- - *NAR Alternate Definition 3: current rhinitis and no answer pollens and dust mites and house dust and animal to Q.25: "What factor triggered or increased these nose problems? (several answers possible)"*

—— *NAR Alternate Definition 4: current rhinitis and No to Q.22: "During your lifetime, have you ever had any nasal allergies including hay fever?" and no answer pollens to Q.25: "What factor triggered or increased these nose problems? (several answers possible)" or no to Q.23.A "Did your eyes itch or cry when you had these nose problems?"*

A.


70%
65%
60%
55%
50%
45%
40%
35%
30%
25%
20%
Percentage
January
February
March
April
May
June
July
August
September
October
November
December

B.

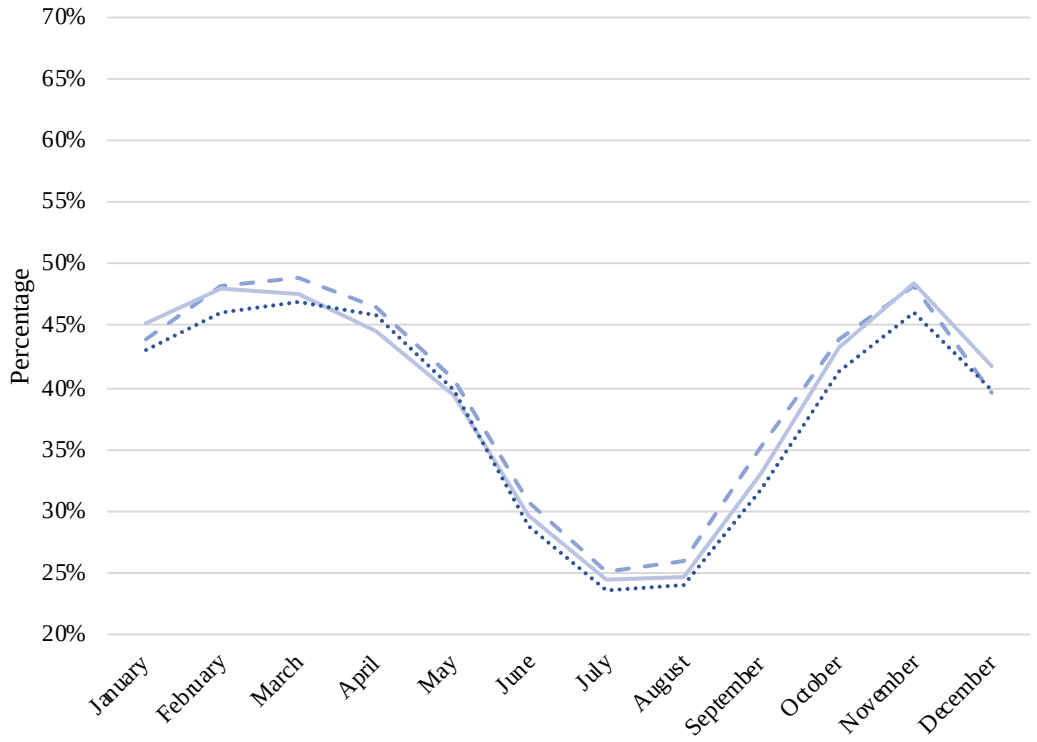

70%
65%
60%
55%
50%
45%
40%
35%
30%
25%
20%
Percentage
January
February
March
April
May
June
July
August
September
October
November
December

Figure S4: Triggers of symptoms (several possible answers)

A: Current Allergic Rhinitis

Current rhinitis: Yes to Q.23 "During your lifetime, 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?"

.... *AR Main definition: current rhinitis and Yes to Q.22: "During your lifetime, have you ever had any nasal allergies including hay fever?"*

- - *AR Alternate Definition 1: current rhinitis and answer pollens or dust mites or house dust or animal to Q.25: "What factor triggered or increased these nose problems? (several answers possible)"*

—— *AR Alternate Definition 2: current rhinitis and Yes to Q.22: "During your lifetime, have you ever had any nasal allergies including hay fever?" or Answer pollens to Q.25: "What factor triggered or increased these nose problems? (several answers possible)" and Yes to Q.23.A "Did your eyes itch or cry when you had these nose problems?"*

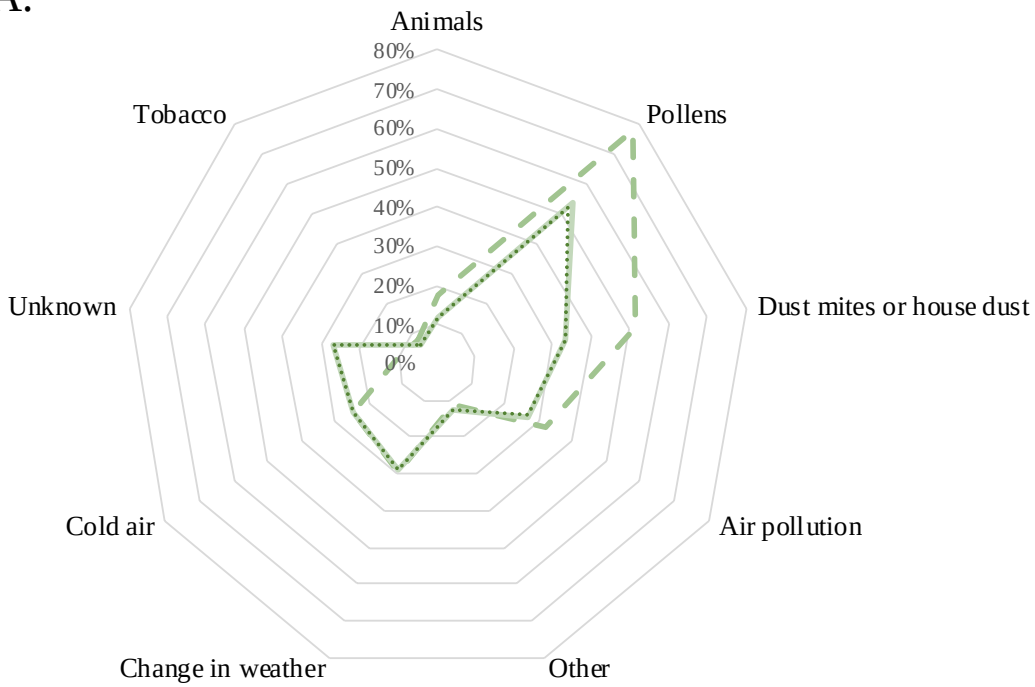
B: Current Non-Allergic Rhinitis

.... *NAR Main definition: current rhinitis and No to Q.22: "During your lifetime, have you ever had any nasal allergies including hay fever?"*

- - *NAR Alternate Definition 3: current rhinitis and no answer pollens and dust mites and house dust and animal to Q.25: "What factor triggered or increased these nose problems? (several answers possible)"*

—— *NAR Alternate Definition 4: current rhinitis and No to Q.22: "During your lifetime, have you ever had any nasal allergies including hay fever?" and no answer pollens to Q.25: "What factor triggered or increased these nose problems? (several answers possible)" or no to Q.23.A "Did your eyes itch or cry when you had these nose problems?"*

A.


Animals
Pollens
Dust mites or house dust
Air pollution
Other
Change in weather
Cold air
Unknown
Tobacco
80%
70%
60%
50%
40%
30%
20%
10%
0%

B.

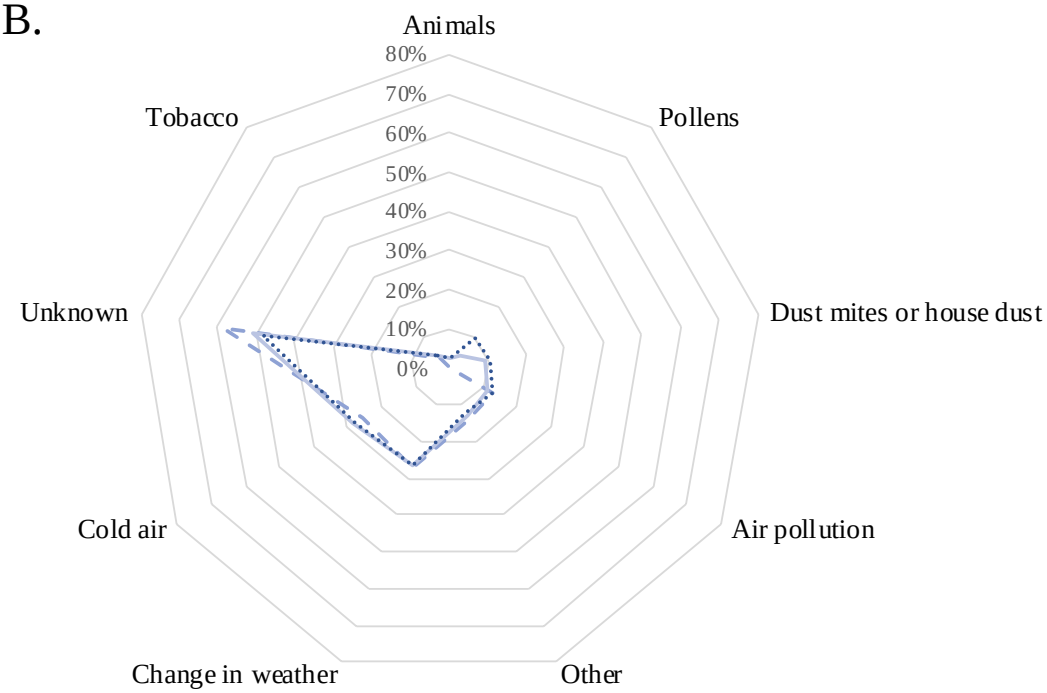
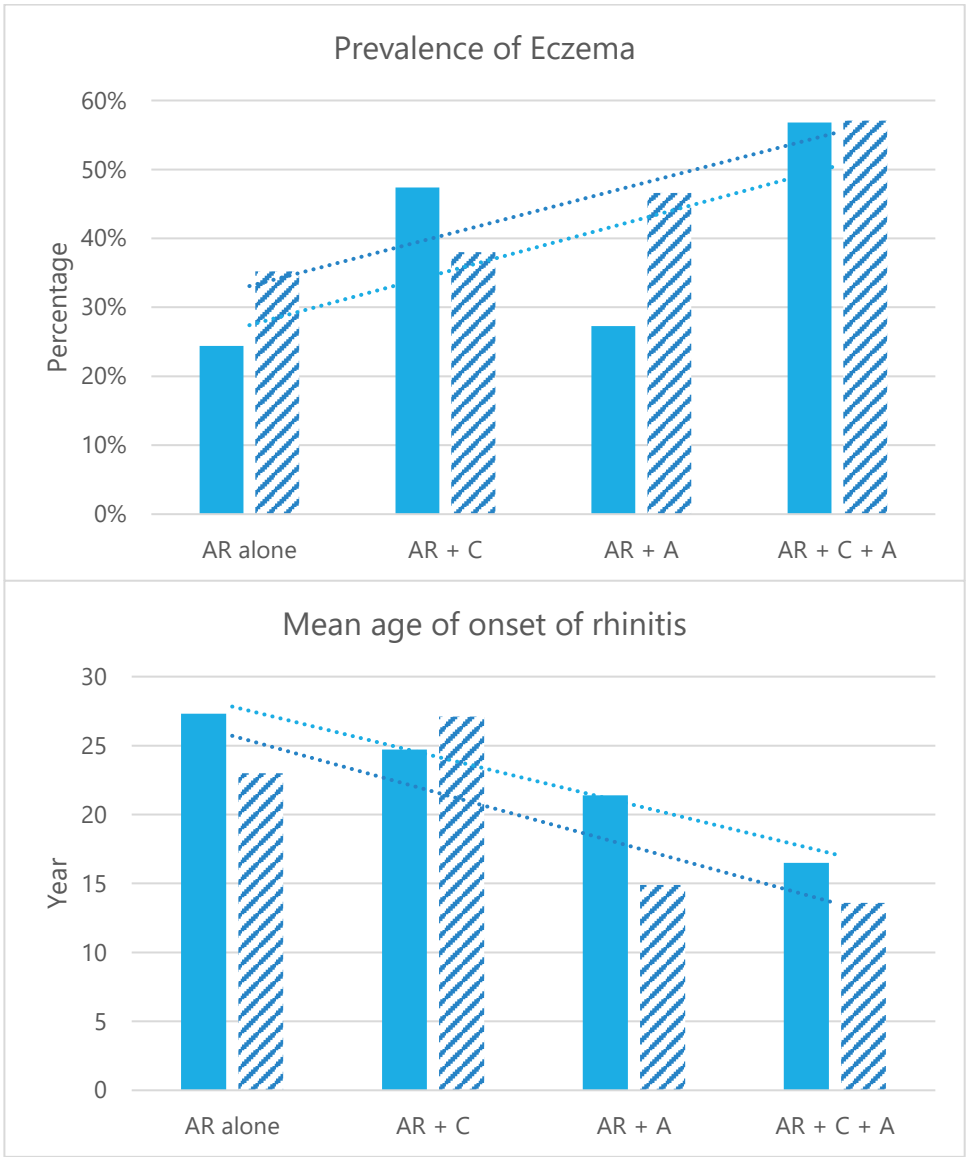
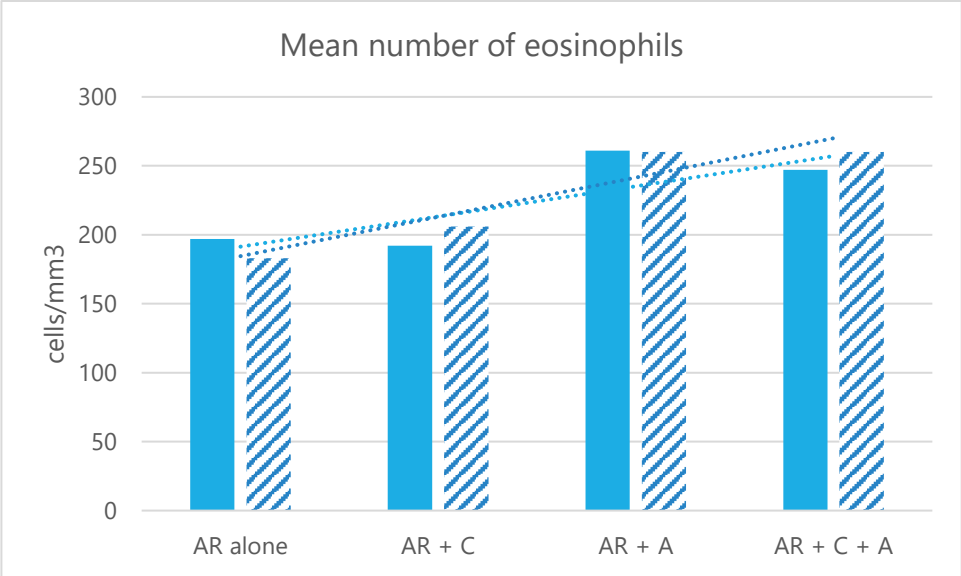

Animals
Pollens
Dust mites or house dust
Air pollution
Other
Change in weather
Cold air
Unknown
Tobacco
80%
70%
60%
50%
40%
30%
20%
10%
0%

Figure S5: Comparison between Constances and EGEA for prevalence of ever-eczema, mean age of onset, and mean eosinophils count

Blue filling: results from Constances
Striped blue filling: results from EGEA
AR alone: current Allergic Rhinitis alone
AR + C: current Allergic Rhinitis and ever-conjunctivitis without ever-asthma
AR + A: current Allergic Rhinitis and ever-asthma without ever-conjunctivitis
AR + C + A: current Allergic Rhinitis and ever-conjunctivitis and ever-asthma




Mean number of eosinophils
300
250
200
150
100
50
0
cells/mm3
AR alone
AR + C
AR + A
AR + C + A

Appendix 6: Influence of asthma on the severity and duration of AR – Supplementary material

Table S1: Comparison of participants included in the analyses with those with missing data for severity or duration

	Not included (n=1,131)	Included (n=4,675)	p
Sex			0.15
Men	459 (40.6%)	2,009 (43.0%)	
Women	672 (59.4%)	2,666 (57.0%)	
Age, years, mean (SD)	57.9 (10.8)	50.2 (12.7)	<0.0001
Tobacco status			0.06
Never-smoker	454 (44.3%)	2,080 (46.4%)	
Ex-smoker	457 (44.6%)	1,832 (40.8%)	
Current smoker	113 (11.0%)	575 (12.8%)	
Educational level			<0.0001
Less than high school	167 (15.0%)	328 (7.1%)	
High school	420 (37.8%)	1,297 (28.0%)	
University	523 (47.1%)	3,005 (64.9%)	
Body-mass index, kg/m^2			0.008
<18.5	21 (1.9%)	103 (2.2%)	
[18.5 - 25[	580 (53.2%)	2,684 (58.5%)	
[25 - 30[	362 (33.2%)	1,328 (29.0%)	
≥ 30	128 (11.7%)	471 (10.3%)	
Asthma			0.0005
Never asthma	880 (79.8%)	3,424 (74.7%)	
Ever asthma	223 (20.2%)	1,160 (25.3%)	
Conjunctivitis			0.04
Never conjunctivitis	363 (41.4%)	1,954 (45.3%)	
Ever conjunctivitis	513 (58.6%)	2,355 (54.7%)	
Eczema			0.60
Never eczema	496 (58.4%)	2,525 (59.4%)	
Ever eczema	354 (41.6%)	1,727 (40.6%)	
Eosinophils count, cells/mm^3, mean (SD)	205.8 (137.9)	209.3 (148.4)	0.50

Data are mean (SD) or n (%)

Table S2: Characteristics of AR according to the four class Total Symptom Score 4

	[0-2] (n=604)	[3-4] (n=1,030)	[5-6] (n=1,183)	≥7 (n=1,767)	p
Sex					<.0001
Men	282 (46.7%)	482 (46.8%)	506 (42.8%)	694 (39.3%)	
Women	322 (53.3%)	548 (53.2%)	677 (57.2%)	1,073 (60.7%)	
Age, years	53.7 (11.9)	51.4 (12.6)	50.1 (12.9)	48.2 (12.6)	<.0001
Tobacco status					0.3849
Never smoker	260 (44.7%)	462 (46.7%)	511 (45.2%)	820 (48.2%)	
Ex-smoker	244 (41.9%)	413 (41.8%)	472 (41.7%)	662 (38.9%)	
Current smoker	78 (13.4%)	114 (11.5%)	148 (13.1%)	219 (12.9%)	
Educational level					0.007
Less than high school	37 (6.2%)	55 (5.4%)	91 (7.7%)	136 (7.8%)	
High school	170 (28.4%)	258 (25.3%)	337 (28.6%)	509 (29.0%)	
University	392 (65.4%)	705 (69.3%)	752 (63.7%)	1,108 (63.2%)	
Body-mass index, kg/m^2					0.1646
<18.5	18 (3.0%)	23 (2.3%)	25 (2.1%)	34 (2.0%)	
[18.5 - 25[	352 (58.8%)	605 (59.9%)	663 (56.7%)	1,019 (59.1%)	
[25 - 30[	176 (29.4%)	286 (28.3%)	355 (30.4%)	482 (28.0%)	
≥30	53 (8.9%)	96 (9.5%)	126 (10.8%)	188 (10.9%)	
Asthma					<.0001
Never asthma	503 (83.3%)	840 (81.6%)	879 (74.3%)	1,202 (68.0%)	
Ever asthma	101 (16.7%)	190 (18.5%)	304 (25.7%)	565 (32.0%)	
Conjunctivitis					<.0001
Never conjunctivitis	330 (59.9%)	493 (52.3%)	505 (45.7%)	586 (36.1%)	
Ever conjunctivitis	221 (40.1%)	450 (47.7%)	601 (54.3%)	1,037 (63.9%)	
Eczema					
Never eczema	363 (66.2%)	628 (66.4%)	667 (61.0%)	821 (51.9%)	
Ever eczema	185 (33.8%)	318 (33.6%)	426 (39.0%)	760 (48.1%)	
Eosinophils count, cells/mm^3	186.2 (128.3)	202.8 (142.0)	207.8 (145.4)	222.1 (160.3)	<.0001
Severity of rhinitis					<.0001
Mild	604 (100.0%)	892 (86.6%)	763 (64.5%)	491 (27.8%)	
Moderate-severe	(0.0%)	138 (13.4%)	420 (35.5%)	1,276 (72.2%)	
Rhinitis duration					<.0001
Intermittent	469 (77.7%)	759 (73.7%)	813 (68.7%)	1,109 (62.8%)	
Persistent	135 (22.4%)	271 (26.3%)	370 (31.3%)	658 (37.2%)	
Reported symptoms*					
Rhinorrhoea	216 (35.8%)	569 (55.2%)	922 (77.9%)	1,686 (95.4%)	<.0001
Nasal congestion/obstruction	180 (29.8%)	620 (60.2%)	934 (79.0%)	1,707 (96.6%)	<.0001
Nasal itching	141 (23.3%)	493 (47.9%)	756 (63.9%)	1,597 (90.4%)	<.0001
Sneezing	181 (30.0%)	609 (59.1%)	901 (76.2%)	1,698 (96.1%)	<.0001
Associated eye symptoms	243 (40.9%)	554 (53.8%)	803 (68.4%)	1,441 (82.3%)	<.0001
Number of reported symptoms	1.6 (0.8)	2.8 (0.8)	3.7 (0.8)	4.6 (0.6)	<.0001
Age of onset of rhinitis, year	27.7 (16.4)	25.1 (15.2)	23.9 (15.1)	20.7 (13.5)	<.0001
Reported triggers of symptoms*					
Dust mites or house dust	139 (23.0%)	294 (28.5%)	395 (33.4%)	792 (44.8%)	<.0001
Animals	32 (5.3%)	103 (10.0%)	139 (11.8%)	313 (17.7%)	<.0001
Pollens	269 (44.5%)	493 (47.9%)	628 (53.1%)	1,094 (61.9%)	<.0001
Air pollution	113 (18.7%)	228 (22.1%)	313 (26.5%)	584 (33.1%)	<.0001

	[0-2] (n=604)	[3-4] (n=1,030)	[5-6] (n=1,183)	≥7 (n=1,767)	p
Change in weather	138 (22.9%)	264 (25.6%)	321 (27.1%)	589 (33.3%)	<.0001
Tobacco	21 (3.5%)	54 (5.2%)	74 (6.3%)	150 (8.5%)	<.0001
Cold air	128 (21.2%)	231 (22.4%)	293 (24.8%)	465 (26.3%)	0.0026
Other	69 (11.4%)	119 (11.6%)	151 (12.8%)	242 (13.7%)	0.0616
Unknown	191 (31.6%)	305 (29.6%)	331 (28.0%)	367 (20.8%)	<.0001
Number of reported triggers	1.8 (1.1)	2.0 (1.1)	2.2 (1.3)	2.6 (1.4)	<.0001
Rhinitis treatment					<.0001
Neither OAH nor INCS	329 (55.1%)	417 (41.0%)	396 (33.8%)	363 (20.8%)	
OAH only	104 (17.4%)	221 (21.7%)	276 (23.6%)	414 (23.7%)	
INCS only	67 (11.2%)	142 (14.0%)	145 (12.4%)	188 (10.8%)	
OAH and INCS	97 (16.3%)	237 (23.3%)	354 (30.2%)	780 (44.7%)	

*Data are mean (SD) or n (%), BMI: Body Mass Index, INCS: Intranasal Corticosteroids, OAH: Oral Antihistamines, *several possible answers*

Table S3: Stratified analyses for variables with a significant interaction coefficient between severity and duration

	Severity						Duration					
	Stratum: Intermittent			Stratum: Persistent			Stratum: Mild			Stratum: Moderate-Severe		
	OR	(CI 95%)	p	OR	(CI 95%)	p	OR	(CI 95%)	p	OR	(CI 95%)	p
Total Symptom Score 4 (TNSS4)	1.99	(1.89 - 2.09)	<.0001	1.78	(1.67 - 1.89)	<.0001	1.10	(1.06 - 1.15)	<.0001	1.06	(1.02 - 1.10)	0.007
Rhinorrhea (ref no)	2.55	(2.14 - 3.06)	<.0001	1.47	(1.15 - 1.88)	0.002	1.43	(1.18 - 1.72)	<.0001	0.82	(0.64 - 1.04)	0.10
Pollens (ref no)	1.05	(0.91 - 1.21)	0.50	1.44	(1.17 - 1.77)	0.0006	0.93	(0.79 - 1.10)	0.39	1.27	(1.05 - 1.54)	0.01
Symptoms in January (ref no)	1.28	(1.09 - 1.51)	0.003	0.88	(0.72 - 1.08)	0.22	4.03	(3.38 - 4.81)	<.0001	2.76	(2.27 - 3.36)	<.0001
Symptoms in February (ref no)	1.25	(1.07 - 1.46)	0.006	0.95	(0.77 - 1.16)	0.60	3.47	(2.92 - 4.13)	<.0001	2.63	(2.17 - 3.19)	<.0001
Symptoms in September (ref no)	1.49	(1.28 - 1.75)	<.0001	1.09	(0.89 - 1.34)	0.42	3.08	(2.59 - 3.67)	<.0001	2.24	(1.85 - 2.72)	<.0001
Symptoms in October (ref no)	1.50	(1.29 - 1.75)	<.0001	0.92	(0.75 - 1.13)	0.44	3.25	(2.74 - 3.87)	<.0001	1.99	(1.65 - 2.41)	<.0001
Symptoms in November (ref no)	1.38	(1.18 - 1.61)	<.0001	0.96	(0.78 - 1.18)	0.68	3.17	(2.66 - 3.77)	<.0001	2.20	(1.82 - 2.66)	<.0001
Symptoms in December (ref no)	1.19	(1.01 - 1.41)	0.04	0.89	(0.73 - 1.09)	0.27	3.55	(2.98 - 4.24)	<.0001	2.65	(2.17 - 3.23)	<.0001

CI: confidence interval; OR: Odds Ratio.

All estimates were from logistic regression models. Moderate-severe rhinitis was compared to mild allergic rhinitis. Persistent allergic rhinitis was compared to intermittent allergic rhinitis

Table S4: Associations between characteristics of allergic rhinitis and its severity

	Univariate analyses			Adjustment on duration		
	OR	(CI 95%)	p	OR	(CI 95%)	p
Sex (ref women)	1.39	(1.23 - 1.56)	<.0001	1.38	(1.22 - 1.55)	<.0001
Age, per 10 years increase	0.76	(0.73 - 0.80)	<.0001	0.76	(0.73 - 0.80)	<.0001
Tobacco status (ref never)						
Ex-smoker	0.90	(0.79 - 1.03)	0.12	0.90	(0.79 - 1.02)	0.11
Current smoker	1.15	(0.96 - 1.39)	0.13	1.17	(0.97 - 1.41)	0.10
Educational level (ref less than high school)						
High school	0.93	(0.73 - 1.19)	0.56	0.94	(0.74 - 1.21)	0.64
University	0.93	(0.74 - 1.17)	0.53	0.93	(0.74 - 1.18)	0.55
Body-mass index (ref <18.5)						
[18·5 - 25[	0.80	(0.54 - 1.20)	0.27	0.84	(0.56 - 1.25)	0.39
[25 - 30[	0.83	(0.55 - 1.24)	0.36	0.87	(0.58 - 1.32)	0.52
≥ 30	0.86	(0.56 - 1.33)	0.49	0.91	(0.59 - 1.41)	0.68
Asthma (ref never)	1.61	(1.41 - 1.84)	<.0001	1.58	(1.38 - 1.81)	<.0001
Conjunctivitis (ref never)	1.40	(1.24 - 1.58)	<.0001	1.37	(1.21 - 1.55)	<.0001
Eczema (ref never)	1.34	(1.19 - 1.52)	<.0001	1.33	(1.18 - 1.51)	<.0001
Eosinophils count, cells/mm^3, per IQR increase	1.11	(1.03 - 1.19)	0.004	1.09	(1.02 - 1.17)	0.01
Total Symptom Score 4 (TNSS4)*	1.92	(1.85 - 1.99)	<.0001	1.91	(1.84 - 1.98)	<.0001
Rhinorrhea (ref no)*	2.15	(1.87 - 2.49)	<.0001	2.12	(1.84 - 2.45)	<.0001
Nasal congestion/obstruction (ref no)	6.63	(5.53 - 8.00)	<.0001	6.50	(5.41 - 7.84)	<.0001
Nasal itching (ref no)	1.59	(1.41 - 1.81)	<.0001	1.59	(1.40 - 1.80)	<.0001
Sneezing (ref no)	1.91	(1.66 - 2.20)	<.0001	1.90	(1.65 - 2.19)	<.0001
Associated eye symptoms (ref no)	1.74	(1.53 - 1.98)	<.0001	1.73	(1.52 - 1.97)	<.0001
Number of reported symptoms	1.70	(1.61 - 1.79)	<.0001	1.68	(1.60 - 1.78)	<.0001
Age of onset of rhinitis, per 10 years increase	0.86	(0.82 - 0.90)	<.0001	0.86	(0.82 - 0.90)	<.0001
Dust mites or house dust (ref no)	1.33	(1.18 - 1.50)	<.0001	1.32	(1.17 - 1.50)	<.0001
Animals (ref no)	1.54	(1.29 - 1.83)	<.0001	1.55	(1.30 - 1.84)	<.0001
Air pollution (ref no)	1.42	(1.25 - 1.62)	<.0001	1.38	(1.21 - 1.57)	<.0001
Change in weather (ref no)	1.53	(1.35 - 1.74)	<.0001	1.58	(1.38 - 1.79)	<.0001
Tobacco (ref no)	1.62	(1.28 - 2.05)	0.0001	1.56	(1.23 - 1.98)	0.0002
Pollens (ref no)*	1.17	(1.04 - 1.32)	0.01	1.17	(1.04 - 1.31)	0.01
Cold air (ref no)	1.22	(1.06 - 1.39)	0.005	1.22	(1.07 - 1.40)	0.004
Other (ref no)	1.41	(1.19 - 1.68)	0.0001	1.39	(1.16 - 1.65)	0.0002
Unknown (ref no)	0.91	(0.80 - 1.04)	0.17	0.88	(0.77 - 1.01)	0.06
Number of reported triggers	1.27	(1.21 - 1.33)	<.0001	1.26	(1.20 - 1.32)	<.0001
Rhinitis treatment (ref neither OAH nor INCS)						
OAH only	1.76	(1.49 - 2.08)	<.0001	1.71	(1.45 - 2.03)	<.0001
INCS only	2.21	(1.80 - 2.70)	<.0001	2.09	(1.71 - 2.57)	<.0001
OAH and INCS	3.00	(2.58 - 3.50)	<.0001	2.80	(2.41 - 3.27)	<.0001
Symptoms in January (ref no)*	1.27	(1.12 - 1.43)	0.0002	1.10	(0.97 - 1.26)	0.14
Symptoms in February (ref no)*	1.27	(1.13 - 1.44)	0.0001	1.13	(1.00 - 1.28)	0.06
Symptoms in March (ref no)	1.22	(1.08 - 1.37)	0.001	1.08	(0.96 - 1.22)	0.19
Symptoms in April (ref no)	1.22	(1.08 - 1.37)	0.002	1.09	(0.96 - 1.24)	0.16
Symptoms in May (ref no)	1.18	(1.04 - 1.33)	0.01	1.06	(0.93 - 1.19)	0.39
Symptoms in June (ref no)	1.21	(1.07 - 1.36)	0.002	1.07	(0.94 - 1.20)	0.31
Symptoms in July (ref no)	1.35	(1.19 - 1.53)	<.0001	1.18	(1.04 - 1.35)	0.01
Symptoms in August (ref no)	1.48	(1.30 - 1.68)	<.0001	1.31	(1.14 - 1.49)	0.0001
Symptoms in September (ref no)*	1.47	(1.30 - 1.66)	<.0001	1.33	(1.17 - 1.51)	<.0001

	Univariate analyses			Adjustment on duration		
	OR	(CI 95%)	p	OR	(CI 95%)	p
Symptoms in October (ref no)*	1.39	(1.24 - 1.57)	<.0001	1.26	(1.12 - 1.43)	0.0002
Symptoms in November (ref no)*	1.34	(1.19 - 1.51)	<.0001	1.21	(1.07 - 1.37)	0.003
Symptoms in December (ref no)*	1.21	(1.07 - 1.37)	0.003	1.06	(0.93 - 1.21)	0.39

CI: confidence interval; INCS: Corticoids Sprays; IQR: Interquartile Range; OAH: Oral Antihistamines; OR: odds ratio.: p value of the interaction coefficient between severity and duration < 0.05, the results of the stratified analyses for these variables are presented in Table S2. All estimates were from logistic regression models. Moderate-severe allergic rhinitis was compared to mild allergic rhinitis.*

Table S5: Associations between characteristics of allergic rhinitis and its duration

	Univariate analyses			Adjustment on severity		
	OR	(CI 95%)	p	OR	(CI 95%)	p
Sex (ref women)	1.12	(0.99 - 1.27)	0.08	1.08	(0.95 - 1.22)	0.26
Age, per 10 years increase	0.97	(0.93 - 1.02)	0.28	1.01	(0.96 - 1.06)	0.76
Tobacco status (ref never)						
Ex-smoker	1.02	(0.89 - 1.17)	0.76	1.04	(0.90 - 1.19)	0.62
Current smoker	0.89	(0.72 - 1.09)	0.26	0.87	(0.71 - 1.07)	0.19
Educational level (ref less than high school)						
High school	0.88	(0.68 - 1.14)	0.33	0.89	(0.68 - 1.15)	0.36
University	0.97	(0.76 - 1.24)	0.78	0.98	(0.77 - 1.25)	0.84
Body-mass index (ref <18.5)						
[18·5 - 25[	0.68	(0.45 - 1.01)	0.06	0.69	(0.46 - 1.04)	0.07
[25 - 30[	0.63	(0.42 - 0.95)	0.03	0.64	(0.42 - 0.97)	0.03
≥ 30	0.60	(0.39 - 0.94)	0.02	0.61	(0.39 - 0.95)	0.03
Asthma (ref never)	1.26	(1.09 - 1.44)	0.002	1.18	(1.03 - 1.36)	0.02
Conjunctivitis (ref never)	1.23	(1.08 - 1.40)	0.002	1.18	(1.04 - 1.35)	0.01
Eczema (ref never)	1.12	(0.98 - 1.28)	0.09	1.08	(0.95 - 1.23)	0.26
Eosinophils count, cells/mm^3, per IQR increase	1.13	(1.05 - 1.21)	0.001	1.11	(1.04 - 1.20)	0.003
Total Symptom Score 4 (TNSS4)*	1.11	(1.09 - 1.14)	<.0001	1.08	(1.05 - 1.11)	<.0001
Rhinorrhea (ref no)*	1.27	(1.10 - 1.47)	0.001	1.17	(1.01 - 1.35)	0.04
Nasal congestion/obstruction (ref no)	1.46	(1.26 - 1.69)	<.0001	1.22	(1.04 - 1.43)	0.01
Nasal itching (ref no)	1.11	(0.97 - 1.26)	0.13	1.04	(0.91 - 1.19)	0.52
Sneezing (ref no)	1.14	(0.99 - 1.32)	0.07	1.06	(0.92 - 1.22)	0.45
Associated eye symptoms (ref no)	1.14	(1.00 - 1.30)	0.06	1.06	(0.93 - 1.22)	0.38
Number of reported symptoms	1.12	(1.07 - 1.18)	<.0001	1.06	(1.01 - 1.12)	0.02
Age of onset of rhinitis, per 10 years increase	1.03	(0.99 - 1.08)	0.15	1.05	(1.01 - 1.11)	0.03
Dust mites or house dust (ref no)	1.09	(0.96 - 1.24)	0.19	1.05	(0.92 - 1.20)	0.45
Animals (ref no)	1.02	(0.85 - 1.23)	0.82	0.97	(0.80 - 1.16)	0.71
Air pollution (ref no)	1.37	(1.20 - 1.57)	<.0001	1.32	(1.15 - 1.51)	0.0001
Change in weather (ref no)	0.84	(0.74 - 0.97)	0.02	0.79	(0.69 - 0.91)	0.001
Tobacco (ref no)	1.47	(1.16 - 1.87)	0.002	1.39	(1.09 - 1.77)	0.01
Pollens (ref no)*	1.09	(0.96 - 1.23)	0.18	1.07	(0.94 - 1.21)	0.31
Cold air (ref no)	0.96	(0.83 - 1.11)	0.62	0.94	(0.81 - 1.09)	0.40
Other (ref no)	1.23	(1.02 - 1.47)	0.03	1.18	(0.98 - 1.41)	0.08
Unknown (ref no)	1.34	(1.17 - 1.54)	<.0001	1.36	(1.19 - 1.57)	<.0001
Number of reported triggers	1.10	(1.05 - 1.16)	<.0001	1.07	(1.02 - 1.13)	0.003
Rhinitis treatment (ref neither OAH nor INCS)						
Oral antihistamines only	1.46	(1.22 - 1.75)	<.0001	1.39	(1.16 - 1.67)	0.0004
Corticoids sprays only	2.01	(1.63 - 2.49)	<.0001	1.88	(1.52 - 2.33)	<.0001
Oral antihistamines and corticoids sprays	2.50	(2.13 - 2.93)	<.0001	2.27	(1.93 - 2.67)	<.0001
Symptoms in January (ref no)*	3.45	(3.02 - 3.93)	<.0001	3.40	(2.99 - 3.88)	<.0001
Symptoms in February (ref no)*	3.11	(2.74 - 3.54)	<.0001	3.07	(2.70 - 3.49)	<.0001
Symptoms in March (ref no)	2.99	(2.62 - 3.41)	<.0001	2.96	(2.60 - 3.38)	<.0001
Symptoms in April (ref no)	2.87	(2.50 - 3.30)	<.0001	2.84	(2.47 - 3.27)	<.0001
Symptoms in May (ref no)	2.84	(2.47 - 3.26)	<.0001	2.82	(2.45 - 3.24)	<.0001
Symptoms in June (ref no)	3.20	(2.81 - 3.64)	<.0001	3.17	(2.79 - 3.61)	<.0001
Symptoms in July (ref no)	3.54	(3.10 - 4.04)	<.0001	3.47	(3.04 - 3.96)	<.0001
Symptoms in August (ref no)	3.43	(3.00 - 3.92)	<.0001	3.33	(2.91 - 3.81)	<.0001
Symptoms in September (ref no)*	2.76	(2.43 - 3.13)	<.0001	2.67	(2.35 - 3.04)	<.0001

Symptoms in October (ref no)*	2.68	(2.36 - 3.04)	<.0001	2.61	(2.30 - 2.97)	<.0001
Symptoms in November (ref no)*	2.75	(2.42 - 3.12)	<.0001	2.69	(2.37 - 3.06)	<.0001
Symptoms in December (ref no)*	3.14	(2.76 - 3.59)	<.0001	3.12	(2.73 - 3.56)	<.0001

*CI: confidence interval; INCS: Corticoids Sprays; IQR: Interquartile Range; OAH: Oral Antihistamines; OR: Odds Ratio. *: p value of the interaction coefficient between severity and duration < 0.05, the results of the stratified analyses for these variables are presented in Table S2. All estimates were from logistic regression models. Persistent allergic rhinitis was compared to intermittent allergic rhinitis.*

Appendix 7: Identification of rhinitis phenotypes using an unsupervised approach in Constances – Supplementary material

Selection of the number of clusters for the K-means algorithm in Constances

- **NbClust R package**

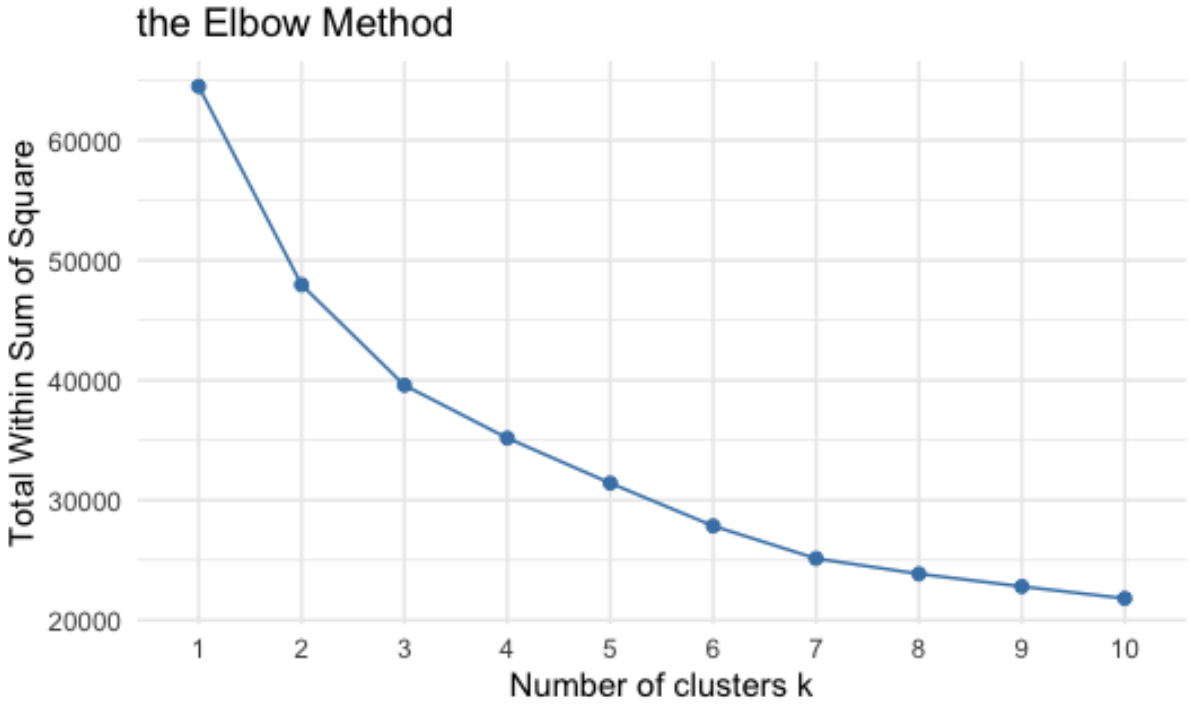
This package provides 30 indices for determining the number of clusters and proposes to user the best clustering scheme from the different results obtained by varying all combinations of number of clusters, distance measures, and clustering methods.

Results:
Among all indices:
** 3 proposed 2 as the best number of clusters*
** 11 proposed 3 as the best number of clusters*
** 1 proposed 6 as the best number of clusters*
** 5 proposed 7 as the best number of clusters*
** 1 proposed 9 as the best number of clusters*
** 2 proposed 10 as the best number of clusters*
****** Conclusion ******
According to the majority rule, the best number of clusters was 3

- **The elbow method**

This method looks at the percentage of variance explained as a function of the number of clusters: One should choose a number of clusters so that adding another cluster doesn't give much better modeling of the data. More precisely, if one plots the percentage of variance explained by the clusters against the number of clusters, the first clusters will add much information (explain a lot of variance), but at some point the marginal gain will drop, giving an angle in the graph. The number of clusters is chosen at this point, hence the "elbow criterion". This "elbow" cannot always be unambiguously identified.

Results: the elbow was located at 3 clusters.



- **Hierarchical Clustering on Principle Components**

Hierarchical clustering does not require to know the number of classes beforehand. It is therefore possible to do a Hierarchical Clustering on Principle Components (HCPC) before the K-means to know the number of classes.
Results: the optimal number of clusters was 2.

- **Bayesian Information Criterion for expectation-maximization, initialized by hierarchical clustering for parameterized Gaussian mixture models**

mclust is a popular R package for model-based clustering, classification, and density estimation based on finite Gaussian mixture modelling. An integrated approach to finite mixture models is provided, with functions that combine model-based hierarchical clustering, EM for mixture estimation and several tools for model selection. Thus, **mclust** provides a comprehensive strategy for clustering, density estimation and discriminant analysis.
Depending on the initialization the optimal number of clusters was 3 or 4.

Table S1: Comparison between participants included and non-included in the analysis

Variables	Levels	Non-included (n=2,664)	Included (n=5,516)	p
Sex	Men	1128 (42.3%)	2,401 (43.5%)	0.32
	Women	1536 (57.7%)	3,115 (56.5%)	
Age, years*	Mean (SD)	56.7 (11.4)	49.6 (13.0)	<0.001
Tobacco status	Never smoker	1077 (43.8%)	2,458 (46.3%)	0.05
	Ex-smoker	1063 (43.2%)	2,139 (40.3%)	
	Current smoker	318 (12.9%)	713 (13.4%)	
Educational level	Less than high school	341 (13.1%)	365 (6.7%)	<0.001
	High school	928 (35.5%)	1,510 (27.6%)	
	University	1342 (51.4%)	3,601 (65.8%)	
Body-mass index, kg/m^2	<18.5	62 (2.4%)	115 (2.1%)	0.14
	[18.5 - 25[	1451 (56.1%)	3,183 (58.8%)	
	[25 - 30[	804 (31.1%)	1,574 (29.1%)	
	≥30	271 (10.5%)	543 (10.0%)	
Asthma*	Never	2068 (82.7%)	4,390 (79.6%)	0.001
	Ever	432 (17.3%)	1,126 (20.4%)	
Conjunctivitis*	Never	849 (47.3%)	3,169 (57.5%)	<0.001
	Ever	946 (52.7%)	2,347 (42.5%)	
Eczema*	Never	990 (56.5%)	3,636 (65.9%)	<0.001
	Ever	763 (43.5%)	1,880 (34.1%)	
Nasal allergies*	Never	698 (27.3%)	1,565 (28.4%)	0.35
	Ever	1855 (72.7%)	3,951 (71.6%)	
Eosinophils count, cells/mm^3	Mean (SD)	202.5 (139.6)	197.7 (139.1)	0.20
Age of onset of rhinitis	Mean (SD)	30.2 (17.5)	25.4 (15.9)	<0.001
Dust mites or house dust trigger*	No	2076 (77.9%)	3,917 (71.0%)	<0.001
	Yes	588 (22.1%)	1,599 (29.0%)	
Animals trigger*	No	2516 (94.4%)	4,932 (89.4%)	<0.001
	Yes	148 (5.6%)	584 (10.6%)	
Air pollution trigger*	No	2092 (78.5%)	4,234 (76.8%)	0.08
	Yes	572 (21.5%)	1,282 (23.2%)	
Change in weather trigger*	No	1902 (71.4%)	3,965 (71.9%)	0.67
	Yes	762 (28.6%)	1,551 (28.1%)	
Tobacco trigger*	No	2528 (94.9%)	5,196 (94.2%)	0.22
	Yes	136 (5.1%)	320 (5.8%)	
Pollens trigger*	No	1724 (64.7%)	3,176 (57.6%)	<0.001
	Yes	940 (35.3%)	2,340 (42.4%)	
Cold air trigger*	No	1972 (74.0%)	4,129 (74.9%)	0.43
	Yes	692 (26.0%)	1,387 (25.1%)	
Other trigger*	No	2328 (87.4%)	4,825 (87.5%)	0.94
	Yes	336 (12.6%)	691 (12.5%)	
Unknown trigger*	No	1666 (62.5%)	3,777 (68.5%)	<0.001
	Yes	998 (37.5%)	1,739 (31.5%)	
Number of reported triggers	Mean (SD)	1.9 (1.2)	2.1 (1.2)	<0.001
Rhinorrhea symptom	No	470 (23.2%)	1,744 (31.6%)	<0.001
	Yes	1559 (76.8%)	3,772 (68.4%)	
Congestion symptom	No	404 (22.0%)	1,634 (29.6%)	<0.001
	Yes	1436 (78.0%)	3,882 (70.4%)	
Itching symptom	No	552 (33.8%)	2,352 (42.6%)	<0.001
	Yes	1083 (66.2%)	3,164 (57.4%)	
Sneezing symptom	No	446 (22.8%)	1,850 (33.5%)	<0.001
	Yes	1509 (77.2%)	3,666 (66.5%)	
Associated eye symptoms	No	648 (33.8%)	2,351 (42.6%)	<0.001
	Yes	1267 (66.2%)	3,165 (57.4%)	
Number of symptoms	Mean (SD)	3.3 (1.4)	3.2 (1.4)	0.15
Rhinorrhea symptom score*	0	470 (23.2%)	1,744 (31.6%)	<0.001
	1	338 (16.7%)	768 (13.9%)	

Variables	Levels	Non-included (n=2,664)	Included (n=5,516)	p
	2	921 (45.4%)	2,185 (39.6%)	
	3	300 (14.8%)	819 (14.8%)	
Congestion symptom score*	0	404 (22.0%)	1,634 (29.6%)	<0.001
	1	197 (10.7%)	557 (10.1%)	
	2	684 (37.2%)	1,771 (32.1%)	
	3	555 (30.2%)	1,554 (28.2%)	
Itching symptom score*	0	552 (33.8%)	2,352 (42.6%)	<0.001
	1	353 (21.6%)	1,231 (22.3%)	
	2	621 (38.0%)	1,648 (29.9%)	
	3	109 (6.7%)	285 (5.2%)	
Sneezing symptom score*	0	446 (22.8%)	1,850 (33.5%)	<0.001
	1	467 (23.9%)	1,216 (22.0%)	
	2	809 (41.4%)	1,908 (34.6%)	
	3	233 (11.9%)	542 (9.8%)	
Associated eye symptoms score*	0	648 (33.8%)	2,351 (42.6%)	<0.001
	1	279 (14.6%)	723 (13.1%)	
	2	774 (40.4%)	1,888 (34.2%)	
	3	214 (11.2%)	554 (10.0%)	
Severity of rhinitis	Mild	755 (65.0%)	3,546 (64.3%)	0.69
	Moderate-Severe	407 (35.0%)	1,970 (35.7%)	
Total Symptom Score 4 (TNSS4)	Mean (SD)	5.3 (2.9)	5.1 (2.8)	0.07
Duration of rhinitis*	Intermittent	1599 (69.3%)	3,884 (70.4%)	0.35
	Persistent	708 (30.7%)	1,632 (29.6%)	
ARIA classification	Mild/Intermittent	492 (48.2%)	2,629 (47.7%)	0.86
	Mild/Persistent	177 (17.4%)	917 (16.6%)	
	Moderate-Severe/Intermittent	222 (21.8%)	1,255 (22.8%)	
	Moderate-Severe/Persistent	129 (12.6%)	715 (13.0%)	
Rhinitis treatment*	Neither OAH nor INCS	1100 (46.5%)	2,473 (44.8%)	<0.001
	OAH only	338 (14.3%)	993 (18.0%)	
	INCS only	358 (15.1%)	682 (12.4%)	
	OAH and INCS	572 (24.2%)	1,368 (24.8%)	
Symptoms in Winter*	No	1396 (52.4%)	2,823 (51.2%)	0.31
	Yes	1268 (47.6%)	2,693 (48.8%)	
Symptoms in Spring*	No	765 (28.7%)	1,271 (23.0%)	<0.001
	Yes	1899 (71.3%)	4,245 (77.0%)	
Symptoms in Summer*	No	1568 (58.9%)	2,903 (52.6%)	<0.001
	Yes	1096 (41.1%)	2,613 (47.4%)	
Symptoms in Autumn*	No	1276 (47.9%)	2,392 (43.4%)	<0.001
	Yes	1388 (52.1%)	3,124 (56.6%)	

*Data are n (%) or mean (SD). *: variables included in the construction of the clusters.*

Table S2: Description and comparison of the three clusters identified in partcipants with never asthma and ever asthma

	Never asthma				Ever asthma			
	Cluster 1 (n=2,250)	Cluster 2 (n=1,755)	Cluster 3 (n=385)	p	Cluster 1 (n=384)	Cluster 2 (n=580)	Cluster 3 (n=162)	p
Sex				<0.001				0.022
Men	1,088 (48.4%)	716 (40.8%)	147 (38.2%)		167 (43.5%)	233 (40.2%)	50 (30.9%)	
Women	1,162 (51.6%)	1,039 (59.2%)	238 (61.8%)		217 (56.5%)	347 (59.8%)	112 (69.1%)	
Age, years	52.3 (13.0)	49.1 (12.7)	45.5 (12.2)	<0.001	49.2 (13.0)	45.6 (12.0%)	43.3 (11.8)	<0.001
Tobacco status				<0.001				0.143
Never smoker	938 (43.3%)	835 (49.3%)	186 (50.5%)		155 (42.6%)	277 (49.3%)	67 (42.9%)	
Ex-smoker	919 (42.4%)	662 (39.1%)	128 (34.8%)		147 (40.4%)	217 (38.6%)	66 (42.3%)	
Current smoker	310 (14.3%)	196 (11.6%)	54 (14.7%)		62 (17.0%)	68 (12.1%)	23 (14.7%)	
Educational level				0.02				0.263
Less than high school	140 (6.3%)	130 (7.5%)	28 (7.3%)		29 (7.7%)	26 (4.5%)	12 (7.5%)	
High school	665 (29.8%)	437 (25.1%)	108 (28.1%)		104 (27.5%)	156 (27.0%)	40 (24.8%)	
University	1,428 (63.9%)	1,176 (67.5%)	248 (64.6%)		245 (64.8%)	395 (68.5%)	109 (67.7%)	
BMI, kg/m^2				0.04				0.125
<18.5	40 (1.8%)	44 (2.5%)	8 (2.1%)		9 (2.4%)	12 (2.1%)	2 (1.3%)	
[18.5 - 25[	1,283 (58.3%)	1,029 (59.6%)	244 (64.9%)		218 (57.8%)	314 (54.5%)	95 (60.5%)	
[25 - 30[	678 (30.8%)	487 (28.2%)	86 (22.9%)		93 (24.7%)	184 (31.9%)	46 (29.3%)	
≥30	201 (9.1%)	167 (9.7%)	38 (10.1%)		57 (15.1%)	66 (11.5%)	14 (8.9%)	
Conjunctivitis				<0.001				<0.001
Never	1,844 (82.0%)	723 (41.2%)	171 (44.4%)		267 (69.5%)	123 (21.2%)	41 (25.3%)	
Ever	406 (18.0%)	1,032 (58.8%)	214 (55.6%)		117 (30.5%)	457 (78.8%)	121 (74.7%)	
Eczema				<0.001				<0.001
Never	1,754 (78.0%)	1,033 (58.9%)	223 (57.9%)		273 (71.1%)	277 (47.8%)	76 (46.9%)	
Ever	496 (22.0%)	722 (41.1%)	162 (42.1%)		111 (28.9%)	303 (52.2%)	86 (53.1%)	
Nasal allergies				<0.001				<0.001
Never	1,320 (58.7%)	108 (6.2%)	27 (7.0%)		103 (26.8%)	4 (0.7%)	3 (1.9%)	
Ever	930 (41.3%)	1,647 (93.8%)	358 (93.0%)		281 (73.2%)	576 (99.3%)	159 (98.1%)	
Eosinophils count, cells/mm^3	176.4 (115.5)	189.0 (127.2)	204.9 (161.6)	<0.001	242.1 (178.2)	247.6 (169.0)	276.9 (172.2)	0.146
Age of onset of rhinitis	31.9 (17.3)	24.3 (14.0)	22.8 (12.5)	<0.001	23.8 (15.5)	16.2 (11.9)	15.4 (12.2)	<0.001
Reported triggers								
Dust mites or house dust trigger	180 (8.0%)	658 (37.5%)	167 (43.4%)	<0.001	104 (27.1%)	398 (68.6%)	92 (56.8%)	<0.001
Animals trigger	21 (0.9%)	212 (12.1%)	66 (17.1%)	<0.001	343 (89.3%)	398 (68.6%)	100 (61.7%)	<0.001
Pollens trigger	184 (8.2%)	1,251 (71.3%)	223 (57.9%)	<0.001	97 (25.3%)	464 (80.0%)	121 (74.7%)	<0.001
Air pollution trigger	225 (10.0%)	572 (32.6%)	140 (36.4%)	<0.001	60 (15.6%)	221 (38.1%)	64 (39.5%)	<0.001
Change in weather trigger	589 (26.2%)	479 (27.3%)	129 (33.5%)	0.01	100 (26.0%)	197 (34.0%)	57 (35.2%)	0.019
Tobacco trigger	74 (3.3%)	92 (5.2%)	41 (10.6%)	<0.001	19 (4.9%)	72 (12.4%)	22 (13.6%)	<0.001
Cold air trigger	599 (26.6%)	396 (22.6%)	95 (24.7%)	0.01	99 (25.8%)	150 (25.9%)	48 (29.6%)	0.597
Other trigger	286 (12.7%)	192 (10.9%)	63 (16.4%)	0.01	46 (12.0%)	70 (12.1%)	34 (21.0%)	0.008
Unknown trigger	1,217 (54.1%)	241 (13.7%)	88 (22.9%)	<0.001	146 (38.0%)	30 (5.2%)	17 (10.5%)	<0.001
Number of reported triggers	1.5 (0.8)	2.3 (1.2)	2.6 (1.4)	<0.001	1.9 (1.1)	3.1 (1.4)	3.2 (1.8)	<0.001
Reported symptoms								
Rhinorrhea symptom	1,277 (56.8%)	1,297 (73.9%)	342 (88.8%)	<0.001	254 (66.1%)	453 (78.1%)	149 (92.0%)	<0.001
Congestion symptom	1,366 (60.7%)	1,268 (72.3%)	348 (90.4%)	<0.001	276 (71.9%)	476 (82.1%)	148 (91.4%)	<0.001
Itching symptom	796 (35.4%)	1,268 (72.3%)	320 (83.1%)	<0.001	171 (44.5%)	461 (79.5%)	148 (91.4%)	<0.001
Sneezing symptom	1,096 (48.7%)	1,372 (78.2%)	351 (91.2%)	<0.001	211 (54.9%)	477 (82.2%)	159 (98.1%)	<0.001
Associated eye symptoms	629 (28.0%)	1,375 (78.3%)	333 (86.5%)	<0.001	178 (46.4%)	499 (86.0%)	151 (93.2%)	<0.001
Severity of rhinitis				<0.001				<0.001
Mild	1,711 (76.0%)	1,243 (70.8%)	0 (0.0%)		248 (64.6%)	344 (59.3%)	0 (0.0%)	
Moderate-Severe	539 (24.0%)	512 (29.2%)	385 (100.0%)		136 (35.4%)	236 (40.7%)	162 (100.0%)	
TNSS4	3.5 (2.0)	5.7 (2.2)	9.5 (2.1)	<0.001	4.5 (2.4)	6.3 (2.1%)	10.2 (1.8)	<0.001
Duration of rhinitis				<0.001				<0.001
Intermittent	1,632 (72.5%)	1,292 (73.6%)	220 (57.1%)		280 (72.9%)	375 (64.7%)	85 (52.5%)	
Persistent	618 (27.5%)	463 (26.4%)	165 (42.9%)		104 (27.1%)	205 (35.3%)	77 (47.5%)	
ARIA classification				<0.001				<0.001

	Never asthma				Ever asthma			
	Cluster 1 (n=2,250)	Cluster 2 (n=1,755)	Cluster 3 (n=385)	p	Cluster 1 (n=384)	Cluster 2 (n=580)	Cluster 3 (n=162)	p
Mild/Intermittent	1,272 (56.5%)	931 (53.0%)	0 (0.0%)		184 (47.9%)	242 (41.7%)	0 (0.0%)	
Mild/Persistent	439 (19.5%)	312 (17.8%)	0 (0.0%)		64 (16.7%)	102 (17.6%)	0 (0.0%)	
Mod-Severe/Intermittent	360 (16.0%)	361 (20.6%)	220 (57.1%)		96 (25.0%)	133 (22.9%)	85 (52.5%)	
Mod-Severe/Persistent	179 (8.0%)	151 (8.6%)	165 (42.9%)		40 (10.4%)	103 (17.8%)	77 (47.5%)	
Rhinitis treatment				<0.001				<0.001
Neither OAH nor INCS	1,591 (70.7%)	556 (31.7%)	73 (19.0%)		190 (49.5%)	54 (9.3%)	9 (5.6%)	
OAH only	111 (4.9%)	529 (30.1%)	86 (22.3%)		53 (13.8%)	171 (29.5%)	43 (26.5%)	
INCS only	411 (18.3%)	144 (8.2%)	29 (7.5%)		56 (14.6%)	32 (5.5%)	10 (6.2%)	
OAH and INCS	137 (6.1%)	526 (30.0%)	197 (51.2%)		85 (22.1%)	323 (55.7%)	100 (61.7%)	

Data are n (%) or mean (SD)

Table S3: Description of the three clusters identified in Constances - Age of onset and eosinophils were added in the cluster analysis (SA1) (n=3,221)

Variables	Levels	Cluster 1 (n=1,316)	Cluster 2 (n=1,531)	Cluster 3 (n=374)	p
Sex	Men	640 (48.6%)	624 (40.8%)	138 (36.9%)	<0.001
	Women	676 (51.4%)	907 (59.2%)	236 (63.1%)	
Age, years*	Mean (SD)	51.9 (13.2)	47.0 (12.4)	44.0 (12.4%)	<0.001
Tobacco status	Never smoker	515 (40.5%)	751 (51.2%)	158 (44.0%)	<0.001
	Ex-smoker	552 (43.4%)	542 (36.9%)	144 (40.1%)	
	Current smoker	205 (16.1%)	174 (11.9%)	57 (15.9%)	
Educational level	Less than high school	73 (5.6%)	88 (5.8%)	26 (7.0%)	0.06
	High school	367 (28.1%)	358 (23.5%)	99 (26.5%)	
	University	864 (66.3%)	1,075 (70.7%)	248 (66.5%)	
Body-mass index, kg/m^2	<18.5	23 (1.8%)	32 (2.1%)	6 (1.6%)	0.11
	[18.5 - 25[	761 (58.7%)	880 (57.9%)	239 (65.1%)	
	[25 - 30[	393 (30.3%)	438 (28.8%)	86 (23.4%)	
	≥30	120 (9.3%)	169 (11.1%)	36 (9.8%)	
Asthma*	Never	1,226 (93.2%)	1,011 (66.0%)	223 (59.6%)	<0.001
	Ever	90 (6.8%)	520 (34.0%)	151 (40.4%)	
Conjunctivitis*	Never	1,041 (79.1%)	558 (36.4%)	135 (36.1%)	<0.001
	Ever	275 (20.9%)	973 (63.6%)	239 (63.9%)	
Eczema*	Never	1,046 (79.5%)	862 (56.3%)	196 (52.4%)	<0.001
	Ever	270 (20.5%)	669 (43.7%)	178 (47.6%)	
Nasal allergies*	Never	700 (53.2%)	49 (3.2%)	19 (5.1%)	<0.001
	Ever	616 (46.8%)	1,482 (96.8%)	355 (94.9%)	
Eosinophils count, cells/mm^3*	Mean (SD)	178.9 (118.7)	213.1 (146.3)	243.0 (176.1)	<0.001
Age of onset of rhinitis*	Mean (SD)	32.4 (17.1)	20.6 (12.6)	19.4 (12.6)	<0.001
Dust mites or house dust trigger*	No	1,195 (90.8%)	805 (52.6%)	169 (45.2%)	<0.001
	Yes	121 (9.2%)	726 (47.4%)	205 (54.8%)	
Animals trigger*	No	1,294 (98.3%)	1,249 (81.6%)	262 (70.1%)	<0.001
	Yes	22 (1.7%)	282 (18.4%)	112 (29.9%)	
Air pollution trigger*	No	1,104 (83.9%)	1,026 (67.0%)	226 (60.4%)	<0.001
	Yes	212 (16.1%)	505 (33.0%)	148 (39.6%)	
Change in weather trigger*	No	976 (74.2%)	1,076 (70.3%)	250 (66.8%)	0.008
	Yes	340 (25.8%)	455 (29.7%)	124 (33.2%)	
Tobacco trigger*	No	1,264 (96.0%)	1,420 (92.7%)	325 (86.9%)	<0.001
	Yes	52 (4.0%)	111 (7.3%)	49 (13.1%)	
Pollens trigger*	No	1,124 (85.4%)	413 (27.0%)	121 (32.4%)	<0.001
	Yes	192 (14.6%)	1,118 (73.0%)	253 (67.6%)	
Cold air trigger*	No	981 (74.5%)	1,165 (76.1%)	280 (74.9%)	0.62
	Yes	335 (25.5%)	366 (23.9%)	94 (25.1%)	
Other trigger*	No	1,132 (86.0%)	1,384 (90.4%)	303 (81.0%)	<0.001
	Yes	184 (14.0%)	147 (9.6%)	71 (19.0%)	
Unknown trigger*	No	651 (49.5%)	1,380 (90.1%)	319 (85.3%)	<0.001
	Yes	665 (50.5%)	151 (9.9%)	55 (14.7%)	
Number of reported triggers	Mean (SD)	1.6 (0.9)	2.5 (1.3)	3.0 (1.6%)	<0.001
Rhinorrhea symptom	No	561 (42.6%)	366 (23.9%)	43 (11.5%)	<0.001
	Yes	755 (57.4%)	1,165 (76.1%)	331 (88.5%)	
Congestion symptom	No	496 (37.7%)	383 (25.0%)	33 (8.8%)	<0.001
	Yes	820 (62.3%)	1,148 (75.0%)	341 (91.2%)	
Itching symptom	No	808 (61.4%)	381 (24.9%)	55 (14.7%)	<0.001
	Yes	508 (38.6%)	1,150 (75.1%)	319 (85.3%)	
Sneezing symptom	No	631 (47.9%)	313 (20.4%)	19 (5.1%)	<0.001
	Yes	685 (52.1%)	1,218 (79.6%)	355 (94.9%)	
Associated eye symptoms	No	870 (66.1%)	291 (19.0%)	38 (10.2%)	<0.001
	Yes	446 (33.9%)	1,240 (81.0%)	336 (89.8%)	
Number of symptoms	Mean (SD)	2.4 (1.2)	3.9 (1.1)	4.5 (0.7)	<0.001
Rhinorrhea symptom score*	0	561 (42.6%)	366 (23.9%)	43 (11.5%)	<0.001

Variables	Levels	Cluster 1 (n=1,316)	Cluster 2 (n=1,531)	Cluster 3 (n=374)	p
	1	257 (19.5%)	159 (10.4%)	9 (2.4%)	
	2	410 (31.2%)	861 (56.2%)	38 (10.2%)	
	3	88 (6.7%)	145 (9.5%)	284 (75.9%)	
Congestion symptom score*	0	496 (37.7%)	383 (25.0%)	33 (8.8%)	<0.001
	1	186 (14.1%)	117 (7.6%)	18 (4.8%)	
	2	361 (27.4%)	636 (41.5%)	49 (13.1%)	
	3	273 (20.7%)	395 (25.8%)	274 (73.3%)	
Itching symptom score*	0	808 (61.4%)	381 (24.9%)	55 (14.7%)	<0.001
	1	303 (23.0%)	395 (25.8%)	38 (10.2%)	
	2	202 (15.3%)	742 (48.5%)	96 (25.7%)	
	3	3 (0.2%)	13 (0.8%)	185 (49.5%)	
Sneezing symptom score*	0	631 (47.9%)	313 (20.4%)	19 (5.1%)	<0.001
	1	355 (27.0%)	315 (20.6%)	26 (7.0%)	
	2	299 (22.7%)	848 (55.4%)	54 (14.4%)	
	3	31 (2.4%)	55 (3.6%)	275 (73.5%)	
Associated eye symptoms score*	0	870 (66.1%)	291 (19.0%)	38 (10.2%)	<0.001
	1	189 (14.4%)	228 (14.9%)	22 (5.9%)	
	2	218 (16.6%)	924 (60.4%)	66 (17.6%)	
	3	39 (3.0%)	88 (5.7%)	248 (66.3%)	
Severity of rhinitis	Mild	987 (75.0%)	1,020 (66.6%)	0 (0.0%)	<0.001
	Moderate-Severe	329 (25.0%)	511 (33.4%)	374 (100.0%)	
TNSS4	Mean (SD)	3.7 (2.1)	5.9 (2.2)	9.7 (2.1)	<0.001
Duration of rhinitis*	Intermittent	935 (71.0%)	1,077 (70.3%)	194 (51.9%)	<0.001
	Persistent	381 (29.0%)	454 (29.7%)	180 (48.1%)	
ARIA classification	Mild/Intermittent	717 (54.5%)	737 (48.1%)	0 (0.0%)	<0.001
	Mild/Persistent	270 (20.5%)	283 (18.5%)	0 (0.0%)	
	Moderate-Severe/Intermittent	218 (16.6%)	340 (22.2%)	194 (51.9%)	
	Moderate-Severe/Persistent	111 (8.4%)	171 (11.2%)	180 (48.1%)	
Rhinitis treatment*	Neither OAH nor INCS	855 (65.0%)	349 (22.8%)	37 (9.9%)	<0.001
	OAH only	88 (6.7%)	484 (31.6%)	100 (26.7%)	
	INCS only	259 (19.7%)	106 (6.9%)	24 (6.4%)	
	OAH and INCS	114 (8.7%)	592 (38.7%)	213 (57.0%)	
Symptoms in Winter*	No	509 (38.7%)	942 (61.5%)	170 (45.5%)	<0.001
	Yes	807 (61.3%)	589 (38.5%)	204 (54.5%)	
Symptoms in Spring*	No	374 (28.4%)	205 (13.4%)	35 (9.4%)	<0.001
	Yes	942 (71.6%)	1,326 (86.6%)	339 (90.6%)	
Symptoms in Summer*	No	818 (62.2%)	653 (42.7%)	114 (30.5%)	<0.001
	Yes	498 (37.8%)	878 (57.3%)	260 (69.5%)	
Symptoms in Autumn*	No	427 (32.4%)	800 (52.3%)	136 (36.4%)	<0.001
	Yes	889 (67.6%)	731 (47.7%)	238 (63.6%)	

*Data are n (%) or mean (SD), *: variables included in cluster analysis*

Table S4: Description of the three clusters identified in Constances – Imputation of the missing values using the regularized iterative FAMD algorithm (n=8,180)

Variables	Levels	Cluster 1 (n=3,952)	Cluster 2 (n=3,394)	Cluster 3 (n=834)	p
Sex	Men	1,863 (47.1%)	1,366 (40.2%)	300 (36.0%)	<0.001
	Women	2,089 (52.9%)	2,028 (59.8%)	534 (64.0%)	
Age, years*	Mean (SD)	54.1 (12.7)	50.5 (12.8)	47.2 (12.7)	<0.001
Tobacco status	Never smoker	1,609 (43.0%)	1,541 (47.6%)	385 (48.8%)	<0.001
	Ex-smoker	1,597 (42.7%)	1,316 (40.7%)	289 (36.6%)	
	Current smoker	538 (14.4%)	378 (11.7%)	115 (14.6%)	
Educational level	Less than high school	348 (8.9%)	281 (8.4%)	77 (9.3%)	0.03
	High school	1,241 (31.7%)	960 (28.6%)	237 (28.8%)	
	University	2,322 (59.4%)	2,111 (63.0%)	510 (61.9%)	
Body-mass index, kg/m^2	<18.5	81 (2.1%)	74 (2.2%)	22 (2.7%)	0.39
	[18.5 - 25[	2,213 (57.3%)	1,937 (58.2%)	484 (59.7%)	
	[25 - 30[	1,186 (30.7%)	974 (29.2%)	218 (26.9%)	
	≥30	381 (9.9%)	346 (10.4%)	87 (10.7%)	
Asthma*	Never	3,576 (92.4%)	2,370 (71.2%)	512 (62.7%)	<0.001
	Ever	294 (7.6%)	960 (28.8%)	304 (37.3%)	
Conjunctivitis*	Never	2,695 (78.4%)	1,060 (34.0%)	263 (34.9%)	<0.001
	Ever	742 (21.6%)	2,061 (66.0%)	490 (65.1%)	
Eczema*	Never	2,611 (74.3%)	1,647 (54.6%)	368 (49.9%)	<0.001
	Ever	905 (25.7%)	1,369 (45.4%)	369 (50.1%)	
Nasal allergies*	Never	2,063 (53.4%)	155 (4.6%)	45 (5.4%)	<0.001
	Ever	1,799 (46.6%)	3,224 (95.4%)	783 (94.6%)	
Eosinophils count, cells/mm^3	Mean (SD)	183.6 (124.7)	210.1 (147.5)	228.3 (159.5)	<0.001
Age of onset of rhinitis	Mean (SD)	32.2 (17.6)	23.5 (14.6%)	21.2 (14.0%)	<0.001
Dust mites or house dust trigger*	No	3,601 (91.1%)	1,947 (57.4%)	445 (53.4%)	<0.001
	Yes	351 (8.9%)	1,447 (42.6%)	389 (46.6%)	
Animals trigger*	No	3,905 (98.8%)	2,884 (85.0%)	659 (79.0%)	<0.001
	Yes	47 (1.2%)	510 (15.0%)	175 (21.0%)	
Air pollution trigger*	No	3,536 (89.5%)	2,258 (66.5%)	532 (63.8%)	<0.001
	Yes	416 (10.5%)	1,136 (33.5%)	302 (36.2%)	
Change in weather trigger*	No	2,958 (74.8%)	2,382 (70.2%)	527 (63.2%)	<0.001
	Yes	994 (25.2%)	1,012 (29.8%)	307 (36.8%)	
Tobacco trigger*	No	3,831 (96.9%)	3,168 (93.3%)	725 (86.9%)	<0.001
	Yes	121 (3.1%)	226 (6.7%)	109 (13.1%)	
Pollens trigger*	No	3,572 (90.4%)	996 (29.3%)	332 (39.8%)	<0.001
	Yes	380 (9.6%)	2,398 (70.7%)	502 (60.2%)	
Cold air trigger*	No	2931 (74.2%)	2,574 (75.8%)	596 (71.5%)	0.024
	Yes	1,021 (25.8%)	820 (24.2%)	238 (28.5%)	
Other trigger*	No	3,462 (87.6%)	3,020 (89.0%)	671 (80.5%)	<0.001
	Yes	490 (12.4%)	374 (11.0%)	163 (19.5%)	
Unknown trigger*	No	1,807 (45.7%)	2,970 (87.5%)	666 (79.9%)	<0.001
	Yes	2,145 (54.3%)	424 (12.5%)	168 (20.1%)	
Number of reported triggers	Mean (SD)	1.5 (0.8)	2.5 (1.3)	2.8 (1.6)	<0.001
Rhinorrhea symptom	No	1,402 (38.8%)	729 (23.1%)	83 (10.7%)	<0.001
	Yes	2,208 (61.2%)	2,427 (76.9%)	696 (89.3%)	
Congestion symptom	No	1,288 (36.5%)	680 (22.3%)	70 (9.1%)	<0.001
	Yes	2,245 (63.5%)	2,374 (77.7%)	699 (90.9%)	
Itching symptom	No	2,066 (62.0%)	732 (23.9%)	106 (14.0%)	<0.001
	Yes	1,266 (38.0%)	2,331 (76.1%)	650 (86.0%)	
Sneezing symptom	No	1,648 (46.7%)	597 (18.9%)	51 (6.5%)	<0.001
	Yes	1,878 (53.3%)	2,558 (81.1%)	739 (93.5%)	

Variables	Levels	Cluster 1 (n=3,952)	Cluster 2 (n=3,394)	Cluster 3 (n=834)	p
Associated eye symptoms	No	2,319 (67.5%)	589 (18.4%)	91 (11.4%)	<0.001
	Yes	1,119 (32.5%)	2,608 (81.6%)	705 (88.6%)	
Number of symptoms	Mean (SD)	2.4 (1.2)	3.9 (1.1)	4.4 (0.8)	<0.001
Rhinorrhea symptom score*	0	1,402 (38.8%)	729 (23.1%)	83 (10.7%)	<0.001
	1	800 (22.2%)	291 (9.2%)	15 (1.9%)	
	2	1,175 (32.5%)	1,842 (58.4%)	89 (11.4%)	
	3	233 (6.5%)	294 (9.3%)	592 (76.0%)	
Congestion symptom score*	0	1,288 (36.5%)	680 (22.3%)	70 (9.1%)	<0.001
	1	478 (13.5%)	247 (8.1%)	29 (3.8%)	
	2	1,008 (28.5%)	1,356 (44.4%)	91 (11.8%)	
	3	759 (21.5%)	771 (25.2%)	579 (75.3%)	
Itching symptom score*	0	2,066 (62.0%)	732 (23.9%)	106 (14.0%)	<0.001
	1	773 (23.2%)	734 (24.0%)	77 (10.2%)	
	2	481 (14.4%)	1,584 (51.7%)	204 (27.0%)	
	3	12 (0.4%)	13 (0.4%)	369 (48.8%)	
Sneezing symptom score*	0	1,648 (46.7%)	597 (18.9%)	51 (6.5%)	<0.001
	1	1,028 (29.2%)	608 (19.3%)	47 (5.9%)	
	2	776 (22.0%)	1,833 (58.1%)	108 (13.7%)	
	3	74 (2.1%)	117 (3.7%)	584 (73.9%)	
Associated eye symptoms score*	0	2,319 (67.5%)	589 (18.4%)	91 (11.4%)	<0.001
	1	506 (14.7%)	444 (13.9%)	52 (6.5%)	
	2	526 (15.3%)	1,980 (61.9%)	156 (19.6%)	
	3	87 (2.5%)	184 (5.8%)	497 (62.4%)	
Severity of rhinitis	Mild	2,394 (75.4%)	1,907 (68.0%)	0 (0.0%)	<0.001
	Moderate-Severe	780 (24.6%)	898 (32.0%)	699 (100.0%)	
Total Symptom Score 4 (TNSS4)	Mean (SD)	3.6 (2.1%)	5.9 (2.2)	9.6 (2.1)	<0.001
Duration of rhinitis*	Intermittent	2,711 (72.2%)	2,357 (72.1%)	415 (51.9%)	<0.001
	Persistent	1,044 (27.8%)	911 (27.9%)	385 (48.1%)	
ARIA classification	Mild/Intermittent	1,745 (56.3%)	1,376 (50.0%)	0 (0.0%)	<0.001
	Mild/Persistent	594 (19.1%)	500 (18.2%)	0 (0.0%)	
	Moderate-Severe/Intermittent	515 (16.6%)	600 (21.8%)	362 (53.2%)	
	Moderate-Severe/Persistent	248 (8.0%)	278 (10.1%)	318 (46.8%)	
Rhinitis treatment*	Neither OAH nor INCS	2,582 (68.5%)	870 (26.4%)	121 (14.9%)	<0.001
	OAH only	220 (5.8%)	942 (28.5%)	169 (20.8%)	
	INCS only	683 (18.1%)	281 (8.5%)	76 (9.4%)	
	OAH and INCS	286 (7.6%)	1,208 (36.6%)	446 (54.9%)	
Symptoms in Winter*	No	1,724 (43.6%)	2,100 (61.9%)	395 (47.4%)	<0.001
	Yes	2,228 (56.4%)	1,294 (38.1%)	439 (52.6%)	
Symptoms in Spring*	No	1,441 (36.5%)	470 (13.8%)	125 (15.0%)	<0.001
	Yes	2,511 (63.5%)	2,924 (86.2%)	709 (85.0%)	
Symptoms in Summer*	No	2,574 (65.1%)	1,573 (46.3%)	324 (38.8%)	<0.001
	Yes	1,378 (34.9%)	1,821 (53.7%)	510 (61.2%)	
Symptoms in Autumn*	No	1,613 (40.8%)	1,767 (52.1%)	288 (34.5%)	<0.001
	Yes	2,339 (59.2%)	1,627 (47.9%)	546 (65.5%)	

*Data are n (%) or mean (SD), *: variables included in cluster analysis*

Table S5: Description and comparison of the two clusters identified in Constances

Variables	Levels	Cluster 1 (n=2,868)	Cluster 2 (n=2,468)	p
Sex	Men	1,363 (47.5%)	1,038 (39.2%)	<0.001
	Women	1,505 (52.5%)	1,610 (60.8%)	
Age, years*	Mean (SD)	52.2 (12.9)	46.8 (12.5)	<0.001
Tobacco status	Never smoker	1,192 (43.2%)	1,266 (49.7%)	<0.001
	Ex-smoker	1,165 (42.2%)	974 (38.2%)	
	Current smoker	404 (14.6%)	309 (12.1%)	
Educational level	Less than high school	196 (6.9%)	169 (6.4%)	0.02
	High school	828 (29.1%)	682 (25.9%)	
	University	1,821 (64.0%)	1,780 (67.7%)	
Body-mass index, kg/m^2	<18.5	59 (2.1%)	56 (2.2%)	0.21
	[18.5 - 25[	1,631 (58.0%)	1,552 (59.6%)	
	[25 - 30[	851 (30.3%)	723 (27.8%)	
	≥30	270 (9.6%)	273 (10.5%)	
Asthma*	Never	2,660 (92.7%)	1,730 (65.3%)	<0.001
	Ever	208 (7.3%)	918 (34.7%)	
Conjunctivitis*	Never	2,259 (78.8%)	910 (34.4%)	<0.001
	Ever	609 (21.2%)	1,738 (65.6%)	
Eczema*	Never	2,208 (77.0%)	1,428 (53.9%)	<0.001
	Ever	660 (23.0%)	1,220 (46.1%)	
Nasal allergies*	Never	1,477 (51.5%)	88 (3.3%)	<0.001
	Ever	1,391 (48.5%)	2,560 (96.7%)	
Eosinophils count, cells/mm^3	Mean (SD)	180.2 (119.6)	216.4 (155.0)	<0.001
Age of onset of rhinitis	Mean (SD)	30.9 (17.1)	20.8 (13.1)	<0.001
Dust mites or house dust trigger*	No	2,555 (89.1%)	1,362 (51.4%)	<0.001
	Yes	313 (10.9%)	1,286 (48.6%)	
Animals trigger*	No	2,824 (98.5%)	2,108 (79.6%)	<0.001
	Yes	44 (1.5%)	540 (20.4%)	
Air pollution trigger*	No	2,518 (87.8%)	1,716 (64.8%)	<0.001
	Yes	350 (12.2%)	932 (35.2%)	
Change in weather trigger*	No	2,114 (73.7%)	1,851 (69.9%)	0.002
	Yes	754 (26.3%)	797 (30.1%)	
Tobacco trigger*	No	2,774 (96.7%)	2,422 (91.5%)	<0.001
	Yes	94 (3.3%)	226 (8.5%)	
Pollens trigger*	No	2,457 (85.7%)	719 (27.2%)	<0.001
	Yes	411 (14.3%)	1,929 (72.8%)	
Cold air trigger*	No	2,126 (74.1%)	2,003 (75.6%)	0.21
	Yes	742 (25.9%)	645 (24.4%)	
Other trigger*	No	2,521 (87.9%)	2,304 (87.0%)	0.34
	Yes	347 (12.1%)	344 (13.0%)	
Unknown trigger*	No	1,439 (50.2%)	2,338 (88.3%)	<0.001
	Yes	1,429 (49.8%)	310 (11.7%)	
Number of reported triggers	Mean (SD)	1.6 (0.8)	2.6 (1.4%)	<0.001
Rhinorrhea symptom	No	1,190 (41.5%)	554 (20.9%)	<0.001
	Yes	1,678 (58.5%)	2,094 (79.1%)	
Congestion symptom	No	1,102 (38.4%)	532 (20.1%)	<0.001
	Yes	1,766 (61.6%)	2,116 (79.9%)	
Itching symptom	No	1,759 (61.3%)	593 (22.4%)	<0.001
	Yes	1,109 (38.7%)	2,055 (77.6%)	
Sneezing symptom	No	1,383 (48.2%)	467 (17.6%)	<0.001
	Yes	1,485 (51.8%)	2,181 (82.4%)	
Associated eye symptoms	No	1,908 (66.5%)	443 (16.7%)	<0.001
	Yes	960 (33.5%)	2,205 (83.3%)	
Number of symptoms	Mean (SD)	2.4 (1.2)	4.0 (1.0)	<0.001
Rhinorrhea symptom score*	0	1,190 (41.5%)	554 (20.9%)	<0.001

Variables	Levels	Cluster 1 (n=2,868)	Cluster 2 (n=2,468)	p
	1	567 (19.8%)	201 (7.6%)	
	2	945 (32.9%)	1,240 (46.8%)	
	3	166 (5.8%)	653 (24.7%)	
Congestion symptom score*	0	1,102 (38.4%)	532 (20.1%)	<0.001
	1	379 (13.2%)	178 (6.7%)	
	2	812 (28.3%)	959 (36.2%)	
	3	575 (20.0%)	979 (37.0%)	
Itching symptom score*	0	1,759 (61.3%)	593 (22.4%)	<0.001
	1	664 (23.2%)	567 (21.4%)	
	2	433 (15.1%)	1,215 (45.9%)	
	3	12 (0.4%)	273 (10.3%)	
Sneezing symptom score*	0	1,383 (48.2%)	467 (17.6%)	<0.001
	1	784 (27.3%)	432 (16.3%)	
	2	636 (22.2%)	1,272 (48.0%)	
	3	65 (2.3%)	477 (18.0%)	
Associated eye symptoms score*	0	1,908 (66.5%)	443 (16.7%)	<0.001
	1	398 (13.9%)	325 (12.3%)	
	2	490 (17.1%)	1,398 (52.8%)	
	3	72 (2.5%)	482 (18.2%)	
Severity of rhinitis	Mild	2,193 (76.5%)	1,353 (51.1%)	<0.001
	Moderate-Severe	675 (23.5%)	1,295 (48.9%)	
Total Symptom Score 4 (TNSS4)	Mean (SD)	3.7 (2.1)	6.8 (2.6)	<0.001
Duration of rhinitis*	Intermittent	2,144 (74.8%)	1,740 (65.7%)	<0.001
	Persistent	724 (25.2%)	908 (34.3%)	
ARIA classification	Mild/Intermittent	1,676 (58.4%)	953 (36.0%)	<0.001
	Mild/Persistent	517 (18.0%)	400 (15.1%)	
	Moderate-Severe/Intermittent	468 (16.3%)	787 (29.7%)	
	Moderate-Severe/Persistent	207 (7.2%)	508 (19.2%)	
Rhinitis treatment*	Neither OAH nor INCS	1,953 (68.1%)	520 (19.6%)	<0.001
	OAH only	208 (7.3%)	785 (29.6%)	
	INCS only	490 (17.1%)	192 (7.3%)	
	OAH and INCS	217 (7.6%)	1,151 (43.5%)	
Symptoms in Winter*	No	1,285 (44.8%)	1,538 (58.1%)	<0.001
	Yes	1,583 (55.2%)	1,110 (41.9%)	
Symptoms in Spring*	No	967 (33.7%)	304 (11.5%)	<0.001
	Yes	1,901 (66.3%)	2,344 (88.5%)	
Symptoms in Summer*	No	1,862 (64.9%)	1,041 (39.3%)	<0.001
	Yes	1006 (35.1%)	1,607 (60.7%)	
Symptoms in Autumn*	No	1,157 (40.3%)	1,235 (46.6%)	<0.001
	Yes	1,711 (59.7%)	1,413 (53.4%)	

*Data are n (%) or mean (SD), *: variables included in cluster analysis*

Table S6: Description and comparison of the four clusters identified in Constances

Variables	Levels	Cluster 1 (n=1,620)	Cluster 2 (n=1,291)	Cluster 3 (n=2,072)	Cluster 4 (n=533)	p
Sex	Men	764 (47.2%)	596 (46.2%)	847 (40.9%)	194 (36.4%)	<0.001
	Women	856 (52.8%)	695 (53.8%)	1,225 (59.1%)	339 (63.6%)	
Age, years*	Mean (SD)	53.2 (12.7)	49.9 (13.3)	47.9 (12.5)	44.8 (12.1)	<0.001
Tobacco status	Never smoker	668 (42.7%)	548 (44.3%)	997 (49.9%)	245 (47.9%)	<0.001
	Ex-smoker	688 (44.0%)	477 (38.5%)	782 (39.2%)	192 (37.6%)	
	Current smoker	208 (13.3%)	213 (17.2%)	218 (10.9%)	74 (14.5%)	
Educational level	Less than high school	107 (6.7%)	94 (7.3%)	121 (5.9%)	43 (8.1%)	0.04
	High school	472 (29.4%)	368 (28.8%)	530 (25.8%)	140 (26.4%)	
	University	1,029 (64.0%)	818 (63.9%)	1,406 (68.4%)	348 (65.5%)	
Body-mass index, kg/m^2	<18.5	28 (1.8%)	33 (2.6%)	44 (2.2%)	10 (1.9%)	0.07
	[18.5 - 25[	888 (55.9%)	769 (60.9%)	1,205 (58.9%)	321 (61.8%)	
	[25 - 30[	506 (31.8%)	349 (27.7%)	584 (28.6%)	135 (26.0%)	
	≥30	167 (10.5%)	111 (8.8%)	212 (10.4%)	53 (10.2%)	
Asthma*	Never	1,519 (93.8%)	1,143 (88.5%)	1,398 (67.5%)	330 (61.9%)	<0.001
	Ever	101 (6.2%)	148 (11.5%)	674 (32.5%)	203 (38.1%)	
Conjunctivitis*	Never	1,282 (79.1%)	960 (74.4%)	734 (35.4%)	193 (36.2%)	<0.001
	Ever	338 (20.9%)	331 (25.6%)	1,338 (64.6%)	340 (63.8%)	
Eczema*	Never	1,261 (77.8%)	941 (72.9%)	1,155 (55.7%)	279 (52.3%)	<0.001
	Ever	359 (22.2%)	350 (27.1%)	917 (44.3%)	254 (47.7%)	
Nasal allergies*	Never	866 (53.5%)	608 (47.1%)	67 (3.2%)	24 (4.5%)	<0.001
	Ever	754 (46.5%)	683 (52.9%)	2,005 (96.8%)	509 (95.5%)	
Eosinophils count, cells/mm^3	Mean (SD)	180.4 (122.7)	184.0 (133.0)	210.5 (144.0)	232.4 (166.0)	<0.001
Age of onset of rhinitis	Mean (SD)	33.5 (17.2)	26.3 (16.2)	21.6 (13.5)	19.9 (12.8)	<0.001
Dust mites or house dust trigger*	No	1,533 (94.6%)	1,012 (78.4%)	1,103 (53.2%)	269 (50.5%)	<0.001
	Yes	87 (5.4%)	279 (21.6%)	969 (46.8%)	264 (49.5%)	
Animals trigger*	No	1,607 (99.2%)	1,246 (96.5%)	1,677 (80.9%)	402 (75.4%)	<0.001
	Yes	13 (0.8%)	45 (3.5%)	395 (19.1%)	131 (24.6%)	
Air pollution trigger*	No	1,564 (96.5%)	937 (72.6%)	1,401 (67.6%)	332 (62.3%)	<0.001
	Yes	56 (3.5%)	354 (27.4%)	671 (32.4%)	201 (37.7%)	
Change in weather trigger*	No	1,562 (96.4%)	460 (35.6%)	1,587 (76.6%)	356 (66.8%)	<0.001
	Yes	58 (3.6%)	831 (64.4%)	485 (23.4%)	177 (33.2%)	
Tobacco trigger*	No	1,605 (99.1%)	1,181 (91.5%)	1,936 (93.4%)	474 (88.9%)	<0.001
	Yes	15 (0.9%)	110 (8.5%)	136 (6.6%)	59 (11.1%)	
Pollens trigger*	No	1,482 (91.5%)	1,051 (81.4%)	453 (21.9%)	190 (35.6%)	<0.001
	Yes	138 (8.5%)	240 (18.6%)	1,619 (78.1%)	343 (64.4%)	
Cold air trigger*	No	1,544 (95.3%)	488 (37.8%)	1,704 (82.2%)	393 (73.7%)	<0.001
	Yes	76 (4.7%)	803 (62.2%)	368 (17.8%)	140 (26.3%)	
Other trigger*	No	1,426 (88.0%)	1,121 (86.8%)	1,843 (88.9%)	435 (81.6%)	<0.001
	Yes	194 (12.0%)	170 (13.2%)	229 (11.1%)	98 (18.4%)	
Unknown trigger*	No	314 (19.4%)	1,177 (91.2%)	1,850 (89.3%)	436 (81.8%)	<0.001
	Yes	1,306 (80.6%)	114 (8.8%)	222 (10.7%)	97 (18.2%)	
Number of reported triggers	Mean (SD)	1.2 (0.5)	2.3 (1.1)	2.5 (1.3)	2.8 (1.6%)	<0.001
Rhinorrhea symptom	No	665 (41.0%)	512 (39.7%)	509 (24.6%)	58 (10.9%)	<0.001
	Yes	955 (59.0%)	779 (60.3%)	1,563 (75.4%)	475 (89.1%)	
Congestion symptom	No	706 (43.6%)	347 (26.9%)	533 (25.7%)	48 (9.0%)	<0.001
	Yes	914 (56.4%)	944 (73.1%)	1,539 (74.3%)	485 (91.0%)	
Itching symptom	No	1,011 (62.4%)	763 (59.1%)	501 (24.2%)	77 (14.4%)	<0.001
	Yes	609 (37.6%)	528 (40.9%)	1,571 (75.8%)	456 (85.6%)	
Sneezing symptom	No	762 (47.0%)	652 (50.5%)	406 (19.6%)	30 (5.6%)	<0.001
	Yes	858 (53.0%)	639 (49.5%)	1,666 (80.4%)	503 (94.4%)	
Associated eye symptoms	No	1,119 (69.1%)	795 (61.6%)	377 (18.2%)	60 (11.3%)	<0.001
	Yes	501 (30.9%)	496 (38.4%)	1,695 (81.8%)	473 (88.7%)	
Number of symptoms	Mean (SD)	2.4 (1.2)	2.6 (1.2)	3.9 (1.1)	4.5 (0.8%)	<0.001
Rhinorrhea symptom score*	0	665 (41.0%)	512 (39.7%)	509 (24.6%)	58 (10.9%)	<0.001

Variables	Levels	Cluster 1 (n=1,620)	Cluster 2 (n=1,291)	Cluster 3 (n=2,072)	Cluster 4 (n=533)	p
	1	346 (21.4%)	206 (16.0%)	204 (9.8%)	12 (2.3%)	
	2	512 (31.6%)	460 (35.6%)	1,163 (56.1%)	50 (9.4%)	
	3	97 (6.0%)	113 (8.8%)	196 (9.5%)	413 (77.5%)	
Congestion symptom score*	0	706 (43.6%)	347 (26.9%)	533 (25.7%)	48 (9.0%)	<0.001
	1	187 (11.5%)	184 (14.3%)	162 (7.8%)	24 (4.5%)	
	2	391 (24.1%)	449 (34.8%)	863 (41.7%)	68 (12.8)	
	3	336 (20.7%)	311 (24.1%)	514 (24.8%)	393 (73.7%)	
Itching symptom score*	0	1,011 (62.4%)	763 (59.1%)	501 (24.2%)	77 (14.4%)	<0.001
	1	342 (21.1%)	324 (25.1%)	512 (24.7%)	53 (9.9%)	
	2	260 (16.0%)	201 (15.6%)	1,049 (50.6%)	138 (25.9%)	
	3	7 (0.4%)	3 (0.2%)	10 (0.5%)	265 (49.7%)	
Sneezing symptom score*	0	762 (47.0%)	652 (50.5%)	406 (19.6%)	30 (5.6%)	<0.001
	1	453 (28.0%)	330 (25.6%)	401 (19.4%)	32 (6.0%)	
	2	373 (23.0%)	270 (20.9%)	1,186 (57.2%)	79 (14.8%)	
	3	32 (2.0%)	39 (3.0%)	79 (3.8%)	392 (73.5%)	
Associated eye symptoms score*	0	1,119 (69.1%)	795 (61.6%)	377 (18.2%)	60 (11.3%)	<0.001
	1	210 (13.0%)	199 (15.4%)	286 (13.8%)	28 (5.3%)	
	2	242 (14.9%)	250 (19.4%)	1,293 (62.4%)	103 (19.3%)	
	3	49 (3.0%)	47 (3.6%)	116 (5.6%)	342 (64.2%)	
Severity of rhinitis	Mild	1,223 (75.5%)	915 (70.9%)	1,408 (68.0%)	0 (0.0%)	<0.001
	Moderate-Severe	397 (24.5%)	376 (29.1%)	664 (32.0%)	533 (100.0%)	
TNSS4	Mean (SD)	3.6 (2.1)	4.0 (2.2)	5.9 (2.2%)	9.7 (2.1)	<0.001
Duration of rhinitis*	Intermittent	1,062 (65.6%)	1,077 (83.4%)	1,455 (70.2%)	290 (54.4%)	<0.001
	Persistent	558 (34.4%)	214 (16.6%)	617 (29.8%)	243 (45.6%)	
ARIA classification	Mild/Intermittent	838 (51.7%)	770 (59.6%)	1,021 (49.3%)	0 (0.0%)	<0.001
	Mild/Persistent	385 (23.8%)	145 (11.2%)	387 (18.7%)	0 (0.0%)	
	Moderate-Severe/Intermittent	224 (13.8%)	307 (23.8%)	434 (20.9%)	290 (54.4%)	
	Moderate-Severe/Persistent	173 (10.7%)	69 (5.3%)	230 (11.1%)	243 (45.6%)	
Rhinitis treatment*	Neither OAH nor INCS	1,096 (67.7%)	839 (65.0%)	471 (22.7%)	67 (12.6%)	<0.001
	OAH only	100 (6.2%)	97 (7.5%)	664 (32.0%)	132 (24.8%)	
	INCS only	290 (17.9%)	227 (17.6%)	130 (6.3%)	35 (6.6%)	
	OAH and INCS	134 (8.3%)	128 (9.9%)	807 (38.9%)	299 (56.1%)	
Symptoms in Winter*	No	720 (44.4%)	483 (37.4%)	1,359 (65.6%)	261 (49.0%)	<0.001
	Yes	900 (55.6%)	808 (62.6%)	713 (34.4%)	272 (51.0%)	
Symptoms in Spring*	No	445 (27.5%)	524 (40.6%)	233 (11.2%)	69 (12.9%)	<0.001
	Yes	1,175 (72.5%)	767 (59.4%)	1,839 (88.8%)	464 (87.1%)	
Symptoms in Summer*	No	868 (53.6%)	1,025 (79.4%)	826 (39.9%)	184 (34.5%)	<0.001
	Yes	752 (46.4%)	266 (20.6%)	1,246 (60.1%)	349 (65.5%)	
Symptoms in Autumn*	No	626 (38.6%)	461 (35.7%)	1,117 (53.9%)	188 (35.3%)	<0.001
	Yes	994 (61.4%)	830 (64.3%)	955 (46.1%)	345 (64.7%)	

*Data are n (%) or mean (SD), *: variables included in cluster analysis*

Appendix 8: Identification of rhinitis endotypes using an unsupervised approach in EGEA – Supplementary material

Table S1: EGEA analysis population (n=328)

	All (n=328)	Never asthma (n=140)	Ever Asthma (n=188)	p
Sex				0.39
Men	146 (44.5%)	58 (41.4%)	88 (46.8%)	
Women	182 (55.5%)	82 (58.6%)	100 (53.2%)	
Age, year	41.3 (16.6)	44.9 (16.4)	38.7 (16.3%)	0.001
Tobacco status				0.22
Never smoker	155 (47.3%)	61 (43.6%)	94 (50.0%)	
Ex-smoker	87 (26.5%)	44 (31.4%)	43 (22.9%)	
Current smoker	86 (26.2%)	35 (25.0%)	51 (27.1%)	
Educational level				0.41
Less than high school	63 (19.3%)	29 (20.7%)	34 (18.2%)	
High school	87 (26.6%)	32 (22.9%)	55 (29.4%)	
University	177 (54.1%)	79 (56.4%)	98 (52.4%)	
Conjunctivitis				0.02
Never	175 (53.4%)	86 (61.4%)	89 (47.3%)	
Ever	153 (46.6%)	54 (38.6%)	99 (52.7%)	
Eczema				0.05
Never	187 (57.0%)	89 (63.6%)	98 (52.1%)	
Ever	141 (43.0%)	51 (36.4%)	90 (47.9%)	
Nasal allergies				<0.001
Never	92 (28.0%)	59 (42.1%)	33 (17.6%)	
Ever	236 (72.0%)	81 (57.9%)	155 (82.4%)	
Age of onset of rhinitis, year	20.5 (16.6)	27.3 (17.2)	15.4 (14.2)	<0.001
Triggers of nasal symptoms†				
Dust mites or house dust	139 (42.4%)	35 (25.0%)	104 (55.3%)	<0.001
Pollens	187 (57.0%)	68 (48.6%)	119 (63.3%)	0.01
Animals	86 (26.2%)	17 (12.1%)	69 (36.7%)	<0.001
Other	41 (12.5%)	28 (20.0%)	13 (6.9%)	0.001
No trigger reported	44 (13.4%)	26 (18.6%)	18 (9.6%)	0.03
Symptoms after a stimulus				
Rhinorrhea after a stimulus	234 (71.3%)	88 (62.9%)	146 (77.7%)	0.005
Sneezing after a stimulus	264 (80.5%)	108 (77.1%)	156 (83.0%)	0.24
Eye symptoms after a stimulus	244 (74.4%)	102 (72.9%)	142 (75.5%)	0.67
Disturbance due to nasal symptoms				0.001
No	164 (50.0%)	83 (59.3%)	81 (43.1%)	
Low	107 (32.6%)	46 (32.9%)	61 (32.4%)	
Medium	41 (12.5%)	9 (6.4%)	32 (17.0%)	
High	16 (4.9%)	2 (1.4%)	14 (7.4%)	
Duration of rhinitis				0.006
<1 month/year	127 (38.7%)	68 (48.6%)	59 (31.4%)	
<4 days/week	87 (26.5%)	33 (23.6%)	54 (28.7%)	
≥4 days/week	114 (34.8%)	39 (27.9%)	75 (39.9%)	
At least one positive SPT				<0.001
No	96 (29.3%)	63 (45.0%)	33 (17.6%)	
Yes	232 (70.7%)	77 (55.0%)	155 (82.4%)	

Data are n (%) or mean (SD), †: several possible answers

Table S2: Description and comparison of the three clusters identified in EGEA – All the variables of interest were selected for the cluster analysis (n=77)

	Cluster 1 (n=20)	Cluster 2 (n=27)	Cluster 3 (n=30)	p
Sex				0.95
Men	8 (40.0%)	11 (40.7%)	11 (36.7%)	
Women	12 (60.0%)	16 (59.3%)	19 (63.3%)	
Age, year	51.4 (14.6)	32.9 (15.3)	32.3 (12.3)	<0.001
Tobacco status				0.22
Never smoker	10 (50.0%)	18 (66.7%)	19 (63.3%)	
Ex-smoker	6 (30.0%)	4 (14.8%)	2 (6.7%)	
Current smoker	4 (20.0%)	5 (18.5%)	9 (30.0%)	
Educational level				0.21
<High school	5 (25.0%)	5 (18.5%)	2 (6.7%)	
High school	2 (10.0%)	8 (29.6%)	10 (33.3%)	
University	13 (65.0%)	14 (51.9%)	18 (60.0%)	
Asthma*				<0.001
Never	14 (70.0%)	3 (11.1%)	8 (26.7%)	
Ever	6 (30.0%)	24 (88.9%)	22 (73.3%)	
Conjunctivitis*				0.97
Never	10 (50.0%)	13 (48.1%)	14 (46.7%)	
Ever	10 (50.0%)	14 (51.9%)	16 (53.3%)	
Eczema*				0.46
Never	12 (60.0%)	15 (55.6%)	13 (43.3%)	
Ever	8 (40.0%)	12 (44.4%)	17 (56.7%)	
Nasal allergies*				<0.001
Never	12 (60.0%)	6 (22.2%)	3 (10.0%)	
Ever	8 (40.0%)	21 (77.8%)	27 (90.0%)	
Age of onset of rhinitis, year*	29.8 (16.5)	12.7 (13.6%)	11.9 (8.6)	<0.001
Triggers of nasal symptoms†				
Dust mites or house dust*	3 (15.0%)	15 (55.6%)	16 (53.3%)	0.009
Pollens*	3 (15.0%)	12 (44.4%)	25 (83.3%)	<0.001
Animals*	0 (0.0%)	12 (44.4%)	13 (43.3%)	0.002
Other*	4 (20.0%)	3 (11.1%)	0 (0.0%)	0.05
No trigger reported*	10 (50.0%)	2 (7.4%)	1 (3.3%)	<0.001
Symptoms after a stimulus†				
Rhinorrhea*	10 (50.0%)	23 (85.2%)	26 (86.7%)	0.005
Sneezing*	16 (80.0%)	24 (88.9%)	30 (100.0%)	0.05
Eye symptoms after*	14 (70.0%)	21 (77.8%)	27 (90.0%)	0.20
Disturbance due to nasal symptoms*				0.45
No	12 (60.0%)	17 (63.0%)	12 (40.0%)	
Low	6 (30.0%)	8 (29.6%)	10 (33.3%)	
Medium	1 (5.0%)	1 (3.7%)	5 (16.7%)	
High	1 (5.0%)	1 (3.7%)	3 (10.0%)	
Duration of rhinitis*				0.72
<1 month/year	6 (30.0%)	13 (48.1%)	14 (46.7%)	
<4 days/week	5 (25.0%)	5 (18.5%)	7 (23.3%)	
≥4 days/week	9 (45.0%)	9 (33.3%)	9 (30.0%)	
Allergy pathway				

	Cluster 1 (n=20)	Cluster 2 (n=27)	Cluster 3 (n=30)	p
At least one positive SPT*	5 (25.0%)	24 (88.9%)	30 (100.0%)	<0.001
IgE, IU/mL*	105.8 (154.4)	163.9 (155.5)	349.2 (466.0)	0.02
IL-1RA, pg/mL*	1.0 (2.1)	0.4 (0.7)	0.4 (0.2)	0.17
IL-5, pg/mL*	0.4 (0.2)	0.2 (0.1)	0.5 (0.3)	<0.001
IL-7, pg/mL*	0.7 (0.4)	0.2 (0.1)	0.7 (0.3)	<0.001
IL-8, pg/mL*	0.4 (0.2)	0.1 (0.1)	0.6 (0.3)	<0.001
IL-10, pg/mL*	1.1 (2.1)	0.3 (0.7)	0.5 (0.4)	0.09
IL-13, pg/mL*	0.6 (0.4)	0.2 (0.1)	0.6 (0.3)	<0.001
Inflammation pathway				
Eosinophils, cells/mm^3*	180.0 (143.1)	196.3 (107.6)	245.3 (182.8)	0.27
Neutrophils, cells/mm^3*	4099.0 (1141.6)	3626.3 (1169.7)	3907.7 (1589.9)	0.48
FeNO 50 mL/s*	14.6 (8.4)	20.9 (19.6)	22.8 (10.7)	0.13
EDN ng/mL*	24.0 (13.5)	29.6 (13.4)	35.3 (21.0)	0.07
ECP ng/mL*	5.2 (4.7)	3.5 (1.6)	15.7 (49.3)	0.29
HS-CRP mg/L*	1.5 (1.3)	1.6 (1.7)	2.1 (4.8)	0.73
CC-16, µg/L*	14.8 (0.9)	14.9 (1.2)	15.1 (0.8)	0.43
TNFa, pg/mL *	0.5 (0.4)	0.2 (0.1)	0.5 (0.2)	<0.001
Leptin, pg/mL*	1.1 (0.6)	0.6 (0.7)	0.7 (0.6)	0.06
TARC plasma EDTA, pg/mL*	92.4 (64.0)	71.4 (77.1)	90.7 (50.0)	0.43
TSLP plasma EDTA, pg/mL*	0.7 (0.3)	0.6 (0.2)	0.6 (0.5)	0.95
Oxidative/Nitrosative pathway				
NO_2/NO_3 plasma, µM*	41.5 (17.8)	45.1 (22.2)	43.6 (30.1)	0.89
NO_2/NO_3 condensate, µM*	3.7 (4.9)	7.3 (8.8)	8.0 (14.8)	0.37
FIOPs, RFU/mL*	95.5 (16.2)	90.8 (18.3)	90.3 (19.5)	0.58
EBC 8-iso, pg/mL*	8.2 (17.8)	10.5 (8.3)	3.7 (2.7)	0.05
SOD U/g*	1227.4 (273.9)	1376.9 (323.5)	1204.2 (254.4)	0.06
GPX U/g*	44.0 (8.0)	38.4 (8.6)	37.1 (6.8)	0.009
Catalase, k/g*	138.6 (29.6)	167.7 (36.0)	166.1 (34.3)	0.008

*Data are n (%) or mean (SD), AR: Allergic Rhinitis, CC-16: Clara Cell protein-16, CRP: C-Reactive Protein, EBC 8-iso: Exalate Breath Condensate 8-isoprostanes, ECP: Eosinophil Cationic Protein, EDN: Eosinophil Derived Neurotoxin, FeNO: Fraction Exhaled Nitric Oxide, FlOP: Fluorescent oxidation product, GPX: Glutathione peroxidase, IgE: Immunoglobulin E, IL: Interleukin, SOD: Superoxide dismutase, SPT: Skin Prick Test, TARC: Thymus and Activation-Regulated Chemokine, TNF: Tumor Necrosis Factor, TSLP: Thymic Stromal Lymphopoietin, †: several possible answers, *: variables included in the construction of the clusters*

Table S3: Description and comparison of the two clusters identified in EGEA – Only biological variables of interest were selected for the cluster analysis (n=437)

Variables	Cluster 1 (n=198)	Cluster 2 (n=239)	p
Sex			<0.001
Men	65 (32.8%)	125 (52.3%)	
Women	133 (67.2%)	114 (47.7%)	
Age, year	47.4 (16.3)	38.9 (15.8)	<0.001
Tobacco status			0.26
Never smoker	96 (48.5%)	113 (47.3%)	
Ex-smoker	58 (29.3%)	58 (24.3%)	
Current smoker	44 (22.2%)	68 (28.5%)	
Educational level			0.06
Less than high school	50 (25.4%)	40 (16.8%)	
High school	50 (25.4%)	77 (32.4%)	
University	97 (49.2%)	121 (50.8%)	
Asthma			<0.001
Never	116 (58.6%)	75 (31.4%)	
Ever	82 (41.4%)	164 (68.6%)	
Conjunctivitis			<0.001
Never	128 (66.7%)	108 (46.2%)	
Ever	64 (33.3%)	126 (53.8%)	
Eczema			0.03
Never	124 (62.9%)	124 (52.3%)	
Ever	73 (37.1%)	113 (47.7%)	
Nasal allergies			<0.001
Never	85 (44.0%)	41 (17.5%)	
Ever	108 (56.0%)	193 (82.5%)	
Age of onset of rhinitis, year	27.8 (18.7)	17.4 (14.3)	<0.001
Triggers of nasal symptoms†			
Dust mites or house dust	55 (27.8%)	119 (49.8%)	<0.001
Pollens	81 (40.9%)	149 (62.3%)	<0.001
Animals	21 (10.6%)	83 (34.7%)	<0.001
Other	46 (23.2%)	20 (8.4%)	<0.001
No trigger reported	45 (22.7%)	17 (7.1%)	<0.001
Symptoms after a stimulus†			
Rhinorrhea	114 (65.1%)	168 (76.0%)	0.02
Sneezing	142 (79.3%)	192 (84.6%)	0.21
Eye symptoms	137 (76.5%)	173 (75.2%)	0.85
Disturbance due to nasal symptoms			0.007
No	119 (60.1%)	114 (47.7%)	
Low	58 (29.3%)	72 (30.1%)	
Medium	16 (8.1%)	36 (15.1%)	
High	5 (2.5%)	17 (7.1%)	
Duration of rhinitis			0.22
<1 month/year	89 (45.2%)	90 (38.0%)	
<4 days/week	50 (25.4%)	60 (25.3%)	
≥4 days/week	58 (29.4%)	87 (36.7%)	
Allergy pathway			
At least one positive SPT*	75 (37.9%)	207 (86.6%)	<0.001
IgE, IU/mL*	74.8 (96.2)	429.3 (611.9)	<0.001
IL-1RA, pg/mL	0.4 (0.7)	0.4 (0.7)	0.99

Variables	Cluster 1 (n=198)	Cluster 2 (n=239)	p
IL-5, pg/mL	0.4 (0.3)	0.5 (0.6)	0.07
IL-7, pg/mL	0.6 (0.3)	0.6 (0.5)	0.14
IL-8, pg/mL	0.4 (0.3)	0.4 (0.4)	0.35
IL-10, pg/mL	0.4 (0.6)	0.5 (0.8)	0.53
IL-13, pg/mL	0.5 (0.3)	0.5 (0.4)	0.07
Inflammation pathway			
Eosinophils, cells/mm^3*	141.8 (89.8)	285.7 (197.2)	<0.001
Neutrophils, cells/mm^3*	3973.5 (1268.7)	4001.2 (1441.4)	0.83
FeNO, 50 mL/s	15.5 (10.6)	24.8 (16.4)	<0.001
EDN, ng/mL*	20.1 (8.1)	36.3 (16.1)	<0.001
ECP, ng/mL*	3.7 (2.5)	7.6 (18.1)	0.003
HS-CRP, mg/L*	2.0 (2.6)	2.9 (5.2)	0.02
CC-16, µg/L*	14.9 (1.0)	15.2 (1.0)	0.001
TNFa, pg/mL	0.3 (0.3)	0.4 (0.4)	0.08
Leptin, pg/mL	0.9 (0.6)	0.8 (0.7)	0.20
TARC plasma EDTA, pg/mL*	91.4 (81.8)	117.0 (217.6)	0.12
TSLP plasma EDTA, pg/mL*	0.6 (0.3)	0.7 (0.5)	0.007
Oxidative/Nitrosative pathway			
NO_2/NO_3 plasma, µM*	47.7 (32.1)	38.5 (21.6)	<0.001
NO2/NO3 condensate, µM	4.1 (6.6)	4.2 (7.2)	0.91
FIOPs, RFU/mL*	98.5 (22.8)	93.7 (23.2)	0.03
EBC 8-iso, pg/mL	9.8 (28.2)	4.9 (5.1)	0.06
SOD, U/g*	1214.2 (279.8)	1289.4 (277.3)	0.005
GPX, U/g*	42.0 (8.7)	38.4 (8.0)	<0.001
Catalase, k/g*	159.6 (39.5)	169.7 (41.1)	0.01

*Data are n (%) or mean (SD), AR: Allergic Rhinitis, CC-16: Clara Cell protein-16, CRP: C-Reactive Protein, EBC 8-iso: Exalate Breath Condensate 8-isoprostanes, ECP: Eosinophil Cationic Protein, EDN: Eosinophil Derived Neurotoxin, FeNO: Fraction Exhaled Nitric Oxide, FlOP: Fluorescent oxidation product, GPX: Glutathione peroxidase, IgE: Immunoglobulin E, IL: Interleukin, SOD: Superoxide dismutase, SPT: Skin Prick Test, TARC: Thymus and Activation-Regulated Chemokine, TNF: Tumor Necrosis Factor, TSLP: Thymic Stromal Lymphopoietin, †: several possible answers, *: variables included in the construction of the clusters*

Table S4: Description and comparison of the two clusters identified in EGEA – Only biological variables of interest were selected for the cluster analysis (n=437) – Stratification according to asthma status

Variables	Levels	Never asthma			Ever asthma		
		Cluster 1 (n=89)	Cluster 2 (n=102)	p	Cluster 1 (n=136)	Cluster 2 (n=110)	p
Sex	Men	28 (31.5)	46 (45.1)	0.075	28 (31.5)	46 (45.1)	0.075
	Women	61 (68.5)	56 (54.9)		61 (68.5)	56 (54.9)	
Age, year	Mean (SD)	48.9 (14.7)	44.8 (17.1)	0.078	48.9 (14.7)	44.8 (17.1)	0.078
Tobacco status	Never smoker	44 (49.4)	47 (46.1)	0.173	44 (49.4)	47 (46.1)	0.173
	Ex-smoker	31 (34.8)	28 (27.5)		31 (34.8)	28 (27.5)	
	Current smoker	14 (15.7)	27 (26.5)		14 (15.7)	27 (26.5)	
Educational level	<High school	23 (25.8)	20 (19.6)	0.375	23 (25.8)	20 (19.6)	0.375
	High school	20 (22.5)	31 (30.4)		20 (22.5)	31 (30.4)	
	University	46 (51.7)	51 (50.0)		46 (51.7)	51 (50.0)	
Conjunctivitis	Never	66 (75.9)	57 (57.6)	0.013	66 (75.9)	57 (57.6)	0.013
	Ever	21 (24.1)	42 (42.4)		21 (24.1)	42 (42.4)	
Eczema	Never	55 (62.5)	70 (68.6)	0.463	55 (62.5)	70 (68.6)	0.463
	Ever	33 (37.5)	32 (31.4)		33 (37.5)	32 (31.4)	
Nasal allergies	Never	48 (56.5)	37 (37.0)	0.012	48 (56.5)	37 (37.0)	0.012
	Ever	37 (43.5)	63 (63.0)		37 (43.5)	63 (63.0)	
Age of onset of rhinitis, year	Mean (SD)	32.0 (18.2)	26.6 (17.2)	0.045	32.0 (18.2)	26.6 (17.2)	0.045
Dust mites or house dust trigger	No	74 (83.1)	71 (69.6)	0.044	74 (83.1)	71 (69.6)	0.044
	Yes	15 (16.9)	31 (30.4)		15 (16.9)	31 (30.4)	
Animals trigger	No	84 (94.4)	87 (85.3)	0.07	84 (94.4)	87 (85.3)	0.07
	Yes	5 (5.6)	15 (14.7)		5 (5.6)	15 (14.7)	
Pollens trigger	No	61 (68.5)	47 (46.1)	0.003	61 (68.5)	47 (46.1)	0.003
	Yes	28 (31.5)	55 (53.9)		28 (31.5)	55 (53.9)	
No trigger reported	No	64 (71.9)	91 (89.2)	0.004	64 (71.9)	91 (89.2)	0.004
	Yes	25 (28.1)	11 (10.8)		25 (28.1)	11 (10.8)	
Other trigger	No	60 (67.4)	86 (84.3)	0.01	60 (67.4)	86 (84.3)	0.01
	Yes	29 (32.6)	16 (15.7)		29 (32.6)	16 (15.7)	
Rhinorrhea after a stimulus	No	31 (41.9)	32 (34.4)	0.406	31 (41.9)	32 (34.4)	0.406
	Yes	43 (58.1)	61 (65.6)		43 (58.1)	61 (65.6)	
Sneezing after a stimulus	No	19 (24.4)	16 (16.8)	0.301	19 (24.4)	16 (16.8)	0.301
	Yes	59 (75.6)	79 (83.2)		59 (75.6)	79 (83.2)	
Eye symptoms after a stimulus	No	21 (26.2)	26 (27.1)	1	21 (26.2)	26 (27.1)	1
	Yes	59 (73.8)	70 (72.9)		59 (73.8)	70 (72.9)	
Disturbance due to nasal symptoms	No	64 (71.9)	60 (58.8)	0.141	64 (71.9)	60 (58.8)	0.141
	Low	21 (23.6)	29 (28.4)		21 (23.6)	29 (28.4)	
	Medium	3 (3.4)	11 (10.8)		3 (3.4)	11 (10.8)	
	High	1 (1.1)	2 (2.0)		1 (1.1)	2 (2.0)	
Duration of rhinitis	None	0 (0.0)	0 (0.0)	0.428	0 (0.0)	0 (0.0)	0.428
	<1 month/year	44 (50.0)	50 (49.5)		44 (50.0)	50 (49.5)	
	<4 days/week	24 (27.3)	21 (20.8)		24 (27.3)	21 (20.8)	
	≥4 days/week	20 (22.7)	30 (29.7)		20 (22.7)	30 (29.7)	
At least one positive SPT*	No	66 (74.2)	36 (35.3)	<0.001	66 (74.2)	36 (35.3)	<0.001
	Yes	23 (25.8)	66 (64.7)		23 (25.8)	66 (64.7)	
Symptoms in Winter	No	35 (40.2)	54 (54.0)	0.083	35 (40.2)	54 (54.0)	0.083
	Yes	52 (59.8)	46 (46.0)		52 (59.8)	46 (46.0)	
Symptoms in Spring	No	30 (34.9)	29 (29.0)	0.483	30 (34.9)	29 (29.0)	0.483
	Yes	56 (65.1)	71 (71.0)		56 (65.1)	71 (71.0)	
Symptoms in Summer	No	34 (39.5)	44 (44.0)	0.641	34 (39.5)	44 (44.0)	0.641
	Yes	52 (60.5)	56 (56.0)		52 (60.5)	56 (56.0)	
Symptoms in Autumn	No	39 (45.3)	48 (48.0)	0.831	39 (45.3)	48 (48.0)	0.831

Variables	Levels	Never asthma			Ever asthma		
		Cluster 1 (n=89)	Cluster 2 (n=102)	p	Cluster 1 (n=136)	Cluster 2 (n=110)	p
	Yes	47 (54.7)	52 (52.0)		47 (54.7)	52 (52.0)	
Eosinophils, cells/mm^3*	Mean (SD)	119.2 (75.8)	241.2 (155.3)	<0.001	119.2 (75.8)	241.2 (155.3)	<0.001
Neutrophils, cells/mm^3*	Mean (SD)	3846.6 (1139.0)	3966.2 (1482.5)	0.537	3846.6 (1139.0)	3966.2 (1482.5)	0.537
FeNO, 50 mL/s	Mean (SD)	14.5 (9.7)	20.4 (11.6)	0.005	14.5 (9.7)	20.4 (11.6)	0.005
EDN, ng/mL*	Mean (SD)	17.7 (6.9)	30.4 (13.1)	<0.001	17.7 (6.9)	30.4 (13.1)	<0.001
ECP, ng/mL*	Mean (SD)	3.2 (2.2)	5.8 (4.2)	<0.001	3.2 (2.2)	5.8 (4.2)	<0.001
HS-CRP, mg/L*	Mean (SD)	1.9 (2.4)	2.4 (4.0)	0.295	1.9 (2.4)	2.4 (4.0)	0.295
CC-16, µg/L*	Mean (SD)	14.7 (1.0)	15.3 (1.0)	<0.001	14.7 (1.0)	15.3 (1.0)	<0.001
TNFa, pg/mL	Mean (SD)	0.3 (0.3)	0.5 (0.6)	0.149	0.3 (0.3)	0.5 (0.6)	0.149
Leptin, pg/mL	Mean (SD)	0.9 (0.6)	0.8 (0.6)	0.357	0.9 (0.6)	0.8 (0.6)	0.357
TARC plasma EDTA, pg/mL*	Mean (SD)	82.5 (68.7)	109.2 (105.3)	0.042	82.5 (68.7)	109.2 (105.3)	0.042
TSLP plasma EDTA, pg/mL*	Mean (SD)	0.6 (0.2)	0.7 (0.4)	0.017	0.6 (0.2)	0.7 (0.4)	0.017
NO_2/NO_3 plasma, µM*	Mean (SD)	51.9 (37.1)	41.3 (27.5)	0.025	51.9 (37.1)	41.3 (27.5)	0.025
NO_2/NO_3 condensate, µM	Mean (SD)	4.0 (6.5)	3.5 (3.9)	0.586	4.0 (6.5)	3.5 (3.9)	0.586
FlOPs, RFU/mL*	Mean (SD)	100.4 (24.2)	97.2 (23.4)	0.341	100.4 (24.2)	97.2 (23.4)	0.341
EBC 8-iso, pg/mL	Mean (SD)	10.2 (20.8)	4.2 (6.1)	0.044	10.2 (20.8)	4.2 (6.1)	0.044
SOD, U/g*	Mean (SD)	1204.2 (288.4)	1292.4 (297.4)	0.04	1204.2 (288.4)	1292.4 (297.4)	0.04
GPX, U/g*	Mean (SD)	42.8 (9.1)	39.0 (7.7)	0.002	42.8 (9.1)	39.0 (7.7)	0.002
Catalase, k/g*	Mean (SD)	160.2 (42.5)	172.2 (34.2)	0.033	160.2 (42.5)	172.2 (34.2)	0.033
IgE, IU/mL*	Mean (SD)	57.2 (80.5)	291.7 (497.2)	<0.001	57.2 (80.5)	291.7 (497.2)	<0.001
IL-1RA, pg/mL	Mean (SD)	0.4 (0.5)	0.3 (0.5)	0.68	0.4 (0.5)	0.3 (0.5)	0.68
IL-5, pg/mL	Mean (SD)	0.4 (0.3)	0.5 (0.6)	0.207	0.4 (0.3)	0.5 (0.6)	0.207
IL-7, pg/mL	Mean (SD)	0.6 (0.4)	0.7 (0.5)	0.303	0.6 (0.4)	0.7 (0.5)	0.303
IL-8, pg/mL	Mean (SD)	0.4 (0.3)	0.5 (0.5)	0.321	0.4 (0.3)	0.5 (0.5)	0.321
IL-10, pg/mL	Mean (SD)	0.5 (0.8)	0.5 (0.6)	0.851	0.5 (0.8)	0.5 (0.6)	0.851
IL-13, pg/mL	Mean (SD)	0.4 (0.3)	0.5 (0.2)	0.179	0.4 (0.3)	0.5 (0.2)	0.179

*Data are n (%) or mean (SD), AR: Allergic Rhinitis, CC-16: Clara Cell protein-16, CRP: C-Reactive Protein, EBC 8-iso: Exalate Breath Condensate 8-isoprostanes, ECP: Eosinophil Cationic Protein, EDN: Eosinophil Derived Neurotoxin, FeNO: Fraction Exhaled Nitric Oxide, FlOP: Fluorescent oxidation product, GPX: Glutathione peroxidase, IgE: Immunoglobulin E, IL: Interleukin, SOD: Superoxide dismutase, SPT: Skin Prick Test, TARC: Thymus and Activation-Regulated Chemokine, TNF: Tumor Necrosis Factor, TSLP: Thymic Stromal Lymphopoietin, †: several possible answers, *: variables included in the construction of the clusters*

Table S5: Description and comparison of the two clusters identified in EGEA after imputation (n=842)

Variables	Levels	Cluster 1 (n=351)	Cluster 2 (n=491)	p
Sex	Men	159 (45.3)	240 (48.9)	0.339
	Women	192 (54.7)	251 (51.1)	
Age, year	Mean (SD)	49.4 (16.2)	35.7 (14.2)	<0.001
Tobacco status	Never smoker	177 (50.4)	255 (52.0)	<0.001
	Ex-smoker	109 (31.1)	97 (19.8)	
	Current smoker	65 (18.5)	138 (28.2)	
Educational level	<High school	100 (30.5)	68 (14.6)	<0.001
	High school	88 (26.8)	149 (32.0)	
	University	140 (42.7)	248 (53.3)	
Asthma*	Never	252 (74.8)	214 (44.8)	<0.001
	Ever	85 (25.2)	264 (55.2)	
Conjunctivitis*	Never	240 (68.8)	245 (50.4)	<0.001
	Ever	109 (31.2)	241 (49.6)	
Eczema*	Never	222 (65.7)	42 (8.6)	<0.001
	Ever	116 (34.3)	444 (91.4)	
Nasal allergies*	Never	32.2 (18.6)	14.1 (10.8)	<0.001
	Ever	293 (83.5)	210 (42.8)	<0.001
Age of onset of rhinitis, year*	Mean (SD)	58 (16.5)	281 (57.2)	
Dust mites or house dust trigger*	No	343 (97.7)	314 (64.0)	<0.001
	Yes	8 (2.3)	177 (36.0)	
Animals trigger*	No	280 (79.8)	134 (27.3)	<0.001
	Yes	71 (20.2)	357 (72.7)	
Pollens trigger*	No	236 (67.2)	483 (98.4)	<0.001
	Yes	115 (32.8)	8 (1.6)	
No trigger reported*	No	235 (67.0)	474 (96.5)	<0.001
	Yes	116 (33.0)	17 (3.5)	
Other trigger*	No	159 (53.9)	69 (15.1)	<0.001
	Yes	136 (46.1)	389 (84.9)	
Rhinorrhea after a stimulus*	No	103 (33.4)	39 (8.5)	<0.001
	Yes	205 (66.6)	422 (91.5)	
Sneezing after a stimulus*	No	128 (41.6)	62 (13.4)	<0.001
	Yes	180 (58.4)	401 (86.6)	
Eye symptoms after a stimulus*	No	243 (69.2)	201 (40.9)	<0.001
	Yes	66 (18.8)	176 (35.8)	
Disturbance due to nasal symptoms*	No	31 (8.8)	78 (15.9)	
	Low	11 (3.1)	36 (7.3)	
	Medium	0 (0.0)	0 (0.0)	<0.001
	High	177 (50.9)	150 (30.8)	
Duration of rhinitis*	None	71 (20.4)	146 (30.0)	
	<1 month/year	100 (28.7)	191 (39.2)	
	<4 days/week	202 (69.2)	44 (10.3)	<0.001
	≥4 days/week	90 (30.8)	384 (89.7)	
At least one positive SPT*	No	121 (35.4)	267 (56.0)	<0.001
	Yes	221 (64.6)	210 (44.0)	
Symptoms in Winter*	No	124 (36.3)	91 (19.1)	<0.001
	Yes	218 (63.7)	385 (80.9)	
Symptoms in Spring*	No	178 (52.0)	152 (31.9)	<0.001
	Yes	164 (48.0)	324 (68.1)	

Variables	Levels	Cluster 1 (n=351)	Cluster 2 (n=491)	p
Symptoms in Summer*	No	136 (39.8)	234 (49.2)	0.01
	Yes	206 (60.2)	242 (50.8)	
Symptoms in Autumn*	No	176.7 (145.7)	264.4 (196.3)	<0.001
	Yes	4076.9 (1386.2)	3934.2 (1419.3)	0.171
Eosinophils, cells/mm^3*	Mean (SD)	16.1 (11.4)	23.0 (16.6)	<0.001
Neutrophils, cells/mm^3*	Mean (SD)	24.0 (11.4)	32.7 (16.9)	<0.001
FeNO, 50 mL/s	Mean (SD)	4.5 (3.2)	6.6 (15.4)	0.045
EDN, ng/mL*	Mean (SD)	2.2 (3.0)	2.7 (5.2)	0.134
ECP, ng/mL*	Mean (SD)	15.0 (1.0)	15.1 (1.0)	0.195
HS-CRP, mg/L*	Mean (SD)	0.6 (1.5)	0.4 (0.7)	0.152
CC-16 zscore*	Mean (SD)	0.9 (0.9)	0.7 (0.6)	0.013
TNFa	Mean (SD)	101.3 (99.7)	108.8 (183.2)	0.565
Leptin	Mean (SD)	0.7 (0.4)	0.7 (0.5)	0.814
TARC plasma EDTA, pg/mL*	Mean (SD)	44.9 (29.0)	38.7 (22.3)	0.002
TSLP plasma EDTA, pg/mL*	Mean (SD)	3.7 (5.4)	4.2 (8.2)	0.443
NO_2/NO_3 plasma*	Mean (SD)	99.3 (29.7)	92.4 (20.7)	<0.001
NO_2/NO_3 condensate	Mean (SD)	7.4 (17.1)	7.6 (19.9)	0.916
FIOPs, RFU/mL*	Mean (SD)	1228.1 (294.9)	1258.7 (286.2)	0.16
Condensate 8-iso, pg/mL	Mean (SD)	39.9 (8.5)	39.6 (8.7)	0.723
SOD, U/g*	Mean (SD)	166.0 (41.4)	163.0 (40.2)	0.326
GPX, U/g*	Mean (SD)	150.2 (356.5)	359.3 (571.8)	<0.001
Catalase, k/g*	Mean (SD)	0.5 (0.9)	0.4 (0.6)	0.068
IgE, IU/mL*	Mean (SD)	0.4 (0.3)	0.5 (0.5)	0.588
IL-1RA, pg/mL	Mean (SD)	0.6 (0.4)	0.6 (0.4)	0.668
IL-5, pg/mL	Mean (SD)	0.4 (0.3)	0.4 (0.3)	0.771
IL-7, pg/mL	Mean (SD)	0.6 (1.2)	0.5 (0.6)	0.16
IL-8, pg/mL	Mean (SD)	0.5 (0.3)	0.5 (0.4)	0.925
IL-10, pg/mL	Mean (SD)	159 (46.5)	313 (65.6)	<0.001
IL-13, pg/mL	Mean (SD)	183 (53.5)	164 (34.4)	

*Data are n (%) or mean (SD), AR: Allergic Rhinitis, CC-16: Clara Cell protein-16, CRP: C-Reactive Protein, EBC 8-iso: Exalate Breath Condensate 8-isoprostanes, ECP: Eosinophil Cationic Protein, EDN: Eosinophil Derived Neurotoxin, FeNO: Fraction Exhaled Nitric Oxide, FlOP: Fluorescent oxidation product, GPX: Glutathione peroxidase, IgE: Immunoglobulin E, IL: Interleukin, SOD: Superoxide dismutase, SPT: Skin Prick Test, TARC: Thymus and Activation-Regulated Chemokine, TNF: Tumor Necrosis Factor, TSLP: Thymic Stromal Lymphopoietin, †: several possible answers, *: variables included in the construction of the clusters*

Table S6: Description of the two clusters identified in participants with never asthma and ever asthma in EGEA after imputation (n=842)

Variables	Levels	Never asthma			Ever asthma		
		Cluster 1 (n=181)	Cluster 2 (n=184)	p	Cluster 1 (n=154)	Cluster 2 (n=323)	p
Sex	Men	76 (42.0)	79 (42.9)	0.939	77 (50.0)	167 (51.7)	0.803
	Women	105 (58.0)	105 (57.1)		77 (50.0)	156 (48.3)	
Age, year	Mean (SD)	50.1 (15.0)	41.9 (15.4)	<0.001	45.3 (18.0)	34.4 (14.0)	<0.001
Tobacco status	Never smoker	91 (50.3)	93 (50.5)	0.279	72 (46.8)	176 (54.7)	0.002
	Ex-smoker	58 (32.0)	48 (26.1)		47 (30.5)	53 (16.5)	
	Current smoker	32 (17.7)	43 (23.4)		35 (22.7)	93 (28.9)	
Educational level	<High school	57 (33.9)	29 (16.5)	0.001	44 (29.9)	38 (12.6)	<0.001
	High school	41 (24.4)	50 (28.4)		43 (29.3)	103 (34.1)	
	University	70 (41.7)	97 (55.1)		60 (40.8)	161 (53.3)	
Conjunctivitis*	Never	138 (79.3)	96 (53.3)	<0.001	104 (71.7)	128 (40.5)	<0.001
	Ever	36 (20.7)	84 (46.7)		41 (28.3)	188 (59.5)	
Eczema*	Never	131 (72.8)	121 (66.5)	0.235	90 (58.8)	143 (44.7)	0.005
	Ever	49 (27.2)	61 (33.5)		63 (41.2)	177 (55.3)	
Nasal allergies*	Never	142 (81.6)	37 (20.4)	<0.001	66 (44.0)	19 (6.0)	<0.001
	Ever	32 (18.4)	144 (79.6)		84 (56.0)	300 (94.0)	
Age of onset of rhinitis, year*	Mean (SD)	35.8 (18.3)	23.3 (14.5)	<0.001	23.7 (17.6)	11.5 (9.4)	<0.001
Dust mites or house dust trigger*	No	157 (86.7)	109 (59.2)	<0.001	121 (78.6)	116 (35.9)	<0.001
	Yes	24 (13.3)	75 (40.8)		33 (21.4)	207 (64.1)	
Animals trigger*	No	181 (100.0)	148 (80.4)	<0.001	149 (96.8)	179 (55.4)	<0.001
	Yes	0 (0.0)	36 (19.6)		5 (3.2)	144 (44.6)	
Pollens trigger*	No	163 (90.1)	42 (22.8)	<0.001	133 (86.4)	76 (23.5)	<0.001
	Yes	18 (9.9)	142 (77.2)		21 (13.6)	247 (76.5)	
No trigger reported*	No	111 (61.3)	183 (99.5)	<0.001	103 (66.9)	322 (99.7)	<0.001
	Yes	70 (38.7)	1 (0.5)		51 (33.1)	1 (0.3)	
Other trigger*	No	109 (60.2)	177 (96.2)	<0.001	104 (67.5)	319 (98.8)	<0.001
	Yes	72 (39.8)	7 (3.8)		50 (32.5)	4 (1.2)	
Rhinorrhea after a stimulus*	No	86 (58.9)	38 (22.9)	<0.001	62 (44.6)	42 (13.9)	<0.001
	Yes	60 (41.1)	128 (77.1)		77 (55.4)	260 (86.1)	
Sneezing after a stimulus*	No	58 (38.2)	13 (7.6)	<0.001	44 (31.0)	27 (8.9)	<0.001
	Yes	94 (61.8)	158 (92.4)		98 (69.0)	277 (91.1)	
Eye symptoms after a stimulus*	No	66 (42.6)	19 (11.4)	<0.001	66 (45.5)	39 (12.8)	<0.001
	Yes	89 (57.4)	147 (88.6)		79 (54.5)	266 (87.2)	
Disturbance due to nasal symptoms*	No	145 (80.1)	91 (49.5)	<0.001	81 (52.6)	127 (39.3)	0.016
	Low	26 (14.4)	66 (35.9)		35 (22.7)	115 (35.6)	
	Medium	7 (3.9)	23 (12.5)		27 (17.5)	52 (16.1)	
	High	3 (1.7)	4 (2.2)		11 (7.1)	29 (9.0)	
Duration of rhinitis*	None	0 (0.0)	0 (0.0)	0.844	0 (0.0)	0 (0.0)	0.004
	<1 month/year	81 (45.0)	87 (47.5)		67 (44.1)	92 (28.8)	
	<4 days/week	39 (21.7)	40 (21.9)		35 (23.0)	103 (32.2)	
	≥4 days/week	60 (33.3)	56 (30.6)		50 (32.9)	125 (39.1)	
At least one positive SPT*	No	120 (83.3)	43 (26.1)	<0.001	68 (52.7)	15 (5.3)	<0.001
	Yes	24 (16.7)	122 (73.9)		61 (47.3)	267 (94.7)	
Symptoms in Winter*	No	52 (29.2)	119 (66.1)	<0.001	43 (29.5)	174 (55.2)	<0.001
	Yes	126 (70.8)	61 (33.9)		103 (70.5)	141 (44.8)	
Symptoms in Spring*	No	71 (39.9)	35 (19.6)	<0.001	52 (35.6)	57 (18.1)	<0.001
	Yes	107 (60.1)	144 (80.4)		94 (64.4)	258 (81.9)	
Symptoms in Summer*	No	76 (42.7)	75 (41.9)	0.964	82 (56.2)	97 (30.8)	<0.001
	Yes	102 (57.3)	104 (58.1)		64 (43.8)	218 (69.2)	
Symptoms in Autumn*	No	64 (36.0)	112 (62.6)	<0.001	46 (31.5)	148 (47.0)	0.002
	Yes	114 (64.0)	67 (37.4)		100 (68.5)	167 (53.0)	
Eosinophils, cells/mm^3*	Mean (SD)	152.9 (133.0)	209.8 (134.8)	<0.001	234.5 (188.9)	276.2 (209.1)	0.047
Neutrophils, cells/mm^3*	Mean (SD)	4004.6 (1293.9)	3811.3 (1339.0)	0.189	4235.8 (1511.5)	3974.3 (1439.8)	0.083
Log10 FeNO, 50 mL/s	Mean (SD)	14.1 (8.7)	19.7 (14.0)	0.003	21.6 (17.4)	23.5 (16.6)	0.45

Variables	Levels	Never asthma			Ever asthma		
		Cluster 1 (n=181)	Cluster 2 (n=184)	p	Cluster 1 (n=154)	Cluster 2 (n=323)	p
Log10 EDN, ng/mL*	Mean (SD)	21.0 (9.7)	27.5 (13.4)	<0.001	29.4 (13.8)	34.0 (17.8)	0.019
Log10 ECP, ng/mL*	Mean (SD)	4.0 (3.1)	5.3 (3.7)	0.005	5.2 (3.3)	7.1 (18.5)	0.299
Log10 HS-CRP, mg/L*	Mean (SD)	2.0 (3.0)	2.0 (3.2)	0.989	2.9 (5.3)	2.8 (5.1)	0.88
CC-16, µg/L*	Mean (SD)	14.9 (1.1)	15.1 (0.9)	0.068	15.0 (1.0)	15.1 (1.0)	0.808
Log10 TNFa, pg/mL	Mean (SD)	0.4 (0.3)	0.8 (2.2)	0.162	0.5 (0.4)	0.4 (0.7)	0.504
Log10 leptin, pg/mL	Mean (SD)	0.9 (0.6)	0.9 (1.1)	0.714	0.8 (0.6)	0.7 (0.6)	0.09
TARC plasma EDTA, pg/mL*	Mean (SD)	97.8 (97.8)	102.8 (90.4)	0.681	102.9 (97.4)	112.7 (215.6)	0.654
TSLP plasma EDTA, pg/mL*	Mean (SD)	0.7 (0.3)	0.6 (0.3)	0.646	0.8 (0.5)	0.7 (0.5)	0.115
Log10 NO_2/NO_3 plasma, µM*	Mean (SD)	48.5 (35.0)	39.9 (26.5)	0.023	39.6 (18.9)	39.0 (20.7)	0.766
Log10 NO_2/NO_3 condensate, µM	Mean (SD)	4.0 (6.1)	3.2 (3.4)	0.216	3.3 (4.4)	4.7 (10.0)	0.178
Log10 FlOPs, RFU/mL*	Mean (SD)	97.9 (20.8)	97.2 (28.5)	0.801	95.6 (29.7)	92.5 (22.1)	0.237
Log10 EBC 8-iso, pg/mL	Mean (SD)	9.1 (20.9)	6.0 (12.4)	0.275	6.1 (11.0)	8.2 (23.2)	0.469
Log10 SOD, U/g*	Mean (SD)	1235.2 (310.6)	1250.3 (286.8)	0.655	1228.8 (286.9)	1257.5 (283.2)	0.334
Log 10 GPX, U/g*	Mean (SD)	41.0 (9.0)	39.3 (8.3)	0.076	38.9 (7.9)	39.7 (8.9)	0.418
Catalase, k/g*	Mean (SD)	165.8 (37.8)	166.6 (40.8)	0.858	162.4 (45.3)	162.9 (39.9)	0.907
Log10 IgE*	Mean (SD)	112.0 (354.4)	189.1 (264.6)	0.026	215.6 (400.9)	436.0 (657.8)	<0.001
Log10 IL-1RA, pg/mL	Mean (SD)	0.4 (0.4)	0.4 (0.7)	0.46	0.6 (1.1)	0.3 (0.4)	0.003
Log10 IL-5, pg/mL	Mean (SD)	0.4 (0.3)	0.5 (0.5)	0.404	0.5 (0.3)	0.4 (0.5)	0.731
Log10 IL-7, pg/mL	Mean (SD)	0.6 (0.4)	0.6 (0.5)	0.496	0.6 (0.4)	0.6 (0.4)	0.486
Log10 IL-8, pg/mL	Mean (SD)	0.4 (0.3)	0.4 (0.4)	0.709	0.4 (0.3)	0.4 (0.3)	0.315
Log10 IL-10, pg/mL	Mean (SD)	0.5 (0.7)	0.6 (1.6)	0.583	0.6 (1.0)	0.4 (0.4)	0.053
Log10 IL-13, pg/mL	Mean (SD)	0.5 (0.3)	0.5 (0.3)	0.75	0.5 (0.4)	0.5 (0.4)	0.633

*Data are n (%) or mean (SD), AR: Allergic Rhinitis, CC-16: Clara Cell protein-16, CRP: C-Reactive Protein, EBC 8-iso: Exalate Breath Condensate 8-isoprostanes, ECP: Eosinophil Cationic Protein, EDN: Eosinophil Derived Neurotoxin, FeNO: Fraction Exhaled Nitric Oxide, FlOP: Fluorescent oxidation product, GPX: Glutathione peroxidase, IgE: Immunoglobulin E, IL: Interleukin, SOD: Superoxide dismutase, SPT: Skin Prick Test, TARC: Thymus and Activation-Regulated Chemokine, TNF: Tumor Necrosis Factor, TSLP: Thymic Stromal Lymphopoietin, †: several possible answers, *: variables included in the construction of the clusters*

Appendix 9: Long-term exposures to $PM_{2.5}$, black carbon and NO_2 and prevalence of current rhinitis in French adults: The Constances Cohort

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Long-term exposures to $PM_{2.5}$, black carbon and NO_2 and prevalence of current rhinitis in French adults: The Constances Cohort

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ABSTRACT

Background: Rhinitis is one of the most common disease worldwide with a high and increasing prevalence. There is limited knowledge on the link between long-term exposure to air pollution and rhinitis.
Objectives: We aim to study the associations between long-term exposure to air pollutants and self-reported current rhinitis among adults from Constances, a large French population-based cohort.
Methods: Current rhinitis was defined at inclusion from questionnaire by the presence of sneezing, runny or blocked nose in the last 12 months without a cold or the flu. Annual concentrations of nitrogen dioxide (NO_2), particulate matter ≤ 2.5 μm ($PM_{2.5}$) and black carbon (BC) were estimated at the participants' residential address by European land-use regression models. Cross-sectional associations between annual exposure to each air pollutant and current rhinitis were estimated using logistic models adjusted for age, sex, smoking, education level and French deprivation index. The health prevention centers were taken into account by marginal models with generalized estimating equations. Several supplementary analyses were performed.
Results: Analyses were performed on 127,108 participants (47 years old on average, 54% women, 19% current smokers). The prevalence of current rhinitis, allergic (AR) and non-allergic (NAR) rhinitis were 36%, 25% and 11% respectively. Adjusted ORs for current rhinitis were 1.13 (1.08, 1.17), 1.12 (1.07, 1.17), and 1.11 (1.06, 1.17) per one interquartile range increase of $PM_{2.5}$ (4.85 μg/m^3), BC ($0.88 \cdot 10^{-5}$ m^{-1}) and NO_2 (17.3 μg/m^3) respectively. Significant and positive associations were also found for both AR and NAR. Results were similar in men and women, and in the different smoking strata, and were consistent with meta-analysis or after imputing missing covariates.
Discussion: An increase of modeled annual average residential exposure to $PM_{2.5}$, BC, and NO_2 was significantly associated with an increase of prevalence of current rhinitis in adults in the French general population. The results suggest that among air pollutants, BC may be of special interest.

1. Introduction

Air pollution is a major risk factor for health in terms of both mortality and morbidity (Schraufnagel et al., 2019a). The respiratory tract is the first organ affected by air pollutants and it is commonly accepted that air pollution exposure has harmful effects on respiratory

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health (Schraufnagel et al., 2019b). There is a substantial body of literature on the long-term effects of pollution on lung function (Edginton et al., 2019) and respiratory diseases such as asthma (Thurston et al., 2020) or chronic obstructive pulmonary disease (Park et al., 2021). However, even if rhinitis is one of the most common medical conditions in the world (Bousquet et al., 2020), the literature on the association between long term exposure to air pollution and rhinitis remains scarce. In the pediatric population, exposures to nitrogen dioxide (NO_2), sulfur dioxide (SO_2), particulate matter $\leq$ 10 μm (PM_{10}) and particulate matter $\leq$ 2.5 μm ($PM_{2.5}$) were associated with the prevalence of allergic rhinitis (AR) (Zou et al., 2018). In adults, the association between long-term exposure to air pollution and rhinitis has been poorly investigated in population-based studies, and the results are inconsistent: exposure to traffic or specific pollutants such as fractions of particulate matter (PM), NO_2 or nitrogen oxide (NO_x) were significantly associated with an increased risk of current AR in some studies (de Marco et al., 2002; Lindgren et al., 2009; Nordeide Kuiper et al., 2020), while others found null or non-significant positive results (Heinrich et al., 2005; Wyler et al., 2000; Zhang et al., 2009). Although there is a growing body of literature showing the harmful effect of black carbon (BC) or soot, a component of PM, on health (Yang et al., 2019), to our knowledge, only one study has examined the association between BC exposure and the prevalence of current AR (Nordeide Kuiper et al., 2020). Furthermore, previous studies have focused solely on AR and have therefore omitted non-allergic rhinitis (NAR), except the paper by Lindgren et al. in which exposure to road traffic was studied in association with both AR and NAR (Lindgren et al., 2009).

The aim of the present study was to assess the associations between long-term exposures to $PM_{2.5}$, BC and NO_2 and the presence of rhinitis symptoms in the past 12 months among adults from Constances, a large French population-based cohort.

2. Material and methods

2.1. Study design

Constances (https://www.constances.fr) is a population-based cohort of more than 200,000 adults aged 18 to 69 at inclusion (2012 – 2019), randomly selected from social security affiliates in France. Recruited participants lived in administrative districts (departments) where one of the 24 participating health prevention centers (HPC) are located (www.constances.fr/centres-examens-sante, see Figure S1). At inclusion, each participant completed standardized questionnaires on occupational exposures, lifestyle and health including a detailed one on respiratory health, and had a complete medical examination (Goldberg et al., 2017; Henny et al., 2020; Ruiz et al., 2016; Zins et al., 2015).

All confidentiality, safety and security procedures were approved by the French legal authorities. According to the French regulations, the Constances Cohort project has obtained the authorization of the National Data Protection Authority (Commission Nationale de l'Informatique et des Libertés-CNIL). In addition, Constances was approved by the National Council for Statistical Information (Conseil National de l'Information Statistique-CNIS), the National Medical Council (Conseil National de l'Ordre des médecins-CNOM), the Institutional Review Board of the National Institute for Medical Research-INSERM and the local Committee for Persons Protection (Comité de protection des personnes).

2.2. Definitions of rhinitis

The definitions of ever rhinitis and current rhinitis were based on the responses from the detailed questionnaire on respiratory health that were previously used and validated in the International study of asthma and allergies in childhood (ISAAC) (Asher et al., 1995). Participants who answered yes 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?*" were considered as having ever rhinitis, otherwise as never having rhinitis. Among participants with ever rhinitis, those who answered yes to "*Have you had these problems in the last 12 months*" were classified as having current rhinitis, otherwise as having non-current rhinitis.

In order to distinguish AR from NAR, we used an adaptation of the question used in the European Community Respiratory Health Survey (ECRHS) to define nasal allergies (ECRHS, 1996; Savouré et al., 2021). Participants with rhinitis who answered yes to "*Have you ever had nasal allergies in your lifetime, including hay fever?*" were classified as AR, otherwise as NAR.

2.3. Estimation of air pollution exposure

Exposure assessment for $PM_{2.5}$, BC and NO_2 was based on estimated annual concentration data from Land Use Regression (LUR) models developed for Western Europe using a supervised linear regression approach based on data from a large regulatory network (de Hoogh et al., 2018). The LUR models were calibrated and validated using annual average $PM_{2.5}$ and NO_2 concentration data derived for 2010 from the AirBase v8 dataset (de Hoogh et al., 2018). For BC, which is not available through AirBase, the annual mean BC concentrations, measured as $PM_{2.5}$ absorbance based on reflectance measurement of the filters, were obtained from the ESCAPE study (Eeftens et al., 2012). Predictors used in the LUR include satellite-derived and chemical transport modeled estimates, land use variables, population density, road density and altitude. The models were applied on a 100 × 100 m grid across Western Europe (de Hoogh et al., 2018). Modeled exposures were assigned at the participants' residential address at inclusion. We used annual averages for each pollutant from year 2010 models at the address of inclusion as a proxy for participants' long-term exposure to air pollution.

2.4. Statistical analyses

The main analyses were complete case analyses, i.e. after excluding participants with missing data for rhinitis, air pollution or adjustment variables. The general characteristics of participants who reported current rhinitis in the last 12 months were compared with those of the reference group, defined as participants with never or non-current rhinitis, with standard statistical tests: Chi2 for categorical variables and Student tests for continuous variables. Spearman correlation coefficients were performed to study the correlations between the different pollutants.

2.5. Main analyses

The cross-sectional associations between long-term exposure to air pollutants and current rhinitis were studied using logistic regression models. Estimates were calculated considering each pollutant separately for an increase of their interquartile range (IQR), thus is 4.85 $\mu g/m^3$ for $PM_{2.5}$, 0.88 10^{-5} m^{-1} for BC and 17.3 $\mu g/m^3$ for NO_2.

As recruited participants lived in departments where HPC are located, analyses were carried out using marginal models with generalized estimating equations (Heagerty and Zeger, 2000) to take into account potential clustering, i.e. that participants living in the same department were likely more similar than those living in other departments.

Associations between each air pollutant and current rhinitis were assessed with several single-pollutant models. Univariate analyses were first performed (model M0). A first level of adjustments for age, sex and smoking status (never smoker, ex-smoker, current smoker) was made on the basis of a priori hypothesis based on the literature (model M1). Further adjustment was made for educational level (no diploma/grade school, high school, university) as a proxy for socioeconomic status at the individual level (model M2). Finally, as the importance of taking both individual and contextual socioeconomic status into account in

studies on the health effects of air pollution (Hajat et al., 2021; Temam et al., 2017), a model with an additional adjustment on the contextual French Deprivation Index (Fdep) was used (model M3 = main model). The Fdep is a score calculated according to the participant's residential address from principal component analysis at the smallest geographical division in France (IRIS - Regrouped statistical information blocks with 2000 inhabitants in average) that considers an accumulation of material and social disadvantages (Rey et al., 2009).

2.6. Supplementary analyses

All supplementary analyses were performed with the main M3 model.

As BC is a component of $PM_{2.5}$, and as they are highly correlated, using a two-pollutant model mutually adjusting one pollutant for the other is precluded. As an alternative to isolate the effect of BC from that of total $PM_{2.5}$, we used the residuals method described by Mostofsky et al. (2012). Following this approach, we regressed BC as response variable on $PM_{2.5}$. These residuals were decorrelated from $PM_{2.5}$ and an increase in these residuals correspond to an increase in BC holding total $PM_{2.5}$ constant. We used these residuals as a new exposure variable in a single-pollutant model.

The analyses were carried out for current AR (reference group: never rhinitis and non-current AR) and current NAR (reference group: never rhinitis and non-current NAR) separately.

As air pollution could lead to different responses between men and women, stratification according to sex was performed. As air pollution and tobacco may share similar underlying biological mechanisms, stratification according to smoking was also performed. Heterogeneity between strata were tested using interaction tests.

As an alternative of the marginal model, models were also performed with HPC as an adjustment variable, in a meta-analysis on HPC or without considering the HPC.

As the main analyses were complete case analyses, additional analyses were also carried out after multiple imputations (n = 10) for missing data on smoking status and diploma using the SAS procedures MI and MIANALYZE.

We also performed analyses by changing the reference group, and by comparing current rhinitis to never rhinitis and current rhinitis to non-current rhinitis separately.

All analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC).

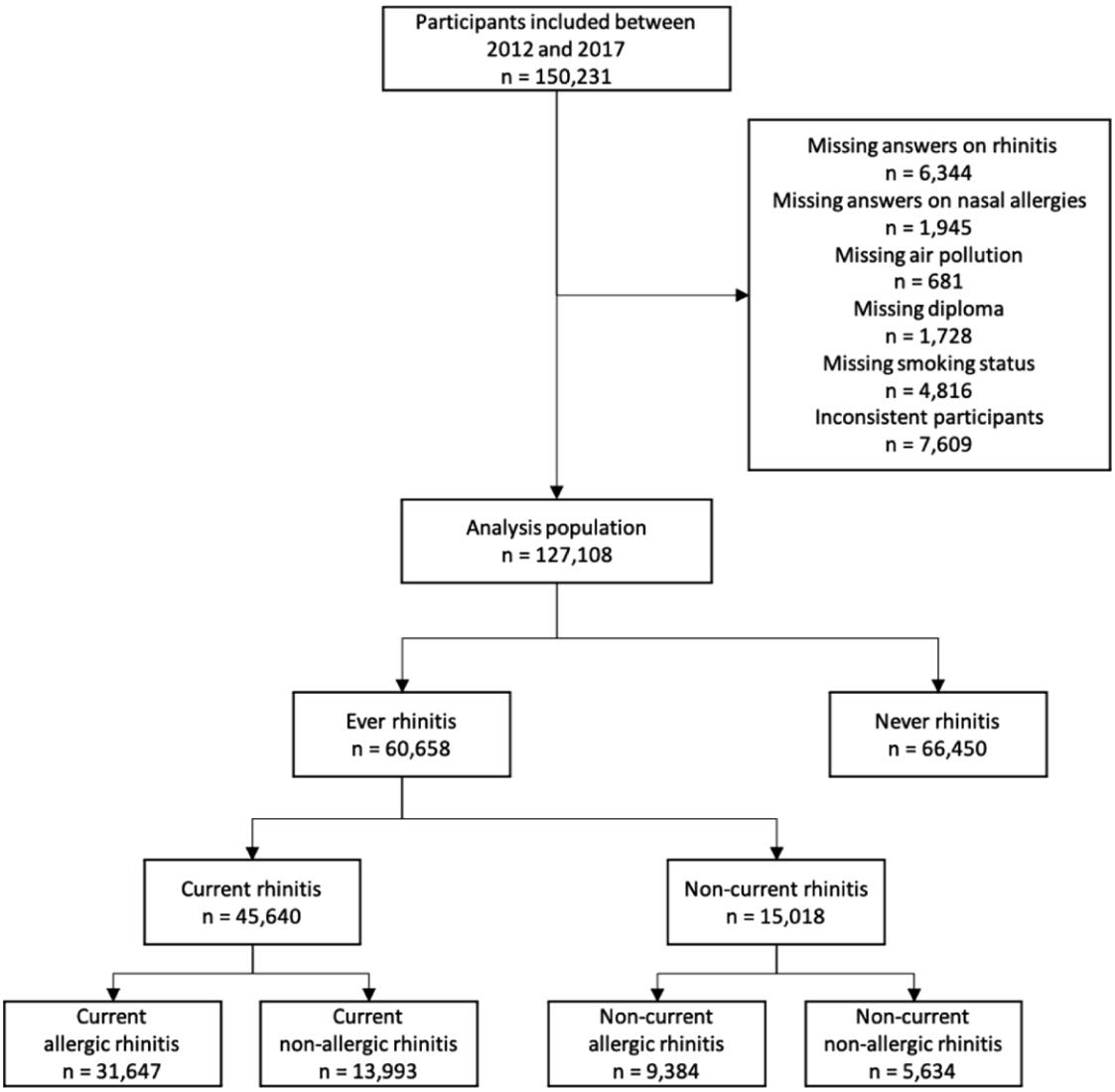

Fig. 1. Flow chart.

3. Results

We analyzed data from participants included in the cohort between 2012 and 2017 (n = 150,231). Participants with missing data regarding the definitions of rhinitis (n = 6344), the presence of nasal allergies (n = 1945), air pollution (n = 681), diploma (n = 1728) or tobacco status (n = 4816) were excluded from the main analyses. Participants who answered yes to "*Have you ever had any nasal allergies including hay fever?*" and no 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?*" were considered inconsistent and were also excluded from the analyses (n = 7609). The flow chart is presented in Fig. 1.

A total of 127,108 adults were included in the main analyses. The differences regarding the main characteristics between participants included and those not included were small, although statistically significant due to the large number of participants (Table S1).

Characteristics of the participants included in the analyses are presented in Table 1. They were on average 47 years old and 53.8% were women. The prevalence of ever rhinitis and current rhinitis were 47.7% and 35.9% respectively. The prevalence of current AR and current NAR were 24.9% and 11.0% respectively. Compared to the reference group, the current rhinitis group comprised more women, a lower average age, higher education level and reported more ever asthma (Table 1). More details about the participants characteristics according to their rhinitis status are given in Table S2.

Table 1
Characteristics of the participants.

	All n = 127,108	Reference population[a] n = 81,468	Current rhinitis n = 45,640	P value
Women, n (%)	68,354 (53.8%)	42,883 (52.6%)	25,471 (55.8%)	<0.0001
Age, year, mean ± SD	47.1 ± 13.6	47.9 ± 13.5	45.7 ± 13.8	<0.0001
BMI, kg/m^2, n (%)				<0.0001
<18.5	3,350 (2.8%)	2,010 (2.6%)	1,340 (3.1%)	
18.5–25	66,309 (54.5%)	41,561 (53.3%)	24,748 (56.5%)	
25–30	37,164 (30.5%)	24,464 (31.4%)	12,700 (29.0%)	
≥ 30	14,936 (12.3%)	9,911 (12.7%)	5,025 (11.5%)	
Smoking status, n (%)				<0.0001
Never	59,922 (47.1%)	38,888 (47.7%)	21,034 (46.1%)	
Ex-smoker	42,943 (33.8%)	27,437 (33.7%)	15,506 (34.0%)	
Current	24,243 (19.1%)	15,143 (18.6%)	9,100 (19.9%)	
Educational level, n (%)				<0.0001
No diploma or grade school	11,355 (8.9%)	7,723 (9.5%)	3,632 (8.0%)	
High school	43,290 (34.1%)	28,888 (35.5%)	14,402 (31.6%)	
University	72,463 (57.0%)	44,857 (55.1%)	27,606 (60.5%)	
Ever asthma, n (%)	17,148 (13.6%)	7,014 (8.7%)	10,134 (22.4%)	<0.0001
Ever rhinitis, n (%)	60,658 (47.7%)	15,018 (18.4%)	45,640 (100%)	<0.0001
Current rhinitis, n (%)	45,640 (35.9%)	/	45,640 (100%)	
Current allergic rhinitis, n (%)	31,647 (24.9%)	/	31,647 (69.3%)	
Current non-allergic rhinitis, n (%)	13,993 (11.0%)	/	13,993 (30.7%)	
$PM_{2.5}$, µg/m^3, mean ± SD	17.1 ± 3.35	17.0 ± 3.31	17.3 ± 3.40	<0.0001
BC, 10^{-5} m^{-1}, mean ± SD	1.82 ± 0.59	1.79 ± 0.58	1.87 ± 0.59	<0.0001
NO_2, µg/m^3, mean ± SD	26.5 ± 12.3	25.9 ± 12.2	27.4 ± 12.5	<0.0001

BC: black carbon; BMI: body mass index; NO_2: nitrogen dioxide; $PM_{2.5}$ particulate matter with an aerodynamic diameter less than 2.5 µm; SD: standard deviation.
a: reference population = never rhinitis + non-current rhinitis

Pollutant levels were variable across HPC and within HCP (Figure S1). Table S3 shows the distribution of pollutants and their correlation coefficients. The annual mean concentration of $PM_{2.5}$ was 17.1 µg/m^3 which is above the World Health Organization (WHO) guideline of 10 µg/m^3, and the annual mean concentration of NO_2 was 26.5 µg/m^3 which is below the WHO guideline of 40 µg/m^3. The annual average concentration of BC was $1.82 \cdot 10^{-5}$ m^{-1}. Correlations between the three pollutants were high (0.80 between $PM_{2.5}$ and BC, 0.87 between $PM_{2.5}$ and NO_2, and 0.93 between BC and NO_2).

Table 2 shows the associations between $PM_{2.5}$, BC and NO_2 and current rhinitis. At all levels of covariate adjustment, an increase of $PM_{2.5}$, BC, or NO_2 was significantly associated with an increased risk of current rhinitis. Adjusted ORs for the main model M3 were 1.13 (95% CI: 1.08, 1.17) per IQR increase in $PM_{2.5}$, 1.12 (95% CI: 1.07, 1.17) per IQR increase in BC and 1.11 (95% CI: 1.06, 1.17) per IQR increase in NO_2.

BC residuals regressed on $PM_{2.5}$ were also significantly associated with an increase of current rhinitis (OR: 1.05, 95% CI: 1.02, 1.07 for an IQR increase of BC residuals).

The results of the supplementary analyses are shown in Fig. 2, Table S4, and Figure S2. Significant and positive associations were also found for both AR and NAR with similar effect estimates between AR and NAR for $PM_{2.5}$ and NO_2. For BC, the adjusted OR was slightly higher in AR compared to NAR (ORs: 1.15 vs 1.09 respectively). The ORs were similar between men and women and there were no significant interactions between each pollutant and sex. Stratification by smoking status yielded similar results for each stratum and there were no significant interactions between each pollutant and smoking status.

Similar results were obtained for $PM_{2.5}$ when not considering the HPC in the model, and the ORs were slightly higher for BC and NO_2. Adjusting on the HPC gave almost the same results as those from the marginal model for all pollutants. Similarly, the meta-analyses gave similar results to those of the main model for $PM_{2.5}$, BC and NO_2, for both fixed and random effects: the heterogeneity was not significant (I^2 = 0%, p = 0.58) for $PM_{2.5}$, and was significant for BC and NO_2 (I^2 = 48%, p = 0.01 and I^2 = 44%, p = 0.02 respectively).

Multiple imputations yielded significant and similar results as those of the main model.

Taking as a reference group only participants who never had rhinitis,

Table 2
OR (95% CI) of the associations between $PM_{2.5}$, BC and NO_2 and current rhinitis.

	OR (95% CI)					
	$PM_{2.5}$		BC		NO_2	
M0	1.16	(1.11,1.22)	1.17	(1.10,1.23)	1.15	(1.08,1.22)
M1	1.13	(1.09,1.19)	1.13	(1.08,1.19)	1.12	(1.07,1.18)
M2	1.12	(1.07,1.17)	1.12	(1.06,1.17)	1.11	(1.05,1.17)
M3 = main model	1.13	(1.08,1.17)	1.12	(1.07,1.17)	1.11	(1.06,1.17)

BC: black carbon; CI: confidence interval; NO_2: nitrogen dioxide; OR: odds ratio; $PM_{2.5}$ particulate matter with an aerodynamic diameter less than 2.5 µm.
All estimates were from logistic regression models, OR (95% CI) were calculated for an increase of an interquartile range (4.85 µg/m^3 for $PM_{2.5}$, 0.88 10^{-5} m^{-1} for BC and 17.3 µg/m^3 for NO_2). The health prevention center was taken into account by marginal models with generalized estimating equations Current rhinitis was compared to never rhinitis + non-current rhinitis. M0: univariate analysis; M1: adjusted for age, sex, and smoking status; M2: adjusted for age, sex, smoking status, and educational level; M3: adjusted for age, sex, smoking status, educational level, and French deprivation index. All p-values were < 10^{-4}.

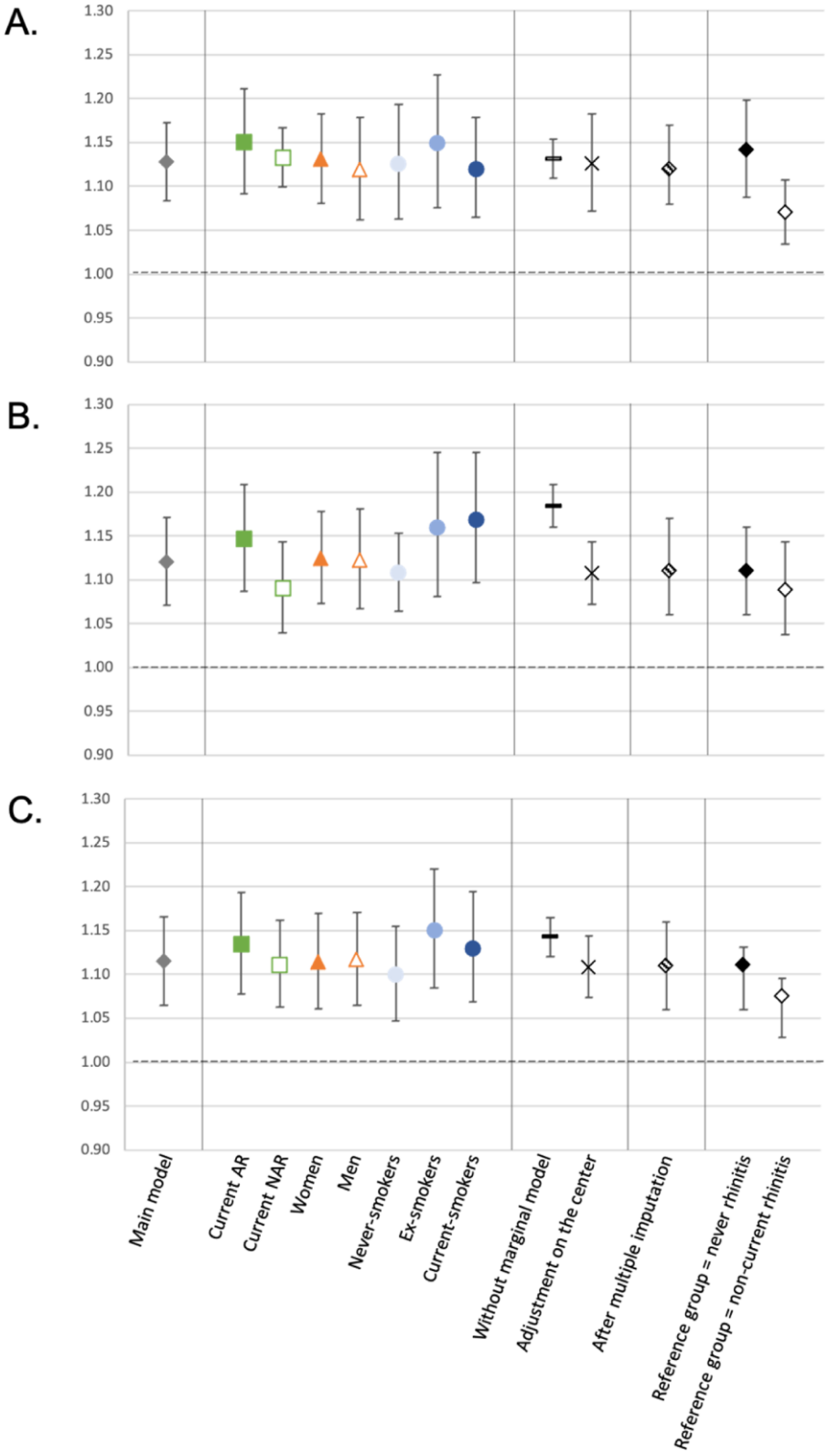

Fig. 2. Associations between exposure to air pollution and current rhinitis OR (95% CI) were calculated: (A) For an increase of an IQR of $PM_{2.5}$ (4.85 µg/m^3). (B) For an increase of an IQR of BC (0.88 10^{-5} m^{-1}). (C) For an increase of an IQR of NO_2 (17.3 µg/m^3). ◆ ■ □ –X ▩ ◆ ◇: adjusted ORs for age, sex, smoking status, educational level, and French deprivation index. ▲ △: adjusted ORs for age, smoking status, educational level, and French deprivation index. ● ● ●: adjusted ORs for age, sex, educational level, and French deprivation index. AR: Allergic Rhinitis; BC: black carbon; CI: confidence interval; NAR: Non-Allergic Rhinitis; NO_2: nitrogen dioxide; OR: odds ratio; $PM_{2.5}$ particulate matter with an aerodynamic diameter less than 2.5 µm. The health prevention center was taken into account by marginal models with generalized estimating equations (except in the model adjusted on the center and in the model without marginal model). All p-values were $< 10^{-4}$.

the ORs were similar to those reported in the main model. In contrast, when only participants with non-current rhinitis were included as a reference group, ORs were still significant but lower than those in the main model.

4. Discussion

In this cross-sectional analysis, an increase of modeled annual average residential exposure to $PM_{2.5}$, BC, and NO_2 was significantly associated with an increased risk of current rhinitis in adults in a large population-based study. These results were consistent regardless of the adjustment, the stratification and the sensitivity analysis.

Our analyses were conducted in the largest French adult population-based cohort, which yielded very high statistical power. Our definition of rhinitis is self-reported and based on the answer to the validated and standardized questions that were used in the ISAAC study (Asher et al., 1995). These questions have the advantage of being based on the main symptoms of AR and NAR and are understandable to all participants which allows all rhinitis to be considered, even those that have not been diagnosed by a doctor. This is especially important as many patients with mild symptoms do not consult a doctor for their rhinitis. Thus taking into account only the medical diagnosis could lead to an underestimation of the actual number of cases of mild to moderate rhinitis (Bousquet et al., 2012; Wise et al., 2018). Skin Prick Tests and/or Immunoglobulin E (IgE) that are the gold standard to differentiate AR from NAR were not available in the Constances study. We have therefore distinguished AR from NAR based on the validated and standardized question of nasal allergies adapted from the ECRHS study (ECRHS, 1996) that has very often been used in the literature to define AR. This definition combined with the ISAAC definition has been shown to be a suitable proxy for AR and NAR (Savouré et al., 2021) even if classification errors cannot be excluded.

In this study, long-term exposure to air pollutants was estimated at the participants' residential address at inclusion using validated European LUR models that provide a fine-scale (100 × 100 m) estimate used to assign (de Hoogh et al., 2018). We considered outdoor pollution, and as participants are not always at home, we acknowledge that this can lead to exposure misclassification. We carried out cross-sectional analyses, so temporality is not defined, and causality cannot be studied. We hypothesize that the measurements performed in 2010 at the inclusion address reflect the long-term air pollution exposure of the participants. It has been shown that the pollution levels from one year to another for the same geographical area are very similar (Hansell et al., 2016). We assume that the annual mean of the pollutants reflects a long-term exposure, which is probably true for those who did not move for several years prior to outcome assessment; unfortunately we did not have the residential history of the participants to perform such a sensitivity analysis. We cannot exclude that the limitations presented above may lead to a non-differential measurement error suggesting that the actual effect of long-term exposure to air pollution on rhinitis may be higher than the one we have identified. Although we adjusted for the main confounders associated with both rhinitis and air pollution, we cannot exclude that a residual confound remains. In Constances, each participant is assigned to an HPC. The estimation of air pollution was based on the same LUR model and rhinitis was assessed by questionnaire which is the same for all participants, independently of the HPC. In our opinion, there is no center effect as classically defined in epidemiology, i.e. meaning that exposure or/and the outcome of interest are differentially assessed across centers. However, it is possible that participants living near the same HPC are more similar in terms of lifestyle or pollen exposure for example, than participants from different HPC. That is why we considered the HPC in a marginal model with generalized equations. The results were similar when considering the HPC in an adjusted model or with the meta-analyses. However, for the meta-analyses the coefficient of heterogeneity was significant for BC and NO_2. This heterogeneity is mainly due to the results for Paris HPC. The results for Paris could be explained by the fact that Parisian participants show less variability in air pollution exposure. Not considering the HPC gave similar results to those of the marginal model for $PM_{2.5}$ and slightly higher ORs for BC and NO_2. Overall, our analyses yielded significant results and the sensitivity analyses we have performed support the robustness of our results.

The existing literature is ambiguous as to which group current rhinitis is compared to, and previous studies have not consistently defined whether or not non-current rhinitis was included in the reference group. In our opinion, participants who have non-current rhinitis may be considered as a "special group" as they used to have rhinitis that is no longer active. Thus, we conducted an extra analysis excluding participants with non-current rhinitis, yielded results nearly identical to those of the main analysis. We also compared current rhinitis to non-current rhinitis. The research question behind the latter analysis was to determine if long-term exposure to air pollution could affect symptom activation among participants with a history of rhinitis. To our knowledge, our study is the first to report this type of comparison. Our results were significant and can be added to the growing literature on the association of air pollution with the severity and exacerbation of rhinitis (Burte et al., 2020; Li et al., 2020a; Naclerio et al., 2020). In addition, our analyses comparing current rhinitis to non-current rhinitis yielded lower ORs than analyses comparing current rhinitis to never rhinitis. This difference in the strength of the associations could be partly explained by the study population: indeed, the comparison between current rhinitis and non-current rhinitis was conducted in a more homogenous population of participants with a rhinitis during their lifetime. These results need to be explored further but they could suggest that air pollution may be associated not only with the presence of rhinitis symptoms but also with the activation of rhinitis symptoms in participants who previously have had rhinitis.

Our main results are difficult to compare with those in the literature as there are only few studies on the association between long-term exposure to air pollution and the prevalence of current rhinitis in adults in population-based cohorts. Three studies in Europe (de Marco et al., 2002; Lindgren et al., 2009; Nordeide Kuiper et al., 2020) have shown that exposure to NO_2 was associated with an increase in the prevalence of current AR in adults. In these studies, as in our results, associations were observed at annual mean concentrations of NO_2 below the WHO recommended value of 40 $\mu g/m^3$, which may suggest that air pollution could have effects on rhinitis even at low levels. To our knowledge only one study (Nordeide Kuiper et al., 2020) has examined the effects of $PM_{2.5}$ and BC on current AR in adults. In the study by Nordeide Kuiper et al., Swedish and Norwegian adults were included and the long-term exposures to $PM_{2.5}$, BC and NO_2 were estimated with the same European LUR as the one used in the present study (de Hoogh et al., 2018). Similarly to our study, long-term exposure to $PM_{2.5}$, BC or NO_2 in the year prior to the report of current AR was significantly associated with an increased risk of current AR (Nordeide Kuiper et al., 2020). Long-term exposures over the lifetime, the period of adolescence, or childhood, of participants were not significantly associated with current AR in adults (Nordeide Kuiper et al., 2020). This may suggest that recent exposure to air pollution may be more important in the occurrence of current rhinitis. To our knowledge, only one study (Lindgren et al., 2009) has considered both AR and NAR. The authors found that road traffic exposure in the adult population was associated with a higher prevalence of AR but not NAR, suggesting that rhinitis should not be treated as a homogeneous disease (Lindgren et al., 2009). In our results, we have observed significant associations between each of the three pollutants and both AR and NAR. The results were very similar between AR and NAR for $PM_{2.5}$ and NO_2, but interestingly for BC the OR was slightly higher for AR compared to NAR. AR and NAR present distinct physiopathological mechanisms, and it is therefore possible that the effect of pollutants is different according to the phenotypes of rhinitis. Given the limited literature that has considered AR and NAR, these hypotheses need to be further explored.

We performed analyses by stratifying according to sex, as air

pollution could lead to different responses between men and women (Clougherty, 2010). The interactions were non-significant between the different pollutants and sex, and the results were similar for women and men. Among adults, evidence of effect modification by sex remains uncertain but the role of biological factors such as hormones, of lung volume or of gender-related factors such as differential accuracy in residence-based exposure assignment could partly explain the greater effects of air pollution observed in women than in men (Clougherty, 2010). As tobacco and air pollutants may share similar underlying biological mechanisms on the onset of respiratory disease (Ni et al., 2020), we have also stratified according to smoking status. We did not observe any interactions between smoking status and the different pollutants, and the results were very similar according to the different strata suggesting that the effect of air pollution on rhinitis would be independent of smoking status.

Due to the high correlation between the three pollutants, we could not perform a two-pollutant or tri-pollutant model by adjusting for the other pollutants (Dominici et al., 2010). As BC is a component of PMs, we used the residual method proposed by Mostofsky et al. to take into account the confounding induced by $PM_{2.5}$ (Mostofsky et al., 2012). Our results with BC residuals were very similar to those of BC, suggesting that BC and closely-linked components are associated with rhinitis independently of total $PM_{2.5}$. Our results reinforce the hypothesis that BC is one of the most harmful components of PMs (Yang et al., 2019) even if further studies between exposure to BC and rhinitis are needed to confirm our findings.

We did not adjust for the different distribution of pollen species in France. However, the marginal model allowed us to consider indirectly, among other things, the differences in the distribution of pollens between the different HPC. The associations between long-term exposure to air pollution, greenspace and rhinitis is understudied. In the recent study by Nordeide Kuiper et al., no significant association was observed between greenspace and rhinitis (Nordeide Kuiper et al., 2020). However, in the study by Markevych et al., early life residence in places with many allergenic trees increased the prevalence of allergic rhinitis later in life. Exposure to greenspace could promote rhinitis by increasing exposure to pollens (Markevych et al., 2020). To our knowledge there is no study on the interaction between long-term exposure to air pollution, greenspace and rhinitis in adults. In their study in 2020, Nordeide Kuiper et al. simultaneously adjusted on greenspace and air pollution in their analyses, but potential interactions were not tested. Considering the relationships between greenspace, air pollution and rhinitis is an interesting research perspective, especially given climate change and its connection with air pollution and respiratory health (D'Amato et al., 2016).

Three major underlying biological pathways have been proposed to explain the link between long-term air pollution and rhinitis: inflammation, oxidative stress, and allergy. They are highly interrelated and can be local, by acting specifically on the nasal epithelium, and/or systemic. The inflammatory effect of air pollutants can be neutrophilic or eosinophilic (Ramanathan et al., 2017; Wei and Tang, 2018). Inflammation can lead to an increase in the permeability of the nasal epithelial barrier leading to an easier access of allergens to the immune system (De Grove et al., 2018). PM, BC and NO_2 can induce the production of reactive oxygen and nitrogen species in the airway epithelium and macrophages, which can subsequently maintain the inflammatory effect and augment immune response (Leikauf et al., 2020; Li et al., 2020b; Niranjan and Thakur, 2017; Rouadi et al., 2020). Finally, regarding AR, air pollutants, in particular diesel particles, could act as adjuvant in synergy with allergens to increase the allergic response which can subsequently induce inflammation (Joubert et al., 2020; Li et al., 2020a; Niranjan and Thakur, 2017). To date, the pathways involved in the association between air pollution and rhinitis have been poorly investigated. Studying the three pathways mentioned above could improve the characterization of the disease, and the understanding of its association with air pollution leading to a better management of rhinitis.

In conclusion, long-term exposure to air pollution was associated with current rhinitis in adults in a large French population-based study. The results suggest that among air pollutants, BC may be of special interest. In view of the high prevalence of rhinitis, these findings have an important public health impact and reinforce the need to reduce the population's exposure to air pollution.

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CRediT authorship contribution statement

Marine Savouré: Conceptualization, Methodology, Formal analysis, Writing – original draft, Visualization. **Émeline Lequy:** Methodology, Resources, Writing – review & editing. **Jean Bousquet:** Writing – review & editing. **Jie Chen:** Methodology, Resources, Writing – review & editing. **Kees de Hoogh:** Methodology, Resources, Writing – review & editing. **Marcel Goldberg:** Resources, Writing – review & editing. **Danielle Vienneau:** Methodology, Resources, Writing – review & editing. **Marie Zins:** Resources, Writing – review & editing. **Rachel Nadif:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Bénédicte Jacquemin:** Conceptualization, Methodology, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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9.B – Supplementary materials

Tables

Table S1: Comparison of included and non-included participants

	Non-included n = 23,123	Included n = 127,108	P value
Women, n (%)	12,155/23,123 (52.6%)	68,354/127,108 (53.8%)	0.0007
Age, year, mean ± SD	49.2 ± 13.7	47.1 ± 13.6	<.0001
BMI, kg/m^2, n (%)	n = 21,848	n = 121,759	<.0001
<18.5	579 (2.7%)	3,350 (2.8%)	
18.5 – 25	11,275 (51.6%)	66,309 (54.5%)	
25 – 30	7,007 (32.1%)	37,164 (30.5%)	
≥ 30	2,987 (13.7%)	14,936 (12.3%)	
Smoking status, n (%)	n = 16,688	n = 127,108	0.04
Never	8,037 (48.2%)	59,922 (47.1%)	
Ex-smoker	5,563 (33.3%)	42,943 (33.8%)	
Current	3,088 (18.5%)	24,243 (19.1%)	
Educational level, n (%)	n = 20,431	n = 127,108	<.0001
No diploma or grade school	2,312 (11.3%)	11,355 (8.9%)	
High school	7,143 (35.0%)	43,290 (34.1%)	
University	10,976 (53.7%)	72,463 (57.0%)	
Ever asthma, n (%)	2,735/19,498 (14.0%)	17,148/126,247 (13.6%)	0.09
Ever rhinitis, n (%)	4,603/9,170 (50.2%)	60,658/127,108 (47.7%)	<.0001
Current rhinitis, n (%)	3,460/9,170 (37.7%)	45,640/127,108 (35.9%)	<.0001

BMI: body mass index; SD: standard deviation.

Table S2: Characteristics of never rhinitis, non-current rhinitis and current rhinitis participants

	Never rhinitis n = 66,450	Non-current rhinitis n = 15,018	Current rhinitis n = 45,640	P value
Women, n (%)	35,077 (52.8%)	7,806 (52.0%)	25,471 (55.8%)	<.0001
Age, year, mean ± SD	47.8 ± 13.5	48.5 ± 13.3	45.7 ± 13.8	<.0001
BMI, kg/m^2, n (%)				<.0001
<18.5	1,686 (2.7%)	324 (2.3%)	1,340 (3.1%)	
18.5 – 25	33,980 (53.5%)	7,581 (52.6%)	24,748 (56.5%)	
25 – 30	19,942 (31.4%)	4,522 (31.4%)	12,700 (29.0%)	
≥ 30	7,936 (12.5%)	1,975 (13.7%)	5,025 (11.5%)	
Smoking status, n (%)				<.0001
Never	31,950 (48.1%)	6,938 (46.2%)	21,034 (46.1%)	
Ex-smoker	22,218 (33.4%)	5,219 (34.8%)	15,506 (34.0%)	
Current	12,282 (18.5%)	2,861 (19.1%)	9,100 (19.9%)	
Educational level, n (%)				<.0001
No diploma or grade school	6,255 (9.4%)	1,468 (9.8%)	3,632 (8.0%)	
High school	23,492 (35.4%)	5,396 (35.9%)	14,402 (31.6%)	
University	36,703 (55.2%)	8,154 (54.3%)	27,606 (60.5%)	
Ever asthma, n (%)	3,784 (5.7%)	3,230 (21.7%)	10,134 (22.4%)	<.0001
Ever rhinitis, n (%)	/	15,018 (100%)	45,640 (100%)	<.0001
Ever allergic rhinitis, n (%)	/	9,384 (62.5%)	31,647 (69.3%)	
Ever non-allergic rhinitis, n (%)	/	5,634 (37.5%)	13,993 (30.7%)	
$PM_{2.5}$, µg/m^3, mean ± SD	16.9 ± 3.31	17.1 ± 3.34	17.3 ± 3.40	<.0001
BC, 10^{-5} m^{-1}, mean ± SD	1.78 ± 0.58	1.81 ± 0.59	1.87 ± 0.60	<.0001
NO_2, µg/m^3, mean ± SD	25.9 ± 12.2	26.3 ± 12.4	27.4 ± 12.5	<.0001

BC: black carbon; BMI: body mass index; NO_2: nitrogen dioxide; $PM_{2.5}$ particulate matter with an aerodynamic diameter less than 2.5 µm; SD: standard deviation.

Table S3: Description of pollutants and Spearman Correlation Coefficient

	Mean	SD	Min	Max	Q1	Med	Q3	IQR	Correlation BC	Correlation NO_2
$PM_{2.5}$, µg/m³	17.1	3.35	4.76	25.8	14.8	16.2	19.6	4.85	0.80	0.87
BC, 10^{-5} m^{-1}	1.82	0.59	0.84	4.66	1.33	1.65	2.21	0.88	/	0.93
NO_2, µg/m³	26.5	12.3	1.59	86.1	17.0	23.4	34.3	17.3	/	/

BC: black carbon; IQR: interquartile range; Max: maximum; Med: median; Min: minimum; NO_2: nitrogen dioxide; $PM_{2.5}$ particulate matter with an aerodynamic diameter less than 2.5 µm; Q1: first quartile; Q3: third quartile; SD: standard deviation.

Table S4: Associations between exposure to air pollution and current rhinitis (result presented in Figure 2)

	Number of participants			OR (95% CI)		
	Total	**Reference**	**Current rhinitis**	**$PM_{2.5}$**	**BC**	**NO_2**
Main model (M3)[a,b]	127,108	81,468	45,640	1.13 (1.08, 1.17)	1.12 (1.07, 1.17)	1.11 (1.06, 1.17)
Allergic status						
Current AR[a,c]	107,481	75,834	31,647	1.15 (1.09, 1.21)	1.15 (1.09, 1.21)	1.13 (1.08, 1.19)
Current NAR[a,d]	86,077	72,084	13,993	1.13 (1.10, 1.17)	1.09 (1.04, 1.14)	1.11 (1.06, 1.16)
Sex[a,e]						
Women	68,354	42,883	25,471	1.13 (1.08, 1.18)	1.12 (1.07, 1.18)	1.11 (1.06, 1.17)
Men	58,754	38,585	20,169	1.12 (1.06, 1.18)	1.12 (1.07, 1.18)	1.12 (1.06, 1.17)
Smoking status[a,f]						
Never	59,922	38,888	21,034	1.13 (1.06, 1.19)	1.11 (1.06, 1.15)	1.10 (1.05, 1.15)
Ex-smoker	42,943	27,437	15,506	1.15 (1.08, 1.23)	1.16 (1.08, 1.25)	1.15 (1.08, 1.22)
Current smoker	24,243	15,143	9,100	1.12 (1.06, 1.18)	1.17 (1.10, 1.25)	1.13 (1.07, 1.19)
Without marginal model[b]	127,108	81,468	45,640	1.13 (1.11, 1.15)	1.18 (1.16, 1.21)	1.14 (1.12, 1.17)
Adjustment on the center[g]	127,108	81,468	45,640	1.13 (1.07, 1.18)	1.11 (1.07, 1.14)	1.11 (1.07, 1.14)
Multiple imputation[a,b]	133,652	85,858	47,794	1.12 (1.08, 1.17)	1.11 (1.06, 1.17)	1.11 (1.06, 1.16)
Change in the reference group						
Never rhinitis[a,h]	112,090	66,450	45,640	1.14 (1.09, 1.20)	1.13 (1.08, 1.18)	1.13 (1.08, 1.18)
Non-current rhinitis[a,i]	60,658	15,018	45,640	1.07 (1.03, 1.11)	1.09 (1.04, 1.14)	1.08 (1.03, 1.12)

AR: Allergic Rhinitis; BC: black carbon; CI: confidence interval; NAR: Non-Allergic Rhinitis; NO_2: nitrogen dioxide; OR: odds ratio; $PM_{2.5}$ particulate matter with an aerodynamic diameter less than 2.5 µm.

OR (95% CI) were calculated for an increase of an interquartile range (4.85 µg/m^3 for $PM_{2.5}$, 0.88 10^{-5} m^{-1} for BC and 17.3 µg/m^3 for NO_2), all p-values were <0.01.

a: Health prevention center taken into account by marginal models with generalized estimating equations.

b: adjusted ORs for age, sex, smoking status, educational level, and French deprivation index. Current rhinitis was compared to never rhinitis + non-current rhinitis.

c: adjusted ORs for age, sex, smoking status, educational level, and French deprivation index. Current AR was compared to never rhinitis + non-current AR.

d: adjusted ORs for age, sex, smoking status, educational level, and French deprivation index. Current NAR was compared to never rhinitis + non-current NAR.

e: adjusted ORs for age, smoking status, educational level, and French deprivation index. Current rhinitis was compared to never rhinitis + non-current rhinitis. Non-significant P-values for interaction between sex and air pollutants.

f: adjusted ORs for age, sex, educational level, and French deprivation index. Current rhinitis was compared to never rhinitis + non-current rhinitis. Non-significant P-values for interaction between sex and air pollutants
g: adjusted ORs for age, sex, smoking status, educational level, French deprivation index and health prevention center. Current rhinitis was compared to never rhinitis + non-current rhinitis.
h: adjusted ORs for age, sex, smoking status, educational level, and French deprivation index. Current rhinitis was compared to never rhinitis.
i: adjusted ORs for age, sex, smoking status, educational level, and French deprivation index. Current rhinitis was compared to non-current rhinitis.

Figure S1: Location of the participating Health Prevention Centers in France
Three health prevention centers were located in Paris.

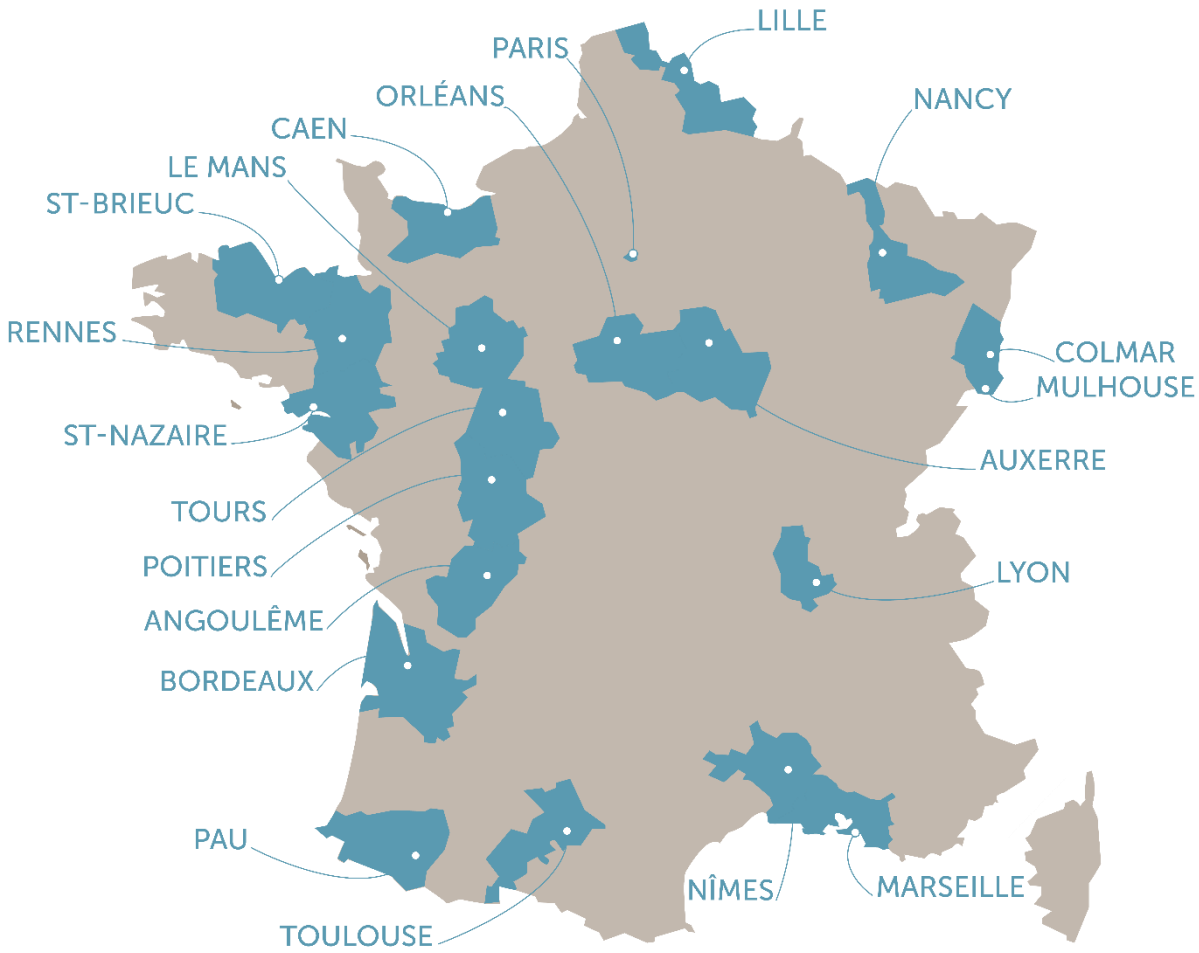


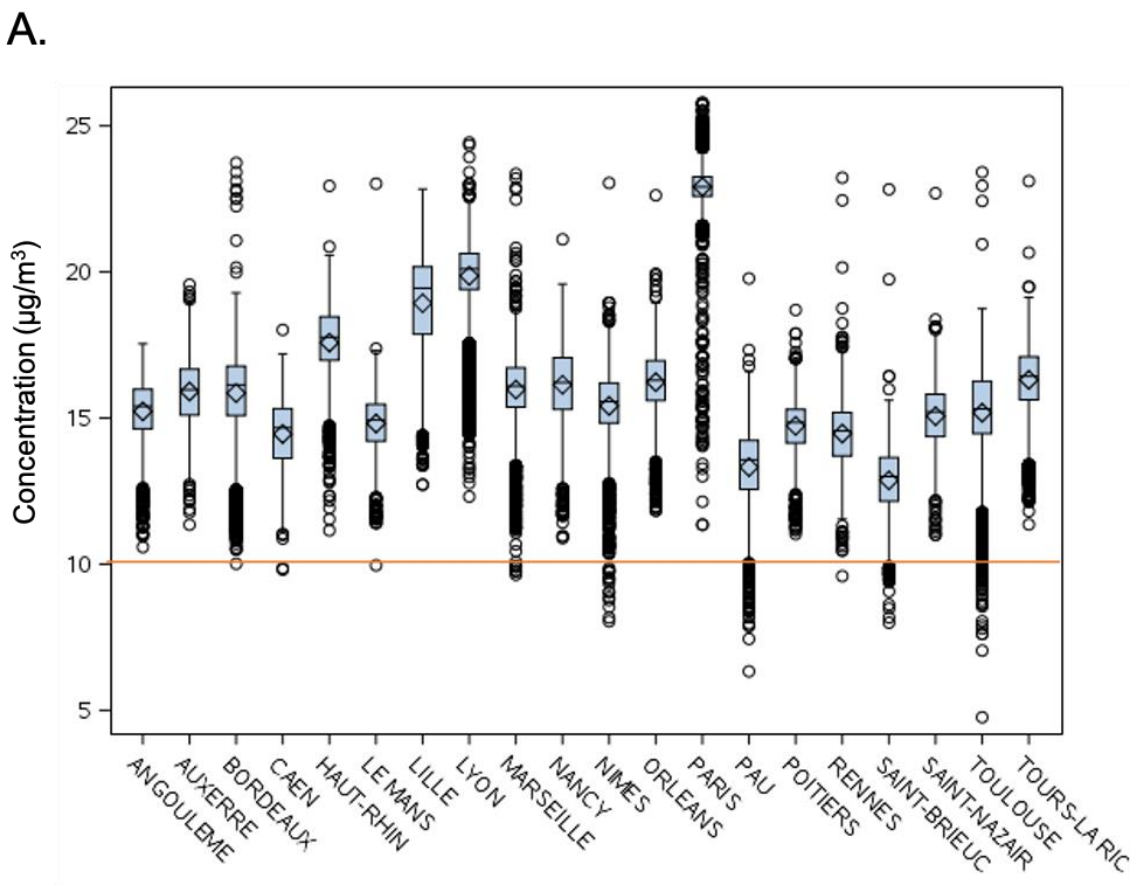
Figure S2: Distribution of air pollutant concentrations by health prevention center

A. $PM_{2.5}$ ($\mu g/m^3$)

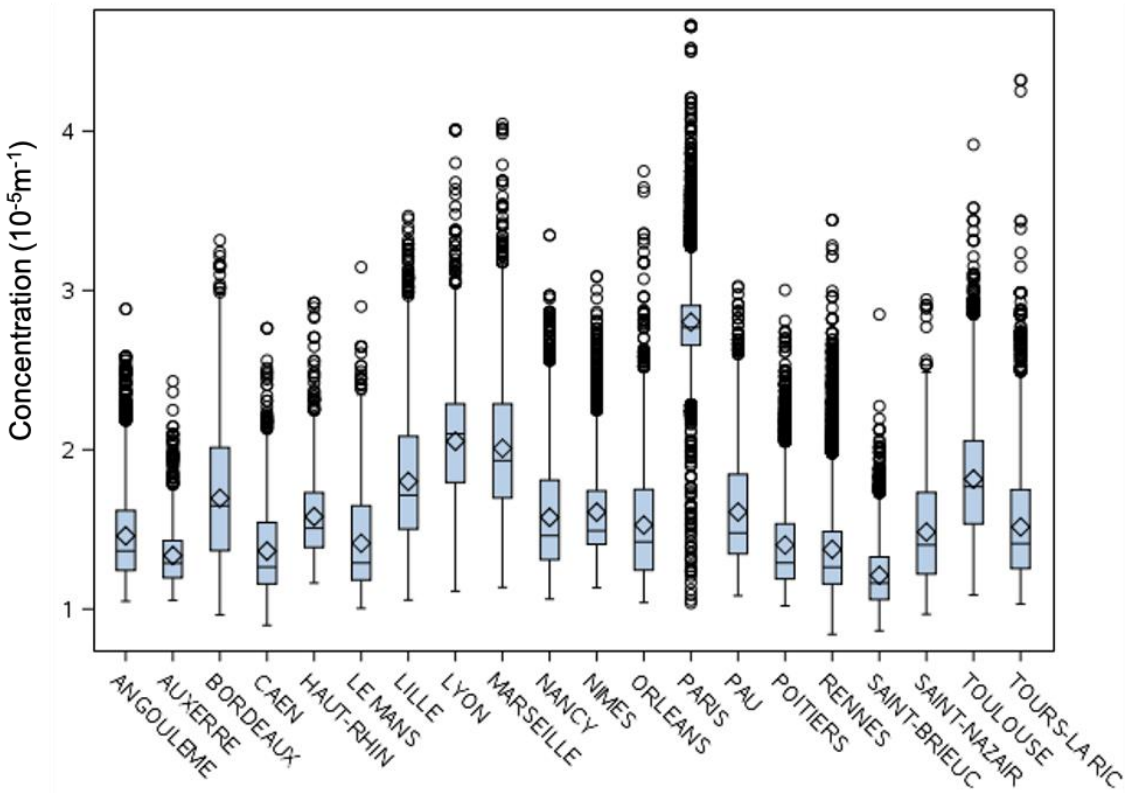
B. BC (10^{-5} m^{-1})

C. NO_2 ($\mu g/m^3$)

— *2005 World Heath Organization air quality guideline (unavailable for BC)*



B.


Concentration (10-5m-1)
1
2
3
4
ANGOULEME
AUXERRE
BORDEAUX
CAEN
HAUT-RHIN
LE MANS
LILLE
LYON
MARSEILLE
NANCY
NIMES
ORLEANS
PARIS
PAU
POITIERS
RENNES
SAINT-BRIEUC
SAINT-NAZAIR
TOULOUSE
TOURS-LA RIC

C.

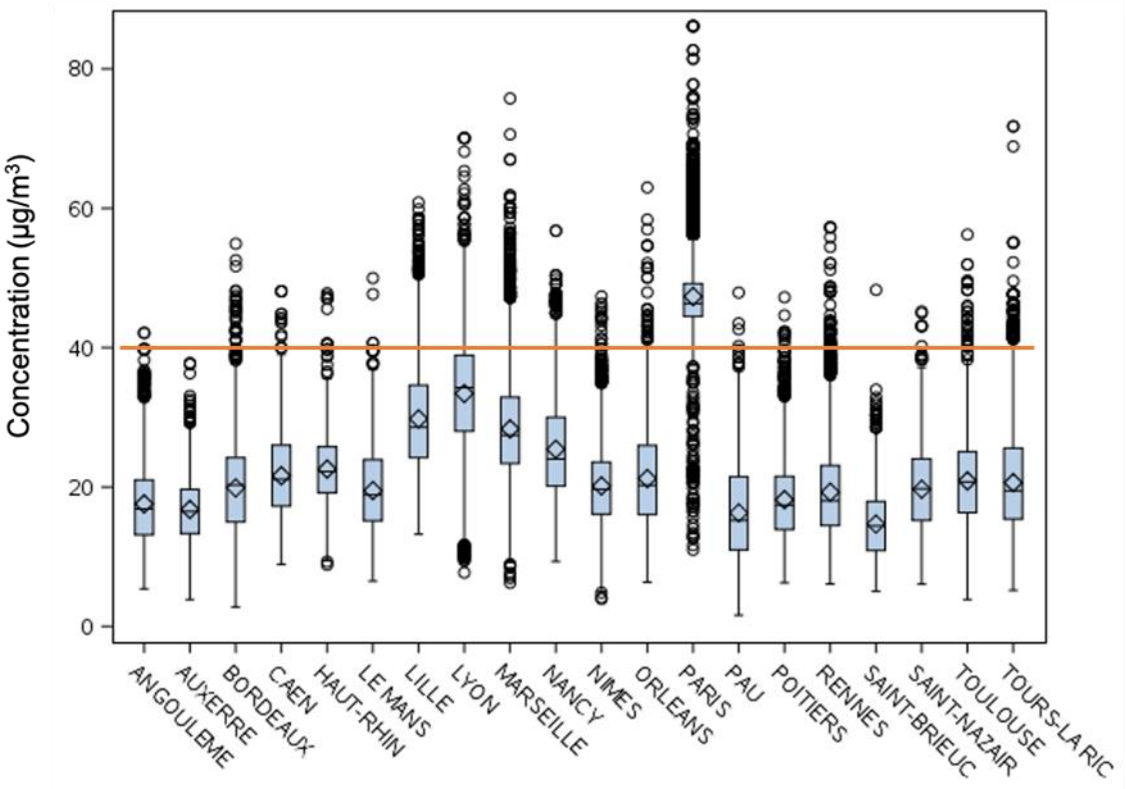

Concentration (µg/m3)
0
20
40
60
80
ANGOULEME
AUXERRE
BORDEAUX
CAEN
HAUT-RHIN
LE MANS
LILLE
LYON
MARSEILLE
NANCY
NIMES
ORLEANS
PARIS
PAU
POITIERS
RENNES
SAINT-BRIEUC
SAINT-NAZAIR
TOULOUSE
TOURS-LA RIC

Figure S3: Meta-analysis

OR (95% CI) were calculated:

A. For an increase of an IQR of $PM_{2.5}$ (4.85 µg/m^3)

B. For an increase of an IQR of BC (0.88 $10^{-5}m^{-1}$)

C. For an increase of an IQR of NO_2 (17.3 µg/m^3)

Adjusted ORs for age, sex, smoking status, educational level, and French deprivation index. Current rhinitis was compared to never rhinitis + non-current rhinitis.

FE: Fixed Effect; RE: Random Effect

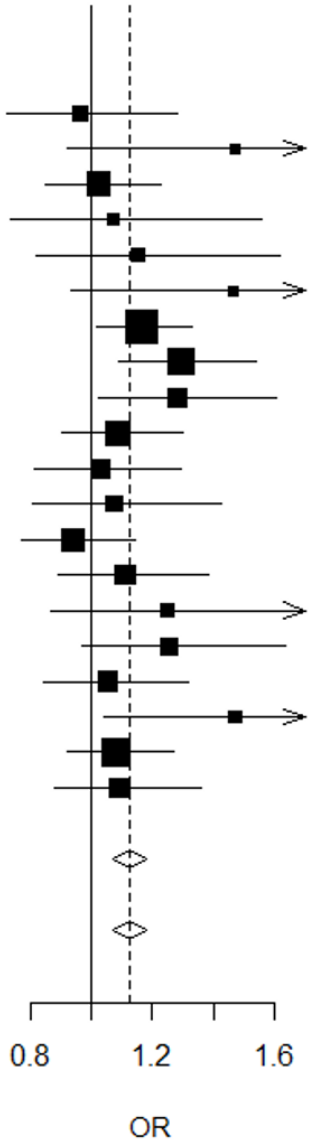
The three centers of Paris were pooled.

Haut Rhin = Colmar + Mulhouse

A.

Center	n Reference	n Current rhinitis	OR	(95% CI)
Angoulème	3,089	1,607	0.96	(0.72, 1.28)
Auxerre	912	446	1.47	(0.92, 2.33)
Bordeaux	4,648	2,843	1.02	(0.85, 1.23)
Caen	1,382	719	1.07	(0.74, 1.56)
Haut-Rhin	1,569	739	1.15	(0.82, 1.62)
Le Mans	1,640	780	1.47	(0.94, 2.29)
Lille	5,627	3,068	1.16	(1.02, 1.33)
Lyon	5,232	3,530	1.30	(1.09, 1.54)
Marseille	3,472	2,427	1.28	(1.02, 1.61)
Nancy	5,534	2,823	1.09	(0.91, 1.30)
Nimes	2,436	1,572	1.03	(0.81, 1.30)
Orléans	3,355	1,722	1.07	(0.81, 1.42)
Paris	12,995	8,663	0.94	(0.77, 1.14)
Pau	3,684	2,053	1.11	(0.89, 1.38)
Poitiers	2,964	1,424	1.25	(0.87, 1.80)
Rennes	4,370	2,045	1.26	(0.97, 1.63)
Saint-Brieux	5,521	2,328	1.05	(0.84, 1.32)
Saint-Nazaire	2,733	1,342	1.47	(1.04, 2.07)
Toulouse	4,831	2,897	1.08	(0.92, 1.27)
Tours-La-Riche	5,474	2,612	1.09	(0.88, 1.36)
FE	81,468	45,640	1.12	(1.07, 1.18)
RE	81,468	45,640	1.12	(1.07, 1.18)

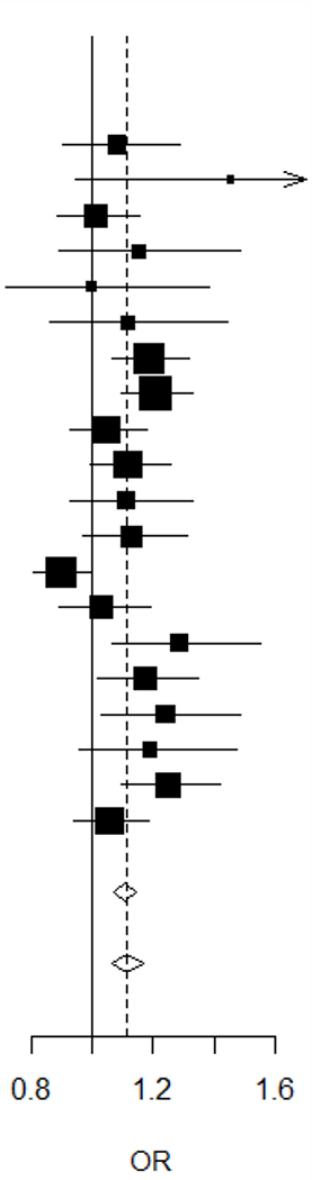
I^2 = 0% (p = 0.58)



B.

Center	n Reference	n Current rhinitis	OR	(95% CI)
Angoulème	3,089	1,607	1.11	(0.93, 1.33)
Auxerre	912	446	1.67	(1.00, 2.79)
Bordeaux	4,648	2,843	1.02	(0.90, 1.15)
Caen	1,382	719	1.06	(0.80, 1.39)
Haut-Rhin	1,569	739	1.04	(0.74, 1.45)
Le Mans	1,640	780	1.08	(0.84, 1.38)
Lille	5,627	3,068	1.17	(1.06, 1.30)
Lyon	5,232	3,530	1.23	(1.10, 1.38)
Marseille	3,472	2,427	1.04	(0.93, 1.17)
Nancy	5,534	2,823	1.13	(1.01, 1.28)
Nimes	2,436	1,572	1.14	(0.94, 1.37)
Orléans	3,355	1,722	1.18	(1.03, 1.37)
Paris	12,995	8,663	0.90	(0.82, 1.00)
Pau	3,684	2,053	1.05	(0.91, 1.20)
Poitiers	2,964	1,424	1.38	(1.14, 1.65)
Rennes	4,370	2,045	1.16	(1.00, 1.34)
Saint-Brieux	5,521	2,328	1.27	(1.03, 1.58)
Saint-Nazaire	2,733	1,342	1.10	(0.90, 1.33)
Toulouse	4,831	2,897	1.16	(1.04, 1.31)
Tours-La-Riche	5,474	2,612	1.07	(0.95, 1.21)
FE	81,468	45,640	1.11	(1.07, 1.14)
RE	81,468	45,640	1.12	(1.06, 1.14)

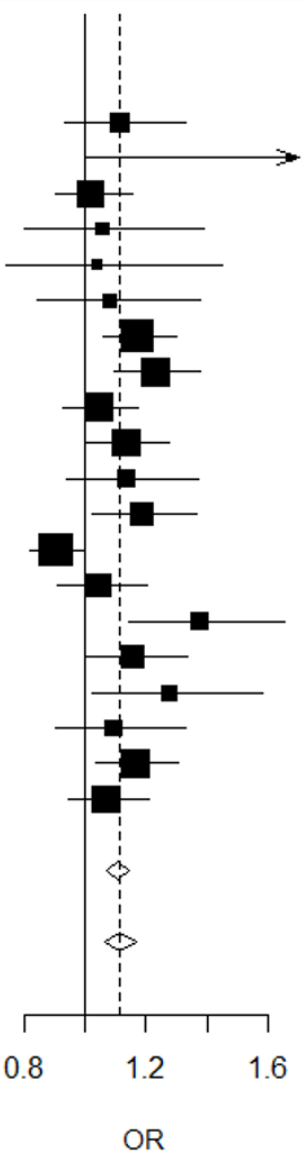
I^2 = 48% (p = 0.01)



C.

Center	n Reference	n Current rhinitis	OR	(95% CI)
Angoulème	3,089	1,607	1.08	(0.90, 1.29)
Auxerre	912	446	1.45	(0.95, 2.23)
Bordeaux	4,648	2,843	1.01	(0.89, 1.16)
Caen	1,382	719	1.15	(0.89, 1.48)
Haut-Rhin	1,569	739	1.00	(0.72, 1.39)
Le Mans	1,640	780	1.12	(0.86, 1.44)
Lille	5,627	3,068	1.19	(1.07, 1.32)
Lyon	5,232	3,530	1.21	(1.10, 1.33)
Marseille	3,472	2,427	1.05	(0.93, 1.18)
Nancy	5,534	2,823	1.12	(0.99, 1.26)
Nimes	2,436	1,572	1.11	(0.93, 1.33)
Orléans	3,355	1,722	1.13	(0.97, 1.31)
Paris	12,995	8,663	0.90	(0.81, 1.00)
Pau	3,684	2,053	1.03	(0.89, 1.19)
Poitiers	2,964	1,424	1.28	(1.06, 1.55)
Rennes	4,370	2,045	1.17	(1.02, 1.35)
Saint-Brieux	5,521	2,328	1.24	(1.03, 1.49)
Saint-Nazaire	2,733	1,342	1.19	(0.96, 1.47)
Toulouse	4,831	2,897	1.25	(1.09, 1.42)
Tours-La-Riche	5,474	2,612	1.06	(0.94, 1.19)
FE	81,468	45,640	1.11	(1.07, 1.15)
RE	81,468	45,640	1.12	(1.07, 1.17)

I^2 = 44% (p = 0.02)



Appendix 10: Effect of long-term exposures to air pollution on rhinitis and asthma multimorbidity – Supplementary material

Table S1: Comparison of included and non-included participants

	Non-included (n=24,737)	Included (n=178,030)	p
Sex			0.001
Men	11,219 (45.4%)	82,718 (46.5%)	
Women	13,518 (54.7%)	95,312 (53.5%)	
Age, years (mean SD)	0.0 (0.0)	46.8 (15.0)	<.0001
Tobacco status			0.032
Never-smoker	7,758 (47.7%)	84,999 (47.7%)	
Ex-smoker	5,605 (34.5%)	60,002 (33.7%)	
Current smoker	2,898 (17.8%)	33,029 (18.6%)	
BMI, kg/m^2			<.0001
<18.5	653 (2.7%)	4,905 (2.8%)	
[18.5-25[	12,270 (51.3%)	95,649 (54.6%)	
[25-30[	7,647 (32.0%)	53,146 (30.4%)	
>=30	3,345 (14.0%)	21,388 (12.2%)	
Educational level			<.0001
Less than high school	2,473 (11.8%)	14,537 (8.2%)	
High school	7,224 (34.6%)	57,505 (32.3%)	
University	11,187 (53.6%)	105,988 (59.5%)	

Data are n (%) or mean (SD)
BMI: body mass index; SD: standard deviation

Table S2: Description of pollutants and Spearman Correlation Coefficient

	Mean	SD	Min	Max	Q1	Med	Q3	IQR	Correlation BC	Correlation NO_2
$PM_{2.5}$, $\mu g/m^3$	17.1	3.31	4.76	25.8	14.8	16.2	19.4	4.66	0.79	0.86
BC, 10^{-5} m^{-1}	1.81	0.59	0.86	4.77	1.33	1.64	2.19	0.87	-	0.92
NO_2, $\mu g/m^3$	26.4	12.2	1.59	86.1	17.1	23.3	33.8	16.7	-	-

BC: black carbon; IQR: interquartile range; Max: maximum; Med: median; Min: minimum; NO_2: nitrogen dioxide; $PM_{2.5}$ particulate matter with an aerodynamic diameter less than 2.5 µm; Q1: first quartile; Q3: third quartile; SD: standard deviation.

Appendix 11: Effect of long-term exposures to air pollution on incident rhinitis – Supplementary material

Table S1: Comparison of included and non-included participants

	Included (n=6,914)	Not included (n=19,823)	p
Sex			0.0007
Men	3,016 (43.6%)	9,117 (46.0%)	
Women	3,898 (56.4%)	10,706 (54.0%)	
Age, years (mean SD)	51.0 (12.3)	50.2 (13.1)	<.0001
Tobacco status			<.0001
Never smoker	3,380 (48.9%)	8,341 (45.0%)	
Ex-smoker	2,460 (35.6%)	6,642 (35.8%)	
Current smoker	1,074 (15.5%)	3,573 (19.3%)	
BMI, kg/m^2			<.0001
<18.5	160 (2.4%)	451 (2.3%)	
[18.5-25[	3,782 (55.5%)	10,261 (52.9%)	
[25-30[	2,141 (31.4%)	6,206 (32.0%)	
≥30	734 (10.8%)	2,492 (12.8%)	
Educational level			<.0001
Less than high school	657 (9.5%)	2,255 (11.6%)	
High school	2,366 (34.2%)	6,672 (34.3%)	
University	3,891 (56.3%)	10,500 (54.1%)	

BMI: body mass index; SD: standard deviation

Table S2: Description of pollutants and Spearman Correlation Coefficient

	Mean	SD	Min	Max	Med	IQR	Correlation BC	Correlation NO_2
PM2.5, µg/m^3	16.64	3.21	7.88	24.68	15.90	3.17	0.78	0.86
BC, 10^{-5} m^{-1}	1.75	0.56	0.88	4.25	1.58	0.77	/	0.91
NO2, µg/m^3	24.81	11.84	5.21	68.97	21.91	13.82	/	/

BC: black carbon; IQR: interquartile range; Max: maximum; Med: median; Min: minimum; NO_2: nitrogen dioxide; $PM_{2.5}$ particulate matter with an aerodynamic diameter less than 2.5 µm; SD: standard deviation.

Appendix 12: Substantial summary in French

Phénotypes de la rhinite : identification et association avec l'exposition à long terme à la pollution atmosphérique dans deux études françaises

La rhinite est l'une des maladies les plus fréquentes et a des conséquences aussi bien économiques que sur le quotidien des patients. Malgré son impact élevé en termes de santé publique, la rhinite est souvent banalisée, sous-diagnostiquée, et de nombreuses lacunes persistent concernant sa prévalence et ses caractéristiques en population générale. Globalement, la prévalence de la rhinite est considérée comme étant en augmentation dans le monde au cours des dernières décennies. L'un des facteurs environnementaux qui pourrait en partie expliquer cette augmentation est la pollution atmosphérique. Il existe cependant peu d'études épidémiologiques portant sur le lien entre l'exposition à long terme à la pollution atmosphérique et la rhinite, notamment chez l'adulte.

L'objectif principal de cette thèse était d'étudier, chez l'adulte, les caractéristiques de la rhinite et de ses phénotypes et leurs associations avec l'exposition à long terme à la pollution atmosphérique. Le premier objectif consistait à identifier et décrire la rhinite, ses phénotypes et endotypes, dans deux études françaises : l'Étude épidémiologique des facteurs Génétiques et Environnementaux de l'Asthme (EGEA) et la cohorte Constances. Le deuxième objectif était d'étudier les associations entre l'exposition à long terme aux particules de diamètre aérodynamique ≤2.5 µm ($PM_{2.5}$), carbone suie (BC) et dioxyde d'azote (NO_2), et la rhinite dans Constances.

1. Objectif 1 : Identification et description de la rhinite, ses phénotypes et endotypes

Il n'y avait pas de revue de la littérature sur la prévalence de la rhinite qui ait porté à la fois sur la rhinite allergique et la rhinite non-allergique. Les revues de la littérature sur la prévalence de la rhinite concernaient uniquement la rhinite allergique, et la plus récente ayant considéré l'ensemble des régions du monde datait de 2008. J'ai donc conduit une revue de la littérature qui a porté sur la prévalence de la rhinite et ses différentes définitions en population générale adulte.
La recherche bibliographique a été effectuée à partir des bases de données Scopus et Pubmed, et 184 articles ont été identifiés, contribuant à 156 définitions différentes de la rhinite. Les définitions ont été regroupées en trois catégories : rhinite allergique, rhinite non-allergique et rhinite non-spécifiée qui correspondait à une définition de la rhinite qui ne distinguait pas la rhinite allergique de la rhinite non-allergique. Selon les études, la prévalence de la rhinite variait de 1 % à plus de 60 %. Les prévalences mondiales médianes de la rhinite allergique, de la rhinite non-allergique et de la rhinite non spécifiée étaient respectivement de 18,1 %, 12,0 % et 28,4 %. La rhinite était principalement définie à partir de questions standardisées, sans qu'il y ait de consensus sur le choix des questions à utiliser. Cette absence de consensus rend difficilement comparable les résultats entre les études et peut expliquer la grande variabilité observée pour la prévalence de la rhinite. Quelle que soit la définition utilisée, la prévalence de la rhinite semblait augmenter au cours du temps. Par ailleurs, si de nombreuses études avaient été conduites en population générale pour estimer la prévalence de la rhinite allergique, peu d'études avaient estimé la prévalence de la rhinite non-allergique. Cette revue de la littérature suggère que de nouvelles études en population générale sont nécessaires pour estimer la prévalence de la rhinite et de ses phénotypes et décrire leurs caractéristiques.

Pour différencier la rhinite allergique de la rhinite non-allergique, les Immunoglobulines E et les tests cutanés aux allergènes (SPTs) sont les deux gold-standards, mais ces mesures ne sont pas toujours disponibles dans les études épidémiologiques, en particulier dans les études réalisées dans de très grands échantillons. C'est pourquoi j'ai cherché à savoir si une définition par questionnaire pouvait être une alternative aux tests cutanés pour différencier la rhinite allergique de la rhinite non-allergique dans les études épidémiologiques. Pour cela, j'ai utilisé les données du premier suivi de l'étude EGEA qui est une étude multicentrique cas-témoin et familiale sur l'asthme. La première enquête s'est déroulée entre 1991 et 1995 (EGEA1, n = 2 047). Un suivi de la cohorte initiale a été réalisé entre 2003 et 2007 (EGEA2, n = 1 601). EGEA présente une large caractérisation phénotypique, environnementale et biologique des participants, dont la réalisation de tests cutanés à plusieurs aéroallergènes. Parmi les adultes, la rhinite actuelle a été définie par la déclaration

d'éternuements ou de rhinorrhée ou de congestion nasale en l'absence de rhume ou de grippe au cours des 12 derniers mois. Parmi les participants présentant de la rhinite actuelle, deux définitions de la rhinite allergique et non-allergique ont été utilisées : l'une basée sur les SPTs et l'autre sur questionnaire. Les participants qui avaient au moins un SPT positif ont été classés dans la catégorie rhinite allergique basée sur SPTs, sinon dans la catégorie rhinite non-allergique basée sur SPTs. Les participants qui ont répondu positivement à la question "*Avez-vous déjà eu une rhinite allergique ?*" ou "*Avez-vous déjà eu un rhume des foins ?*" ont été classés dans la catégorie rhinite allergique basée sur questionnaire, sinon dans la catégorie rhinite non-allergique basée sur questionnaire.
J'ai montré que, la définition par questionnaire et par SPT présentaient des caractéristiques similaires pour la rhinite allergique comme pour la rhinite non-allergique. Ces résultats suggèrent que la définition par questionnaire pourrait être utilisée comme un proxy approprié en l'absence de mesures biologiques.

A l'aide de définitions par questionnaire similaires à celles utilisées dans EGEA, j'ai ensuite pu estimer la prévalence de la rhinite en population générale dans Constances. Constances est la plus grande cohorte épidémiologique en population générale chez l'adulte en France avec 220 000 participants âgés de 18 à 69 ans inclus de 2012 à 2020. Les prévalences pondérées de la rhinite, et des rhinites allergique et non-allergique ont été estimées à l'inclusion. La rhinite actuelle a été définie par la déclaration d'éternuement, rhinorrhée ou congestion nasale dans les 12 derniers mois en l'absence de rhume ou de grippe. Parmi les participants avec de la rhinite actuelle, ceux ayant déclaré avoir eu au cours de leur vie des allergies nasales, rhume des foins inclus, ont été considérés comme ayant de la rhinite allergique, sinon comme ayant de la rhinite non-allergique. Des poids de sondages disponibles pour les années d'invitations comprises entre 2013 et 2017 ont été utilisés afin d'obtenir des prévalences pondérées. Suivant l'année d'invitation, les prévalences pondérées de la rhinite actuelle, de la rhinite allergique et de la rhinite non-allergique variaient de 33,7 % à 34,7 %, de 23,0 % à 24,2 %, et de 10,2 % à 11,4 % respectivement. Ces estimations apportent de nouvelles connaissances sur la prévalence de la rhinite et en particulier de la rhinite non-allergique pour laquelle il existe actuellement très peu de données.

J'ai ensuite décrit dans Constances les phénotypes de la rhinite à partir des réponses au questionnaire de suivi annuel de 2014 qui comporte des questions détaillées sur la rhinite et ses caractéristiques. Ce questionnaire a été envoyé à 26 737 adultes, 21 507 y ont répondu et 19 663 ont été inclus dans les analyses. La rhinite actuelle, la rhinite allergique et la rhinite non-allergique ont été définies de la même manière que dans le paragraphe précédent.
Les participants du groupe rhinite allergique déclaraient en moyenne plus d'asthme, de conjonctivite et d'eczéma au cours de leur vie que les participants du groupe rhinite

non-allergique. Ils déclaraient également plus de déclencheurs allergiques (pollens, acariens ou poussières de maison) et plus de la moitié d'entre eux rapportaient avoir des symptômes au printemps. Les participants du groupe rhinite allergique rapportaient également davantage de rhinite persistante (31,6 % contre 25,1 %) et modérée à sévère (40,1 % contre 24,2 %) que les participants du groupe rhinite non-allergique. L'âge de début des symptômes était en moyenne plus précoce pour les participants avec de la rhinite allergique comparé aux participants avec de la rhinite non-allergique (moyenne : 24,3 ans *versus* 34,6 ans). Les participants présentant à la fois de la rhinite et de l'asthme avaient un nombre moyen d'éosinophiles sanguins plus élevé, un âge de début de rhinite en moyenne plus précoce, ainsi que plus de symptômes sévères que les participants ayant seulement de la rhinite. Les participants ayant à la fois de l'asthme, de la conjonctivite et de la rhinite allergique rapportaient un âge de début de la rhinite encore plus précoce, plus de rhinite sévère et avaient un nombre moyen d'éosinophiles sanguins plus élevé que les participants des autres groupes. Ces analyses ont été également effectuées avec les données de l'étude EGEA2 et des résultats très similaires ont été observés.
En résumé, dans une grande cohorte en population générale, j'ai retrouvé les caractéristiques connues de la rhinite allergique et la rhinite non-allergique. La prévalence de rhinite modérée-sévère était plus faible que celle rapportée en pratique clinique, ce qui était attendu car les patients qui consultent un médecin ont généralement des rhinites plus sévères, mais cela n'avait jamais montré auparavant. Que ce soit dans l'étude Constances ou dans l'étude EGEA, inclure l'asthme et la conjonctivite permettait d'identifier des sous-phénotypes de rhinite avec des caractéristiques spécifiques. Ces sous-phénotypes pourront faire l'objet de recherche ciblée pour une meilleure prise en charge de la rhinite.

Toujours avec les données du questionnaire de suivi annuel de 2014 de la cohorte Constances, j'ai décrit la rhinite selon la classification établie par l'Allergic Rhinitis and Its Impact on Asthma (ARIA) qui est une référence dans le domaine. Cette classification permet de définir la sévérité (légère ou modérée-sévère) et la persistance (intermittente ou persistante) de la rhinite. En combinant ces catégories, quatre classes de rhinite peuvent être définies : légère/intermittente, légère/persistante, modérée-sévère/intermittente, modérée-sévère/persistante. L'asthme étant une multimorbidité majeure de la rhinite et compte tenu des résultats précédents, j'ai également étudié si le fait de prendre en compte l'asthme impactait ces quatre classes.
Parmi les 4 584 participants avec de la rhinite allergique inclus dans les analyses, 44,0 % ont été classés en rhinite légère/intermittente, 15,9 % légère/persistante, 24,7 % modérée-sévère/intermittente, et 15,3 % modérée-sévère/persistante. Les quatre classes présentaient des caractéristiques cliniques propres. Pour chacune des classes, comparés aux participants avec de la rhinite seule, ceux avec de la rhinite et de l'asthme avaient significativement plus de conjonctivite, un nombre moyen d'éosinophiles

sanguins plus élevé et rapportaient plus de traitements combinant anti-histaminiques par voie orale et corticostéroïdes inhalés.
Ces analyses conduites dans une grande étude en population générale chez l'adulte, montrent pour la première fois que prendre en compte le statut asthmatique pourrait modifier la classification ARIA. La rhinite seule et la rhinite avec asthme semble être deux phénotypes présentant des caractéristiques différentes. Ce résultat est un argument solide pour créer de nouvelles classifications de rhinite incluant l'asthme.

Les phénotypes présentés ci-dessus ont été construits à partir de classifications cliniques basées sur des hypothèses *a priori*, une approche dite « candidate ». Une des limites de cette approche est sa subjectivité dans le choix des classifications à utiliser pour identifier les phénotypes de la rhinite. Complémentaire à l'approche candidate, l'approche dite « non-supervisée » ne nécessite pas de connaissances *a priori*, et permet de s'affranchir de cette subjectivité. Cette approche a été peu utilisée pour identifier les phénotypes de la rhinite dans des études en population générale ; je l'ai donc appliquée dans Constances.
A partir des données du questionnaire de 2014 et sur la base de 25 variables décrivant les caractéristiques et multimorbidités de la rhinite, une analyse factorielle des données mixtes suivie d'un clustering via un algorithme K-means a permis d'identifier trois phénotypes (clusters).
Le cluster 1 (n = 2 586, 46,9 %) était majoritairement caractérisé par des participants ayant déclaré une rhinite avec peu de déclencheurs allergiques (acariens, animaux et pollens) et 53,1 % d'entre ne savaient pas quel était le déclencheur de leurs symptômes. Dans les clusters 2 (n = 2 379, 43,1 %) et 3 (n = 551, 10,0 %), plus de 95 % des participants rapportaient des allergies nasales. Le cluster 3 était, en plus, caractérisé par 100 % de participants rapportant une rhinite modérée-sévère. Comparé aux deux autres clusters, le cluster 3 présentait également le nombre moyen d'éosinophiles sanguins et le pourcentage de déclaration de traitements combinant antihistaminiques par voie orale et corticostéroïdes inhalés les plus élevés.
Les caractéristiques de ces clusters sont assimilables à celles des phénotypes rhinite non-allergique, rhinite allergique et rhinite allergique sévère. Ces résultats montrent l'importance majeure des phénotypes de rhinite allergique et non-allergique et de la sévérité de la rhinite.

Les différences observées dans les caractéristiques de la rhinite allergique légère et de la rhinite allergique sévère pourraient en partie être liées à des mécanismes biologiques sous-jacents différents, comme suggéré par le nombre moyen d'éosinophiles sanguins élevé observé dans le cluster rhinite allergique sévère identifié dans Constances. Identifier des endotypes de rhinite, c'est à dire des sous-groupes de rhinite combinant des caractéristiques cliniques et biologiques, est d'intérêt pour répondre à cette question. Cette approche nécessite de nombreuses variables biologiques, et une large

biobanque étant disponible à EGEA2, j'ai cherché à identifier des endotypes de la rhinite en utilisant une approche non-supervisée.
Parmi les adultes d'EGEA2, en intégrant 35 variables décrivant les caractéristiques et multimorbidités de la rhinite, ainsi que des marqueurs appartenant à différentes voies biologiques (inflammation, stress oxydant, stress nitrosant, allergie), une analyse factorielle des données mixtes suivie d'un clustering via un algorithme K-means a permis d'identifier deux endotypes (clusters).
Le cluster 1 (n = 130, 39,6 %) était majoritairement caractérisé par des participants déclarant peu de rhinite allergique/rhume des foins et présentant peu de marqueurs de l'allergie alors que dans le cluster 2 (n = 198, 60,4 %) quasiment tous les participants avaient au moins un SPT positif et déclaraient de la rhinite allergique ou un rhume des foins. Des résultats similaires ont été observés en stratifiant selon le statut asthmatique.
En conclusion, l'analyse non-supervisée dans EGEA a permis d'identifier deux clusters principalement discriminés par les voies biologiques de l'allergie et qui peuvent être assimilés à de la rhinite non-allergique et de la rhinite allergique.

2. Objectif 2 : Exposition à long-terme à la pollution atmosphérique et associations avec la rhinite

La revue de la littérature réalisée dans l'objectif 1 a mis en évidence une augmentation de la prévalence de la rhinite dans le monde durant les dernières décennies. L'un des facteurs environnementaux qui pourrait en partie expliquer cette augmentation est la pollution atmosphérique.

J'ai donc étudié les associations entre l'exposition à long terme à la pollution atmosphérique et la rhinite actuelle dans Constances. La rhinite actuelle a été définie à l'inclusion (2012-2017) à partir des mêmes questions que celles utilisées dans l'objectif 1. Les expositions annuelles aux $PM_{2.5}$, BC et NO_2 ont été estimées à l'adresse résidentielle des participants à l'inclusion par un modèle de Land Use Regression. Des analyses transversales entre l'exposition annuelle à chaque polluant atmosphérique et la rhinite actuelle ont été effectuées à l'aide de modèles logistiques marginaux (sur le centre d'examen de santé) ajustés sur l'âge, le sexe, le statut tabagique, le niveau d'éducation et l'indice de déprivation français (FDep). Plusieurs analyses complémentaires ont été réalisées (données imputées, méta-analyse) ainsi que des analyses conduites séparément pour la rhinite allergique et la rhinite non-allergique, ou stratifiées selon le sexe ou le statut tabagique (non-fumeurs, ex-fumeurs ou fumeurs actuels).
La population d'analyse était constituée de 127 108 participants (47 ans en moyenne, 53,8 % de femmes, 19,1 % de fumeurs actuels). La prévalence de la rhinite actuelle était de 35,9 %, celle de la rhinite allergique de 24,9 %, et celle de la rhinite non allergique de 11,0 %. Une augmentation d'un intervalle interquartile de $PM_{2.5}$ (4,85 µg/m^3), de BC (0,88 $10^{-5}m^{-1}$) ou de NO_2 (17,3 µg/m^3) était associée à une augmentation de la rhinite actuelle avec des Odds Ratio ajustés (Intervalles de Confiance à 95%) de 1,13 (1,08-1,17), 1,12 (1,07-1,17) et 1,11 (1,06-1,17) respectivement. Les résultats des modèles en ajustant sur le centre ou après imputation sur les données manquantes des covariables étaient similaires à ceux du modèle principal, soulignant la robustesse des résultats. Des associations significatives et positives ont également été mises en évidence pour la rhinite allergique et la rhinite non-allergique. Les résultats étaient similaires chez les hommes et les femmes et quel que soit le statut tabagique.
Ces résultats montrent que l'exposition résidentielle moyenne annuelle aux $PM_{2.5}$, BC et NO_2 était significativement associée à une augmentation de la prévalence de la rhinite actuelle chez les adultes en population générale française. Les résultats suggèrent que parmi les polluants atmosphériques, le BC peut présenter un intérêt particulier et devrait faire l'objet d'action plus ciblées pour le contrôle de l'exposition à la pollution atmosphérique.

Mes travaux ont montré que la présence d'asthme impactait les caractéristiques de la rhinite (objectif 1) et que l'exposition à la pollution atmosphérique était significativement associée à la rhinite. J'ai donc étudié l'association entre la pollution atmosphérique et la rhinite associée ou non à l'asthme. Pour cette analyse, la rhinite actuelle a été définie comme précédemment. L'asthme actuel correspondait à la déclaration d'asthme au cours de la vie et à la déclaration au cours des 12 derniers mois de : prise de traitement pour l'asthme, crise d'asthme, sifflements, réveil dû à une gêne respiratoire, essoufflement au repos, essoufflement à l'effort ou réveil dû à un essoufflement. Quatre groupes ont été considérés : les participants sans rhinite actuelle et sans asthme actuel (R-A-), les participants avec rhinite actuelle seule (R+A-), les participants avec asthme actuel seul (R-A+), et les participants avec rhinite actuelle et asthme actuel (R+A+). Des analyses transversales à l'inclusion entre l'exposition annuelle à chaque polluant atmosphérique et ces quatre catégories ont été effectuées à l'aide de modèles de régression logistique multinomiale ajustés sur l'âge, le sexe, le tabagisme, le niveau d'éducation et le FDep.
Parmi les 178 030 participants inclus dans les analyses (47 ans en moyenne, 53,5 % de femmes, 18,6 % de fumeurs actuels), 111 142 (62,4 %) étaient classés R-A-, 49 992 (28,1 %) R+A-, 6 436 (3,6 %) R-A+ et 10 460 (5,9 %) R+A+. En prenant comme référence R-A-, pour les trois polluants atmosphériques, une augmentation d'un IQR était significativement associée à chacun des autres groupes. Ainsi une augmentation d'un IQR de BC (0,87 $10^{-5}m^{-1}$) était significativement associée à R+A- (OR ($IC95_{\%}$) : 1,18 (1,16-1,20)), R-A+ (1,07 (1,04-1,11)), et à R+A+ (1,12 (1,08-1,16)). Quel que soit le polluant considéré, les associations étaient significativement plus fortes pour le groupe R+A- comparés aux trois autres groupes.
Ces résultats montrent que l'exposition à chaque polluant était associée à la rhinite actuelle avec et sans asthme actuel et à l'asthme actuel avec et sans rhinite actuelle. Les associations les plus fortes étaient observées pour le groupe rhinite actuelle sans asthme actuel, suggérant que ce groupe pourrait être davantage sensible aux effets de la pollution atmosphérique.

Enfin, j'ai étudié les associations entre la pollution atmosphérique et l'incidence de la rhinite dans Constances. A l'inclusion (en 2012/2013) et au suivi en 2014, la rhinite incidente a été définie comme : 1) « Incidence générale » : lorsque le participant déclarait ne jamais avoir eu de rhinite à l'inclusion et déclarait une rhinite au suivi ; 2) « Incidence stricte » : lorsqu'en plus l'âge de début de la rhinite était supérieur ou égal à l'âge à l'inclusion. Les associations entre chaque polluant atmosphérique et la rhinite incidente ont été évaluées à l'aide de modèles de régression logistiques de Poisson avec prise en compte du temps entre les deux suivis et ajustés sur l'âge, le sexe, le tabagisme, le niveau d'éducation et le FDep. Plusieurs analyses complémentaires ont été réalisées (données imputées, modèles marginaux, modèles logistiques et modèles de Cox) ainsi que des analyses conduites séparément pour la rhinite allergique et la rhinite non-allergique, ou stratifiées selon le sexe ou le statut tabagique.

Parmi les 9 226 participants inclus dans les analyses, 6 777 n'avaient jamais déclaré de rhinite, 2 450 ont été classés dans la catégorie des rhinites « incidentes générales » et 138 dans celle des rhinites « incidentes strictes ». Les Incidence Rate Ratios (IRR) ajustés pour « l'incidence stricte » étaient de 1,20 (1,00-1,86), de 1,28 (0,99-1,66) et de 1,22 (0,98-1,52) pour une augmentation d'un IQR de $PM_{2,5}$, BC et NO_2 respectivement. Les IRRs étaient plus élevés pour les femmes que pour les hommes, et des associations significatives ont été trouvées chez les femmes pour le BC (1,43 (1,06-1,93)) et le NO_2 (1,31 (1,01-1,69)). Des associations significatives pour chacun des trois polluants ont été observées dans la strate des personnes n'ayant jamais fumé, dans les deux autres strates aucune association significative n'a été observée. Les IRRs étaient plus élevés pour la rhinite non-allergique par rapport à la rhinite allergique, avec un IRR significatif pour le BC et la rhinite non-allergique (1,38 (1,01-1,89)).
En conclusion, ces résultats montrent que la pollution atmosphérique pourrait augmenter le risque de rhinite incidente chez les adultes en population générale, et suggèrent que les femmes et les non-fumeurs pourraient être des populations plus sensibles aux effets de la pollution.

Discussion générale et conclusion

L'objectif général de cette thèse était d'étudier, chez l'adulte, les caractéristiques de la rhinite et de ses phénotypes et leurs associations avec l'exposition à long terme à la pollution atmosphérique.
La revue de la littérature que j'ai réalisée sur les définitions et les prévalences de la rhinite dans le monde a souligné la nécessité d'un consensus sur des définitions standardisées de la rhinite à utiliser dans les études épidémiologiques. A partir des données de l'étude EGEA, j'ai étudié une définition de la rhinite allergique et de la rhinite non-allergique basée sur un questionnaire et j'ai montré que cette définition est appropriée pour être utilisée comme un proxy en l'absence de mesures biologiques. Cette définition a été utilisée dans Constances et pourrait l'être dans tout autre étude épidémiologique en raison de sa simplicité. Les analyses effectuées dans Constances sur les phénotypes de rhinite apportent de nouvelles données en population générale sur la rhinite et les données de prévalence pourraient être utilisées dans des études pharmaco-épidémiologiques et/ou d'économie de la santé. Au-delà de ces résultats, tout au long de cette thèse, il a été observé que le statut asthmatique apportait des informations importantes sur les phénotypes de rhinite. Il s'agit d'un changement de paradigme et le statut asthmatique devrait être pris en compte pour établir de nouvelles classifications de rhinite. Globalement, les résultats de cette thèse contribuent à une meilleure compréhension de la rhinite, et donc à terme à une meilleure prise en charge ainsi qu'à une diminution de son fardeau économique et social. Ceci est d'un intérêt majeur car la prévalence de la rhinite continue d'augmenter. Enfin cette thèse s'est concentrée sur les effets à long-terme de la pollution atmosphérique sur la rhinite et contribue au niveau de preuve que la pollution atmosphérique a un effet néfaste sur la santé, même à de faibles niveaux d'exposition. La réduction de l'exposition à la pollution atmosphérique est aujourd'hui une priorité de santé publique mais un véritable défi pour les politiques de santé. Au regard du fardeau que représente la pollution atmosphérique sur la santé et sur l'environnement, il est indéniable que réduire la pollution atmosphérique aura des effets bénéfiques sur l'ensemble de la société.

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Titre : Phénotypes de la rhinite : identification et association avec l'exposition à long terme à la pollution atmosphérique dans deux études françaises

Mots clés : rhinite, pollution atmosphérique, phénotypes, endotypes, multimorbidité

Résumé :
L'objectif principal de cette thèse était d'étudier, chez l'adulte, les caractéristiques de la rhinite et de ses phénotypes et leurs associations avec l'exposition à long terme à la pollution atmosphérique dans deux études françaises. Nous avons montré dans l'étude EGEA qu'une définition par questionnaire pouvait être un bon proxy pour identifier la rhinite allergique (RA) et la rhinite non allergique (RNA). A partir de cette définition et des données de la cohorte en population générale Constances, nous avons estimé les prévalences de la rhinite, de la RA et de la RNA et décrit leurs caractéristiques. Nous avons également étudié les différences phénotypiques entre la rhinite seule ou avec de l'asthme et décrit la RA en fonction de sa sévérité et de sa persistance. Dans Constances, à l'aide d'une approche non supervisée, nous avons identifié trois phénotypes assimilés à la RA, à la RA sévère et à la RNA. Dans EGEA, l'approche non supervisée a identifié deux endotypes assimilés à la RA et à la RNA. Ces résultats fournissent une description approfondie de la rhinite et montrent que la prise en compte de l'asthme permet d'identifier de nouveaux phénotypes de rhinite avec des caractéristiques spécifiques. Ils suggèrent que l'asthme devrait être considéré pour classifier la rhinite. Lors d'analyses transversales menées dans Constances, l'exposition aux particules fines ($PM_{2,5}$), carbone suie (BC) ou dioxide d'azote (NO_2) était significativement associée à la rhinite actuelle. En considérant la multimorbidité rhinite et asthme, quel que soit le polluant, les associations étaient plus élevées pour la rhinite actuelle sans asthme, renforçant l'hypothèse que la rhinite seule et la rhinite avec de l'asthme sont des maladies différentes avec des facteurs de risque probablement différents. Lors d'analyses longitudinales, des associations proches de la significativité ont été observées entre les $PM_{2,5}$, le BC et le NO_2 et l'incidence de la rhinite. Des associations significatives ont été observées parmi les non-fumeurs et les femmes, suggérant que ces populations pourraient être plus sensibles à la pollution atmosphérique. Compte tenu de la forte prévalence de la rhinite, les résultats issus de cette thèse ont des implications en pratique clinique ainsi qu'un impact important sur la santé publique. Ils renforcent également la nécessité de réduire l'exposition de la population à la pollution atmosphérique.

Title: Phenotypes of rhinitis: identification and association with long-term exposure to air pollution in two French studies

Keywords: rhinitis, air pollution, phenotypes, endotypes, multimorbidity

Abstract:
The main objective of this thesis was to study, among adults, the characteristics of rhinitis and of its phenotypes and their associations with long-term exposure to air pollution in two French studies. We first showed in the EGEA study that a questionnaire definition is a good proxy for identifying allergic (AR) and non-allergic (NAR) rhinitis. Then, based on this definition and from the data of the population-based cohort Constances, we estimated the prevalences of rhinitis, AR and NAR and described their characteristics. We also studied the phenotypic differences between rhinitis alone or with asthma and described AR according to its severity and duration. In Constances, using an unsupervised approach, we identified three phenotypes assimilated to AR, severe AR and NAR. In EGEA, the unsupervised approach identified two endotypes assimilated to AR and NAR. Overall, these results provide an in-depth description on rhinitis and showed that considering asthma allows to identify new phenotypes of rhinitis with specific characteristics. They also suggested that asthma should be considered for future classifications of rhinitis. In cross-sectional analyses in Constances, exposure to Particulate Matter ≤2.5 µm ($PM_{2.5}$), Black Carbon (BC) or nitrogen dioxide (NO_2) was significantly associated with current rhinitis. When considering rhinitis and asthma multimorbidity, whatever the pollutant, associations were the highest for current rhinitis without asthma strengthen the hypothesis that rhinitis alone and rhinitis with asthma are different diseases with probably different risk factors. In longitudinal analyses, considering all participants, associations at the borderline significance were observed between $PM_{2.5}$, BC, and NO_2 and incident rhinitis. Significant associations were observed in the never smoker group and in women suggesting these populations more sensitive to air pollution. As the prevalence of rhinitis is high, the findings from this thesis have implications in clinical practice and have an important public health impact. They reinforce the need to reduce the population's exposure to air pollution.