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# Contribution of real-life databases of adult patients suffering from allergic rhinitis

Davide Caimmi

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# Sorbonne Université

Ecole doctorale Pierre Louis de Santé publique :  
Epidémiologie et sciences de l'information biomédicale

*ED393 Laboratoire IPLESP, Equipe EPAR*

## **Contribution of real-life databases of adult patients**

### **suffering from allergic rhinitis**

#### *Allergic rhinitis severity and control*

Par Davide Paolo Caimmi

Thèse de doctorat d'épidémiologie clinique

Dirigée par Pascal Demoly et Isabella Annesi-Maesano

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Devant un jury composé de :

Demoly Pascal, PU-PH, Directeur  
Annesi-Maesano Isabella, DR1 INSERM, Co-directeur  
Chenivesse Cécile, MCU-PH, Rapporteur  
Dubus Jean Christophe, PU-PH, Rapporteur  
Bernaudin Jean-François, PU-PH  
Calderon Moises, PU  
Guilleminault Laurent, MCU-PH  
Marseglia Gian Luigi, PU-PH



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*Alla mia famiglia*

*e a chi crede sempre ai propri sogni*

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## List of abbreviations

AD	Allergy Diary
AIT	Allergen Immunotherapy
AR	Allergic Rhinitis
ARCT	Allergic Rhinitis Control Test
ARIA	Allergic Rhinitis and its Impact on Asthma
ARPhyS	Allergic Rhinitis Physician Score
CARAT	Control of Allergic Rhinitis and Asthma Test
CDSS	Clinical Decision Support System
CNIL	Commission Nationale Informatique et Liberté
COPD	Chronic Obstructive Pulmonary Disease
EAACI	European Academy of Allergy and Clinical Immunology
GA2LEN	Global Allergy and Asthma European Network
GINA	Global Initiative for Asthma
HRQL	Health-Related Quality of Life
ICC	Intraclass Correlation Coefficient
ICT	Information and Communication Technology
LAR	Local Allergic Rhinitis
LTRAs	Leukotriene Receptor Antagonists
MASK	MACVIA ARIA Sentinel network
NAR	Non-Allergic Rhinitis
OTC	Over The Counter
QoL	Quality of Life
RCAT	Rhinitis Control Assessment Test
RAPP	RhinAsthma Patient Perspective
RQLQ	Rhino-conjunctivitis Quality of Life Questionnaire
RTSS	Rhinitis Total Symptom Score
SCIT	Sub-Cutaneous Immunotherapy
SLIT	Sub-Lingual Immunotherapy
SPT	Skin Prick Tests
TNSS	Total Nasal Symptoms Score
TSS	Total Symptoms Score
T4SS	Total Four Symptom Score
VAS	Visual Analogue Scale

## Introduction

Allergic rhinitis (AR) affects up to 50% of some populations, especially in “westernized” countries and its prevalence, in France, tripled over the last 25 years and according to last figures is around 31% [1,2]. AR is associated with sleep disorders, poor quality of life, loss of performance at work and thus with an important socioeconomic burden. The control and severity of AR have been defined [3-5] and several attempts have been made by physicians to find the best way to reduce the impairment due to AR.

Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines try to categorize patients by differentiating between those suffering from “mild” symptoms and those with “moderate to severe” forms of rhinitis [6-8]. There is not a unanimous way to define patients as simply “severe”, even though it seems important to highlight this specific group, because of the consistent burden associated to these patients, in terms of increased morbidity and therefore direct healthcare and indirect socio-economic cost [9,10].

More recently, ARIA guidelines focus on the control of symptoms to better assess the efficacy of the prescribed treatment [7], and to improve patient’s quality of life (QoL) while reducing allergic symptoms. Measures of AR control include symptom scores, patients self-administered visual analogue scales (VAS), patients reported outcomes, such as QoL, objective measures of nasal obstruction, and a recent modification of the ARIA severity classification [11,12].

Even though current guidelines are clear and standardized when it comes to choose the proper treatment to administer to patients suffering from AR, there is no unanimous consensus on which tool is the best to evaluate severity prior to treatment and control during patients’ follow-up. The main purpose of this PhD Thesis was to fill this gap using a big data approach based on real-life assessments.

Two databases have been evaluated for the present PhD project: the MASK database and the POLLIN’Air database. The analysis of these two databases of adults suffering from AR had the goal to look for a solution for the previous unresolved question on how to evaluate severity and control in *real-life* settings. The MASK database was used to validate the Allergy Diary (now called MASK-Air®) App, which allow users to assess their AR

control on a phone screen [13]. The POLLIN'AIR database was evaluated to assess the best method to discriminate severity in patients suffering from seasonal AR [14].



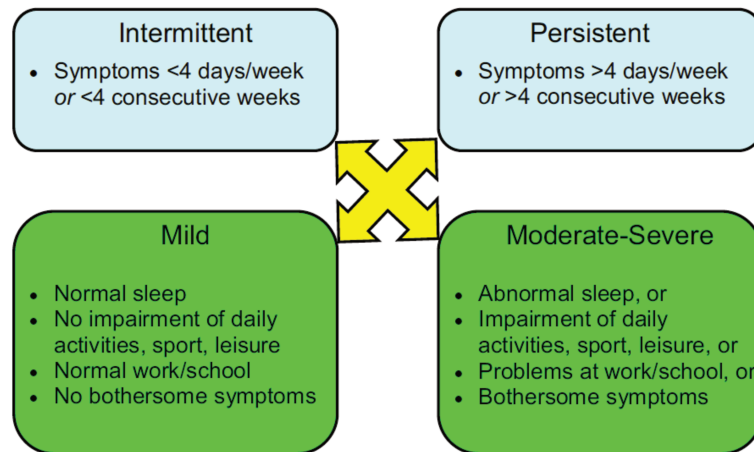
## Allergic rhinitis

In Europe 150 million people suffer from allergy [15]. One out of 3 children are allergic and present estimations suggest that, within the next 10 years, 50% of Europeans will suffer from allergy [15]. Chronic respiratory diseases, such as AR, asthma, chronic obstructive pulmonary disease (COPD), and rhinosinusitis account for 4% of the global burden of chronic diseases [16]. Even with their vast prevalence, relative severity and huge impact on quality of life, allergic diseases are invariably trivialized [17]. In medical schools, students are not fully taught about allergies and such subject is only marginal in their medical formation [17]. Politics, social media, and research funding look at allergies less seriously than other medical potentially lethal conditions [17]. Even patients consider allergic diseases as trivial: in fact, more than 50% of individuals suffering from AR do not consult a physician over the year and almost one-third prefer non-prescription medications, considering unnecessary to see a doctor for their respiratory allergies [17,18].

AR is one of the most common chronic diseases worldwide, affecting 10-30% of adults and up to 40% of children [19]. Its global prevalence continues to increase, with over 500 million individuals affected worldwide [19,20]. In the European population, the prevalence of the disease, confirmed by clinical examination, seems to be approximately 23% [18,20]. However, the prevalence may vary between countries from 16.9% in Italy to 28.5% in Belgium [20]. Data from the Burden of Rhinitis in America study reported the prevalence of rhinitis in the case of seasonal or perennial rhinitis to range between 11.9% and 30.2% depending on duration of symptoms and physician diagnosis [20]. At any rate, the prevalence of AR is also increasing in those countries that previously showed a low prevalence while plateauing in areas of highest prevalence, where it can already affect up to 50% of the population [19].

AR is an IgE-mediated disease affecting the nasal membranes characterized by one or more symptoms including nasal congestion, rhinorrhea, sneezing and itching on consecutive days [19,20]. To enhance the effectiveness and quality of management for AR, several international guidelines and consensus statements have been developed [21]. The ARIA workshop (organized by the World Health Organization), was the first evidenced-based guidelines. ARIA guidelines suggest categorizing AR as intermittent or persistent [8]. This is motivated by the fact that aeroallergens may be present seasonally in one area and year-round

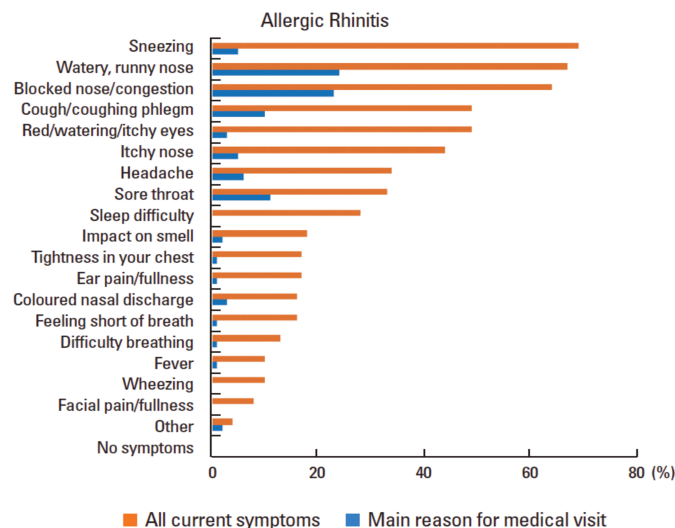
in other areas [19]. In the ARIA classification system, intermittent refers to symptoms occurring less than 4 days a week or for less than 4 consecutive weeks, while persistent refers to symptoms present more than 4 days per week and for more than 4 consecutive weeks [8]. The ARIA working group additionally classifies severity of AR as mild and moderate/severe, in untreated patients [8]. Patients have mild AR if they do not have any of the following characteristics: sleep disturbance, impairment of daily activities, impairment of school/work and symptoms [8]. Patients with one or more of the above characteristics are considered to have moderate/ severe AR, as shown in Figure 1 [8].



**Figure 1** : ARIA classification of allergic rhinitis according to symptom duration and severity. From: [8].

Alternatively, the Joint Task Force guidelines by the American Academy of Allergy, Asthma and Immunology, American College of Allergy, Asthma and Immunology, and the Joint Council on Allergy, Asthma and Immunology, classify AR as seasonal, perennial and episodic [22]. Perennial AR is typically caused by sensitization to indoor allergens such as dust mites, mold and animal dander, while seasonal AR is most often due to sensitization to pollen allergens [22]. Episodic AR results from sporadic exposures to aeroallergens that are not typically encountered, such as visiting a farm or home with animal allergens that an individual would not typically encounter [22].

The most common symptoms are sneezing, itchy nose, rhinorrhea, and/ or nasal congestion [18,23], with many patients experiencing symptoms of at least moderate severity; one study estimated that 93% of patients with AR who consulted general practitioners had symptoms that were moderate-to-severe [18]. Even though patients may present several different symptoms at the same time, they tend to consult their doctor especially because of nasal congestion and watery nose [24], as shown in Figure 2.



**Figure 2 :** Symptoms presented by AR patients and main reason for consulting a physician. Adapted from: [24].

Indeed, nasal congestion is one of the most frequent and generally the most bothersome symptom in both adults and children [23]. In adults, 60% report it as the most common symptom during the worst time of the year, and in the pediatric population (4 to 17 years) patients present such symptom every day or most days in 52% of cases [23]. Postnasal drip, runny nose, and sneezing are similarly common and more so than nasal itch [23]. Postnasal drip and runny nose, however, are generally more bothersome than either sneezing or nasal itch [23]. The presentation of AR in childhood is more frequent in boys, but in adults, it is more common in women [23]. Children with a bilateral family history of atopy may develop symptoms more frequently and at a younger age than those with a unilateral family history [23]. Aeroallergen sensitization rarely begins before 6 months of age but may start between 6 months and 2 years of life [23]. Infants born in atopic families are sensitized to pollen aeroallergens more frequently than to indoor aeroallergens in the first year of life [23].

The frequency of sensitization to inhalant allergens is increasing and is more than 40% in many populations in the United States and Europe [23]. Seasonal AR symptoms generally do not develop until 2 to 7 years of age [23]. The prevalence of seasonal AR is higher in children and adolescents, whereas perennial AR has a higher prevalence in adults [23].

Risk factors for the development of AR include: the previously mentioned family history of atopy; total serum IgE greater than 100 IU/mL before the age of 6; the presence of a positive allergy skin prick test and higher socioeconomic class [23]. Recently, tobacco smoking [25,26], air pollution [27,28], or diet [29] have been suggested as potential factors, as well.

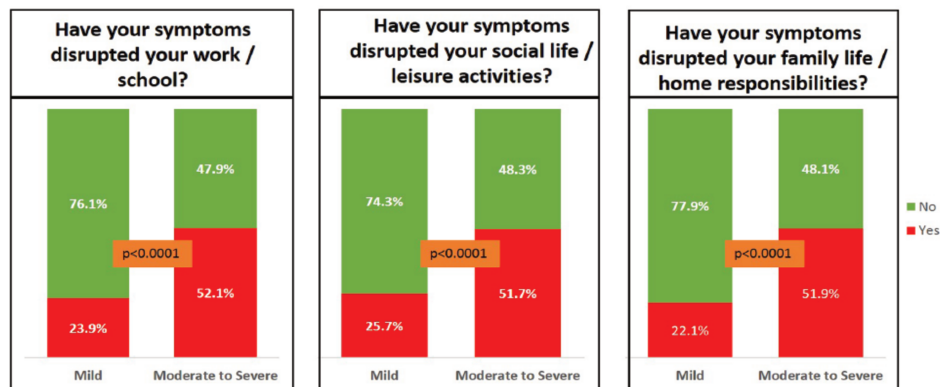
The influence of early childhood exposure to infections (the hygiene hypothesis), animals, and secondary tobacco smoke on the development of atopy and allergic rhinitis is still unclear [23].

## **Allergic rhinitis burden**

AR is a global public health issue: patients are daily burdened with the misery of nasal and ocular symptoms, making them tired and irritable [15,30]. AR burden refers to the overall impact of the disease both on patients and on society: indeed, not only it includes how patients are physically and mentally affected by AR, how their daily life is conditioned by their symptoms and how they struggle to control them to improve their quality of life, but also how much the disease costs in term of medical and pharmaceutical costs and of decreased ability to work or perform daily activities. Although clinical measures provide information on the affected organ systems, they do not capture the patient's overall perception of the disease burden caused by the physical, emotional, and social impairments in everyday life [18]. The burden of AR is now being recognized both by the European Academy of Allergy & Clinical Immunology (EAACI) as well as at the EU parliament level [31]. It is now also acknowledged in the ARIA guidelines, which classify its severity based both on symptoms and its effect on Health-Related Quality of Life (HRQL) [18].

Unfortunately, in *real-life*, the burden of AR is often under-estimated since the disease is trivialized [20]. Nevertheless, no aspect of patients' lives, from sleep to cognitive functions,

mood, and associated comorbid conditions, such as asthma and conjunctivitis, escapes the rhinitis touch, including an increased risk of road traffic accidents [15,30]. Ultimately, AR deeply affects patients' QoL and work and school performances [30], and may lead to depression and anxiety [20]. Patients suffering from moderate-to-severe AR show a significant deterioration of their QoL, as shown in Figure 3.



**Figure 3 :** Impact of AR severity based on the ARIA classification on activities of daily living. Adapted from: [20].

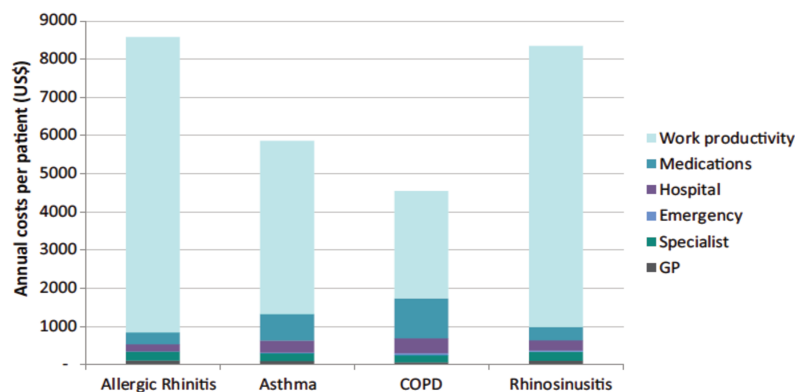
In the US, approximately 1 in 4 adults (22%) report they are unable to sleep or are awakened most days or every day and 26% to 45% of children experience sleep disruption because of nasal allergy symptoms [23]. Almost twice as many patients with AR compared with adults without nasal allergies say that their AR limits them in daytime physical indoor activities (20% vs. 11%) and outdoor activities (44% vs. 21%) [23]. In a Spanish study, the negative impact on daily activities for patients with AR was greater (27%) than for patients with type 2 diabetes mellitus (17%) and hypertension (9%); it was less than for symptomatic depression (59%) [23]. In athletes with rhinitis, factors with a potential negative effect on sports performance include outdoor exposure to pollens and pollutants (ozone and particulate matter) and sports-specific environmental conditions (e.g. cold temperatures, dry air, and indoor chlorine) [23]. In a US survey, adults were questioned about how much their AR, during the worst month of allergy symptoms, affected their emotional domain regarding their mood and feelings; 85% of patients answering “sometimes” or “frequently” for the item “fatigue”, 67% for “irritable”, 60% for “miserable”, 28% for “depressed or blue”, 25% for

“anxious”, and 15% felt “embarrassed” [23]. Indeed, most studies indicate a close association between nasal allergies and anxiety/mood syndromes [23]. There are several mechanisms that might mediate this relationship: allergic reactions triggering the immune system and cytokines, allergies impairing sleep through nasal obstruction, and allergies negatively affecting cognitive function [23].

The impact of nasal allergies on patient-perceived health status is therefore substantial [23]. In the US, Latin America and Asia-Pacific surveys, between 35% and 50% of adults reported that nasal allergies have at least a moderate effect on daily life [23]. Although most patients with AR have reported a good overall sense of their health (excellent, 11%; very good, 29%; and good, 34%), when compared with adults without nasal allergies, it is evident that AR patients rated their overall health significantly lower [23]. Nearly twice as many adults without nasal allergies described their health as excellent (23%) and at the other extreme, nearly twice as many AR patients rated their health as only fair/poor/very poor (27%) compared with adults without nasal allergies (15%) [23].

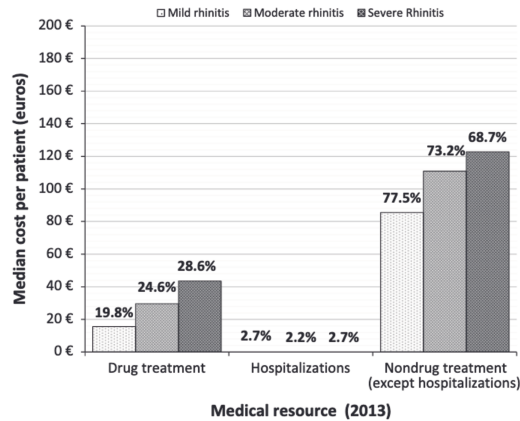
The burden of the disease becomes even more important when AR is uncontrolled [32]. The ramifications of poorly controlled AR extend into other disease states, most notably asthma, where the likelihood of exacerbations or flare-ups is elevated [32]. The lack of symptoms control seems the basic motivation for patients to seek medical aid and undergo therapy [23]. In fact, patients appear reluctant to seek professional advice until their symptoms become ‘intolerable’ [15]. A UK study found that only 18% of patients with AR had consulted their doctor about the condition in the preceding 2 years [18]. In a French study, up to 20% of patients avoided consulting their doctor about the problem, despite 90% reporting that nasal symptoms affected their daily lives, over half complaining of sleepiness and headaches, and 8% reporting that they had taken time off work because of their rhinitis [18]. On the other side, unfortunately, even many physicians under-estimate AR severity and undertreat it [15]. Undertreated rhinitis may have a substantial negative impact on patients’ QoL impairments in work productivity, school performance, social interactions, sleep and driving performance, which contributes to the overall disease burden [33]. It has been evaluated that only 10% of AR patients are being treated optimally [17]. The number of untreated or incorrectly treated patients, who are consequently partly or fully symptomatic, in all studies is approximately 90% [17].

Patients, therefore, struggle to alleviate their misery, frequently use over the counter (OTC) drugs and homeopathic remedies and take several different drugs as relief therapy [15]. Patients with mild AR have less impact on the health economy, with costs of around a quarter of those with moderate-to-severe disease [16]. The societal costs of a disease are commonly described as direct and indirect costs [34]. The formers are instigated by health-care visits, use of medication and hospitalization, whereas the latter are mainly related to absence from work (absenteeism) and reduced working capacity at work (presenteeism) [34]. Overall cost for AR is more important than the cost for other chronic respiratory diseases, such as asthma, COPD, and rhinosinusitis (Figure 4).



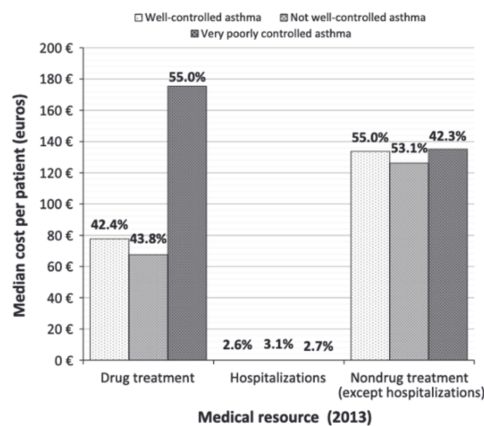
**Figure 4** : Annual directed and indirect costs for chronic respiratory diseases, based on primary diagnosis. From: [16].

In Europe, the total societal cost of persistent allergic rhinitis and its comorbidities in 2002 was estimated at 355.06€ per patient per month [23]. In a French study, the authors assessed, through national Electronic Health Records, medical resource utilization and related direct cost for perennial AR, with or without concomitant allergic asthma [35]. They highlighted that, in 2013, the median annual cost reimbursed by the French social security system for a patient with perennial AR was 159€, ranging from 111€ to 188€ in more severe forms, as show in Figure 5 [35]. Also, a gradient of median costs per patient appeared between the three subgroups of perennial AR severity for drug treatment (from 15.51€ to 4.57€), and nondrug treatment (from 85.52€ to 122.72€) [35].



**Figure 5 :** Median cost in 2013 in France, for patients suffering from perennial AR. From: [35].

They also found that in patients suffering from perennial AR and allergic asthma, the median annual cost varied between 266€ and 375€, and drug treatment accounted for 42-55% of the costs, depending on asthma control, as shown in Figure 6 [35]. Patients with very poorly controlled asthma had a high median cost per patient for drug treatment of 175.5€ per year, while patients with well-controlled asthma it was 77.71€ per year, and 67.6€ per year for patients with not well-controlled asthma [35]. Medical resource utilization for nondrug treatments was stable between the three subgroups (around 130€ per year per patient), as well as hospitalizations [35].



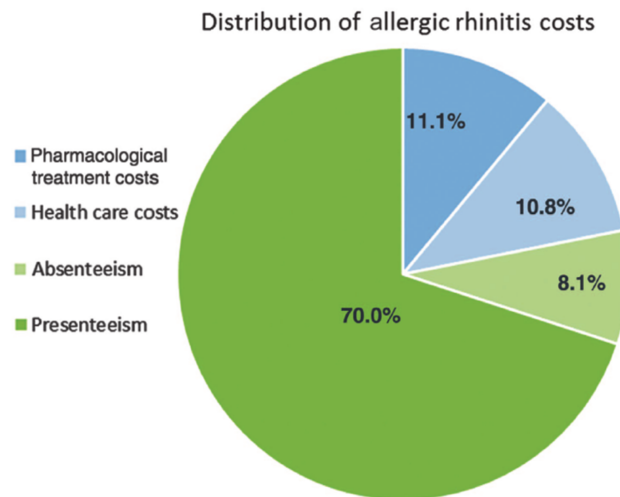
**Figure 6 :** Median cost in 2013 in France, for patients suffering from perennial AR and allergic asthma, according to asthma control. From: [35].

The total direct medical cost for AR in the US is approximately \$3.4 billion per year, with almost half attributable to prescription medications [23]. Compared with matched controls, patients with AR have an approximately 2-fold increase in medication costs and a 1.8-fold



increase in the number of visits to health care practitioners [23]. In Sweden, the total annual cost of self-reported AR is estimated at €1.3 billion per year, which is three to four times the estimated total cost of asthma in the same Country [34]. Based on the Swedish results, if we assume that the demographics and health-care costs were comparable in other EU countries, the annual cost of AR in Germany, France and Great Britain would be between €9.4 and €9.9 billion each [34].

As previously mentioned, drugs cost for AR is indeed a major direct cost of the disease, but it does not represent the main cost related to the disease. Indeed, AR imposes a high socioeconomic burden worldwide, particularly in terms of indirect costs [31], higher than that induced by asthma, diabetes and heart disease [15]. Indirect cost in the US ranges between \$5.5–\$9.7 billions per year [23]. The economic burden of allergic diseases in the working population (between the ages of 15 and 65) of the European Union was previously investigated by the Global Allergy and Asthma European Network (GA2LEN) [36]. The study found that the high socioeconomic cost of allergies was due to the high prevalence of allergies in the studied age group, and the associated presenteeism (working while feeling sick) and absenteeism, which were mainly caused by under-treatment and were thus avoidable [37]. The GA2LEN study indicated that cost savings of over €100 billion could be realistically expected through better treatment of allergic diseases [36]. In the United States AR patients show low absenteeism (1.7%) but their overall work impairment ranged from 35% to 40% of normal productivity [16]. Indeed, recent studies agree that AR substantially impairs at-work productivity (evaluated as presenteeism) and only minimally absenteeism, as shown in Figure 7. Nevertheless, further studies assessing daily work productivity and severity of symptoms at the same time over prolonged periods and comparing with other chronic diseases are needed to better characterize the impact of AR [30].



**Figure 7 :** Distribution of direct and indirect costs for AR. From: [34].

The high financial costs associated with poorly managed rhinitis, including the direct treatment-related costs and indirect costs through lost wages and reduced productivity, create a substantial socioeconomic burden on individuals and society [33]. The possible annual cost for working impairment in the European Union caused by undertreated AR is shown in Table 1. Improved adherence to guidelines might ease the economic burden on society [34].

**Table 1:** Annual cost for EU employers due to working impairment caused by undertreated AR. Adapted from: [34].

	Assuming a 20% prevalence of relevant allergic diseases and 10% impairment	Assuming a 20% prevalence of relevant allergic diseases and 20% impairment	Assuming a 35% prevalence of relevant allergic diseases and 20% impairment
Cost of absenteeism/worker/annum	€ 528	€ 528	€ 528
Cost of presenteeism/worker/annum	€ 845	€ 1.690	€ 1.690
Total cost/worker/annum	€ 1.373	€ 2.218	€ 2.218
Number of workers with allergic disease	44 million	44 million	76 million
Number of workers with undertreated allergy	40 million	40 million	68 million
Total allergy cost	€ 54.9 billion	€ 88.7 billion	€ 150.8 billion
Total additional costs for guideline-approved treatment of untreated population	€ 5 billion	€ 5 billion	€ 8.5 billion
<b>Total potential savings</b>	<b>€ 50 billion</b>	<b>€ 84 billion</b>	<b>€ 142 billion</b>

## Management of allergic rhinitis

Management of AR may be a difficult task for specialists, considering the previously mentioned fact that patient do not frequently consult a doctor for their nasal symptoms [32]. Indeed, patients may fail to recognize the impact of the disorder on their quality of life and, tend to perceive their illness as a ‘minor’ ailment, which they can easily manage themselves [32, 38]. When they do consult a doctor, they usually underreport their AR symptoms, making the diagnosis of AR often a challenge for general practitioners [39]. Early detection and optimal management of AR allows patients to minimize the impact of AR on the patient [39].

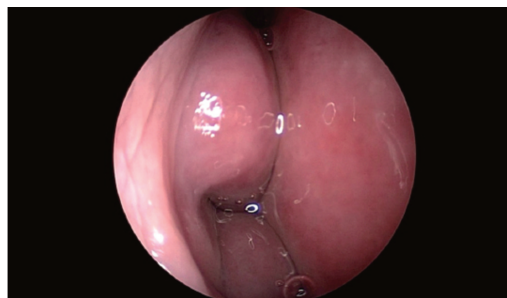
Several different classifications have been created to distinguish different types of rhinitis. Such disease may be classified as IgE-mediated (allergic), and Non-Allergic Rhinitis (NAR). The difference between AR and other forms is the presence of positive skin prick tests or the detection of serum specific IgE [40]. Local AR (LAR) is a newly described form of AR, and an exception to such definition [41]. LAR is generally diagnosed in individuals without classic systemic atopy, but with a positive nasal provocation test and/or with specific IgE detected in nasal secretions [40,41]. NAR has many subtypes, including infectious, autonomic (drug-induced, gustatory, hormone-induced, atrophic, senile), and idiopathic rhinitis, as shown in Table 2 [38,40].

**Table 2:** etiological classification of rhinitis. Adapted from: [38].

Type	Description
IgE-mediated (allergic)	<ul style="list-style-type: none"><li>• IgE-mediated inflammation of the nasal mucosa, resulting in eosinophilic and Th2-cell infiltration of the nasal lining</li><li>• Further classified as intermittent or persistent</li></ul>
Autonomic	<ul style="list-style-type: none"><li>• Vasomotor</li><li>• Drug-induced (rhinitis medicamentosa)</li><li>• Hypothyroidism</li><li>• Hormonal</li><li>• Non-allergic rhinitis with eosinophilia syndrome (NARES)</li></ul>
Infectious	<ul style="list-style-type: none"><li>• Precipitated by viral (most common), bacterial or fungal infection</li></ul>
Idiopathic	<ul style="list-style-type: none"><li>• Etiology cannot be determined</li></ul>

In both AR and NAR, nasal symptoms may also be due to or accentuated by structural or mechanical issues, as well as systemic conditions (cystic fibrosis, primary ciliary dyskinesia, eosinophilic granulomatosis and polyangiitis, sarcoidosis, and amyloidosis) [40]. Patients may present different types of rhinitis at the same time, leading to a mixed phenotype or endotype or both [40].

The initial evaluation of a patient presenting with evocative symptoms of AR starts with a complete collection of personal and family clinical history; personal history should include careful attention to environmental exposures with a focus on precipitating factors and quality of life assessment [19]. Physical examination should include rhinoscopy, or nasal endoscopy, in specialized centers, to assess the possible inflammation of the nasal mucosa, as shown in Figure 8. Physical exam findings may include rhinorrhea, enlargement and pallor of the inferior nasal turbinates, conjunctival injection and increased lacrimation, Dennie-Morgan lines, allergic shiners, nasal crease, and sinus tenderness [19].



**Figure 8** : Endoscopic image of nasal mucosa in a patient suffering from AR. From: [41].

Diagnosis of AR is strictly clinical. Nevertheless, further diagnostic testing may be necessary to confirm the allergen responsible for allergic symptoms [38]. To evaluate responsible allergens, skin prick tests should be performed to assess sensitization and possibly allergy, whenever the exposure to an allergen relates to the appearance of clinical symptoms. Skin-prick testing for the allergens relevant to the patient's environment is considered the primary method for identifying specific allergic triggers of rhinitis. Although allergen skin prick testing is preferred, *in vitro* assays for serum allergen specific IgE may be performed for patients who cannot undergo skin testing (ex: extensive eczema, dermographism, recent oral antihistamine use...), is the *in vitro* testing for allergen-specific IgE. However, skin prick tests are still considered as the gold standard, are more sensitive, less expensive, and give

immediate results, and the sensitivity of specific IgE in vitro assays compared with skin prick tests is approximately 70-75% [19,38].

Differential diagnosis of AR from other forms of rhinitis is not easily defined as AR rarely presents in isolation [32]. The disease is frequently associated to mainly two comorbidities: conjunctivitis and asthma. Ocular allergic symptoms are strongly associated with AR, even though they are often underdiagnosed – at least in mild forms – and consequently undertreated [42]. Conjunctivitis is now increasingly recognized as the most frequent comorbidity of AR [8], strongly participating to AR QoL impairment. As for asthma, over 80% of asthmatics have AR while 10-40% of individuals with AR have asthma [19]. AR is a risk factor for asthma, and the diagnosis of AR may precede asthma [19]. Studies of both adult and pediatric populations provide evidence for an increased risk of asthma development in individuals previously suffering from AR [19]. Even though the precise mechanisms underlying comorbid asthma and AR have yet to be fully elucidated AR seems to contribute to asthma severity and poor asthma control [19,31]. Patients reporting severe rhinitis exhibit poorer asthma control than those with mild disease, with a negative impact equivalent to that of tobacco smoking [31]. For such reason, an appropriate treatment of AR is essential in asthmatic patients, being able to possibly reduce the odds of asthma-related healthcare (specifically, emergency room visits and hospitalizations), by up to 80% [19].

Once the diagnosis of AR is reached, AR management is mainly based on allergen (trigger) avoidance, relief medication (including OTC and prescription medicines), patient education, allergen immunotherapy (AIT) and, occasionally, surgical treatment [21,40,43]. An appropriate treatment is related to an improvement in patients' QoL [18]. However, since allergen avoidance is often not effective and AIT is limited to a minor group of patients, AR treatment is based on relief therapy in most cases [43]. Such treatment may be self-prescribed by patients, or advised by a general practitioner or by an allergy specialist.

Although treatment guidelines are well established, treated patients may report poor levels of satisfaction, with a frequent search for extra medications (mainly OTC drugs) to better reduce their nasal/ocular symptoms [21]. Also, given that the management of AR is not straightforward, it requires proper medical guidance for self-management as well [32]. Adherence to prescribed treatment is key to ensuring achievement of the clinician's desired therapeutic effect [39]. However poor adherence remains a crucial problem in AR, leading to increased symptoms, lower patients' QoL, and higher direct and indirect costs [44]. Patients

may have an easy access to AR medications, and, while not being aware of the importance of appropriate treatment, they get used to living with sub-optimally managed AR [32,43]. It has been shown that AR may be present since childhood, but that a proper diagnosis is often reached on the average 7 years after the first reported symptom, and after seeing multiple physicians, before finding a suitable treatment [43]. Dissatisfaction towards doctors and previously proposed treatments leads to decreased compliance and increased reliance on multiple therapies, including OTC medications [45]. In fact, through multiple doctor consultations and personal internet researches, patients believe they have learned enough about their disease and grow confidence in being able to self-manage AR [43]. 60% of AR patients are “very interested” in finding a new medication, and 25% are “constantly” trying different medications to find one that really “works” [45]. AR patients also frequently feel that their doctor does not take their disease seriously and does not understand their personal treatment needs [45]. Also, doctor’s appointments become a significant impingement on patients’ time, besides being an extra cost to manage the disease [43]. Therefore, at the end, optimal management of AR is further compromised with patients’ bypassing the medical consultation, and with 70% of them self-selecting medication for their AR symptoms [39]. Nevertheless, only 15% of patients select appropriate OTC medications: in fact, they mainly choose oral antihistamines, which are not classified as the most effective medication for moderate-to-severe AR symptoms [39]. Also, many OTC drugs for the treatment of AR may induce sedation and should be avoided [46]. Therefore, despite the high dependence on medications, AR sufferers remain undertreated or not adequately treated [39].

Lack of treatment, under-treatment, and nonadherence to treatment have all been seen to increase both the impact and direct and indirect costs of AR [23,44]. Therefore, each patient should receive an appropriate therapy, not only to completely control AR symptoms, but also to substantially reduce overall disease costs [23]. At the same times, AR treatment should include appropriate therapy, after evaluation, for specific AR symptoms and possible co-existing comorbidities, as shown in Table 3 [45,47].

**Table 3:** AR symptoms and effectiveness of different drugs. Adapted from: [46].

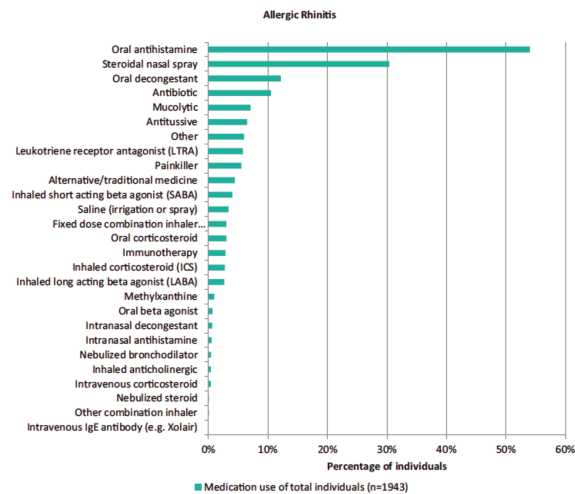
	Sneezing	Rhinorrhea	Nasal Obstruction	Nasal itch	Eye symptoms
<b>H1-antihistamines</b>					
Oral	□ □	□ □	□	□ □ □	□ □
Intranasal	□ □	□ □	□	□ □	0
Eye drops	0	0	0	0	□ □ □
<b>Corticosteroids</b>					
Intranasal	□ □ □	□ □ □	□ □	□ □	□ □
<b>Chromones</b>					
Intranasal	□	□	□	□	0
Eye drops	0	0	0	0	□
<b>Decongestants</b>					
Intranasal	0	0	□ □ □ □	0	0
Oral	0	0	□	0	0
LTRAs	0				□ □
Intranasal combination corticosteroids and anti H1	□ □ □	□ □ □	□ □ □	□ □ □	□ □ □

AR treatment goals include erasing any possible influence the disease may have on sleep and daily activities (including work and school attendance, and leisure activities), making residual symptoms no troublesome at all, without being associated to side effects [46]. Unfortunately, many patients with AR continue to live with uncontrolled disease [45]. To properly understand how AR control may be achieved in real-life, it is necessary to understand the complexity of the AR management landscape.

### Treatments for allergic rhinitis

Allergic disease may be managed through environmental control, pharmacologic intervention and AIT, which is the only curative treatment for the management of allergic diseases [41,48]. The treatment goal for AR is symptoms control [45]. Unfortunately, studies of patients consulting general practitioners for AR reported that 18-48% had symptoms that were not controlled by pharmacotherapy alone [18]. Many medications are advised in current guidelines at several steps of AR severity and duration, including antihistamines (oral and intranasal), intranasal corticosteroids, combination intranasal corticosteroid/antihistamine sprays, leukotriene receptor antagonists, and chromones (intranasal and eye drops) [37,46]. Anti-cholinergics and decongestants (intranasal and oral) may be used for short-term courses

(<10 days), due to the risk of a rebound swelling effect of the nasal mucosa, possible appearance of rhinitis medicamentosa, and tachyphylaxis [46]. Medications used by patients reporting a diagnosis of AR are shown in Figure 9.



**Figure 9 :** Medication use in subjects reporting a diagnosis of AR. From: [16].

Intranasal glucocorticoids and second-generation antihistamines and have been recommended for the treatment of AR symptoms and have been found to improve patient QoL as shown by studies utilizing the Rhino-conjunctivitis Quality of Life Questionnaire (RQLQ) surveys [36].

Standardized comprehensive therapy may achieve optimal symptom control and significant improvement in the QoL of patients [41]. If mild and intermittent, AR may be effectively managed through avoidance measures and oral antihistamines; nevertheless, most patients present with moderate-to-severe AR and, for them, intranasal corticosteroids are the best therapeutic relief option [38].

### Allergen avoidance

As an important part of prevention and treatment strategy, environmental control should focus on avoidance or reduction of allergens (such as house dust mites, animals, exposure to specific pollens...) and irritants (such as tobacco smoke) [38,41]. Several advises



may be given to patients to avoid the allergen responsible for the AR symptoms [38]. Avoidance strategies may effectively improve the symptoms of AR, and patients should be advised to use a combination of measures for optimal results [38]. However, existing measures are often difficult to achieve complete control of AR [41]. Therefore, pharmacotherapy and AIT remain the main treatments for AR [41].

### Intranasal Corticosteroids

Intranasal corticosteroids are the first-line therapeutic options for patients with mild persistent or moderate/severe symptoms and may be used alone or in combination with oral antihistamines [38]. They reduce nasal mucosa inflammation and are superior to oral antihistamines and leukotriene receptor antagonists in controlling AR, ocular, and lower airway symptoms [38,49]. They are capable to decrease the upper and lower airways inflammation and help therefore control clinical manifestations of coexisting AR and asthma [49]. They should be used before exposure to the allergen since their efficacy needs several days before being clinically evident, and should be used regularly. Most common side effects include nasal irritation/stinging and epistaxis: these effects may usually be prevented by an appropriate use of the intranasal device [38]. For such reason, physicians should take some time to correctly educate patients on the use of such drugs.

### Oral Antihistamines

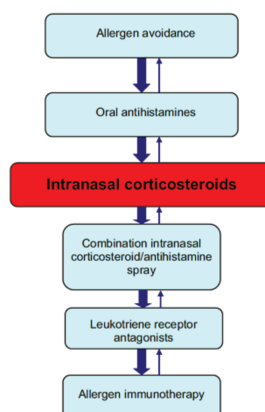
Second-generation oral anti-histamines are the first-line treatment in controlling mild intermittent AR [49]. They are capable of effectively reduce sneezing, itching and rhinorrhea when taken regularly at the time of maximal symptoms or before exposure to an allergen [38]. Even though they are not included as asthma treatment, they may be able to delay asthma development in high-risk atopic infants and have beneficial effects on asthma outcomes when used to treat AR [49]. They are associated with improvement of AR and QoL [49]. Although first-generation sedating antihistamines are also effective in relieving symptoms, they have been shown to negatively impact cognition and functioning and, therefore, they are not routinely recommended for the treatment of AR [38].

## Intranasal antihistamines

Intranasal antihistamines have broadened the landscape of intranasal medications for the treatment of AR and are included in the ARIA guidelines as an important option as relief therapy for AR [40]. They have a faster onset than oral antihistamines and show similar effects in terms of efficacy, while being more effective in reducing nasal congestion [40]. They improve the total nasal symptom score (TNSS) as well as each individual nasal symptom score including sneezing, rhinorrhea, nasal congestion, and nasal itching with faster onset and similar efficacy when compared with intranasal steroids [40]. They may also be associated with intranasal corticosteroids: such association seems more effective than the individual components in controlling AR symptoms and in improving patients' QoL [38,40].

## Leukotriene receptor antagonists (LTRAs)

Anti-leukotrienes may be considered as a beneficial anti-asthma treatment targeting both upper and lower airways in asthma and allergic rhinitis [49]. Nevertheless, they are not as effective as intranasal corticosteroids in controlling AR symptoms [38]. Even in patients receiving a combination of LTRAs and antihistamines, treatment efficacy is hardly comparable to that obtained by intranasal corticosteroids [38]. LTRAs should therefore only be considered when oral antihistamines, intranasal corticosteroids and/or combination corticosteroid/antihistamine sprays are not well tolerated or are ineffective; if the combination of LTRAs and all other mentioned therapies is not sufficient to control AR symptoms, AIT should be prescribed, as shown in Figure 10.



**Figure 10 :** Simplified algorithm for AR treatment. From: [38].

### Allergen immunotherapy (AIT)

AIT is the only curative treatment of respiratory allergy, being able to cure the real cause of the symptoms [50]. The benefit of AIT has been proven in AR (improvement of symptom score and quality of life with decrease in medication use) and asthma (increase in time to first asthma exacerbation following weaning of inhaled corticosteroids) [49]. AIT reduce the risk for the future development of asthma in children with AR, and improves asthma symptoms and BHR in patients with AR [38,49].

AIT may mainly be divided into subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT), based on route of allergen administration [48]. SLIT may be prescribed with drops or with oral tablets. Although SCIT has been employed for a longer period of time, the use of SLIT has also become of increasing interest [48]. Also, SLIT showed a more favorable safety profile than SCIT [38]. The risk of systemic allergic reactions is much lower with SLIT compared to traditional injections, and the most common side effects of the sublingual route include local reactions such as oral pruritus, throat irritation, and ear pruritus [38].

AIT should be reserved for patients in whom optimal avoidance measures and pharmacotherapy are insufficient to control symptoms or are not well tolerated [38]. Evidence suggests that at least 3 years of AIT provides beneficial effects in patients with AR that can persist for several years after discontinuation of therapy [38].

### Monoclonal antibodies

Two monoclonal antibodies seem to be a therapeutic option in in patients with both severe allergic asthma and AR: omalizumab and dupilumab. Omalizumab, an anti-IgE therapy, is effective in preventing asthma exacerbations and in improving asthma/rhinitis symptoms and quality of life in this population [49]. Dupilumab, an anti-IL-4 receptor- $\alpha$  antibody (and anti-IL-13), at a dose of 300 mg every 2 weeks, significantly improves AR-associated nasal symptoms in patients with uncontrolled persistent asthma [49].

### Other therapies

New possible therapies for AR include new formulation nasal sprays, novel H3/H4 antihistamines, alternative routes of AIT, and addition of adjuvants to improve allergy [51].

Intranasal sodium cromoglycate may reduce sneezing, rhinorrhea and nasal itching, even though with less efficacy than intranasal corticosteroids [38]. It may be used as a first-line therapy in pregnancy since no teratogenic effects have been noted in humans or animals [38]. Oral corticosteroids are often prescribed (or self-prescribed) in patients with severe AR refractory to oral antihistamines and intranasal corticosteroids [38]: patients and physicians should be aware of the possible side effects related to such therapy, even given in short courses and try to avoid the use of oral corticosteroids in AR patients. Oral and intranasal decongestants are useful for relieving nasal congestion in patients with allergic rhinitis, only if used for short courses [38]. Surgical therapy has limited indications in AR.

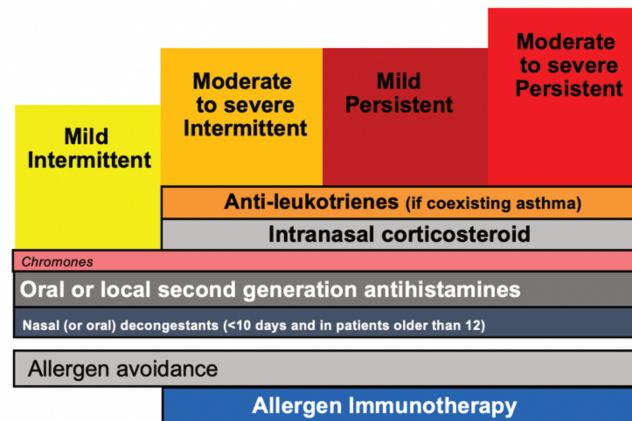
### Complementary and alternative medicines

More and more patients wish to pursue complementary and alternative medicines for the management of AR. Nevertheless, there is a paucity of randomized controlled studies evaluating these approaches and they are not included in current guidelines [40]. They include traditional Chinese medicines, acupuncture, homeopathy, and herbal therapies [38]. Acupuncture has the greatest amount of data and shows promise in smaller randomized studies [38,40]. In a number of studies, acupuncture has been shown to provide modest benefits for patients with AR [38].

### ARIA guidelines and approach

ARIA guidelines recommend a step-wise approach for treating AR [8]. The management strategies mentioned above are validated by the guidelines, as shown in Figure 11. ARIA focuses on the need to assess AR severity and initially adapt the patient's treatment and then to re-evaluate them and consequently modulate treatment, based on the control of

symptoms [52]. Unfortunately, the level of AR control is often overestimated by both patients and physicians: therefore, classical guidelines alone seem not complete enough to determine the assessment of AR control, which may result in failure to make the necessary adjustments to medication [21].



**Figure 11** : ARIA stepwise approach for AR treatment. Adapted from: [8].

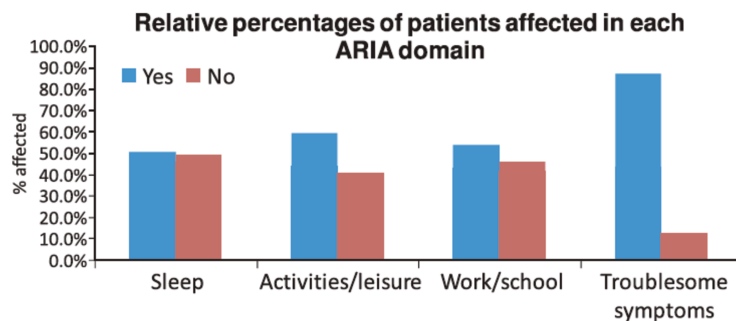
For such reasons, in its latest revision, ARIA introduced integrated care pathways for the management of AR and asthma by a multidisciplinary group centered around the patients using shared decision making with interventional therapy evidence-based tools, thus empowering the patient to make treatment decisions focused on disease control, by using the guided self-management plan proposed by their healthcare professionals [49].

## Allergic rhinitis severity and control

Recommendations for drug management in AR are currently based on the classification of the disease severity and persistence of symptoms [53]. These recommendations may be easily applied to untreated patients, but are less useful to evaluate changes over time and cannot measure response to treatment [53]. Therefore, if severity needs

to be assessed to properly target an appropriate treatment, the follow-up of patients suffering from AR should be based upon symptoms control. Although "disease severity", "disease control" and "responsiveness to treatment" are related, they are different metrics, not mutually exclusive [2].

Disease severity may be defined as a loss of physiological function caused by the disease process [2]. It is well known that the more severe AR, the more symptoms and the lower degree of QoL in allergic patients. For such reason, in the ARIA guidelines, the severity of AR is based upon both QoL and symptom severity [54]. Severity is indeed based on the impact of the disease on daily life, assessed by the impairment of four HRQL items: sleep, daily activities/sport/leisure, work productivity/school performance, and troublesome symptoms [55,56]. ARIA guidelines propose a grading of severity (mild and moderate/severe) that includes such items [44], that seems to be the most important issues in patients suffering from AR, as shown in Figure 12. AR is mild when there is no impairment of any of these items, whereas it is moderate/severe when one or more of these items are impaired [55]. It has also been recently proposed to better differentiate severity and, while maintaining the four items, to classify symptoms as mild (no affected items), moderate (1–3 affected items), and severe (all four affected items) [57].



**Figure 12 :** Relative percentages of patients affected in each ARIA domain. From: [58].

The concept of AR control is based on an analogy with the Global Initiative for Asthma (GINA) guidelines on asthma [59], and is only applicable to treated patients [21]. It has been introduced given the difficulties to reach full remission in affected patients and the need for a new individualized medical care approach, known as precision medicine [60]. Control assessment may be able to improve and simplify management in AR patients [61].

Nevertheless, the evaluation of disease control in AR is challenging due to the difficulty of including several different dimensions in a single measurement tool [60]. Recent papers developed under the aegis of ARIA indicate that disease control is being considered for future initiatives and that methods for measuring severity and control in allergic disease must be uniform [21]. The generalization of the "control" is now being considered as a trend in the management of patients suffering from AR, but there is no unanimous definition, even though it has been suggested that it could be a way to improve clinical decisions [2]. It may be considered as the degree of symptom reduction and of achievement of the treatment's goals, and its measure should allow to evaluate treatment outcomes and simplify monitoring [21,23]. It could be said that control defines a status in which the treatment objectives are reached, and symptoms are minimized [60]. Better AR control is associated with improved QoL and therefore with a reduction in indirect costs [23]. Guidelines have not been implemented effectively by many clinicians, adherence to recommendations is commonly lacking, and poor control of the disease is widespread [23]. Accurate assessment of rhinitis control is an essential element in a strategy to simplify and improve management [23].

Even though it could seem easy to link severity and control, there are too many parameters that may influence these two aspects of the disease that they often do not correlate. In fact, sometimes, a non-severe form of AR may be uncontrolled because patients are not compliant to prescribed treatment, or because they are too exposed to the culprit allergen or for other psychological reasons [21]. On the other hand, sometimes severe forms of AR may be easily controlled, for example, in targeted patients properly treated with AIT. Nevertheless, when comorbidities are associated to AR, they usually not only make the overall symptoms more severe, but also more difficult to be controlled, with a strong impact on patients' QoL [62]. Main comorbidities and symptoms reported by patients suffering from severe forms of AR, besides conjunctivitis, asthma and rhinosinusitis, include olfactory dysfunction, gastroesophageal reflux, impaired sleep quality and nocturnal sleep, sexual dysfunction, and psychological disorders such as anxiety and depression [23,62]. Many recent studies focus on patients altered nocturnal sleep: congestion is a risk factor for respiratory sleep-disordered breathing, including snoring, hypopnoea, and apnoea [58]. Also, fatigue, which usually considered as a side effect of allergy medication, may be the result of nasal congestion and associated sleep disruption [58].

It is therefore important both to clearly target patients with severe AR and to optimize patients with uncontrolled symptoms, to improve their QoL and possibly reduce the overall cost of the disease. Both severity and control can be measured in a multitude of ways, with both objective and subjective measurements and patient-reported vs. physician-reported outcomes [2]. Patient-reported metrics are growing in importance in clinical research and, increasingly, in patient care, although there is debate over whether the physician or the patient should be considered as the best judge to assess control [2].

### Severity assessment

Although the ARIA severity classification has been validated in primary care patients, surveys have found that both primary care physicians and specialists are not necessarily aware of this tool [2]. Also, the ability to assess the severity of respiratory diseases is difficult in clinical setting, especially for AR [63]. Patients often are not capable of verbally communicate how severe their disease is because they learn to tolerate more and more their respiratory symptoms [63]. Indeed, for example, chronic nasal congestion becomes normal to them [63]. According to physicians' assessments, 46.2% suffer from persistent AR, and 41.4% from intermittent AR; almost two thirds (63%) have moderate or severe disease [23]. On the other hand, when comparing physicians' and patients' evaluations of AR severity, it seems like patients rates their disease as more severe than their physicians [23]. Indeed, in a patient-reported assessment study, more than 85% of patients reported to have moderate-to-severe symptoms, according to ARIA classification, as shown in Table 4 [58].

**Table 4:** AR classification by severity. Adapted from: [58].

ARIA severity classification		Modified ARIA classification [52]	
Grade	Frequency (%)	Grade	Frequency (%)
Mild Persistent	3.6%	Mild	12.4%
Mild Intermittent	8.8%	Moderate	59.9%
Moderate/Severe Persistent	46.2%	Severe	27.7%
Moderate /Severe Intermittent	41.4%		



Several symptoms score, each with a different number of evaluated items, have been developed and validated for the assessment of AR severity. Symptoms reported by a patient can be added up: the lower the score, the less severe the disease. The most used ones include the previously mentioned TNSS, which is the sum of 4 individual symptom scores for rhinorrhea, nasal congestion, nasal itching, and sneezing, resulting in a possible score of 0 to 12; a shorter version, the Total Four Symptom Score (T4SS), was also proposed for pediatric patients [55,63]. Another established possibility of determining illness-related impairments experienced by AR patients is the Rhinitis Total Symptom Score (RTSS) [64].

Nevertheless, in *real-life*, the most feasible and practical instrument to evaluate the presence, severity and control of symptoms remains the VAS, consisting in a single patient-reported outcome of the effect of the disease and of the treatment [65]. VAS seems to adequately correlate with severity according to ARIA items, as well [55]. VAS are quantitative measures largely validated in many diseases, and extensively used to assess both AR severity and control [54]. VAS may be used as a simple and quantitative method for the assessment of rhinitis severity in both intermittent and persistent rhinitis [54]. A cut-off level of 5.5 out of 10 cm was proposed to discriminate between mild and moderate/severe patients with AR, highlighting a negative predictive value of 93.4% and a positive predictive value of 73.6% [54].

As mentioned above, severity is often associated to a reduced QoL. For such reason, tools to evaluate HRQL in AR patients will be discussed in this section, even though they have sometimes been used to assess symptoms control as well. One of the most frequently used instrument to measure HRQL is the previously mentioned RQLQ [56]. This questionnaire has since become the gold standard for determining quality of life in clinical studies involving rhinoconjunctivitis patients [64]. The original version of the validated questionnaire consists of 28 items in seven dimensions, and a shorter version of the questionnaire, the Mini-Rhinoconjunctivitis Quality of Life Questionnaire (MiniRQLQ) has been proposed as well [56]. The RhinAsthma Patient Perspective (RAPP) is a validated tool of 8 questions that provides evaluation of HRQL of patients with asthma and/or rhinitis in clinical practice [67,68]. Patients are asked to evaluate how bothersome their symptoms have been over the previous 2 weeks using a 5-point Likert scale (not at all, a little, quite, a lot, and very much) [69]. The score may range between 8 and 40, and a cutoff of 15 was shown to be able to discriminate the achievement of an optimal HRQL [69].

## **Control assessment**

Despite the availability of effective therapies, total control of AR is difficult to achieve for many patients [21]. The evaluation of AR control can be performed using standardized questionnaires, in a similar way to the evaluation of control proposed for the management of asthma [60]. In the absence of a “gold standard”, many scales, scores and instruments have been used to evaluate AR symptoms control [70]. They mainly include nasal symptom scores, total (nasal and ocular) symptom scores, individual symptom scores, medication-adjusted symptom scores, medication scores, QoL scores, combined symptom-medication scores, VAS, and satisfaction questionnaires [70]. The time-period of assessment ranges from 1-4 weeks prior to the consultation, long enough to assess changes and short enough to avoid recall bias [21]. In general, control measurement depends on the variables considered by the different available tools [21]. Measurements of control must be reproducible, easy to perform, easy to interpret and should focus on the impact of the disease in everyday life [21]. For patients, measures should be easily obtained and allow patients to self-medicate, while for physician, tools must have a low burden in a busy clinical practice and should guide clinical action following the test result [21].

### The Control of Allergic Rhinitis and Asthma Test (CARAT)

CARAT was the first questionnaire developed to assess the level of control of both asthma and AR using a single tool [71,72]. CARAT is a self-administered questionnaire that includes 17 questions with a Likert scale [73]. The reference period is four weeks [2]. Subsequently, a simply 10-item version of CARAT (CARAT10) was validated as well, and is shown in Figure 13 [74]. The range of possible scores for CARAT10 is 0 (absence of control) to 30 (complete control), and the reference/evaluation period is 4-6 weeks. CARAT10 has good test-retest reliability, responsiveness and longitudinal validity, and it may be used to assess control of allergic rhinitis and asthma, both to compare groups in clinical studies and to evaluate individual patients in clinical practice [75].

Please mark the following boxes with a cross (☒).

Due to your allergic respiratory diseases (asthma, rhinitis, allergies) in the last **four weeks**, on average, how many times did you have:

	Never	1 or 2 days per week	More than 2 days per week	Almost every day
1. Blocked nose?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Sneezing?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Itchy nose?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Runny nose?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Shortness of breath/dyspnoea?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Wheezing in the chest?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Chest tightness upon physical exercise?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. Tiredness/ limitations in doing daily tasks because of your allergic respiratory diseases?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. Woke up during the night because of your allergic respiratory diseases?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

In the last **4 weeks**, because of your allergic respiratory diseases (asthma, rhinitis, allergies), how many times did you:

	I'm not taking any medicines	Never	Less than 7 days	7 or more days
1. Increased the use (dosage or frequency) of your medicines?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

\_\_\_\_ Score  
(Sum of all 10 questions, 0 = worst, best = 30)

Date \_\_\_/\_\_\_/\_\_\_

**Figure 13 :** Control of Allergic Rhinitis and Asthma Test. From: [76].

More recently, then Control of Allergic Rhinitis and Asthma Test for Children (CARATKids) was developed to evaluate AR and asthma control in 6-12 years old children [77]. The initial version of CARATKids has 17-item and was developed from CARAT and other pediatric questionnaires; it uses a dichotomous scale, with easily understandable questions and images for children [71], as shown in Figure 14.

**CARAT** Control of Allergic Rhinitis and Asthma Test for kids

Due to your allergies, have you had:

- Blocked nose? Yes  No
- Sneezing? Yes  No
- Itchy nose? Yes  No
- Runny nose? Yes  No
- Itchy throat? Yes  No
- Itchy or irritated eyes? Yes  No
- Shortness of breath? Yes  No
- Wheezing in the chest? Yes  No
- Cough? Yes  No
- Chest tightness, cough, wheezing upon physical exercise or laugh due to your allergies? Yes  No

**CARAT** Control of Allergic Rhinitis and Asthma Test for kids

Due to your allergies:

- Have you felt tiredness/limitation in doing daily tasks due to your allergies? Yes  No
- Have you woken up during the night due to your allergies? Yes  No
- Have you had complaints/symptoms when you wake up in the morning due to your allergies? Yes  No

In the last **2 WEEKS**:

- Did you have to miss school or your activities due to your Asthma/Rhinitis/Allergy? Yes  No
- Did you have to use more medication than usual due to your Asthma/Rhinitis/Allergy? Yes  No
- Did you need to go to a doctor due to deterioration of your Asthma/Rhinitis/Allergy? Yes  No
- Did you need to be admitted to a hospital due to your Asthma/Rhinitis/Allergy? Yes  No

**Figure 14 :** CARATkids – children’s version. From: [77].

## Rhinitis Control Assessment Test (RCAT)

RCAT is a 26-item instrument developed for the assessment of control of nasal and ocular symptoms during the previous week [78]. It was afterwards refined to a 6-item self-administered questionnaire (including frequency of nasal congestion, sneezing, watery eyes, sleep interference, activity avoidance and self-assessed control), as shown in Figure 15. These 6 items were most predictive ( $p < 0.001$  for all) of the allergist's overall rating of rhinitis symptom control [2]. For each question, patients are asked to choose a rating that describes their condition over the past week, from a range of 5, which is the best the person could be, to 1, which is the worst they could be [21,23]. Total score may therefore range from 6 (poor control) to 30 (complete control). Based on its sensitivity and specificity, a cut-point score of 21 or less was suggested to identify AR control [21]. Scores of 21 or less indicate uncontrolled rhinitis; a score of 17 or less suggests poor control and referral to a specialist may be appropriate [23]. Finally, a 3 or more point-change from a previous RCAT assessment indicates a clinically meaningful change, either a relevant improvement or a relevant worsening [23].

<i>During the past week, how often did you have nasal congestion?</i>				
Never 5	Rarely 4	Sometimes 3	Often 2	Extremely Often 1
<i>During the past week, how often did you sneeze?</i>				
Never 5	Rarely 4	Sometimes 3	Often 2	Extremely Often 1
<i>During the past week, how often do you have watery eyes?</i>				
Never 5	Rarely 4	Sometimes 3	Often 2	Extremely Often 1
<i>During the past week, to what extent did your nasal or other allergy symptoms interfere with your sleep?</i>				
Never 5	Rarely 4	Sometimes 3	Often 2	Extremely Often 1
<i>During the past week, how often did you avoid activities (for example, visiting a house with a dog or cat, gardening) because of your nasal or other allergy symptoms?</i>				
Never 5	Rarely 4	Sometimes 3	Often 2	Extremely Often 1
<i>During the past week, how well were your nasal or other allergy symptoms controlled?</i>				
Completely (5)	Very (4)	Somewhat (3)	A little (2)	Not at all (1)

**Figure 15 :** Rhinitis Control Assessment Test: questionnaire. From: [79].

The RCAT has also been proposed as a short alternative for the RQLQ [66]. The RCAT is a simple and validated tool that can rapidly measure control at home, in a pharmacy,

or in a health care provider’s office [23,79]. In facts, patients may use the RCAT to assess their level of rhinitis control at home, since the tool generates a rhinitis score that can be easily understood [61]. For physicians, the RCAT gives a rapid and accurate assessment of rhinitis control, suitable for use in clinical practice, that can be compared to the previous values [61].

### Allergic Rhinitis Control Test (ARCT)

The self-assessment Allergic Rhinitis Control Test (ARCT) was developed and validated in adults by a multidisciplinary group associating allergists, pulmonologists, ENT physicians and methodologists, and is shown in Figure 16 [12]. It is a multidimensional five-item tool, with similarities to the Asthma Control Test (ACT) [2]. The 5 items include the impact on professional/personal activities, sleep disturbance, medication and overall assessment of the disease [21]. A 2-week recall is used in ARCT [21]. A score of 20 is considered as the optimal cut-off for poorly vs. well-controlled rhinitis (sensitivity: 67%; specificity: 82%; negative predictive value: 32%; positive predictive value: 95%) [2]. The questionnaire is currently being validated in adolescents and in children aged more than 5 years.

During the last 2 weeks, has your allergic rhinitis had an effect on your professional/personal activities?					
Permanently	Very often	Often	Not often	Never	Points
1	2	3	4	5	
During the last 2 weeks, has your allergic rhinitis made you irritable?					
Permanently	Very often	Often	Not often	Never	Points
1	2	3	4	5	
During the last 2 weeks, has your allergic rhinitis disturbed your sleep (going to sleep, waking at night)?					
Permanently	Very often	Often	Not often	Never	Points
1	2	3	4	5	
During the last 2 weeks, have you needed to use an additional treatment not prescribed by your doctor to treat your allergic rhinitis?					
Four nights or more per week	Two to three nights per week	One night per week	One to two times in all	Never	Points
1	2	3	4	5	
During the last 2 weeks, how would you assess your allergic rhinitis?					
Not controlled at all	Very slightly controlled	Somewhat controlled	Well controlled	Completely controlled	Points
1	2	3	4	5	
Total score					

Each patient circled their score for each question depending on their condition and wrote the number in the box in the right-hand column.

**Figure 16 :** Allergic Rhinitis Control Test. From: [12].

### Visual Analog Scale (VAS)

Initially developed as a simple tool to measure AR severity, VAS has turned out to be a possible tool to assess AR control [21,65]. Patients with a VAS > 5 are considered not controlled [65]. In a *post hoc* analysis assessing VAS at inclusion and after 15 days of treatment, the change of VAS greater than 30 mm was considered as significant in relation to the improvement of QoL and of symptom score [21]. Also, a 0 to 10 cm VAS score proved to be significantly correlated to the RQLQ score [2]. The VAS assessment well correlates with the structured CARAT questionnaire as well, and with the relevant symptoms of AR [65].

### Allergy-Control-SCORE™

The "Allergy-Control-SCORE"™ [80] is a combined score that measures (i) the severity of 10 nasal and non-nasal symptoms on a 4-point scale) and (ii) medication use (out of a catalogue of 745 different medications) and combines the two metrics with equal weighting [80]. It is significantly correlated with the global assessment of allergy severity, the RQLQ score and the number of medical consultations due to allergy within the previous year [2].

## Objectives of the PhD studies

Two studies on *real-life* databases of adults suffering from AR were carried out for the present PhD project: the first one to validate the use of a VAS on smartphone screens to assess patients' control and the second one to detect a simple and reliable tool able to discriminate seasonal AR severity in a clinical setting.

### MASK

Most validated tools for AR to evaluate disease control use patient-reported assessments of the intensity of the main symptoms. Administration of currently available paper-and-pencil tools is either through patient self-administration or through interviews with patients or caregivers. Emerging methods use computer-assisted questionnaire administration, or computer-tailored assessments. Today, the most practical, reliable and easy tool seems the administration of a 10 cm VAS that allows users to simply evaluate the degree of impairment, and physicians to assess the overall intensity of allergic symptoms [81-83]. VAS has already been used even on computer screens, and may incorporate symptoms and QoL evaluation [84].

MACVIA-France (Fighting chronic diseases for active and healthy ageing in France, <http://macvia.cr-languedocroussillon.fr>) is one of the reference sites of the European Innovation Partnership on Active and Healthy Ageing [85]. It initiated the project AIRWAYS ICPs (integrated care pathways for airway diseases) [86,87] and the allergy sentinel network MASK (MACVIA-ARIA Sentinel NetworK) [3,88]. MASK-rhinitis [89] is a simple Information and Communication Technology (ICT) tool to implement care pathways for AR from patients to health care providers using a common language and a clinical decision support system [81], through a smartphones and tablets application. The corresponding app, previously called "ARIA Allergy Diary" (AD), and since 2019 MASK-Air® may be downloaded for free both using an Android or an iOs system and is currently available in 23 European countries, Canada, Mexico, Brazil, and Australia. Users may self-evaluate their AR control by a VAS that appears on their phone screen. Preliminary data showed that the App enables baseline and simple phenotypic characteristics collection [90].

The aim of the first study for the present PhD project was therefore to assess the validity of the MASK-rhinitis VAS, as it appears in the AD app, in users who reported to suffer from AR.

## **Pollin'Air**

ARIA guidelines look for duration and types of symptoms reported to or diagnosed by the physician, to assess AR severity prior to treatment [7,8,90]. Nevertheless, the real goal, both in the previous classical ARIA guidelines and in the new digitally-enabled ones, is to assess the control of the disease, regardless its severity. We previously showed that severity and control are strictly related in AR patients, and severe forms often characterize patients who are not able to control their symptoms even if an appropriate high-dose treatment is prescribed and their compliance is good. Therefore, an appropriate assessment of both is needed to optimize AR management. We already discussed the fact that several scores have been previously validated to assess AR both control and severity, and a few papers try to categorize patients based on symptoms severity [54,57,83,91,92]. Some authors assessed severe AR, by analyzing patients in clusters, and stratify them, based on the severity of their symptoms [93-95]. Therefore, in literature, severe forms may be identified through physicians' questionnaire, self-assessment methods, or by analyzing the results of published cluster analysis. Besides identifying the best tool to stratify patients, it is debated whether physician's or patient's assessment would serve as the best guide to classify the patient's severity.

The aim of the second study for the present PhD project was therefore to assess in a large *real-life* database, the best method to stratify patients suffering from seasonal AR and then to propose cut-offs able to determine which patients suffer from severe forms of rhinitis.



# Evaluated cohorts, methods

## MASK

### Collected data

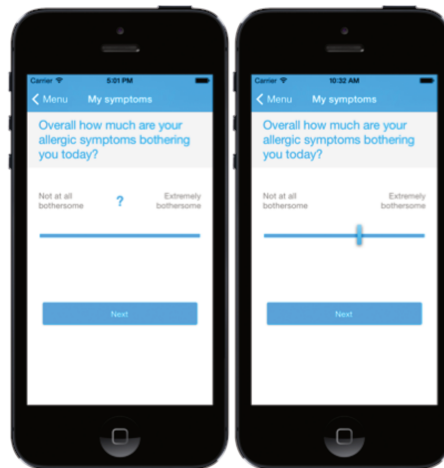
In the MASK study, we included all users that logged into the AD app, since August 1<sup>st</sup> 2015, until July 31<sup>st</sup> 2016 (12-month period). The app collects information on AR symptoms experienced by users, who assess their daily symptom control using the touchscreen functionality on their smart phone. To do so, users need to click on 4 consecutive VAS (i.e. general allergy symptoms, nasal symptoms, ocular symptoms, and asthma symptoms). At the time of the study, the system was deployed in 20 countries and in 15 languages (translated and back-translated, culturally adapted and legally compliant). After the download, and before using the app, users need to approve both the terms of use and the privacy policy, which also have been translated and legally adapted for each country in which the app is available. By accepting the use of the app, subjects agree to the fact that their data could be used also for research and scientific purposes.

Data collected by the AD app, after the registration process are:

- the user's sex and age;
- the severity of the symptoms, as indicated through 4 VAS detailed below, each time users log into the app; users may evaluate their symptoms as many times as they want during the day. Of note, there is no reminder, nor a precise time imposed to score symptoms;
- the possible medications taken to control their symptoms (whether prescribed by a physician or OTC);
- the diagnosis, which is a self-diagnosis: when patients register, they answer "I have allergic rhinitis" and/or "I have asthma".

During the evaluated period, the VAS included four items, each of which targets a specific domain. Specific domains include an organ or related disease. To complete the VAS, users are invited to touch anywhere along a line that appears on the screen to indicate how bothersome their symptoms are: the left edge means their symptoms are "not at all

bothersome” while the right edge is equal to “extremely bothersome”, as indicated on the screen. Once users touch the line, a slider appears and they may move it, if necessary, to provide a more accurate response (Figure 17).



**Figure 17 :** VAS for overall allergic symptoms as it appears on smartphones screens. From: [13].

Users are asked to answer to one general and three symptom-specific questions that yield therefore to 4 different VAS, as follows:

- VAS 1 (Overall symptoms): Overall, how much are your allergic symptoms bothering you today?
- VAS 2 (Rhinitis): How much are your nose symptoms bothering you today?
- VAS 3 (Conjunctivitis): How much are your eye symptoms bothering you today?
- VAS 4 (Asthma): How much are your asthma symptoms bothering you today? (since current ARIA guidelines [7,83] advise to evaluate the possible asthma co-morbidity in patients suffering from allergic rhinitis, this question was included for all patients from June 1<sup>st</sup> 2016; previously, users were asked to answer this question only if they answered, during the registration process, that they were asthmatic).

## Statistical methods

The associations between the different VAS were assessed using a Spearman test and a chi-square test for all users, and for users logging into the app more than once as follows:

- associations between the overall symptoms (VAS 1) and rhinitis (VAS 2); VAS1 and conjunctivitis (VAS 3); VAS1 and asthma (VAS 4); VAS1 and rhino-conjunctivitis, as the average of the collected values for VAS 2 and VAS 3; and VAS1 and all organ symptoms, as the average of the collected values for VAS 2, VAS 3 and VAS 4.
- the association between VAS 1, and the cumulative VAS score given by the average of all VAS scores.

For the chi-square analysis, we categorized patients into 3 different classes: class 0, for asymptomatic patients (VAS < 20); class 1, for those presenting with mild symptoms ( $\leq 20$  VAS < 50); and class 2, for those as with moderate to severe symptoms (VAS  $\geq 50$ ). As for the asthma question (VAS 4) we also evaluated the association with the overall symptoms VAS before June 1<sup>st</sup> (when only asthmatic users answered to the fourth question) and after June 1<sup>st</sup> 2016 (when all users were asked to complete VAS 4 as well).

The analysis of the psychometric characteristics of the AD app, in compliance with the COSMIN guidelines [96], aimed to verify for this tool:

- the *internal consistency*. It was assessed through the Cronbach's alpha coefficient and the test-retest procedure, evaluating the results given by users logging into the App and filling the VAS for two consecutive days, when no change in medications intake is recorded;
- the *reliability*. It was assessed by analyzing correlations between VAS measures taken twice in the same day, through Intraclass Correlation Coefficients (ICCs). As the magnitude of correlation coefficients is affected by the range of scores included in the sample, increasing as the range of scores increases, ICCs were calculated separately for VAS scores above and below 50 mm;
- the *sensitivity*. It was evaluated by the Cronbach' alpha coefficient, the difference of measures and the standard deviation in the VAS, for those users logging into the app more than once per day, but self-assessing their symptoms with a interval of less than three hours (thus, eliminating bias related to possible changes in allergen exposure and/or drug intake).
- the *external validity*. It has already been described in a previous paper [90].

We also verified the population *acceptability*, that we arbitrarily defined as (i) the persistence of self-assessment over at least two consecutive days in more than 40% of users using the app, and (ii) the persistence of self-assessment at least 4 days a week in more than 30% of users downloading the app.

All analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA). All *p-values* <0.05 were considered as statistically significant.

## **Pollin’Air**

In the Pollin’Air multicenter French study, we analyzed a large dataset from 36.397 adult patients with a previous medical diagnosis of seasonal AR and consulting a physician. All patients were consulting either a general practitioner or an otolaryngologist, or an allergist, or a dermatologist, or a pulmonologist. A total of 8,143 doctors distributed over the whole French territory participated to the study. The Pollin’Air study was approved by local authority bodies by the National Committee for Information Management on medical research (Comité Consultatif sur le Traitement de l’Information en Matière de Recherche dans le domaine de la santé) and by the National Commission on informatics and health (CNIL, Commission Nationale Informatique et Liberté). The approval by an ethic committee was not necessary in 2005m when the study was performed. Information was provided to included subjects or to their caregivers through a written document. Informed written consent to participate in the survey was obtained for all patients by the physicians. The CNIL approved in 2016 that all data acquired prior to 2016, without the previous need of an authorization of an Ethic Committee, could still be exploited. The survey and its methodology have been described in detail elsewhere [83,97].

## **Collected data**

Each doctor interviewed the patients after confirming the previous medical diagnosis of seasonal AR through a clinical visit, and answered 17 questions for each included patient; each question focused on one item, and the physician was supposed to rate every symptom

from 0 to 4 in a 5-point Likert scale (0: absent, 1: mild, 2: moderate, 3: severe, and 4: very severe). Evaluated symptoms were: 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, and sleep alteration. Other collected data included age, gender, location (rural / urban), disease onset (years before), duration of episode (days), reported history of asthma, conjunctivitis, atopic dermatitis, food allergy, or hives, results of skin-prick tests to respiratory allergens (positive / negative), positivity of serum specific IgE to respiratory allergens (positive / negative), previous or concomitant allergen immunotherapy (yes / no), and region (center, east, north-west, Paris agglomeration, south-east, south-west and west). On the day of the visit, patients completed a VAS on a paper, indicating, on a 10-cm line, how severe they believed their rhinitis was (“how bothersome are your allergic rhinitis symptoms?”).

## **Statistical methods**

Five approaches to classify patients according to AR severity were assessed:

1. K-means clustering (KMC) [98] was used as unsupervised classification on standardized variables to categorize AR patients. A group of three clusters were then selected for further analyses.
2. Agglomerative hierarchical clustering (AHC) [99] was used as unsupervised classification on standardized variables to categorize AR patients. A group of three clusters were then selected for further analyses.
3. Allergic Rhinitis Physician Score (ARPhyS), previously described as “Global Symptomatic Score (GSS-20)” [83,97] was calculated, based on five physician-diagnosed symptoms. These symptoms were assessed by each doctor during the interview with the patients. To each nasal (nasal obstruction, rhinorrhea, sneezes and nasal pruritus) and ocular symptom (ocular pruritus), doctors attributed a severity score ranging from 0 to 4, as described above. This score could therefore possibly range from a minimum of 0 to a maximum of 20 points. The score was categorized into three tertiles.
4. Total Symptoms Score (TSS-17) [100,101], which is the global score resulting from adding up the evaluation of the 17 items rated by physicians for each included patient.

This score could therefore possibly range from a minimum of 0 to a maximum of 68 points. The score was categorized into three tertiles.

5. VAS [54,91], which is a global self-assessment wellness score reported by each patient, and ranging from 0 (= no discomfort) to 100 (= maximal discomfort). The score was categorized into three tertiles.

Classification in three groups (clusters and tertiles) had been chosen to follow current guidelines on AR severity and their adaptation [6,102,103]. For validation, K-means algorithm and agglomerative hierarchical clustering models were carried out 10 times by the leave-one-out method to ensure stability and repeatability of the models.

Classical statistical methods were used for the analysis comparing the groups [98-100,104-106]. Discrimination analyses was conducted with Fisher linear and quadratic discriminant analysis, along with non-parametric kernel density estimation methods [107] and allowed to evaluate miss-classification of the patients among the three categories on each of the five scales. Cross-validation check was used to assess the validity of each scale [108]. Reliability of the ARPhyS scale and of the TSS-17 were evaluated through Cronbach's alpha coefficient. At last, Cohen's  $\kappa$  coefficient was computed to study the degree of agreement between the five scales.

All analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA). All *p-values* <0.05 were considered statistically significant.

## Evaluated cohorts, results

### **MASK**

#### **VAS Acceptability – Description of the users**

Between August 1<sup>st</sup> 2015 and July 31<sup>st</sup> 2016, the AD app was used 14,612 times, by 2,497 individuals. 1,272 subjects used the app only once, while 1,225 (49.1%) subjects used it at least twice (12,076 accesses): 845 individuals used it for 2 to 7 days, 154 for one to 2 weeks, 128 for 2 to 4 weeks, and 98 for more than 30 days. The VAS were completed on two consecutive days for 6328 times.

Out of the 1,225 users connecting to the AD more than once, 809 logged into the app for at least two consecutive days (66.0%, and 32.4% of the whole cohort). In the same group, 461 subjects (37.6%) entered their VAS for at least 4 days during the same week. Also, 196 out of these 461 users (42.5%), assessed their symptoms for at least two consecutive weeks and 90 (19.5%) for at least 4 consecutive weeks. Considering only these subjects, the mean value of consecutive weeks during which they used the app for at least 4 days per week was 2.41 weeks (min 1, max 23, SD 2.66).

The associations between the different VAS for all users, and for users logging into the AD app more than once are shown in Table 5 and Table 6. In both groups, when considering one organ only, the highest correlation coefficient was observed between rhinitis (VAS 2) and conjunctivitis (VAS 3) (Table 5). The correlation was very elevated when considering together rhinitis and conjunctivitis. The association with asthma was less strong compared to the other symptoms. These results were confirmed when analyzing the VAS once categorized into the three previously described classes (Table 6). Figure 18 shows the correlation between the overall symptoms (VAS 1) and the average values obtained by all the other three VAS, both for all users using the app and for those using it more than once.

**Table 5:** association between overall symptoms (VAS 1) and rhinitis (VAS 2), conjunctivitis (VAS 3), asthma (VAS 4), rhino-conjunctivitis (average value of VAS 2 and VAS 3), and all organ symptoms (average value of VAS 2, VAS 3, and VAS 4), in all subjects who ever used the app, and in those who used it more than once, through Spearman test. Adapted from: [13].

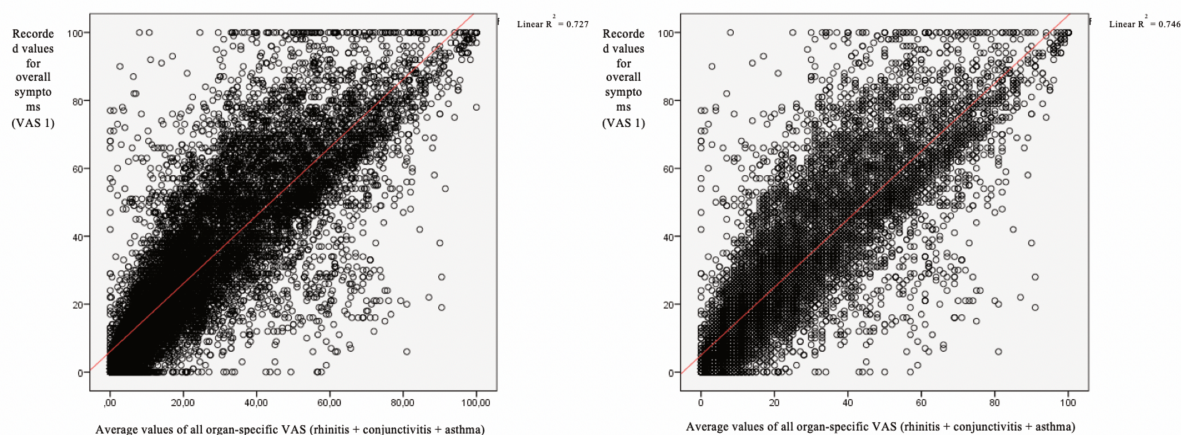
	VAS 1			
	All users (total data = 14612)		Users logging in more than once (total data = 12076)	
	Spearman's coefficient of correlation	<i>p-value</i>	Spearman's coefficient of correlation	<i>p-value</i>
<b>VAS 2</b>	0.879	< 0.001	0.878	< 0.001
<b>VAS 3</b>	0.656	< 0.001	0.692	< 0.001
<b>VAS 4</b>	0.583	< 0.001	0.595	< 0.001
<b>VAS 2 and 3</b>	0.889	< 0.001	0.894	< 0.001
<b>VAS 2, 3 and 4</b>	0.893	< 0.001	0.897	< 0.001
<b>VAS 4: before June 1<sup>st</sup>, 2016</b>	0.668	< 0.001	0.642	< 0.001
<b>VAS 4: after June 1<sup>st</sup>, 2016</b>	0.478	< 0.001	0.522	< 0.001

**Table 6:** relation between overall symptoms (VAS 1) and rhinitis (VAS 2), conjunctivitis (VAS 3), asthma (VAS 4), and all organ symptoms (average value of VAS 2, VAS 3, and VAS 4), in all subjects who ever used the app, and in those who used it more than once, through chi-squared test. Adapted from: [13].

		VAS 1			<i>p-value</i>	VAS 1			<i>p-value</i>
		Data from all users (N = 14612)				Data from users logging in more than once (N = 12076)			
		Class 0	Class 1	Class 2		Class 0	Class 1	Class 2	
<b>VAS 2</b>	Class 0	<b>86.49%</b>	15.42%	4.74%	< 0.0001	<b>86.67%</b>	16.80%	4.62%	< 0.0001
	Class 1	11.19%	<b>67.05%</b>	16.36%		11.42%	<b>64.93%</b>	17.00%	
	Class 2	2.33%	17.53%	<b>78.90%</b>		1.91%	18.28%	<b>74.20%</b>	
<b>VAS 3</b>	Class 0	<b>91.01%</b>	54.58%	23.86%	< 0.0001	<b>91.25%</b>	49.58%	22.97%	< 0.0001
	Class 1	6.93%	<b>34.97%</b>	25.15%		7.09%	<b>39.29%</b>	23.79%	
	Class 2	2.06%	10.46%	<b>50.99%</b>		1.66%	11.13%	<b>53.24%</b>	
<b>VAS 4</b>	Class 0	<b>94.51%</b>	74.95%	60.92%	< 0.0001	<b>94.32%</b>	71.69%	58.13%	< 0.0001
	Class 1	4.20%	<b>18.62%</b>	13.84%		4.47%	<b>21.36%</b>	13.98%	
	Class 2	1.29%	6.43%	<b>25.24%</b>		1.21%	6.94%	<b>27.89%</b>	
<b>Average of VAS 1, 2 and 3</b>	Class 0	<b>95.02%</b>	63.47%	43.28%	< 0.0001	<b>93.96%</b>	37.12%	20.77%	< 0.0001
	Class 1	4.11%	<b>31.23%</b>	25.84%		5.30%	<b>57.72%</b>	25.02%	
	Class 2	0.86%	5.30%	<b>30.88%</b>		0.75%	5.16%	<b>54.21%</b>	

Class 0 = asymptomatic (VAS < 20), class 1 = mild symptoms ( $\leq 20$  VAS < 50), and class 2 = severe symptoms (VAS  $\geq 50$ ).





**Figure 18 :** Correlation between the results of the overall symptoms VAS (VAS 1), and all organ symptoms (average value of VAS 2, VAS 3, and VAS 4). On the left, in all subjects who ever used the app; and, on the right, in those who used the app more than once. Adapted from: [13].

### VAS validation – Internal consistency

The Cronbach's alpha coefficient for each VAS and for the average values of all collected VAS in subjects using the app for two consecutive days (n=6328) were as follows:

- VAS 1, overall allergic symptoms: alpha coefficient 0.85;
- VAS 2, nose symptoms: alpha coefficient 0.84;
- VAS 3, ocular symptoms: alpha coefficient 0.85;
- VAS 4, asthma symptoms: alpha coefficient 0.89;
- Average of all collected VAS by each patient: alpha coefficient 0.88.

When evaluating for test-retest the group of users logging into the app for two consecutive days (n=809), we highlighted the following ICCs:

- VAS 1, overall allergic symptoms: ICC 0.737 (CI 95%, 0.725-0.748, p<0.0001);
- VAS 2, nose symptoms: ICC 0.727 (CI 95%, 0.715-0.738, p<0.0001);
- VAS 3, ocular symptoms: ICC 0.748 (CI 95%, 0.737-0.759, p<0.0001);
- VAS 4, asthma symptoms: ICC 0.797 (CI 95%, 0.785-0.808, p<0.0001);
- Average of all collected VAS by each patient: ICC 0.799 (CI 95%, 0.789-0.808, p<0.0001).

## VAS validation – Reliability and sensitivity

521 individuals recorded the VAS more than once over three consecutive hours. Reliability was evaluated considering no external interaction effect, in this population, and then in the subgroups of users reporting a VAS of more and less than 50%, as shown in Table 7. ICCs were higher than 0.87 and thus excellent in the entire population and in users reporting VAS values < 50, and between good and excellent in users reporting VAS values > 50. Sensitivity was evaluated as good for each VAS, through classical statistical analysis, t-student test, and alpha coefficient, as shown in Table 8.

**Table 7:** Intraclass correlation coefficients (ICC) in all subjects who used the app twice in the same day (whole population), and in those evaluating their symptoms as moderate to severe (VAS $\geq$ 50) and not (VAS<50). The analysis was conducted for each VAS completed by users (n=521). Adapted from: [13].

		Included subjects	ICC	Min-Max (95% CI)	p-value
Whole population	VAS 1	498	0.924	0.909-0.936	< 0.001
	VAS 2	521	0.928	0.914-0.939	< 0.001
	VAS 3	521	0.949	0.940-0.957	< 0.001
	VAS 4	316	0.959	0.949-0.967	< 0.001
VAS > 50	VAS 1	169	0.645	0.520-0.738	< 0.001
	VAS 2	165	0.619	0.482-0.720	< 0.001
	VAS 3	119	0.661	0.513-0.764	< 0.001
	VAS 4	52	0.841	0.724-0.909	< 0.001
VAS < 50	VAS 1	329	0.889	0.862-0.911	< 0.001
	VAS 2	356	0.865	0.834-0.891	< 0.001
	VAS 3	402	0.913	0.895-0.929	< 0.001
	VAS 4	264	0.891	0.861-0.914	< 0.001

ICC: intraclass correlation coefficient; CI: confidence interval; Min: Minimum; Max: Maximum

**Table 8:** Sensitivity of the four VAS, in users evaluating their symptoms with a less than three-hours-interval. Adapted from: [13].

	Cronbach's alpha coefficient	Mean difference	Standard Deviation	CI 95%	t-Student test
VAS 1	0.858	1,143	14,993	-0,177 ; 2,463	1,701
VAS 2	0.865	0,495	14,917	-0,789 ; 1,779	0,758
VAS 3	0.904	1,207	12,58	0,125 ; 2,29	2,19
VAS 4	0.922	-0,003	10,464	-1,161 ; 1,155	-0,005

CI: confidence interval; Min: Minimum; Max: Maximum

## Pollin’Air

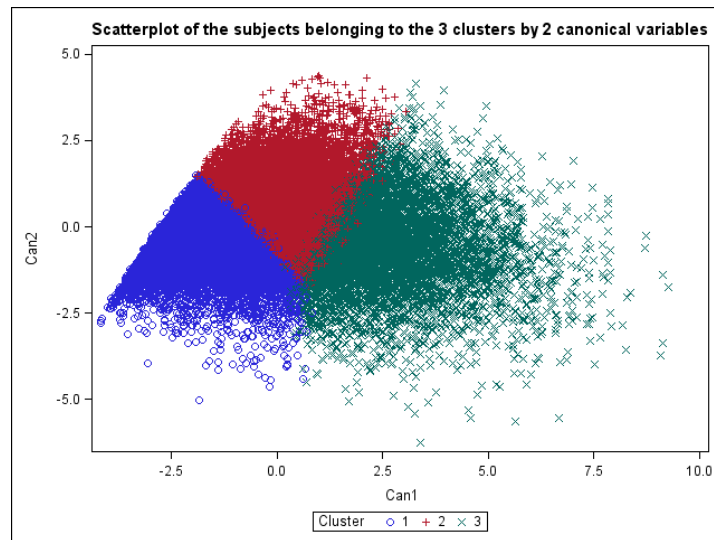
### Patients’ stratification

Out of the 36,397 subjects initially included in the trial, 8,288 were excluded from further analysis, because of missing data. The other 28,109 patients were then categorized in three classes, of “mild”, “moderate”, and “severe” AR, as shown in Table 9. Stratification by cluster analysis is shown in Figure 19 and Figure 20. There were 10,617 patients in the mild, 9,446 patients in the moderate and 8046 patients in the severe category based on the ARPhyS scale (Table 9).

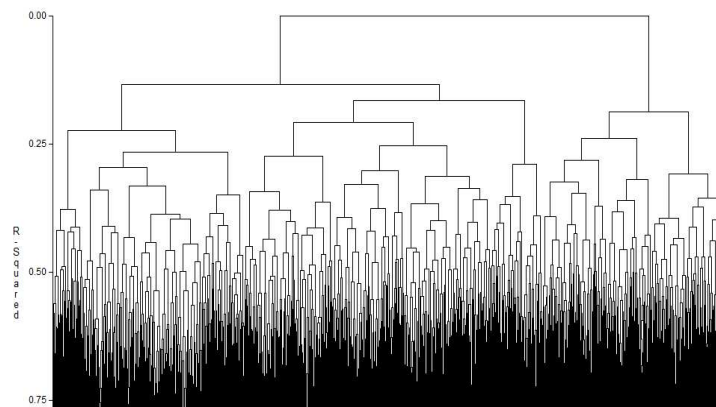
**Table 9:** Distribution of mild, moderate, and severe patients, based on the five approaches used in the study. From: [14].

	Mild		Moderate		Severe	
	Included subjects, n (%)	Cumulated frequency (n) Cumulated Percentage (%)	Included subjects (n)	Cumulated frequency (n) Cumulated Percentage (%)	Included subjects (n)	Cumulated frequency (n) Cumulated Percentage (%)
KMC	11358 (40.41)	11358 40.41	10163 (36.16)	21521 76.56	6588 (23.44)	28109 100.00
AHC <sub>l</sub>	8021 (28.54)	8021 25.54	12403 (44.12)	20424 72.66	7685 (27.34)	28109 100.00
ARPhyS	10617 (37.77)	10617 37.77	9446 (33.60)	20063 71.38	8046 (28.62)	28109 100.00
TSS-17	9579 (34.08)	9579 34.08	9177 (32.65)	18756 66.73	9353 (33.27)	28109 100.00
VAS	9247 (32.90)	9247 32.90	9689 (34.47)	18936 67.37	9173 (32.63)	28109 100.00

The difference in terciles group is due to the TIES = Low option (default): ties are assigned to lower categories. CV: cross-validation; KD: kernel density; KMC: k-means clustering; AHC: agglomerative hierarchical clustering; ARPhyS: Allergic Rhinitis Physician Score; TSS-17: Total Symptom Score with 17 items; VAS: Visual Analogue Scale (0–100).



**Figure 19 :** Cluster analysis (all variables standardized): agglomerating hierarchical clustering dendrogram, with y-axis that shows the  $R^2$  as the distance measure ( $R^2=16.5\%$ ). Adapted from: [14].



**Figure 20 :** Cluster analysis (all variables standardized): k-means clustering, non-hierarchical clustering approach;  $k = 3$  (Cluster 1 = ‘mild’ allergic rhinitis; Cluster 2 = ‘moderate’ allergic rhinitis; Cluster 3 = ‘severe’ allergic rhinitis). Adapted from: [14].

## Discrimination and cross-validation

When considering all the five approaches, the best discrimination was offered by the ARPhyS scale, followed by the KMC, and then by the TSS-17 and by the AHC, while the VAS produced the worst results (Table 10).

**Table 10:** Overall error (misclassification) rates and cross-validation error rates according to the approaches and the different discrimination methods. From: [14].

Discrimination methods	KMC		AHC		ARPhyS		TSS-17		VAS	
	Error rates (%)	CV error rates (%)	Error rates (%)	CV error rates (%)	Error rates (%)	CV error rates (%)	Error rates (%)	CV error rates (%)	Error rates (%)	CV error rates (%)
Linear	4.30	4.40	22.39	22.48	3.08	3.18	8.31	8.36	43.93	44.06
Quadratic	10.96	11.20	23.36	23.58	2.89	3.06	9.34	9.48	45.43	45.95
KD with equal bandwidth	0.04	11.50	0.67	15.62	0.00	7.92	0.00	11.43	1.85	48.53
KD with unequal bandwidth	0.99	15.43	5.62	23.97	0.12	8.11	2.43	16.18	8.07	50.87

CV: cross-validation; KD: kernel density; KMC: k-means clustering; AHC: agglomerative hierarchical clustering; ARPhyS: Allergic Rhinitis Physician Score; TSS-17: Total Symptom Score with 17 items; VAS: Visual Analogue Scale (0–100). Smoothing parameter for hierarchical clusters was varied from 0.4 to 1.0 for sensitivity analysis. A moderate smoothing bandwidth (0.8) showed the best results for all analyses. Linear discrimination was better than quadratic discrimination for all analysis. ARPhyS, TSS-17 and VAS are divided into tertiles; KMC and AHC are grouped into 3 clusters.

For validation, K-means algorithm and agglomerative hierarchical clustering models were carried out 10 times by the leave-one-out method to ensure stability and repeatability of the models. These methods showed 95.6% and 94.8% repeatability. The ArPhyS scale showed the best results in terms of error rates and cross-validation error rates, as highlighted in Table 10. Based on the ARPhyS stratification in mild, moderate and severe symptoms, the characteristics of the included patients are shown in Table 11. The duration of the rhinitis episode did not have a statistically significant impact on the ARPHYs scale, despite the large sample size. The proportion of rural population was significantly higher in the severe category compared to the mild category by approximately 3%; no statistically significant difference was noted in gender distributions across the categories (Table 11). The number of patients presenting with a history of conjunctivitis, asthma, atopic dermatitis, food allergy, and hives, and with positive Skin Prick Tests (SPT) or specific IgE or with a previous or concomitant allergen immunotherapy significantly increased with severity.

**Table 11:** Characteristics of the patients according to allergic rhinitis severity as assessed with the ARPhyS Scale. Adapted from: [14].

Characteristics	Mild (N = 10,617)		Moderate (N = 9,446)		Severe (N = 8,046)		p-value <sup>1</sup>
	Mean	SE	Mean	SE	Mean	SE	
Age (years)	35.12	0.15	34.30	0.15	33.32	0.16	< 0.001
Onset (years ago)	6.85	0.07	7.38	0.07	7.91	0.08	< 0.001
Duration of episode (days)	19.64	0.22	19.23	0.23	19.70	0.26	0.500
Loss of appetite	0.22	0.00	0.42	0.01	0.69	0.01	< 0.001
Nasal congestion	2.18	0.01	2.63	0.01	3.02	0.01	< 0.001
Daily activity disturbed	0.80	0.01	1.16	0.01	1.54	0.01	< 0.001
Sneezing	1.68	0.01	2.52	0.01	3.17	0.01	< 0.001
Tiredness	0.83	0.01	1.20	0.01	1.63	0.01	< 0.001
Painful throat	0.55	0.01	0.76	0.01	1.11	0.01	< 0.001
Irritability	0.46	0.01	0.78	0.01	1.16	0.01	< 0.001
Lacrimation	0.95	0.01	1.54	0.01	2.27	0.01	< 0.001
Earache	0.14	0.01	0.22	0.01	0.38	0.01	< 0.001
Nasal obstruction	0.94	0.01	1.58	0.01	2.25	0.01	< 0.001
Ears/Throat itching	0.45	0.01	0.82	0.01	1.33	0.01	< 0.001
Nasal itching	1.12	0.01	1.97	0.01	2.79	0.01	< 0.001
Ocular itching	0.60	0.01	1.32	0.01	2.29	0.01	< 0.001
Rhinorrhoea	1.87	0.01	2.56	0.01	3.13	0.01	< 0.001
Sleep disturbed	0.87	0.01	1.25	0.01	1.64	0.01	< 0.001
Headache	0.60	0.01	0.88	0.01	1.20	0.01	< 0.001
Cough	0.73	0.01	1.00	0.01	1.27	0.01	< 0.001
	<b>N (%)</b>	<b>SE</b>	<b>N, %</b>	<b>SE</b>	<b>N, %</b>	<b>SE</b>	
Female	5,550 (52.27)	0.48	4,933 (52.22)	0.51	4,191 (52.09)	0.56	0.970
Rural	4,332 (40.80)	0.48	4,013 (42.48)	0.51	3,532 (43.90)	0.55	< 0.001
History of conjunctivitis	6,349 (59.80)	0.49	6,762 (71.59)	0.48	6,679 (83.01)	0.43	< 0.001
History of asthma	2,227 (20.98)	0.41	2,402 (25.43)	0.47	2,404 (29.88)	0.53	< 0.001
History of atopic dermatitis	1,472 (13.86)	0.35	1,554 (16.45)	0.40	1,521 (18.91)	0.46	< 0.001
History of food allergy	647 (6.09)	0.24	662 (7.01)	0.28	691 (8.59)	0.33	< 0.001
History of hives	1,766 (16.63)	0.38	1,780 (18.84)	0.42	1,761 (21.89)	0.48	< 0.001
Positive SPT	2,064 (19.44)	0.44	1,962 (20.77)	0.47	2,052 (25.52)	0.55	< 0.001
Positive specific IgE	1,042 (9.81)	0.32	1,104 (11.69)	0.37	1,153 (14.33)	0.43	< 0.001
Previous or concomitant AIT	813 (7.66)	0.26	660 (6.99)	0.27	721 (8.96)	0.33	< 0.001
Region							
- Centre	755 (7.11)	0.25	706 (7.47)	0.27	585 (7.27)	0.29	
- East	1,232 (11.60)	0.31	1,210 (12.81)	0.34	1,068 (13.27)	0.38	
- North-west	1,518 (14.30)	0.34	1,317 (13.94)	0.36	1,022 (12.70)	0.37	
- Paris agglomeration	2,020 (19.03)	0.38	1,643 (17.39)	0.39	1,442 (17.92)	0.43	< 0.001
- South-east	2,068 (19.48)	0.38	1,975 (20.91)	0.42	1,766 (21.95)	0.46	
- South-west	1,615 (15.21)	0.35	1,410 (14.93)	0.37	1,245 (15.47)	0.40	
- West	1,409 (13.27)	0.33	1,185 (12.54)	0.34	918 (11.41)	0.35	

Legend – SPT: skin prick tests; AIT: Allergen Immunotherapy; SE: Standard Error.

<sup>1</sup> Kruskal-Wallis test for continuous or ordinal variables, and  $\chi^2$ -test for categorical variables.

## Reliability, agreement and stratification

Score reliability, assessed through Cronbach's  $\alpha$  coefficient, was acceptable (0.626, computed on the original raw scores) for the ARPhyS scale, and excellent for the TSS-17 (0.864). Maximum variability was observed in the first canonical component direction explaining 99.8% of the total variability for the ARPhyS scale. As for agreement between scores, VAS showed the lowest agreement if compared with all the other scores, as shown in Table 12.

**Table 12:** Cohen's  $\kappa$  matrix showing agreement between the different methods of

	KMC	AHC	ARPhyS	TSS-17	VAS
KMC	1	0.49	0.41	0.67	0.28
AHC	0.49	1	0.33	0.54	0.24
ARPhyS	0.41	0.33	1	0.45	0.25
TSS-17	0.67	0.54	0.45	1	0.32
VAS	0.28	0.24	0.25	0.32	1

classification. Adapted from: [14].

Legend – KMC: k-means clustering; AHC: agglomerative hierarchical clustering; ARPhyS: Allergic Rhinitis Physician Score; TSS-17: Total Symptom Score with 17 items; VAS: Visual Analogue Scale (0-100). ARPhyS, TSS-17 and VAS are divided into terciles; KMC and AHC are grouped into 3 clusters.

In order to choose cut-offs able to properly stratify patients, based on the ARPhyS scale, we identified those values that would be best associated to equivalent previously highlighted terciles: we propose therefore cut-offs at a score of 8-9 for mild to moderate symptoms and of 11-12 for moderate to severe symptoms. To summarize, patients were classified as presenting with “mild” symptoms if they scored 0 to 8 with the ARPhyS scale; they had “moderate” symptoms if they scored 9 to 11; they should be considered as “severe” whenever they scored 12 to 20 (Table 13).

## Missing data analysis

When analyzing data from the 8,288 patients excluded from the cohort, because of missing data, no significant statistical difference was highlighted when considering sex, age, history of conjunctivitis, asthma, atopic dermatitis, food allergy, hives, and positive SPT.

Significant difference was on the contrary pointed out when evaluating other items: proportion of rural population included in the analysis was significantly higher than the one who was not included due to missing data (43.4% vs. 39.9%;  $p < 0.001$ ); same consideration as for positive specific IgE (11.9% vs. 11.0%;  $p = 0.036$ ); at last, the included population underwent previous or concomitant allergen immunotherapy almost significantly more than the excluded group (7.9% vs. 7.3%;  $p = 0.048$ ).

**Table 13:** The ARPhyS score, with cut-offs level to identify patient's severity.  
Adapted from: [14].

<b>ARPhyS</b>						
Please, rate the severity of each of the following symptoms as presented in this moment by your patient:						
						Score
A Nasal obstruction	0 Absent	1 Mild	2 Moderate	3 Severe	4 Very severe	
B Rhinorrhea	0 Absent	1 Mild	2 Moderate	3 Severe	4 Very severe	
C Sneezes	0 Absent	1 Mild	2 Moderate	3 Severe	4 Very severe	
D Nasal pruritus	0 Absent	1 Mild	2 Moderate	3 Severe	4 Very severe	
E Ocular pruritus	0 Absent	1 Mild	2 Moderate	3 Severe	4 Very severe	
Total Score						
If total score is 8 or less, then your patient presents <b>mild</b> symptoms						
If total score is between 9 and 11, then your patient presents <b>moderate</b> symptoms						
If total score is 12 or more, then your patient presents <b>severe</b> symptoms						



## Discussion

### Control may be assessed through a VAS even on smartphones

Current AR guidelines emphasize that AR control is a key therapeutic goal and recommend evaluating symptoms control to guide step therapy [6]. So far, no tool is considered as a gold standard for AR. Nevertheless, current trend in assessing different aspects of diseases is the use of a simple tool for both patients to complete and for physicians to evaluate, namely a VAS. Another advantage of the VAS is that it may be used in most age groups and in a wide variety of languages, and that it may assess the severity of the disease as well [54,82]. If VAS has largely been validated to assess AR severity according to ARIA guidelines [54,104], its validation for control has less been carried out. Through a survey at the 2013 EAACI congress, physicians were asked to evaluate and approved the usefulness of a VAS to monitor AR control as well [109].

Since the use of ICT, such as apps running on consumer smartphones, is increasingly popular and has the potential to profoundly affect healthcare, MASK-rhinitis developed an app, as one of the implementation tools of the B3 Action Plan of the European Innovation Partnership on Active and Healthy Ageing (EIP on AHA) [85,86,89]. The app is currently included as a tool of the ARIA guidelines to monitor users' symptoms [6]. The MASK-Air® app, known as ARIA Allergy Diary app at the time of the study, uses a quick VAS system for the assessment of AR control, though 4 simple questions. A pilot study has been completed in AR to assess the relevance of the AD app and showed the importance of the tool to stratify users, and assess their symptoms severity and control and highlighted the external validity of the app [90].

The tool proved its acceptability following defined criteria, with 49% of users logging into the app more than once and more than 30% using it for at least 4 times a week. When an app is free to download, its usefulness is important for the users, and a great number of people may download it without even knowing the purpose of it. The fact that almost a half of all people who downloaded the app used it more than once makes its acceptability verified.

Internal consistency was validated both by alpha coefficient and test-retest. Cronbach's alpha showed an excellent internal consistency ( $\geq 0.84$ ) for each VAS and for all

the average VAS, when evaluating users answering to the 4 questions over two consecutive days. Test-retest showed an acceptable ICC for each VAS and for all the average VAS, in the same group of users, as well (ICC >0.7,  $p < 0.0001$ ).

Reliability was confirmed by the assessment of ICCs in users answering to the 4 VAS twice in the same day. Intraclass coefficients were excellent when considering the whole population (>0.9,  $p < 0.001$ ), and users with no to mild symptoms, i.e. with a VAS <50 (>0.8,  $p < 0.001$ ). On the other hand, users with elevated values of VAS showed lower values of ICC (>0.6,  $p < 0.001$ ) and reliability is to considered as adequate. Nevertheless, in this group of moderate to severe patients (VAS >50), reliability was excellent in those users with moderate to severe symptoms of asthma (0.841, 95% CI, 0.724-0.909,  $p < 0.001$ ).

The mean difference and the standard deviation of the values entered by users when logging into the app twice in less than 3 hours proved a good sensitivity of the tool.

At last, VAS showed a good association between overall symptoms and rhinitis symptoms, rhino-conjunctivitis symptoms and all organ symptoms through Spearman test. Eyes symptoms and asthma symptoms showed a weaker association with the “overall symptoms” VAS, if compared with the other variables. Also, until June 1<sup>st</sup> 2016, users were not obliged to answer to the asthma question, if they claimed not to suffer from this condition, while after that date, each user was required to answer the question (VAS 4). The Spearman test showed an even weaker association between asthma symptoms and overall symptoms after that date. All these considerations are valid for both analysis run on all the subjects who downloaded the app (n=2497) and those who used it at least twice (n=1272). When evaluating results with a chi-squared test, we categorized users according to their VAS: no symptoms if their VAS was <20, mild symptoms when  $\leq 20$  VAS <50 and moderate to severe when VAS  $\geq 50$ . We run the same analysis both on all the subjects who ever used the app (n=2497) and on those who used it more than once (n=1272). In both case, the chi-squared test resulted significant ( $p < 0.0001$ ). We noticed that when users reported to have no overall symptoms, their answer was strongly correlated with the answers to the other three VAS. On the contrary, when overall symptoms are mild, they correlate well with nasal symptoms, but users mainly respond not to be bothered by eyes and asthma symptoms. Moreover, when overall symptoms are moderate to severe, they correlate very well with nasal symptoms and well with eyes symptoms, but most of users claim to have no asthma symptoms. These results may be explained by the fact that not all patients suffer from asthma, and it could therefore be a bias

in our analysis. Nevertheless, we could also hypothesize that what bothers allergic patients are mostly their nasal symptoms and secondly their eyes symptoms when their allergic condition becomes severe, and that asthma symptoms are either less important or patients are used to those chronic symptoms and thus, they seem less bothersome during an allergy peak.

The first study of this PhD project validated therefore the use of a VAS for AR on smartphone screens. Indeed, we highlighted the acceptability, the internal consistency, the reliability and sensitivity of the tool. External validity was demonstrated in a previous paper [90]. Even though the acceptability criterion was satisfied, the drop-off rate was quite big. The reasons for this could probably be linked to the fact that the app is free to download and anyone might use it, without being consistent.

### **Severity may be assessed by physicians through the ARPhys questionnaire**

When a physician examines patients reporting AR symptoms, he/she should be able to easily detect those presenting severe forms. The importance of detecting severe AR is associated to a possible search mainly for comorbidities and impaired QoL, in order to minimize the cost of the disease and provide proper efficient treatments.

In recent years, cluster analysis has become more and more common to identify subgroups of patients: it consists of applying unsupervised statistical methods to a population with a wide distribution of related symptoms, and then identifying possible homogeneous phenotypes, with minimum overlap between each other [93]. In a work by Burte et al., the authors highlighted three different clusters of rhinitis (allergic and non-allergic), from a population of 983 adults, but they do not differentiate them based on severity [95]. In a work by Bousquet PJ et al., on the contrary, the authors identified clusters of severe AR, in a population of 990 patients, and then compared them with the ARIA classification [93]. They found that, in *real-life*, physicians prescribe a therapy, with no regard to nasal symptoms severity [93], and therefore current guidelines and proposed cluster do not help general practitioners in stratifying the severity of patients presenting with AR. In this second study of the present PhD study, we identified three clusters, through two different methods, in a population of 28,109 patients. Clusters showed no overlap between each other. After evaluation through Fisher linear and quadratic discriminant analysis, and non-parametric

kernel density estimation methods, we found that cluster analysis does not provide the best results in terms of discrimination, error rate and cross-validation, if compared to other assessed methods (Table 10).

Visual Analogue Scales, on the other hand, that we previously even validated as a control assessment tool on smartphones screens, through the first PhD study [13], are usually used as a severity assessment tool as well, in patients suffering from AR [90,91]. Del Cuvillo et al. showed in a population of 3,572 patients that a VAS lower than 7 cm is a reliable score to identify non-severe patients (Negative Predictive Value, NPV: 98.6%; specificity: 88.6%) [91]. On the other hand, the previously mentioned paper by Bousquet PJ et al., on a cohort of 3,052 patients, proposed a 5-cm cut-off for mild forms, while moderate to severe patients were to be considered for a VAS of over 6 cm (with a NPV of 56.5% and a PPV of 94.3%) [54]. The two papers found two different cut-offs, but in the study by Bousquet PJ et al., the authors only differentiated “mild” patients from “moderate/severe”, while the study by del Cuvillo categorized patients into three severity groups (mild, moderate, and severe). On the other hand, in a paper by Rouve et al., it seemed that categorizing AR severity in patients through VAS brought to an exaggerated inclusion in the severe group [83]. In the PhD 2<sup>nd</sup> paper, we found that VAS proved the worst results in terms of discrimination and cross-validation (Table 10), and the least agreement in terms of results if compared with the other 4 tested methods (Table 12). Considering our findings from a very large cohort of patients, we may speculate that VAS is a useful tool for diagnosis and assessment of disease control, for both patients and physicians, but not the best tool for classifying patients according to severity by physicians. Another possible explanation of the discrepancy between our results and those from del Cuvillo and Bousquet PJ is that we only included patients suffering from seasonal AR, while the previous authors did not use such selection criterion.

In contrast with the ARIA guidelines, we found that the duration of the disease does not have a significant impact on the severity of symptoms, and such result confirms what had been previously stated by Bousquet PJ et al. [93]. Rather than differentiating the disease between intermittent and persistent, attention should be focused on nasal and ocular symptoms, based on our findings. In a study by Valero et al., the authors evaluated a TSS-4 to stratify AR patients, based on the clinical items proposed by the ARIA guidelines [57], and in a following study the authors validated the TSS-4 as a tool to assess severe forms [92]. Through these papers, Valero et al. underlined that total symptoms scores seem to be practical

methods for physicians to target severe patients, following current ARIA guidelines. Based on such considerations, in our study, even though the ARPhyS scale showed a Cronbach's alpha-coefficient inferior to the TSS-17, we chose the first questionnaire because, besides being superior as a discriminating method, it is also quicker and easier to use in everyday clinical practice. Also, the ARPhyS scale (Table 13) allowed us to identify tertiles that maximally correlated in the first canonical dimension and therefore to propose simple cut-offs to categorize AR into "mild", "moderate", and "severe". [54]. The PRPhyS score is indeed able to specifically recognize severe patients, who may need a specialized approach in order to control their symptoms and comorbidities.

A possible limit of the study is that patients visiting physicians were only evaluated during spring and summer seasons, which might limit the generalizability of our results to patients visiting during autumn and winter seasons. However, the large sample size provides robustness in the results and, through the study, we proposed a practical tool for physicians, which is fast and obtained from a *real-life* database.

## **Strengths, limitations, and future perspectives**

Our results show some important strengths. First, analyzed data are driven from *real-life* studies and included subjects are drawn from the general population. Most clinical trials, in fact, imply inclusion and exclusion criteria that are difficult to apply to the general population in everyday clinical settings, while our analysis reflect what really happens in patients' and physicians' daily practice. Also, the MASK study included patients covering a large geographical area, over 20 countries worldwide, and the Pollin'Air study included patients distributed all over France. Such aspect might be helpful in reducing possible bias due to local habits both for patients and doctors. Another important aspect is that the two validated tools are based on standardized instruments that are easily applicable in daily settings. As for the MASK study, the fact that patients decided on their own to download the application and answer to the VAS makes our results stronger, since they were not conditioned by the fact that they were in a clinical study: in fact, it seems like patients included in research studies tend to better follow physicians' recommendations and not to act as they would in real-life. As for the Pollin'Air study, the diagnosis of AR was made by

specialized physicians, thus reducing the risk of possible misclassification.

We should also highlight some limitations in our results. In both study, some data were missing. Nevertheless, for the Pollin'Air study, an *intention-to-treat* analysis including missing data showed no differences from the results obtained through the *post-hoc* analysis. Another important limitation of the studies is that possible confounders were not taken into account: for the MASK study, AR was declared by users, without a sure medical diagnosis, and, at that time, the amount of drugs taken by users, the quantity of pollen they were exposed to, and possible not-allergic comorbidities were not included in the data analysis; for the Pollin'Air study, patients were all tested during the same season, non-allergic comorbidities (such as flue) were not assessed, and only patients with seasonal AR were included. Also, for the MASK study, it is more likely that older patients, who are probably less prone to use smartphones applications, were not significantly represented in the cohort, and that a real follow-up of patients was missing, to assess the evolution of their disease control.

Even though the MASK-Air® application has been largely developed since the study was performed, a *real-life* evaluation from the doctors and pharmacists point of view, together with a follow-up of users, is still missing. The real problem, in a world where applications for smartphones are developed at a very high rate, is to be able to keep users connected to the app, and to stimulate them to access it daily, without having an immediate benefit from it. ARIA guidelines are pushing specialized doctors to advise their patients to use the app, without considering that allergists are not the only doctors seeing AR patients and that probably only a few GPs know the evolution of these guidelines. Implementation and dissemination of the new ARIA recommendations are therefore a mandatory first step to see if this electronic clinical decision support system will still be alive and effective in the next years. As for the ARPhyS scale, it seems very similar to other 5-symptoms scales, employed, for example, in other allergy trials, such as those for testing the efficacy of oral antihistamines. The score system proposed in our study is easy to use and to implement in clinical practice, but it would need to be validated from a patients' and doctors' perspective prior to be proposed as a *real-life* instrument to assess patients' severity.

## Conclusion

AR may seem like a non important disease: physicians tend to minimize its burden, patients get used to their symptoms and they perceive it as a minor health problem, and health care policies look at it as a minor issue [17]. If we look closer to AR and its burden, though, we realize that it has a major impact in patients QoL and total direct and indirect costs may be up to € 9 billion per year in a country like France [23,34,35], simply because of its high prevalence and the subset of patients with a severe form of the disease. ARIA guidelines are well known by specialists, but, in clinical practice, they are not followed by general practitioners nor by patients, who try too often to self-medicate and to avoid a specialized consultation [21,32].

Several treatments are available to control AR symptoms: nasal corticoids and antihistamines (or a nasal spray associating corticoids and antihistamines) are the best option in most patients as relief therapy [38,46]. The only causative treatment remains AIT, generally prescribed by specialists [50]. AIT allows to control symptoms, lower the possibility of developing allergic asthma, and/or lower the consumption of AR and asthma drugs. Nevertheless, in consideration of the fact that many patients avoid consulting a specialist, over-the-counter drugs are the most used by allergic patients, who keep searching for their best option to control AR symptoms [15].

If on one hand the disease burden and its cost are important, on the other hand ARIA guidelines could help better manage the symptoms of AR and its comorbidities and drastically reduce the indirect cost of the disease [8,34]. For such reasons, current guidelines have tried to focus on two crucial aspects of AR: severity and control [7,8]. The first one should be assessed in patients prior to treatment, mainly to highlight those who present severe symptoms and that therefore risk to significantly lower their QoL and cost more because of drug consumption, possible work absenteeism, and, most important, impaired presenteeism. Control should be used to follow-up patients suffering from AR: modulating the prescribed treatment based on symptoms control should lead to a better management of the disease and of its overall burden. Several tools have been developed to assess severity and control: most

of them have been validated in clinical studies but, at least in France, only few, such as the ARCT, are used in routine clinical practice by general practitioners and even by allergists.

In general, therefore, it seems that, even if there are specific AR guidelines, patients follow different paths. Also, physicians are not aware or not aware enough of the available tools and therefore they are limited in their daily work, trying to find the best and simplest way to assist their patients. For such reason, an analysis of *real-life* data seems important to both empower patients and to understand what could really help both them and their physicians to properly manage this disease. Through the present PhD thesis, we analyzed two *real-life* databases and highlighted a possible easy tool to assess AR severity and control [13,14].

The MASK study started in 2015, as a possible way to implement ARIA guidelines through a free app for smartphones [3]. Since then, more than 20 papers have been published on the app, that was previously known as “The Allergy Diary” and is now called “MASK-Air®”. The MASK-Air app has been used to assess work productivity and adherence to treatment in AR patients, and to implement care pathway and create a clinical decision support system to integrate in the ARIA guidelines [6,8,46,89,90,110,111]. One of the first step to validate the app was to validate the use of a VAS on mobile phone screens. VAS is classically a paper-and-pencil tool, and is composed by a 10-cm long line, on which patients may assess a symptom or the importance of a feeling. Mobile phones have different shapes and different sizes. It was therefore important to validate the use of VAS even in such setting.

Therefore, through the first study, we validated the VAS as a tool to assess AR control on smartphones screen, as in the MASK-Air® (previously AD) app. The tool and the app were well accepted by both patients and physicians. We demonstrated that the VAS on the MASK-Air® app is capable to stratify users and evaluate control, indicating if their symptoms are well controlled, partially controlled or uncontrolled [13]. At the time of the study, the implementation of the app, through a CDSS and a health care providers’ version, was ongoing and not released yet. Today, the app is validated as an important part of the newest version of ARIA guidelines, with three specific versions: one for patients, to help them assess disease control and better communicate with their doctor or the pharmacist; one for pharmacists, to guide them in advising the best OTC medications and to refer uncontrolled users to physician; and one for doctors, to prescribe appropriate treatment based on the app results [112,113]. Although ICT is certainly an avenue to explore, several issues arise,



including the persistence of the use, with a lot of patients opting out rather quickly and the storing and ownership of the data by a private company at a time of open science... time will tell [114].

The Pollin'Air study is a large study that was carried out on more than 36,000 patients with a physician's diagnosis of a non-complicated and non-treated seasonal AR, between May and August 2004 in France. For each patient, a physician assessed AR severity by calculating a 17-items score corresponding to the intensity of the symptoms as felt by the patient but also using a VAS. In previous studies on this cohort, it was highlighted that severity level may vary according to different used tools [83,97].

Through the second paper for this PhD thesis, we evaluated the different tools used at the time by the physicians. We created, from the 17-items score, a new 5-items one, the ARPhyS scale. We also analyzed all data in cluster, and then compared severity groups through 5 methods: two different cluster analysis, the 17-items score, the ARPhyS scale and the VAS. When comparing our new tool to the other tested methods, we found that the ARPhyS scale is the best in terms of discrimination and cross-validation [14]. Also, this tool seemed very easy and practical for physicians and we were able to find some cut-off values able to differentiate mild patients from moderate, and, most important, from severe ones. The ARPhyS could therefore be implemented in daily practice to identify severe patients that need a specialized intervention or anyway a more important therapeutic treatment.

The *real-life* databases analyzed in this project showed important strengths: they were able to validate two new tools, one to assess AR severity in daily clinical settings through an easy score, and one to assess control on smartphone screens through VAS. Both tools are simple and very practical, and could be implemented in physicians practice when dealing with patients suffering from AR. Nevertheless, the MASK-Air® app needs to be truly disseminated and used by patients, while the ARPhyS is still not used by physicians. Compliance to medications and doctor instructions is another issue that needs to be taken into account. The real goal for the future is therefore to guide patients and push them to use the smartphones application, and to communicate to physicians that the ARPhyS could be an easy system to assess severity in patients reporting AR symptoms, to properly prescribe an adapted treatment.

# Résumé extensif

## Introduction

La prévalence de la rhinite allergique (RA) est en augmentation dans le monde entier et elle a triplé en France au cours des 25 dernières années [1,2]. La clé pour la gestion de cette pathologie est l'évaluation de sa sévérité et le contrôle des symptômes chez les patients atteints [3-5]. Les recommandations ARIA (*Allergic Rhinitis and its Impact on Asthma*) soulignent l'importance de bien cibler les patients atteints d'une forme légère par rapport à ceux avec des symptômes modérés à sévères [6-8]. Malgré cela, il n'existe pas de classification univoque pour cibler les formes sévères de la maladie. Ces patients, par contre, sont ceux qui présentent un risque accru de comorbidités et d'augmentation des coûts directs et indirects liés à la RA [9,10]. Selon les recommandations ARIA, une fois que le diagnostic est posé et le patient traité, il est important d'évaluer dans le suivi le contrôle des symptômes, pour vérifier si le traitement prescrit est efficace et pour améliorer la qualité de vie (QoL) des patients rhinitiques [7]. Malheureusement, à ce jour, il n'y a pas d'outil standardisé pour évaluer la sévérité de la rhinite et le contrôle des symptômes. L'objectif principal de cette thèse de science était de pallier ce manque en utilisant une approche de type données massives.

Au cours de cette thèse de science, j'ai évalué deux larges bases de données : la base MASK et la base Pollin'Air. L'analyse de ces deux bases de patients adultes avec une RA a eu comme objectif d'essayer de trouver des méthodes pour évaluer la sévérité et le contrôle des symptômes dans des études de vraie vie. La base MASK a été exploitée pour valider l'utilisation de l'application *Allergy Diary* (maintenant connue sous le nom de MASK-Air®), pour l'évaluation du contrôle de la RA sur des smartphones [13]. La base Pollin'Air a été analysée pour déterminer la meilleure méthode pour différencier les patients selon le degré de sévérité de leurs symptômes de RA [14].

## Rhinite allergique

En Europe, il y a environ 150 millions d'allergiques [15]. Un enfant sur trois est allergique et avant 2050 la moitié de la population européenne souffrira d'une allergie [15].

Dans la population européenne, la prévalence de la maladie, confirmée par un examen clinique, semble être aujourd'hui d'environ 23% [18,20]. Malgré ces données, les maladies allergiques sont considérées comme un souci de santé peu important : il n'y a pas beaucoup d'espace pour l'allergologie au cours des études de médecine et les médias sociaux, les politiciens et les financements publics gardent aux allergies de façon une place moins sérieuse, par rapport à d'autres maladies potentiellement mortelles [17]. Même les patients considèrent les maladies allergiques comme banales : en fait, plus de 50 % des personnes souffrant de RA ne consultent pas un médecin au cours de l'année et près d'un tiers préfèrent les médicaments en vente libre, considérant inutile de consulter un médecin pour leurs maladies allergiques respiratoires [17,18].

La RA est une maladie IgE-médiée, qui affecte la muqueuse nasale et qui se caractérise par un ou plusieurs symptômes, dont la congestion nasale, la rhinorrhée, les éternuements et le prurit pendant plusieurs jours consécutifs [19,20]. Les recommandations ARIA suggèrent de classer la RA comme intermittente ou persistante [8] selon la chronologie. Les symptômes intermittents se manifestent moins de 4 jours par semaine ou pendant moins de 4 semaines consécutives, tandis que les symptômes persistants se manifestent plus de 4 jours par semaine et pendant plus de 4 semaines consécutives [8]. Selon les recommandations ARIA, la sévérité peut être classée comme légère et modérée/sévère, chez les patients non traités [8]. Les patients présentent une RA légère s'ils ne présentent aucune des caractéristiques suivantes : troubles du sommeil, troubles des activités quotidiennes, atteints au cours de la journée scolaire ou au travail [8]. Les patients présentant une ou plusieurs des caractéristiques ci-dessus sont considérés comme ayant une RA modérée/sévère (Figure 1) [8]. Les symptômes les plus courants sont les éternuements, le prurit nasal, la rhinorrhée et/ou la congestion nasale [18,23]. Une étude a estimé que 93% des patients atteints de RA ayant consulté des médecins généralistes présentaient des symptômes allant de modéré à sévère [18]. Même si les patients peuvent présenter plusieurs symptômes différents en même temps, ils ont tendance à consulter leur médecin, surtout à cause de la congestion nasale et de l'écoulement nasal (Figure 2) [24].

En effet, la congestion nasale est l'un des symptômes les plus fréquents et généralement les plus gênants chez les adultes et les enfants [23]. La rhinite et l'écoulement nasal sont généralement plus gênants que les éternuements ou le prurit [23]. Il existe des facteurs de risque pour le développement de la RA [23]. Il s'agit notamment des antécédents

familiaux d'atopie, des IgE sériques totaux supérieurs à 100 UI/mL avant l'âge de 6 ans, du statut socioéconomique élevé, de la présence d'un prick test cutané (*skin prick tests*, SPT) positif à un allergène respiratoire [23]. L'influence de l'exposition de la petite enfance aux infections (hypothèse hygiénique), aux animaux et à la fumée du tabac sur le développement de l'atopie et de la RA est encore incertaine [23].

L'Académie européenne d'allergie et d'immunologie clinique (EAACI) et le Parlement européen [31] reconnaissent maintenant le fardeau de la RA. Elle est maintenant reconnue dans les lignes directrices de l'ARIA, qui classent sa sévérité non seulement en fonction des symptômes, mais aussi de son effet sur la qualité de vie (QoL) [18]. Malheureusement, dans la vie réelle, le fardeau de la RA est souvent sous-estimé puisque la maladie n'est pas mortelle [20]. Néanmoins, aucun aspect de la vie des patients, du sommeil aux fonctions cognitives, à l'humeur et aux comorbidités liées à la maladie, comme l'asthme et la conjonctivite, n'échappe à la RA, y compris un risque accru d'accidents de la route [15,30]. En fin de compte, la RA a une incidence profonde sur la qualité de vie des patients, leur rendement au travail et à l'école [30], et peut entraîner dépression et anxiété [20]. Les patients atteints de RA modérée à grave présentent une détérioration importante de leur QoL (Figure 3). L'impact de la RA sur l'état de santé perçu du patient est donc considérable [23]. Le fardeau de la maladie devient encore plus important lorsque la RA n'est pas contrôlée [32]. L'absence de contrôle des symptômes semble être la motivation de base pour les patients de demander une aide médicale et de suivre un traitement [23]. En fait, les patients sont en général réticents à consulter un professionnel jusqu'à ce que leurs symptômes deviennent « intolérables » [15]. De l'autre côté, malheureusement, de nombreux médecins sous-estiment la sévérité de la RA et la sous-traitent [15]. Il a été évalué que seulement 10% des patients atteints de RA sont traités de manière optimale [17]. Dans toutes les études, le nombre de patients non traités ou mal traités, qui présentent donc des symptômes partiels ou complets, est d'environ 90% [17]. Les patients luttent donc pour soulager leur misère, consomment fréquemment des médicaments en vente libre et des remèdes homéopathiques, et prennent plusieurs médicaments différents comme traitement symptomatique [15].

Les patients atteints de RA légère ont moins d'impact sur l'économie de la santé, avec des coûts d'environ un quart de ceux atteints de maladie modérée à sévère [16]. Les coûts d'une maladie sont généralement décrits comme des coûts directs et indirects [34]. Les coûts directs sont liés aux consultations médicales, à la prise de médicaments et aux

hospitalisations, alors que les coûts indirects sont principalement liés à l'absence au travail (absentéisme) et à une capacité de travail réduite (présentéisme) [34]. Le coût global de la RA est plus important que le coût des autres maladies respiratoires chroniques, comme l'asthme, la bronchopathie chronique obstructive, et la rhino-sinusite (Figure 4). En Europe, le coût social total de la RA persistante et de ses comorbidités en 2002 a été estimé à 355,06€ par patient par mois [23]. Dans une étude française, les auteurs ont évalué, après une analyse des dossiers électroniques nationaux de santé, l'utilisation des ressources médicales et les coûts de la RA perannuelle, associée ou pas à l'asthme allergique [35]. En 2013, le coût annuel médian remboursé par le système de sécurité sociale français pour un patient souffrant d'une RA perannuelle était de 159€, allant de 111€ à 188€ selon la sévérité (Figure 5) [35], en sachant que les médicaments de la RA sont remboursés à 15% (antihistaminiques) et 30% (corticoïdes nasaux) et que le nombre de sujets concernés est colossal. De plus, un gradient des coûts médians par patient a été mis en évidence entre les trois sous-groupes de sévérité par rapport aux traitements médicamenteux (de 15,51€ à 4,57€) et non médicamenteux (de 85,52€ à 122,72€) [35]. Ils ont également constaté que chez les patients souffrant de RA perannuelle et d'asthme allergique, le coût annuel médian variait entre 266€ et 375€, et que le traitement médicamenteux représentait 42-55% des coûts, selon le niveau de contrôle de l'asthme (Figure 6) [35]. Le coût pour l'utilisation des ressources médicales pour les traitements non médicamenteux (environ 130€ par an par patient) et pour les hospitalisations était stable entre les trois sous-groupes [35]. Une étude suédoise a estimé que le coût annuel global de la RA en Allemagne, en France et en Grande-Bretagne se situerait entre 9,4 et 9,9 milliards d'euros chacun [34]. En général, le coût des médicaments pour la RA ne représente pas le coût principal lié à la maladie. En effet, le coût principal semble être lié au présentéisme associé (travailler pendant qu'on se sent malade) et à l'absentéisme (Figure 7), qui sont évitables avec un traitement approprié [37]. Une meilleure conformité aux recommandations sur la prise en charge de la RA pourrait donc alléger la charge économique pesant sur la société [34]. Les coûts ultérieurs liés aux effets secondaires des corticoïdes oraux, trop souvent prescrits, n'est pas évalué ici.

La prise en charge de la RA peut être une tâche difficile pour les spécialistes, compte tenu du fait que le patient ne consulte pas souvent un médecin pour ses symptômes nasaux [32]. En effet, les patients peuvent ne pas reconnaître l'impact du trouble sur leur qualité de vie (étant malades depuis l'enfance, ils ne savent ce qu'est « être bien ») et, ont tendance à percevoir leur maladie comme une maladie « mineure », qu'ils peuvent facilement gérer eux-

mêmes [32,38]. Lorsqu'ils consultent un médecin, ils sous-déclarent habituellement leurs symptômes de RA, ce qui rend le diagnostic de RA souvent difficile pour les généralistes [39].

L'évaluation initiale d'un patient présentant des symptômes évocateurs de RA commence par un recueil complet de ses antécédents personnels et familiaux ; les antécédents personnels devraient inclure une attention particulière aux expositions environnementales, en mettant l'accent sur les facteurs précipitants et l'évaluation de la qualité de vie [19]. L'examen physique devrait inclure une rhinoscopie, ou une endoscopie nasale, dans des centres spécialisés, pour évaluer l'inflammation possible de la muqueuse nasale (Figure 8).

Le diagnostic de RA est strictement clinique. Néanmoins, d'autres tests diagnostiques peuvent être nécessaires pour confirmer l'allergène responsable des symptômes allergiques [38]. Pour évaluer les allergènes responsables, des SPT devraient être effectués pour évaluer une possible sensibilisation ou même une allergie, dans les cas où l'exposition à un allergène s'associe à l'apparition de symptômes cliniques. Les SPT pour les allergènes pertinents pour l'environnement du patient sont considérés comme la principale méthode pour identifier les déclencheurs allergiques spécifiques de la rhinite. Bien qu'il soit préférable d'effectuer des SPT, des dosages *in vitro* des IgE spécifiques peuvent être réalisés pour des patients chez qui les tests cutanés sont contre-indiqués (p. ex., eczéma important, dermographisme, utilisation récente d'antihistaminiques par voie orale...). Cependant, les SPT sont toujours considérés comme le *gold standard*, sont plus sensibles, moins coûteux et donnent des résultats immédiats, et la sensibilité des tests *in vitro* IgE spécifiques par rapport aux SPT est d'environ 70-75% [19,38]. La maladie est fréquemment associée à deux comorbidités : la conjonctivite et l'asthme. Les symptômes allergiques oculaires sont fortement associés à la RA, même s'ils sont souvent sous-diagnostiqués et donc sous-traités [42]. La conjonctivite est de plus en plus reconnue comme la comorbidité la plus fréquente de la RA [8], participant fortement à la déficience de la QoL de la RA. Pour ce qui est de l'asthme, plus de 80 % des asthmatiques ont une RA, alors que 10 à 40 % des personnes atteintes d'une RA ont de l'asthme [19]. La RA est un facteur de risque pour l'asthme, et le diagnostic de RA peut précéder l'asthme [19]. Des études sur des populations adultes et pédiatriques fournissent des preuves d'un risque accru de développement d'asthme chez des personnes souffrant auparavant de RA [19]. Les patients qui déclarent une rhinite sévère présentent un contrôle de l'asthme plus faible que ceux qui ont une maladie bénigne, avec un impact négatif équivalent à celui du tabagisme [31]. Pour

cette raison, un traitement approprié de la RA est essentiel chez les patients asthmatiques, étant en mesure de réduire les risques de soins de santé liés pour l'asthme (en particulier, les accès aux urgences et les hospitalisations), jusqu'à 80 % [19].

Une fois le diagnostic de RA posé, la prise en charge de la RA est principalement fondée sur l'éviction des allergènes responsables des symptômes, les médicaments symptomatiques, l'éducation des patients, et l'immunothérapie allergénique (AIT), qui est le seul traitement curatif pour la prise en charge des maladies allergiques [21,40,41,43,48]. Un traitement approprié est lié à une amélioration de la qualité de vie des patients [18]. Toutefois, comme l'évitement des allergènes n'est souvent pas efficace et que l'AIT se limite à un petit groupe de patients, le traitement de la RA est basé sur une thérapie symptomatique dans la plupart des cas [43]. Ce traitement peut être auto-prescrit par les patients, conseillé par un médecin généraliste ou par un spécialiste des allergies. Bien que les recommandations par rapport aux traitements soient bien établies, les patients traités peuvent déclarer de faibles niveaux de satisfaction, avec une recherche fréquente de médicaments supplémentaires (principalement des médicaments en vente libre) pour mieux réduire leurs symptômes nasaux/oculaires [21]. De plus, étant donné que la gestion de la RA n'est pas simple, elle nécessite également des conseils médicaux appropriés pour l'autogestion [32]. Le respect du traitement prescrit est essentiel pour garantir l'obtention de l'effet thérapeutique souhaité par le clinicien [44]. Toutefois, la mauvaise observance reste un problème crucial dans la RA, ce qui entraîne une augmentation des symptômes, une baisse de la QoL des patients et une hausse des coûts directs et indirects tous [44]. Le manque de traitement, le sous-traitement et le non-respect du traitement augmentent tous l'impact et les coûts directs et indirects de la RA [23,44]. Par conséquent, chaque patient devrait recevoir un traitement approprié, non seulement pour contrôler complètement les symptômes de la RA, mais aussi pour réduire considérablement le coût global de la maladie [23]. L'objectif du traitement de la RA est donc le contrôle des symptômes [45]. Malheureusement, des études menées auprès de patients qui consultaient des médecins généralistes pour une RA ont révélé que 18 à 48 % présentaient des symptômes qui n'étaient pas contrôlés par la pharmacothérapie seule [18]. De nombreux médicaments sont recommandés dans les lignes directrices actuelles selon la sévérité et de la durée de la RA (Figure 11), et ils comprennent :

- Les corticostéroïdes intranasaux : ils sont les options thérapeutiques de première intention pour les patients présentant des symptômes légers persistants ou

modérés/sévères et peuvent être utilisés seuls ou en association avec des antihistaminiques oraux ou locaux [38].

- Antihistaminiques oraux de deuxième génération : ils sont le traitement de première ligne pour contrôler la légère RA intermittente [49].
- Antihistaminiques intranasaux : ils agissent plus rapidement que les antihistaminiques oraux et présentent des effets similaires en termes d'efficacité, tout en étant plus efficaces pour réduire la congestion nasale [40]. Ils doivent par contre être administrés en 2 prises quotidiennes. Ils peuvent aussi être associés à des corticostéroïdes intranasaux, association qui semble plus efficace que les composants individuels pour contrôler les symptômes de la RA et améliorer la QoL des patients [38,40].
- Antagonistes des récepteurs des leucotriènes : ils ne sont pas aussi efficaces que les corticostéroïdes intranasaux pour contrôler les symptômes de la RA [38]. Ils ne sont indiqués en France qu'en présence d'un asthme léger.
- Immunothérapie allergénique (AIT) : elle est le seul traitement curatif de l'allergie respiratoire, capable de guérir la cause réelle des symptômes [50]. L'AIT devrait être réservée aux patients chez lesquels les mesures d'éviction et la pharmacothérapie sont insuffisantes pour contrôler les symptômes ou ne sont pas bien tolérées [38].

Autres traitements incluent les anticorps monoclonaux (omalizumab et dupilumab, qui n'ont pas d'AMM pour la RA) ; des nouvelles thérapies en cours d'étude, telles que de nouvelles formulations de spray nasaux, de nouveaux antihistaminiques H3/H4, des voies alternatives de AIT et l'ajout d'adjuvants pour améliorer l'allergie [51] ; le cromoglycate de sodium intranasal (traitement de première intention pendant la grossesse puisqu'aucun effet tératogène n'a été observé chez les humains ou les animaux [38]) ; les corticostéroïdes oraux, qui exposent par contre le patient à des effets secondaires importants ; les décongestionnants oraux et intranasaux, uniquement s'ils sont utilisés pour des traitements de courte durée [38] ; la chirurgie, qui par contre a des indications très limitées dans le traitement de la RA ciblant uniquement l'obstruction nasale ; les médicaments complémentaires et alternatifs, dont surtout l'acupuncture [38].

Les recommandations pour la prise en charge des médicaments dans la RA sont actuellement fondées sur la classification de la sévérité de la maladie et de la persistance des symptômes [53]. Ces recommandations peuvent être facilement appliquées aux patients non traités, mais elles sont moins utiles pour évaluer les changements au fil du temps et ne



peuvent pas mesurer la réponse au traitement [53]. Par conséquent, si la sévérité doit être évaluée pour cibler adéquatement un traitement approprié, le suivi des patients souffrant de RA devrait être fondé sur le contrôle des symptômes. Bien que la "sévérité de la maladie", le "contrôle de la maladie" et la "réponse au traitement" soient liés, il s'agit de paramètres différents, qui ne s'excluent pas mutuellement [2]. La sévérité de la maladie peut être définie comme une perte de fonction physiologique causée par le processus de la maladie [2]. Il est bien connu que plus la RA est sévère, plus les symptômes sont nombreux et plus la QoL est faible chez les patients allergiques. Pour cette raison, dans les recommandations ARIA, la sévérité de la RA est fondée à la fois sur la QoL et sur la sévérité des symptômes [54]. Plus récemment il a été proposé de mieux différencier la sévérité et de classer les symptômes comme étant légers, modérés et sévères, alors qu'avant on ne différenciait pas les formes modérées des sévères [57].

Le concept de contrôle de la RA est basé sur une analogie avec les lignes directrices de la Global Initiative for Asthma (GINA) sur l'asthme [59], et ne s'applique qu'aux patients traités [21]. L'évaluation du contrôle peut permettre d'améliorer et de simplifier la prise en charge chez les patients atteints de RA [61]. La généralisation du "contrôle" est maintenant considérée comme une tendance dans la prise en charge des patients souffrant de RA, mais il n'y a pas de définition unanime, même s'il a été suggéré qu'elle pourrait être un moyen d'améliorer les décisions cliniques [2]. Il peut être considéré comme le degré de réduction des symptômes et de réalisation des objectifs du traitement, et sa mesure devrait permettre d'évaluer les réponses au traitement et de simplifier le suivi [21,23]. On pourrait dire que le contrôle définit un état dans lequel les objectifs de traitement sont atteints, et les symptômes sont minimisés [60]. Un meilleur contrôle des RA est associé à une amélioration de la QoL et donc à une réduction des coûts indirects [23]. Une évaluation précise du contrôle de la rhinite est un élément essentiel d'une stratégie visant à simplifier et à améliorer la gestion [23].

Même s'il peut sembler facile d'établir un lien entre la sévérité et le contrôle, il y a trop de paramètres qui peuvent influencer sur ces deux aspects de la maladie qu'ils ne recourent souvent pas. En fait, parfois, une forme non sévère de RA peut ne pas être contrôlée parce que les patients ne se conforment pas au traitement prescrit, ou parce qu'ils sont trop exposés à l'allergène coupable ou pour d'autres raisons psychologiques [21]. D'autre part, des formes parfois sévères de RA peuvent être facilement contrôlées, par exemple, chez des patients ciblés traités correctement avec AIT. Néanmoins, lorsque les comorbidités sont associées à la

RA, elles rendent généralement non seulement les symptômes globaux plus graves, mais aussi plus difficiles à contrôler, ce qui a un impact important sur la QoL des patients [62]. Il est donc important à la fois de cibler clairement les patients atteints de RA sévère et d'optimiser le traitement chez les patients présentant des symptômes non contrôlés, d'améliorer leur QoL et de réduire éventuellement le coût global de la maladie. La sévérité et le contrôle peuvent être mesurés de multiples façons, avec des mesures objectives et subjectives et des résultats déclarés par les patients ou par les médecins [2]. Les paramètres rapportés par les patients prennent de plus en plus d'importance dans la recherche clinique et, de plus en plus, dans les soins aux patients, bien qu'il y ait un débat sur la question de savoir si le médecin ou le patient devrait être considéré comme le meilleur juge pour évaluer le contrôle [2].

En ce qui concerne la sévérité, selon les évaluations des médecins, 46,2 % des patients souffrent d'une RA persistante et 41,4 % d'une RA intermittente ; près des deux tiers (63 %) souffrent d'une maladie modérée ou sévère [23]. Par contre, lorsqu'on compare les évaluations de la sévérité des médecins et des patients, il semble que les patients estiment que leur maladie est modérée ou sévère dans 85 % des cas [58]. Plusieurs scores de symptômes, chacun comportant un nombre différent d'éléments, ont été élaborés et validés pour l'évaluation de la sévérité de la RA. Les symptômes rapportés par un patient peuvent être additionnés : plus le score est bas, moins la maladie est sévère. Les principales méthodes utilisées pour évaluer la sévérité incluent :

- le TNSS est la somme de 4 scores de symptômes individuels pour rhinorrhée, congestion nasale, démangeaisons nasales, et éternuements, marqué chacun de 0 (pas de gêne) à 3 (gêne majeure altérant la QoL), ce qui donne un score possible de 0 à 12 ; peu ou pas de données de validation psychométrique sont disponibles ;
- le T4SS (Total 4 Symptoms Score), une version plus courte, proposée pour les patients pédiatriques [50,58] ;
- le RTSS (Rhinitis Total Symptoms Score) [64] ;
- le VAS (Visual Analogue Scale), qui est l'instrument le plus réalisable et le plus pratique pour évaluer non seulement la sévérité, mais aussi le contrôle de la RA. Il a été proposé qu'avec un VAS de 10 cm, un seuil de 5,5 cm est utile pour distinguer les patients légers des patients modérés à sévères atteints de RA, avec une valeur prédictive négative de 93,4 % et une valeur prédictive positive de 73,6 % [54].

En ce qui concerne le contrôle, en l'absence d'un *gold standard*, de nombreux instruments ont été inventés et sont utilisés pour l'évaluer dans la RA [70]. Les mesures de contrôle doivent être reproductibles, faciles à effectuer, faciles à interpréter et doivent se concentrer sur l'impact de la maladie dans la vie quotidienne [21]. Pour les patients, les mesures devraient être faciles à obtenir et permettre aux patients de s'auto-médicamenter, tandis que pour les médecins, les outils doivent avoir un faible fardeau dans une pratique clinique occupée et doivent guider l'action clinique après le résultat du test [21]. Ils comprennent principalement :

- le CARAT (Test de contrôle de la rhinite allergique et de l'asthme) : il a été le premier questionnaire conçu pour évaluer le niveau de contrôle de l'asthme et de la RA à l'aide d'un seul outil [71,72]. Le CARAT est un questionnaire auto-administré qui comprend 17 questions avec une échelle de Likert [73]. Par la suite, une version simple de CARAT (CARAT10) en 10 points a également été validée, comme le montre (Figure 13) [74]. Les scores possibles varient de 0 (absence de contrôle) à 30 (contrôle complet), et la période de référence/d'évaluation est de 4 à 6 semaines. Le CARATKids, adapté pour les enfants de 6 à 12 ans [77], utilise une échelle dichotomique, avec des questions et des images facilement compréhensibles pour les enfants (Figure 14) [71].
- le RCAT (Test d'évaluation du contrôle de la rhinite) : est un outil de 26 items développé pour l'évaluation du contrôle des symptômes nasaux et oculaires au cours de la semaine précédente [78]. Il a été ensuite réduit en un questionnaire auto-administré en six points (Figure 15). Le score total varie de 6 (mauvais contrôle) à 30 (contrôle complet). Compte tenu de sa sensibilité et de sa spécificité, il a été suggéré que le contrôle est défini par les patients avec un score supérieur à 21 [21].
- l'ARCT (Test de contrôle de la rhinite allergique) : ce test d'auto-évaluation a été élaboré et validé chez les adultes par un groupe multidisciplinaire associant des allergologues, des pneumologues, des médecins ORL et des méthodologistes (Figure 16) [12]. Il s'agit d'un outil multidimensionnel à cinq éléments, avec des similitudes avec le test de contrôle de l'asthme (ACT) [2]. Les cinq éléments comprennent l'impact sur les activités professionnelles/personnelles, les troubles du sommeil, les médicaments et l'évaluation globale de la maladie [21]. Un rappel de 2 semaines est utilisé dans ARCT [21]. Un score de 20 est considéré comme le seuil optimal pour une

rhinite mal contrôlée ou bien contrôlée (sensibilité : 67 % ; spécificité : 82 % ; valeur prédictive négative : 32 % ; valeur prédictive positive : 95 %) [2]. Le questionnaire est actuellement en cours de validation chez les adolescents et les enfants de plus de 5 ans.

- la VAS : initialement développée comme un outil pour la sévérité de la RA, il peut être aussi utilisé pour évaluer le contrôle [21,65]. Les patients présentant une VAS > 5 sont considérés comme non contrôlés [65]. Dans une analyse post hoc évaluant la VAS à l'inclusion et après 15 jours de traitement, un changement supérieur à 30 mm a été considéré comme significatif par rapport à l'amélioration de la QoL et du score des symptômes [21].
- le Allergy-Control-SCORE<sup>TM</sup> : est un score combiné qui associe la mesure de la sévérité (avec 10 symptômes nasaux et non nasaux sur une échelle de 4 points) et l'utilisation de médicaments (sur un catalogue de 745 médicaments différents) et combine les deux mesures avec une pondération égale [80].

## **Objectifs des études**

Deux études sur des bases de données en vie réelle chez des adultes souffrant de RA ont été réalisées dans le cadre du présent projet doctoral : le premier pour valider l'utilisation d'une VAS sur les écrans des smartphones pour évaluer le contrôle des symptômes de RA, et le deuxième pour détecter un outil simple et fiable capable de discerner la sévérité de la RA saisonnière dans un contexte clinique.

La plupart des outils pour évaluer le contrôle des symptômes de RA sont sur papier. Aujourd'hui, l'outil le plus pratique, fiable et facile semble être l'administration d'une VAS de 10 cm pour évaluer l'intensité globale des symptômes allergiques [81-83]. L'application pour smartphones « The Allergy diary » (maintenant téléchargeable avec le nom « MASK-Air® ») est un outil simple de technologie de l'information et de la communication (ICT) qui peut être téléchargé gratuitement à l'aide d'un système Android ou iOS. Les utilisateurs peuvent autoévaluer leur contrôle de la RA par e VAS qui apparaît sur leur écran téléphonique. L'objectif de la première étude du présent projet de doctorat était donc d'évaluer la validité de la VAS sur les écrans des smartphones, chez les utilisateurs ayant déclaré souffrir de RA, et utilisant l'application « The Allergy Diary ».

Plusieurs scores ont déjà été validés pour évaluer la sévérité de la RA. L'objectif de la deuxième étude pour la présente thèse de science était d'évaluer dans une large base de données en vie réelle, la meilleure méthode pour stratifier les patients souffrant de RA saisonnière et de proposer des cut-offs pour discriminer les patients atteints d'une forme sévère.

## **Méthodes**

Dans l'étude MASK, nous avons inclus tous les utilisateurs qui se sont connectés à l'application AD, depuis le 1<sup>er</sup> août 2015, jusqu'au 31 juillet 2016 (période de 12 mois). L'application était téléchargeable dans 20 pays à l'époque de l'étude. L'application recueille de l'information sur les symptômes de RA éprouvés par les utilisateurs, qui évaluent leur contrôle quotidien des symptômes en utilisant la fonctionnalité d'écran tactile sur leur smartphone. Pour ce faire, les utilisateurs doivent cliquer sur 4 VAS consécutives (c.-à-d. symptômes allergiques généraux, symptômes nasaux, symptômes oculaires et symptômes d'asthme). Les données collectées par l'application AD, après le processus d'enregistrement sont : le sexe et l'âge de l'utilisateur ; la sévérité des symptômes ; les médicaments pris pour contrôler leurs symptômes ; le diagnostic, qui est un autodiagnostic (« J'ai une rhinite allergique » et/ou « J'ai de l'asthme »). Pour remplir la VAS, les utilisateurs sont invités à toucher n'importe où le long d'une ligne qui apparaît à l'écran pour indiquer à quel point leurs symptômes sont gênants, c'est-à-dire que le bord gauche signifie que leurs symptômes ne sont pas du tout gênants, tandis que le bord droit est égal à « extrêmement gênant », comme indiqué à l'écran. Une fois que les utilisateurs touchent la ligne, un curseur apparaît et ils peuvent la déplacer, au besoin, pour fournir une réponse plus précise (figure 17). L'application demande aux utilisateurs de répondre à une question générale et à trois questions propres aux symptômes qui donnent donc quatre VAS différentes, comme suit :

- VAS 1 (symptômes généraux) : « En général, dans quelle mesure vos symptômes allergiques vous dérangent-ils aujourd'hui ? »
- VAS 2 (rhinite) : « Dans quelle mesure vos symptômes du nez vous dérangent-ils aujourd'hui ? »
- VAS 3 (conjonctivite) : « Dans quelle mesure vos symptômes oculaires vous dérangent-ils aujourd'hui ? »

- VAS 4 (Asthme) : « Dans quelle mesure vos symptômes d’asthme vous dérangent-ils aujourd’hui ? » Puisque les recommandations ARIA [7,83] conseillent d’évaluer l’asthme comme possible comorbidité chez tous les patients souffrant de RA, cette question a été incluse pour tous les patients à partir du 1<sup>er</sup> juin 2016; auparavant, l’application demandait aux utilisateurs de répondre à cette question seulement s’ils avaient répondu, pendant le processus d’inscription, qu’ils étaient asthmatiques).

Les associations entre les différentes VAS ont été évaluées à l’aide d’un test Spearman et d’un test chi carré pour tous les utilisateurs, et pour les utilisateurs se connectant à l’application plus d’une fois. Pour l’analyse du chi carré, nous avons classé les patients en trois catégories différentes : la classe 0, pour les patients asymptomatiques ( $VAS < 20$ ) ; la classe 1, pour ceux qui présentent des symptômes bénins ( $20 < VAS < 50$ ) ; et la classe 2, pour ceux qui présentent des symptômes modérés à sévères ( $VAS > 50$ ). En ce qui concerne la question sur l’asthme (VAS 4), nous avons également évalué l’association avec les symptômes globaux (VAS) avant le 1 juin (lorsque seuls les utilisateurs asthmatiques ont répondu à la quatrième question) et après le 1<sup>er</sup> juin 2016 (lorsque tous les utilisateurs devaient également remplir la VAS 4).

L’analyse des caractéristiques psychométriques de l’application AD, conformément aux directives COSMIN [96], visait à vérifier pour cet outil la cohérence interne, la fiabilité, et la sensibilité. La validité externe avait déjà été décrite dans un article précédent [90]. Nous avons également vérifié l’acceptabilité de la population, définie comme (i) la persistance de l’auto-évaluation pendant au moins deux jours consécutifs dans plus de 40 % des utilisateurs utilisant l’application, et (ii) la persistance de l’auto-évaluation au moins 4 jours par semaine dans plus de 30% des utilisateurs. Toutes les analyses ont été effectuées à l’aide du programme SAS 9.4 (SAS Institute Inc, Cary, NC, É.-U.). Tous les *p-value*  $< 0,05$  ont été considérées comme statistiquement significatifs.

Dans l’étude multicentrique française Pollin’Air, nous avons analysé les données de 36,397 patients adultes ayant déjà reçu un diagnostic de RA saisonnière et consulté un médecin. Tous les patients consultaient soit un généraliste, soit un ORL, soit un allergologue, soit un dermatologue, soit un pneumologue. Au total, 8 143 médecins répartis sur l’ensemble du territoire français ont participé à l’étude. L’étude Pollin’Air a été approuvée en France en 2005. L’enquête et sa méthodologie ont été décrites dans des publications précédentes [83,97].

Chaque médecin a interviewé les patients après avoir confirmé le diagnostic médical de RA saisonnière au cours d'une visite clinique et a répondu à 17 questions pour chaque patient inclus; chaque question portait sur un seul symptôme (congestion nasale, obstruction nasale, rhinorrhée, prurit nasal, éternuements, maux de tête, fatigue, perte d'appétit, irritabilité, larmoiement, prurit oculaire, odynophagie, toux, prurit de la gorge, otalgie, altération de l'activité quotidienne et altération du sommeil) évalué par le médecin de 0 à 4 sur une échelle de Likert à 5 points (0 : absent, 1 : léger, 2 : modéré, 3 : sévère et 4 : très sévère). Les autres données recueillies comprenaient l'âge, le sexe, le lieu de vie (rural/urbain), le début de la maladie (années avant), la durée de l'épisode de rhinite (jours), les antécédents d'asthme, la présence de conjonctivite, de dermatite atopique, d'allergie alimentaire, d'urticaire, les résultats des tests cutanés, la positivité des IgE spécifiques, l'utilisation d'une ITA antérieure ou concomitante, et la région de provenance. Le jour de la visite, les patients ont rempli un VAS sur papier.

Cinq approches ont été évaluées pour classer les patients selon la sévérité de la RA et pour chaque modèle, une ségrégation en trois classes de sévérité a été calculé :

1. l'analyse en cluster par k-means (KMC) [98] ;
2. l'analyse en cluster hiérarchique agglomérative (AHC) [99] ;
3. le score pour la RA donné par le médecin (ARPhyS), décrit précédemment comme étant le « score symptomatique global (ESG-20) » [83,97], et calculé en fonction des cinq symptômes diagnostiqués par un médecin (obstruction nasale, rhinorrhée, éternuements, prurit nasal et prurit oculaire) ;
4. le TSS-17 (score total des symptômes) [100,101] ;
5. le VAS [54,91].

La classification en trois groupes avait été choisie pour suivre les lignes directrices actuelles sur la sévérité de la RA et leur adaptation [6,102,103]. Des méthodes statistiques classiques ont été utilisées pour l'analyse [98-100,104-106]. Des analyses de discrimination ont été effectuées à l'aide de l'analyse linéaire de Fisher et quadratique discriminante, ainsi que des méthodes non paramétriques d'estimation de la densité de kernel [107] et ont permis d'évaluer les erreurs de classification des patients parmi les trois catégories pour chacune des cinq méthodes. Une vérification de cross-validation a été réalisée pour évaluer la validité de chaque échelle [108]. La fiabilité de l'échelle

ARPhyS et de la TSS-17 ont été calculés avec le coefficient alpha de Cronbach. Enfin, le coefficient  $\kappa$  de Cohen a été calculé pour étudier le degré d'accord entre les cinq échelles.

Toutes les analyses ont été effectuées à l'aide du programme SAS 9.4 (SAS Institute Inc, Cary, NC, É.-U.). Tous les *p-value* < 0,05 ont été jugées statistiquement significatifs.

## Résultats

Pour l'étude MASK, entre le 1<sup>er</sup> août 2015 et le 31 juillet 2016, l'application a été utilisée 14 612 fois, par 2 497 personnes. 1 272 sujets ont utilisé l'application une seule fois, tandis que 1 225 (49,1 %) sujets l'ont utilisée au moins deux fois (12 076 accès) : 845 personnes l'ont utilisée pendant 2 à 7 jours, 154 pendant une à 2 semaines, 128 pendant 2 à 4 semaines et 98 pendant plus de 30 jours. La VAS a été évaluée 6328 fois sur deux jours consécutifs. Sur les 1 225 utilisateurs qui se sont connectés à l'application plus d'une fois, 809 se sont connectés à l'application pendant au moins deux jours consécutifs (66,0 %, et 32,4 % de l'ensemble de la cohorte). Dans le même groupe, 461 sujets (37,6 %) ont évalué leur VAS pendant au moins 4 jours au cours de la même semaine. De plus, 196 de ces 461 utilisateurs (42,5 %) ont évalué leurs symptômes pendant au moins deux semaines consécutives et 90 (19,5 %) pendant au moins quatre semaines consécutives. En ne tenant compte que de ces sujets, la valeur moyenne des semaines consécutives pendant lesquelles ils ont utilisé l'application pendant au moins 4 jours par semaine était de 2,41 semaines (min 1, max 23, ET 2,66).

Les associations entre les différentes VAS pour tous les utilisateurs, et pour les utilisateurs se connectant à l'application plus d'une fois sont montrées dans le tableau 5 et le tableau 6. Dans les deux groupes, lorsque l'on considère un seul organe, le coefficient de corrélation le plus élevé a été observé entre la rhinite (VAS 2) et la conjonctivite (VAS 3) (Tableau 5). La corrélation était très élevée quand on considère ensemble la rhinite et la conjonctivite. L'association avec l'asthme était moins forte que pour les autres symptômes. Ces résultats ont été confirmés lors de l'analyse des VAS une fois classées dans les trois catégories décrites précédemment (Tableau 6). La Figure 18 montre la corrélation entre les symptômes globaux (VAS 1) et les valeurs moyennes obtenues par les trois autres VAS, tant pour tous les utilisateurs de l'application que pour ceux qui l'utilisent plus d'une fois.



Le coefficient alpha de Cronbach pour chaque VAS et pour les valeurs moyennes de tous les VAS recueillies chez les sujets utilisant l'application pendant deux jours consécutifs (n=6328) était le suivant :

- VAS 1, symptômes allergiques généraux : coefficient alpha 0,85 ;
- VAS 2, symptômes du nez : coefficient alpha 0,84 ;
- VAS 3, symptômes oculaires : coefficient alpha 0,85 ;
- VAS 4, symptômes d'asthme : coefficient alpha 0,89 ;
- Moyenne de toutes les VAS recueillies par chaque patient : coefficient alpha 0,88.

Lors de l'évaluation avec la méthode du test-retest du groupe d'utilisateurs se connectant à l'application pendant deux jours consécutifs (n=809), nous avons mis en évidence les ICC suivants :

- VAS 1, symptômes allergiques généraux : ICC 0,737 (IC 95 %, 0,725-0,748, P0,0001) ;
- VAS 2, symptômes du nez : ICC 0,727 (IC 95 %, 0,715-0,738, P0,0001) ;
- VAS 3, symptômes oculaires : ICC 0,748 (IC 95 %, 0,737-0,759, P0,0001) ;
- VAS 4, symptômes d'asthme : ICC 0,797 (IC 95 %, 0,785-0,808, P0,0001) ;
- Moyenne de toutes les VAS recueillies par chaque patient : ICC 0,799 (IC 95 %, 0,789-0,808, P0,0001).

521 personnes ont évalué leur VAS plus d'une fois pendant trois heures consécutives. La fiabilité a été évaluée en tenant compte de l'absence d'effet d'interaction externe dans cette population, puis, de façon distincte, dans les sous-groupes d'utilisateurs qui ont déclaré une VAS supérieure et inférieure à 50 %. Les CCI étaient supérieures à 0,87 et étaient donc excellentes dans l'ensemble de la population et chez les utilisateurs qui ont déclaré des valeurs de VAS < 50, et entre bonnes et excellentes chez les utilisateurs qui ont déclaré des valeurs de VAS > 50 (Tableau 7). La sensibilité a été évaluée comme étant bonne pour chaque VAS, par analyse avec un test t-student et le coefficient alpha (Tableau 8).

Pour l'étude Pollin'Air, sur les 36 397 sujets initialement inclus dans l'essai, 8 288 ont été exclus de l'analyse ultérieure en raison de données manquantes. Les 28 109 autres patients

ont ensuite été classés en trois catégories, soit la sévérité de leur RA (légère, modérée, sévère) (Tableau 9). Selon le score ARPhyS 10 617 étaient « légers », 9446 « modérés » et 8046 « sévères » (Tableau 9). Si l'on considère les cinq méthodes, la meilleure discrimination a été offerte par l'échelle ARPhyS, suivie par la KMC, puis par la TSS-17 et l'AHC, tandis que la VAS a produit les pires résultats (Tableau 10).

Pour la validation, les deux analyses en clusters ont été réalisées 10 fois par la *leave-one-out* méthode pour assurer la stabilité et la répétabilité des modèles. Ces méthodes ont montré une répétabilité de 95,6 % et de 94,8 %. Le score ArPhyS a donné les meilleurs résultats en termes de taux d'erreur et cross-validation de taux d'erreur (Tableau 10). Pour la stratification des patients avec le score ARPhyS, les caractéristiques des patients inclus sont présentées au Tableau 11. La durée de l'épisode de rhinite n'a pas eu d'incidence statistiquement significative sur le score ARPhyS, malgré la grande taille de l'échantillon. La proportion de la population rurale était significativement plus élevée dans la catégorie des cas sévères que dans la catégorie des cas légers d'environ 3 % ; aucune différence statistiquement significative n'a été observée dans la répartition des sexes entre les catégories (Tableau 11). Le nombre de patients présentant des antécédents de conjonctivite, d'asthme, de dermatite atopique, d'allergie alimentaire et d'urticaire, et des SPT positifs ou IgE spécifiques positives ou avec un traitement concomitant ou antérieure par AIT augmentait significativement avec la sévérité.

La fiabilité des scores, évaluée par le coefficient  $\alpha$  de Cronbach, était acceptable (0,626, calculé à partir des scores bruts initiaux) pour l'échelle ARPhyS, et excellente pour la TSS-17 (0,864). Afin de choisir des seuils capables de stratifier correctement les patients, sur la base de l'échelle ARPhyS, nous avons identifié des valeurs qui seraient le mieux associées aux terciles équivalents mis en évidence précédemment : nous proposons donc un cut-off de 8-9 pour les symptômes légers à modérés et de 11-12 pour les symptômes modérés à sévères. En résumé, les patients présentaient des symptômes « légers » s'ils avaient un score de 0 à 8 avec l'ARPhyS ; ils présentaient des symptômes « modérés » s'ils avaient un score de 9 à 11 ; ils devraient être considérés comme « sévères » chaque fois qu'ils avaient un score de 12 à 20 (Tableau 13).

## Discussion

Les recommandations ARIA soulignent que le contrôle de la RA est un objectif thérapeutique clé et recommandent d'évaluer le contrôle des symptômes pour guider le traitement [6]. Jusqu'à présent, aucun outil n'est considéré comme un *gold-standard* pour la RA. Néanmoins, la tendance actuelle dans l'évaluation de différents aspects des maladies est l'utilisation d'un outil simple pour les patients à remplir et pour les médecins à évaluer, à savoir une VAS. Puisque l'utilisation des ICT, telles que les applications pour smartphones, est de plus en plus populaire, le groupe MASK a développé une application pour l'évaluation du contrôle de la RA. Cette application, le Allergy Diary ou, maintenant, MASK-Air®, est actuellement incluse dans les recommandations ARIA [6]. L'application utilise un système d'évaluation rapide par VAS, à l'aide de 4 simples questions. A travers l'étude réalisée dans le cadre de cette thèse, nous avons prouvé l'acceptabilité de l'outil. La cohérence interne a été jugée comme excellente ( $\geq 0.84$ ) après analyse par coefficient alpha et par test-retest. Les tests ont montré un ICC acceptable pour chaque VAS et pour toutes les VAS moyennes, dans le même groupe d'utilisateurs (ICC  $> 0,7$ ,  $p < 0,0001$ ). La fiabilité a été confirmée par l'évaluation des CCI chez les utilisateurs qui ont répondu aux 4 EAV deux fois le même jour. Les coefficients intraclassés étaient excellents si l'on tient compte de l'ensemble de la population ( $> 0,9$ ,  $p < 0,001$ ), et des utilisateurs qui présentaient soit pas de symptômes soit des symptômes légers, avec une VAS  $< 50$  ( $> 0,8$ ,  $p < 0,001$ ). D'autre part, les utilisateurs ayant des valeurs élevées de VAS ont montré des valeurs plus faibles de ICC ( $> 0,6$ ,  $p < 0,001$ ) et la fiabilité est considérée comme adéquate. Néanmoins, dans ce groupe de patients modérés à sévères (VAS  $> 50$ ), la fiabilité était excellente chez les utilisateurs présentant des symptômes d'asthme modérés à sévères (0,841, IC à 95 %, 0,724-0,909,  $p < 0,001$ ). La différence moyenne et l'écart-type des valeurs saisies par les utilisateurs lors de la connexion à l'application deux fois en moins de 3 heures ont prouvé une bonne sensibilité de l'outil. Enfin, la VAS a montré une bonne association entre les symptômes globaux et les symptômes de rhinite, les symptômes de rhino-conjonctivite et tous les symptômes des organes grâce au test de Spearman.

La première étude de ce doctorat a donc validé l'utilisation d'une VAS pour le contrôle de la RA sur les écrans des smartphones. En effet, nous avons souligné l'acceptabilité, la cohérence interne, la fiabilité et la sensibilité de l'outil. La validité externe a été démontrée dans un document précédent [90]. Bien que le critère d'acceptabilité ait été

satisfait, le taux de rejet était assez élevé. Les raisons à cela pourraient probablement être liées au fait que l'application est gratuite à télécharger et n'importe qui pourrait l'utiliser, sans être cohérent ou persistant.

Avec la deuxième étude, nous nous sommes concentrés sur la sévérité de la RA. Nous pouvons conseiller donc aux médecins d'évaluer la sévérité de leurs patients rhinitiques avec le questionnaire ARPhys. Lorsqu'un médecin examine des patients qui présentent des symptômes de RA, il devrait être en mesure de détecter facilement ceux qui présentent des formes sévères. L'importance de détecter la RA sévère est associée à une recherche possible principalement de comorbidités et de QoL altérée, afin de minimiser le coût de la maladie et de fournir des traitements efficaces appropriés. Compte tenu de nos résultats dans une très grande cohorte de patients, nous pouvons supposer que la VAS est un outil utile pour l'évaluation du contrôle de la RA, tant pour les patients que pour les médecins, mais il n'est pas le meilleur outil pour classer les patients en fonction de la sévérité. Contrairement aux lignes directrices de l'ARIA, nous avons constaté que la durée de la maladie n'a pas d'incidence significative sur la sévérité des symptômes, et ce résultat confirme ce qui avait été précédemment déclaré par Bousquet PJ et al. [93]. Plutôt que de faire la distinction entre la maladie intermittente et la maladie persistante, nous devrions nous concentrer sur les symptômes nasaux et oculaires, en fonction de nos constatations. Dans notre étude, même si le score ARPhyS a montré un coefficient alpha de Cronbach inférieur au TSS-17, nous avons choisi le premier questionnaire parce que, en plus d'être supérieure comme méthode discriminante, il est également plus rapide et plus facile à utiliser dans la pratique clinique quotidienne. De plus, le score ARPhyS (Tableau 13) nous a permis d'identifier les tertiles qui correspondaient au maximum à la première dimension canonique et, par conséquent, de proposer des seuils simples pour classer la RA en « légère », « modérée » et « sévère ». [54]. Le score PRPhyS est en effet capable de reconnaître spécifiquement les patients sévères, qui peuvent avoir besoin d'une approche spécialisée afin de contrôler leurs symptômes et comorbidités.

## **Conclusions**

La RA peut sembler être une maladie non importante : les médecins ont tendance à en minimiser le fardeau, les patients s'habituent à leurs symptômes et perçoivent cela comme un

problème de santé mineur, et les politiques de santé la considèrent comme un aspect médical mineur [17]. Si nous nous rapprochons de la RA et de son fardeau, nous nous rendons compte qu'elle a un impact majeur sur la QoL des patients et que les coûts directs et indirects totaux peuvent atteindre 9 milliards d'euros par an dans un pays comme la France [23,34,35], simplement en raison de sa prévalence élevée et du sous-groupe de patients atteints d'une forme sévère. Les recommandations ARIA sont bien connues des spécialistes, mais, en pratique clinique, elles ne sont pas suivies par les généralistes ni par les patients, qui essaient trop souvent de s'auto-médiquer à l'occasion d'exacerbations et d'éviter une consultation spécialisée [21,32]. Plusieurs traitements sont disponibles pour contrôler les symptômes de la RA : corticoïdes nasaux et antihistaminiques sont la meilleure option chez la plupart des patients comme traitement symptomatique [38,46]. Le seul traitement causal reste l'ITA, généralement prescrite par des spécialistes [50]. Néanmoins, compte tenu du fait que de nombreux patients évitent de consulter un spécialiste, les médicaments en vente libre sont souvent sur-utilisés par les patients allergiques, qui continuent de chercher leur meilleure option pour contrôler les symptômes de la RA [15]. Si, d'une part, le fardeau de la maladie et son coût sont importants, d'autre part, les recommandations de l'ARIA pourraient aider à mieux gérer les symptômes de la RA et de ses comorbidités et à réduire considérablement le coût indirect de la maladie [8,34]. Pour ces raisons, ARIA se concentre aujourd'hui sur deux aspects cruciaux de la RA : la sévérité et le contrôle [7,8]. La première devrait être évaluée chez les patients avant le traitement, principalement pour mettre en évidence ceux qui présentent des symptômes sévères et qui, par conséquent, risquent de réduire considérablement leur QoL et coûtent plus chers en raison de la consommation de médicaments, de l'absentéisme possible au travail, et, le plus important, d'un présentéisme. Le contrôle devrait être utilisé pour suivre les patients souffrant de RA : la modulation du traitement prescrit en fonction du contrôle des symptômes devrait conduire à une meilleure prise en charge de la maladie et de son fardeau global. Plusieurs outils ont été développés pour évaluer la sévérité et le contrôle : la plupart d'entre eux ont été validés dans des études cliniques mais, au moins en France, peu, tels que l'ARCT, sont utilisés dans la pratique clinique de routine par les généralistes et même par les allergologues.

En général, il semble donc que, même s'il existe des recommandations précises sur la RA, les patients suivent des voies différentes. De plus, les médecins ne connaissent pas ou ne connaissent pas suffisamment les outils disponibles et, par conséquent, ils sont limités dans leur travail quotidien, essayant de trouver la façon la meilleure et la plus simple d'aider leurs

patients. Pour cette raison, une analyse des données de vie réelle semble importante pour mieux comprendre comment gérer ces deux aspects de la RA. Dans le cadre de cette thèse de doctorat, nous avons analysé deux bases de données de vie réelle et mis en évidence deux outils faciles pour évaluer la sévérité et le contrôle de la RA [13,14]. L'étude MASK a débuté en 2015, comme moyen possible de mettre en œuvre les recommandations ARIA grâce à une application gratuite pour smartphones [3]. Depuis, plus de 20 articles ont été publiés sur l'application, qui s'appelait auparavant « The Allergy Diary » et qui s'appelle maintenant « MASK-Air® ». Avec notre étude, nous avons validé l'utilisation d'une VAS sur les écrans des smartphones pour évaluer le contrôle des symptômes chez des sujets reportant un diagnostic de RA. Bien que les ICT soient certainement une avenue à explorer, plusieurs questions se posent, y compris la persistance de l'utilisation, avec beaucoup de patients qui se désistent assez rapidement et le stockage et la propriété des données par une entreprise privée à une époque où la science est de plus en plus « open » ... le temps le dira [114]. De l'autre côté, l'étude Pollin'Air nous a permis de détecter un outil simple et rapide pour évaluer la sévérité de la RA, l'ARPhyS. Cet outil pourrait donc être mis en œuvre dans la pratique quotidienne pour identifier les patients graves qui ont besoin d'une intervention spécialisée ou de toute façon d'un traitement thérapeutique plus important.

Les bases de données réelles analysées dans le cadre de cette thèse de science ont pu valider deux nouveaux outils, l'un pour évaluer la sévérité de la RA dans des contextes cliniques quotidiens grâce à un score facile, et un autre pour évaluer le contrôle de symptômes sur les écrans des smartphones par une VAS. Les deux outils sont simples et très pratiques et pourraient être mis en œuvre dans la pratique des médecins lorsqu'ils se trouvent à gérer des patients souffrant de RA. Néanmoins, l'application MASK-Air® doit encore être vraiment diffusée et utilisée par les patients, alors que l'ARPhyS n'est toujours pas utilisé par les médecins. La conformité aux médicaments et aux instructions du médecin est une autre question dont il faut tenir compte. Le véritable objectif pour l'avenir est donc de guider les patients et de les pousser à utiliser l'application pour smartphones, et de communiquer aux médecins que l'ARPhyS pourrait être un système facile pour évaluer la sévérité chez les patients présentant des symptômes de RA, et, en conséquence, pour prescrire correctement un traitement adapté.

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# Attachments

## Paper 1 – Validation of the MASK-rhinitis visual analogue scale on smartphone screens to assess allergic rhinitis control

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### ORIGINAL ARTICLE

WILEY

#### Asthma and Rhinitis

## Validation of the MASK-rhinitis visual analogue scale on smartphone screens to assess allergic rhinitis control

D. Caimmi<sup>1,2</sup> | N. Baiz<sup>2</sup> | L. K. Tanno<sup>1</sup>  | P. Demoly<sup>1,2</sup> | S. Arnavielhe<sup>3</sup> | R. Murray<sup>4</sup> | A. Bedbrook<sup>5</sup> | K. C. Bergmann<sup>6,7</sup> | G. De Vries<sup>8</sup> | W. J. Fokkens<sup>9</sup> | J. Fonseca<sup>10,11</sup> | T. Haahtela<sup>12</sup> | T. Keil<sup>13,14</sup> | P. Kuna<sup>15</sup> | J. Mullol<sup>16</sup> | N. Papadopoulos<sup>17,18</sup> | G. Passalacqua<sup>19</sup> | B. Samolinski<sup>20</sup> | P. V. Tomazic<sup>21</sup> | A. Valiulis<sup>22</sup> | M. van Eerd<sup>8</sup> | M. Wickman<sup>23,24</sup> | I. Annesi-Maesano<sup>2</sup> | J. Bousquet<sup>5,25,26</sup>  | the MASK Study Group

<sup>1</sup>Allergy Unit, Département de Pneumologie et Addictologie, Hôpital Anaud de Villeneuve, CHRU de Montpellier, Montpellier, France

<sup>2</sup>Sorbonnes Universités, UPMC, UMR-S 1136, IPLESP, Equipe EPAR, Paris, France

<sup>3</sup>Kyomed, Montpellier, France

<sup>4</sup>Medical Communications Consultant, MedScript Ltd, Dundalk, Co Louth, Ireland

<sup>5</sup>MACVIA-France, Contre les Maladies Chroniques pour un Vieillissement Actif en France European Innovation Partnership on Active and Healthy Ageing Reference Site, Montpellier, France

<sup>6</sup>Comprehensive Allergy-Centre-Charité, Department of Dermatology and Allergy, Charité, Universitätsmedizin Berlin, Berlin, Germany

<sup>7</sup>Global Allergy and Asthma European Network (GA2LEN), Berlin, Germany

<sup>8</sup>Peercode DV, Amsterdam, The Netherlands

<sup>9</sup>Department of Otorhinolaryngology, Academic Medical Centre, Amsterdam, The Netherlands

<sup>10</sup>Center for Health Technology and Services Research, CINTESIS, Faculdade de Medicina, Universidade do Porto, Porto, Portugal

<sup>11</sup>Allergy Unit, CUF Porto Instituto & Hospital, Porto, Portugal

<sup>12</sup>Skin and Allergy Hospital, Helsinki University Hospital, Helsinki, Finland

<sup>13</sup>Institute of Social Medicine, Epidemiology and Health Economics, Charité, Universitätsmedizin Berlin, Berlin, Germany

<sup>14</sup>Institute for Clinical Epidemiology and Biometry, University of Wuerzburg, Wuerzburg, Germany

<sup>15</sup>Division of Internal Medicine, Asthma and Allergy, Barlicki University Hospital, Medical University of Lodz, Lodz, Poland

<sup>16</sup>Clinical & Experimental Respiratory Immunology, ENT Department, Hospital Clinic, IDIBAPS, Universitat de Barcelona, Barcelona, Spain

<sup>17</sup>Center for Pediatrics and Child Health, Institute of Human Development, Royal Manchester Children's Hospital, University of Manchester, Manchester, UK

<sup>18</sup>Allergy Department, 2<sup>nd</sup> Pediatric Clinic, Athens General Children's Hospital "P&A Kyriakou", University of Athens, Athens, Greece

<sup>19</sup>Allergy and Respiratory Diseases, IRCCS San Martino Hospital-IST-University of Genoa, Genoa, Italy

<sup>20</sup>Department of Prevention of Environmental Hazards and Allergology, Medical University of Warsaw, Warsaw, Poland

<sup>21</sup>Department of ENT, Medical University of Graz, Graz, Austria

<sup>22</sup>Vilnius University Clinic of Children's Diseases and Public Health Institute, Vilnius, Lithuania, European Academy of Paediatrics (EAP/UEMS-SP), Brussels, Belgium

<sup>23</sup>Sachs' Children and Youth Hospital, Södersjukhuset, Stockholm

<sup>24</sup>Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden.

<sup>25</sup>INSERM, VIMA: Ageing and Chronic Diseases, Epidemiological and Public Health Approaches, U1168, Paris, France

<sup>26</sup>UVSQ, UMR-S 1168, Université Versailles St-Quentin-en-Yvelines, Paris, France

**Correspondence**

Davide Caimmi, Allergy Unit, Département de Pneumologie et Addictologie, Hôpital Arnaud de Villeneuve, CHRU de Montpellier, France.  
Email: davide.caimmi@gmail.com

**Summary**

**Background:** Visual Analogue Scale (VAS) is a validated tool to assess control in allergic rhinitis patients.

**Objective:** The aim of this study was to validate the use of VAS in the MASK-rhinitis (MACVIA-ARIA Sentinel Network for allergic rhinitis) app (Allergy Diary) on smartphones screens to evaluate allergic rhinitis symptoms and disease control.

**Methods:** Each user filled 4 different VAS measuring overall, nasal, ocular, and asthma symptoms at least once. Following COSMIN guidelines, we evaluated internal consistency, (Cronbach's alpha coefficient and test-retest), reliability (intraclass correlation coefficients), sensitivity, and acceptability of the MASK-Rhinitis VAS.

**Results:** Between 1 August 2015 and 31 July 2016, the app was used 14 612 times in 15 countries. A total of 1225 users used it more than once, during the evaluated period. The tool resulted to be statistically satisfactory, showing excellent internal consistency (Cronbach's test > 0.84, test-retest > 0.7), reliability (>0.9), and acceptability. In addition, the tool had a good sensitivity when users (n = 521) answered the VAS twice in less than 3 hours.

**Conclusions and Clinical Relevance:** The MASK-rhinitis VAS is a reliable and valid tool to assess allergic control on smartphone screens, at the population level.

**KEYWORDS**

allergic rhinitis, allergy, control, MASK, visual analogue scale

**1 | INTRODUCTION**

The control and severity of AR have been defined,<sup>1-3</sup> and several attempts have been made by physicians to find the best way to reduce the impairment due to AR. Current guidelines mainly focus on the control of symptoms to better assess the efficacy of the prescribed treatment<sup>4</sup> and to improve patient's quality of life (QOL) while reducing allergic symptoms.

Measures of AR control include symptom scores, patients self-administered visual analogue scales (VAS), patients reported outcomes, such as QOL, objective measures of nasal obstruction, and a recent modification of the ARIA severity classification.<sup>5,6</sup> A few tools have been validated for AR to evaluate disease control or the impact of symptoms on QOL. Most tools use patient-reported assessments of the intensity of the main symptoms. Administration of currently available paper-and-pencil tools is either through patient self-administration or through interviews with patients or caregivers. Emerging methods use computer-assisted questionnaire administration or computer-tailored assessments. A practical, reliable, and easy tool is the administration of a VAS that allows users to simply evaluate the degree of impairment, and physicians to assess the overall intensity of allergic symptoms,<sup>7-9</sup> and that has been used even on computer screens. VAS in AR incorporates symptoms and QOL.<sup>10</sup>

MACVIA-France (Fighting chronic diseases for active and healthy ageing in France, <http://macvia.cr-languedocroussillon.fr>) is one of

the reference sites of the European Innovation Partnership on Active and Healthy Ageing.<sup>11</sup> It initiated the project AIRWAYS ICPs (integrated care pathways for airway diseases)<sup>12,13</sup> and the allergy sentinel network MASK (MACVIA-ARIA Sentinel Network).<sup>14</sup> MASK-rhinitis<sup>15</sup> is a simple ICT (Information and Communication Technology) tool to implement care pathways for AR from patients to healthcare providers using a common language and a clinical decision support system,<sup>7</sup> through a smartphones and tablets application. The corresponding app, called "ARIA Allergy Diary" (AD), may be downloaded for free both using an Android or an iOS system and is currently available in 15 European countries, Canada, Mexico, Brazil, and Australia, and will soon be available in the USA. Users may self-evaluate their AR control by a VAS that appears on their phone screen. Preliminary data showed that the app enables baseline and simple phenotypic characteristics collection.<sup>16</sup>

The aim of this paper was to assess the validity of the MASK-rhinitis visual analogue scale (VAS), as it appears in the AD app, in users who reported to suffer from AR.

**2 | METHODS****2.1 | Collected data**

In this study, we included all users that logged into the AD app, since 1 August 2015, until 31 July 2016 (12-month period). The app

collects information on AR symptoms experienced by users, who assess their daily symptom control using the touchscreen functionality on their smart phone. To do so, users need to click on 4 consecutive VAS (ie, general allergy symptoms, nasal symptoms, ocular symptoms, and asthma symptoms). The system has been deployed in 20 countries and in 15 languages (translated and back-translated, culturally adapted, and legally compliant).

After the download, and before using the app, users need to approve both the terms of use and the privacy policy, which also have been translated and legally adapted for each country in which the app is available. By accepting the use of the app, subjects agree to the fact that their data could be used also for research and scientific purposes. Data collected by the AD app after the registration process are as follows:

- The user's sex and age;
- The severity of the symptoms, as indicated through 4 VAS (see below) each time users log in the app; users may evaluate their symptoms as many times as they want during the day. Of note, there is no reminder, nor a precise time imposed to score symptoms;
- The possible medications taken to control their symptoms (whether prescribed by a physician or over the counter);
- The diagnosis, which is a self-diagnosis: when patients register, they answer "I have allergic rhinitis" and/or "I have asthma."

During the evaluated period, the VAS included four items, each of which targets a specific domain. Specific domains include an organ or related disease. To complete the VAS, users are invited to touch anywhere along a line that appears on the screen to indicate how bothersome their symptoms are the left edge means their symptoms are "not at all bothersome" while the right edge is equal to "extremely bothersome," as indicated on the screen. Once users touch the line, a slider appears and they may move it, if necessary, to provide a more accurate response (Figure 1).

Users are asked to answer to one general and three symptom-specific questions that yielded to 4 VAS as follows:

- VAS 1 (Overall symptoms): Overall, how much are your allergic symptoms bothering you today?
- VAS 2 (Rhinitis): How much are your nose symptoms bothering you today?
- VAS 3 (Conjunctivitis): How much are your eye symptoms bothering you today?
- VAS 4 (Asthma): How much are your asthma symptoms bothering you today? (as current ARIA guidelines<sup>4,9</sup> advise to evaluate the possible asthma co-morbidity in patients suffering from allergic rhinitis, this question was included for all patients from 1 June 2016; previously, users were asked to answer this question only if they answered, during the registration process, that they were asthmatic).



**FIGURE 1** VAS for overall allergic symptoms as it appears on smartphones screens

## 2.2 | Statistical methods

The associations between the different VAS were assessed using a Spearman test and a chi-square test for all users and for users logging into the app more than once as follows:

- Associations between the overall symptoms (VAS 1) and
  - Rhinitis, VAS 2,
  - Conjunctivitis, VAS 3,
  - Asthma, VAS 4,
  - Rhino-conjunctivitis, as the average of the collected values for VAS 2 and VAS 3,
  - All organ symptoms, as the average of the collected values for VAS 2, VAS 3, and VAS 4.
- The association between the overall symptoms (VAS 1), and the cumulative VAS score given by the average of all VAS scores.

For the chi-square analysis, we categorized patients into 3 different classes: class 0, for asymptomatic patients ( $VAS < 20$ ); class 1, for those presenting with mild symptoms ( $20 \leq VAS < 50$ ); and class 2, for those as with moderate-to-severe symptoms ( $VAS \geq 50$ ). As for the asthma question (VAS 4), we also evaluated the association with the overall symptoms VAS before 1 June (when only asthmatic users answered to the fourth question) and after 1 June 2016 (when all users were asked to complete VAS 4 as well).

The analysis of the psychometric characteristics of the AD app, in compliance with the COSMIN guidelines,<sup>17</sup> aimed to verify for this tool:

- The *internal consistency*. It was assessed through the Cronbach's alpha coefficient and the test-retest procedure, evaluating the results given by users logging into the app and filling the VAS for two consecutive days, when no change in medications intake is recorded;
- The *reliability*. It was assessed by analysing correlations between VAS measures taken twice in the same day, through intraclass correlation coefficients (ICCs). As the magnitude of correlation coefficients is affected by the range of scores included in the sample, increasing as the range of scores increases, ICCs were calculated separately for VAS scores above and below 50 mm;
- The *sensitivity*. It was evaluated by the Cronbach' alpha coefficient, the difference of measures and the standard deviation in the VAS, for those users logging into the app more than once per day, but self-assessing their symptoms with a interval of less than 3 hours (thus, eliminating bias related to possible changes in allergen exposure and/or drug intake).
- The *external validity* having already been described in a previous paper.<sup>16</sup>

We also verified the population *acceptability*, defined as the persistence of self-assessment over at least two consecutive days in more than 40% of users using the app and the persistence of self-assessment at least 4 days a week in more than 30% of users downloading the app.

All analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA). All *P-values* < .05 were considered as statistically significant.

### 3 | RESULTS

#### 3.1 | VAS acceptability—Description of the users

Between 1 August 2015 and 31 July 2016, the AD app was used 14 612 times, by 2497 individuals. A total of 1272 subjects used the app only once, while 1225 (49.1%) subjects used it at least twice (12 076 accesses): 845 individuals used it for 2 to 7 days, 154 for one to 2 weeks, 128 for 2 to 4 weeks, and 98 for more than 30 days. The VAS was completed on two consecutive days for 6328 times.

Of the 1225 users connecting to the AD more than once, 809 logged into the app for at least two consecutive days (66.0% and 32.4% of the whole cohort). In the same group, 461 subjects (37.6%) entered their VAS for at least 4 days during the same week. Also, 196 of these 461 users (42.5%) assessed their symptoms for at least two consecutive weeks and 90 (19.5%) for at least 4 consecutive weeks. Considering only these subjects, the mean value of consecutive weeks during which they used the app for at least 4 days per week was 2.41 weeks (min 1, max 23, SD 2.66).

The associations between the different VAS for all users and for users logging into the AD app more than once are shown in Table 1 and Table 2. In both groups, when considering one organ only, the

**TABLE 1** Association between overall symptoms (VAS 1) and rhinitis (VAS 2), conjunctivitis (VAS 3), asthma (VAS 4), rhinoconjunctivitis (average value of VAS 2 and VAS 3), and all organ symptoms (average value of VAS 2, VAS 3, and VAS 4), in all subjects who ever used the app, and in those who used it more than once, through Spearman test

	VAS 1			
	All users (total data = 14612)		Users logging in more than once (total data = 12076)	
	Spearman's coefficient of correlation	<i>P-value</i>	Spearman's coefficient of correlation	<i>P-value</i>
VAS 2	.879	<.001	.878	<.001
VAS 3	.656	<.001	.692	<.001
VAS 4	.583	<.001	.595	<.001
VAS 2 and 3	.889	<.001	.894	<.001
VAS 2, 3 and 4	.893	<.001	.897	<.001
VAS 4: before 1 June 2016	.668	<.001	.642	<.001
VAS 4: after 1 June 2016	.478	<.001	.522	<.001

highest correlation coefficient was observed between rhinitis (VAS 2) and conjunctivitis (VAS 3) (Table 1). The correlation was very elevated when considering together rhinitis and conjunctivitis. The association with asthma was less strong compared to the other symptoms. These results were confirmed when analysing the VAS once categorized into the three previously described classes (Table 2).

Figure 2 shows the correlation between the overall symptoms (VAS 1) and the average values obtained by all the other three VAS, both for all users using the app and for those using it more than once.

#### 3.2 | VAS validation—Internal consistency

The Cronbach's alpha coefficient for each VAS and for the average values of all collected VAS in subjects using the app for two consecutive days (*n* = 6328) was as follows:

- VAS 1, overall allergic symptoms: alpha coefficient 0.85;
- VAS 2, nose symptoms: alpha coefficient 0.84;
- VAS 3, ocular symptoms: alpha coefficient 0.85;
- VAS 4, asthma symptoms: alpha coefficient 0.89;
- Average of all collected VAS by each patient: alpha coefficient 0.88.

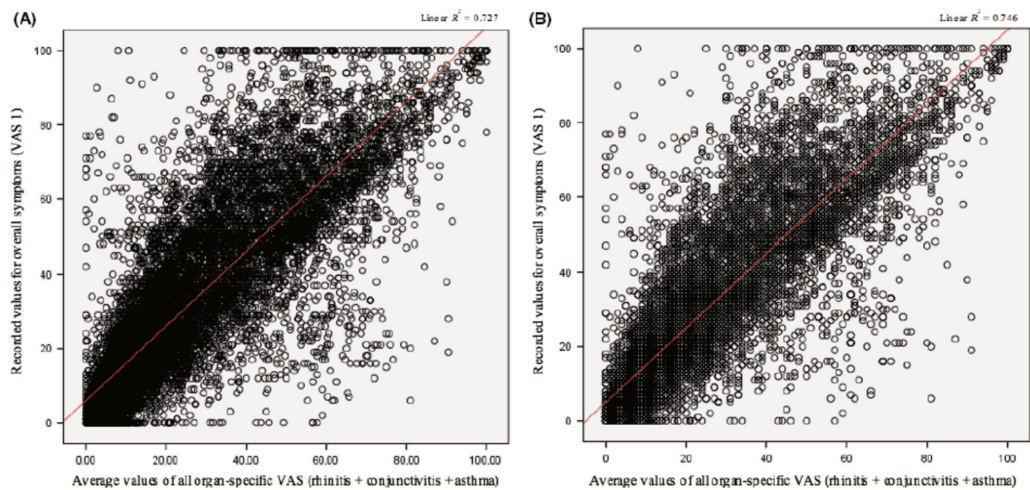
When evaluating for test-retest the group of users logging into the app for two consecutive days (*n* = 809), we highlighted the following ICCs:

- VAS 1, overall allergic symptoms: ICC 0.737 (CI 95%, 0.725-0.748, *P* < .0001);

**TABLE 2** Relation between overall symptoms (VAS 1) and rhinitis (VAS 2), conjunctivitis (VAS 3), asthma (VAS 4), and all organ symptoms (average value of VAS 2, VAS 3, and VAS 4), in all subjects who ever used the app, and in those who used it more than once, through chi-squared test

		VAS 1				VAS 1			
		Data from all users (N = 14612)				Data from users logging in more than once (N = 12076)			
		Class 0	Class 1	Class 2	P-value	Class 0	Class 1	Class 2	P-value
VAS 2	Class 0	<b>86.49%</b>	15.42%	4.74%	<.0001	<b>86.67%</b>	16.80%	4.62%	<.0001
	Class 1	11.19%	<b>67.05%</b>	16.36%		11.42%	<b>64.93%</b>	17.00%	
	Class 2	2.33%	17.53%	<b>78.90%</b>		1.91%	18.28%	<b>74.20%</b>	
VAS 3	Class 0	<b>91.01%</b>	54.58%	23.86%	<.0001	<b>91.25%</b>	49.58%	22.97%	<.0001
	Class 1	6.93%	<b>34.97%</b>	25.15%		7.09%	<b>39.29%</b>	23.79%	
	Class 2	2.06%	10.46%	<b>50.99%</b>		1.66%	11.13%	<b>53.24%</b>	
VAS 4	Class 0	<b>94.51%</b>	74.95%	60.92%	<.0001	<b>94.32%</b>	71.69%	58.13%	<.0001
	Class 1	4.20%	<b>18.62%</b>	13.84%		4.47%	<b>21.36%</b>	13.98%	
	Class 2	1.29%	6.43%	<b>25.24%</b>		1.21%	6.94%	<b>27.89%</b>	
Average of VAS 1, 2 and 3	Class 0	<b>95.02%</b>	63.47%	43.28%	<.0001	<b>93.96%</b>	37.12%	20.77%	<.0001
	Class 1	4.11%	<b>31.23%</b>	25.84%		5.30%	<b>57.72%</b>	25.02%	
	Class 2	0.86%	5.30%	<b>30.88%</b>		0.75%	5.16%	<b>54.21%</b>	

Class 0 = asymptomatic (VAS < 20), class 1 = mild symptoms (≤20 VAS < 50), and class 2 = severe symptoms (VAS ≥ 50). Bold values highlight the correlation between values considered from the same class of patients.



**FIGURE 2** Correlation between the results of the overall symptoms VAS (VAS 1) and all organ symptoms (average value of VAS 2, VAS 3, and VAS 4) (A) in all subjects who ever used the app; and (B) in those subjects who used the app more than once

- VAS 2, nose symptoms: ICC 0.727 (CI 95%, 0.715-0.738, P < .0001);
- VAS 3, ocular symptoms: ICC 0.748 (CI 95%, 0.737-0.759, P < .0001);
- VAS 4, asthma symptoms: ICC 0.797 (CI 95%, 0.785-0.808, P < .0001);
- Average of all collected VAS by each patient: ICC 0.799 (CI 95%, 0.789-0.808, P < .0001).

### 3.3 | VAS validation—Reliability and sensitivity

A total of 521 individuals recorded the VAS more than once over three consecutive hours. Reliability was evaluated considering no external interaction effect, in this population, and then in the sub-groups of users reporting a VAS of more and less than 50%, as shown in Table 3. ICCs were higher than 0.87 and thus excellent in the entire population and in users reporting VAS values < 50,

**TABLE 3** Intraclass correlation coefficients (ICC) in all subjects who used the app twice in the same day (whole population) and in those evaluating their symptoms as moderate-to-severe (VAS  $\geq$  50) and not (VAS < 50). The analysis was conducted for each VAS completed by users (n = 521)

		Included subjects	ICC	Min-Max (95% CI)	P-value
Whole population	VAS 1	498	0.924	0.909-0.936	<.001
	VAS 2	521	0.928	0.914-0.939	<.001
	VAS 3	521	0.949	0.940-0.957	<.001
	VAS 4	316	0.959	0.949-0.967	<.001
VAS > 50	VAS 1	169	0.645	0.520-0.738	<.001
	VAS 2	165	0.619	0.482-0.720	<.001
	VAS 3	119	0.661	0.513-0.764	<.001
	VAS 4	52	0.841	0.724-0.909	<.001
VAS < 50	VAS 1	329	0.889	0.862-0.911	<.001
	VAS 2	356	0.865	0.834-0.891	<.001
	VAS 3	402	0.913	0.895-0.929	<.001
	VAS 4	264	0.891	0.861-0.914	<.001

ICC, intraclass correlation coefficient; CI, confidence interval; Min, minimum; Max, maximum.

and between good and excellent in users reporting VAS values > 50.

Sensitivity was evaluated as good for each VAS, through classical statistical analysis, t-student test, and alpha coefficient, as shown in Table 4.

#### 4 | DISCUSSION

Current AR guidelines emphasize that allergic rhinitis control is a key therapeutic goal and recommend evaluating symptoms control to guide step therapy.<sup>18</sup> So far, no tool is considered as a gold standard for AR. Nevertheless, current trend in assessing different aspects of diseases is the use of a simple Visual Analogue Scale, a simple tool for both patients to complete and for physicians to evaluate. Another advantage of the VAS is that it may be used in most age groups and in a wide variety of languages and that it may assess the severity of the disease as well.<sup>9,19</sup> The VAS, as a tool to assess AR severity, according to ARIA (Allergic Rhinitis and its Impact on Asthma) guidelines, has already been validated and is considered as an easy-to-use tool.<sup>19,20</sup> A VAS score of 50/100 mm (or 60/100,

**TABLE 4** Sensitivity of the four VAS, in users evaluating their symptoms with a less than 3 h of interval

	Cronbach's alpha coefficient	Mean difference	Standard Deviation	CI 95%	t-Student test
VAS 1	0.858	1.143	14.993	-0.177; 2.463	1.701
VAS 2	0.865	0.495	14.917	-0.789; 1.779	0.758
VAS 3	0.904	1.207	12.58	0.125; 2.29	2.19
VAS 4	0.922	-0.003	10.464	-1.161; 1.155	-0.005

CI, confidence interval; Min, minimum; Max, maximum.

based on different studies) is suggestive of moderate-to-severe AR.<sup>18,21</sup> Such considerations lead to conduct a survey at the 2013 congress of the European Academy of Allergy and Clinical Immunology (EAACI), where physicians were asked to evaluate and approve the usefulness of a VAS to monitor AR control.<sup>22</sup>

As the use of information and communications technology (ICT), such as apps running on consumer smartphones, is increasingly popular and has the potential to profoundly affect health care, MASK-rhinitis developed an app, as one of the implementation tools of the B3 Action Plan of the European Innovation Partnership on Active and Healthy Ageing (EIP on AHA).<sup>11,12,15</sup> The app is currently included as a tool of the ARIA guidelines to monitor users' symptoms.<sup>18</sup> The ARIA Allergy Diary app uses a quick VAS system for the assessment of AR control, although 4 simple questions. A pilot study has been completed in AR to assess the relevance of the AD app and showed the importance of the tool to stratify users and assess their symptoms severity and control and highlighted the external validity of the app.<sup>16</sup>

The tool proved its acceptability following defined criteria, with 49% of users logging into the app more than once and more than 30% using it for at least 4 times a week. When an app is free to download, its usefulness is important for the users, and a great number of people may download it without even knowing the purpose of it. The fact that almost a half of all people who downloaded the app used it more than once makes its acceptability verified.

Internal consistency was validated both by alpha coefficient and test-retest. Cronbach's alpha showed an excellent internal consistency ( $\geq$ 0.84) for each VAS and for all the average VAS, when evaluating users answering to the 4 questions over two consecutive days. Test-retest showed an acceptable ICC for each VAS and for all the average VAS, in the same group of users, as well (ICC > 0.7,  $P$  < .0001).

Reliability was confirmed by the assessment of ICCs in users answering to the 4 VAS twice in the same day. Intraclass coefficients were excellent when considering the whole population ( $>$ 0.9,  $P$  < .001) and users with no to mild symptoms, that is with a VAS <50 ( $>$ 0.8,  $P$  < .001). On the other hand, users with elevated values of VAS showed lower values of ICC ( $>$ 0.6,  $P$  < .001) and reliability is to considered as adequate. Nevertheless, in this group of moderate-to-severe patients (VAS > 50), reliability was excellent in those users with moderate-to-severe symptoms of asthma (0.841, 95% CI, 0.724-0.909,  $P$  < .001).

The mean difference and the standard deviation of the values entered by users when logging into the app twice in less than 3 hours proved a good sensitivity of the tool.



At last, the VAS showed a good association between overall symptoms and rhinitis symptoms, rhino-conjunctivitis symptoms and all organ symptoms through Spearman test. Eyes symptoms and asthma symptoms showed a weaker association with the "overall symptoms" VAS, if compared with the other variables. Also, until 1 June 2016, users were not obliged to answer to the asthma question, if they claimed not to suffer from this condition, while after that date, each user was required to answer the question (VAS 4). The Spearman test showed an even weaker association between asthma symptoms and overall symptoms after that date. All these considerations are valid for both analysis run on all the subjects who downloaded the app ( $n = 2497$ ) and those who used it at least twice ( $n = 1272$ ). When evaluating results with a chi-squared test, we categorized users according to their VAS: no symptoms if their VAS was  $< 20$ , mild symptoms when  $\leq 20$  VAS  $< 50$  and moderate-to-severe when VAS  $\geq 50$ . We run the same analysis both on all the subjects who ever used the app ( $n = 2497$ ) and on those who used it more than once ( $n = 1272$ ). In both case, the chi-squared test resulted significant ( $P < .0001$ ). We noticed that when users reported to have no overall symptoms, their answer was strongly correlated with the answers to the other three VAS. On the contrary, when overall symptoms are mild, they correlate well with nasal symptoms, but users mainly respond not to be bothered by eyes and asthma symptoms. Moreover, when overall symptoms are moderate-to-severe, they correlate very well with nasal symptoms and well with eyes symptoms, but most of users claim to have no asthma symptoms. These results may be explained by the fact that not all patients suffer from asthma, and it could therefore be a bias in our analysis. Nevertheless, we could also hypothesize that what bothers allergic patients are mostly their nasal symptoms and secondly their eyes symptoms when their allergic condition becomes severe and that asthma symptoms are either less important or patients are used to those chronic symptoms and thus, they seem less bothersome during an allergy peak.

The present study showed that the use of a VAS for AR on smartphone screens can be validated. Indeed, we highlighted the acceptability, the internal consistency, the reliability and sensitivity of the tool. External validity was demonstrated in a previous paper.<sup>16</sup> Even though the acceptability criterion was satisfied, the drop-off rate was quite big. The reasons for this could probably be linked to the fact that the app is free to download and anyone might use it, without being consistent. The implementation of the app with the clinical decision support system and the healthcare-provider version will be more appealing and useful and we might speculate that the patients who would actually benefit from the app will use it more consistently. For the same reason, data on medication used should be better exploited in further analysis.


As a conclusion, VAS can be considered as a validated tool to assess allergic rhinitis control in users suffering from AR even on smartphones screen, as in the AD app, and is well accepted by physicians. The MASK-rhinitis tool uses VAS to stratify users and evaluate symptom severity and control, through the ARIA Allergy Diary app for smartphones. The implementation of the app, through

a clinical decision support system (CDSS) and a healthcare providers' version, will help not only users to better handle their symptoms, but also both the pharmacists, to guide them in the prescription of OTC medications and refer uncontrolled users to physicians, and the doctors, to prescribe appropriate treatment and assess symptom control in their patients. The current study is of great importance for the transfer of innovation to the Reference Sites of the European Innovation Partnership on Active and Healthy Ageing.<sup>23,24</sup>

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#### ORCID

L. K. Tanno  <http://orcid.org/0000-0003-3236-1225>  
J. Bousquet  <http://orcid.org/0000-0001-9226-7762>

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# Paper 2 - Looking for the best method to discriminate severe seasonal allergic rhinitis. Results from a large nation-wide database



## RESEARCH ARTICLE

# Discriminating severe seasonal allergic rhinitis. Results from a large nation-wide database

Davide Caimmi<sup>1,2\*</sup>, Nour Baiz<sup>2</sup>, Shreosi Sanyal<sup>2</sup>, Soutrik Banerjee<sup>2</sup>, Pascal Demoly<sup>1,2</sup>, Isabella Annesi-Maesano<sup>2</sup>

**1** Unité d'allergologie, Département de Pneumologie et Addictologie, University Hospital of Montpellier, CHU de Montpellier, France, **2** Epidemiology of Allergic and Respiratory Diseases Department (EPAR), Sorbonne Université, INSERM, Pierre Louis Institute of Epidemiology and Public Health, Saint-Antoine Medical School, Paris, France

\* [davide.caimmi@gmail.com](mailto:davide.caimmi@gmail.com)



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**Data Availability Statement:** For detailed data, current French regulation in agreement with EC GDPR does not allow to share them publicly, but they are all available at our lab. Data set used to reach the conclusions drawn in the manuscript with related metadata and methods, and any additional data required to replicate the reported study findings are available in the present paper and in previous published papers (references 10 and 18 in the present manuscript). Interested researchers will be able to request the minimal underlying meta-data set. Meta-data requests may

## Abstract

Allergic rhinitis (AR) is a chronic disease affecting a large amount of the population. To optimize treatment and disease management, it is crucial to detect patients suffering from severe forms. Several tools have been used to classify patients according to severity: standardized questionnaires, visual analogue scales (VAS) and cluster analysis. The aim of this study was to evaluate the best method to stratify patients suffering from seasonal AR and to propose cut-offs to identify severe forms of the disease. In a multicenter French study (PollinAir), patients suffering from seasonal AR were assessed by a physician that completed a 17 items questionnaire and answered a self-assessment VAS. Five methods were evaluated to stratify patients according to AR severity: k-means clustering, agglomerative hierarchical clustering, Allergic Rhinitis Physician Score (ARPhyS), total symptoms score (TSS-17), and VAS. Fisher linear, quadratic discriminant analysis, non-parametric kernel density estimation methods were used to evaluate miss-classification of the patients and cross-validation was used to assess the validity of each scale. 28,109 patients were categorized into "mild", "moderate", and "severe", through the 5 different methods. The best discrimination was offered by the ARPhyS scale. With the ARPhyS scale, cut-offs at a score of 8–9 for mild to moderate and of 11–12 for moderate to severe symptoms were found. Score reliability was also acceptable (Cronbach's  $\alpha$  coefficient: 0.626) for the ARPhyS scale, and excellent for the TSS-17 (0.864).

The ARPhyS scale seems the best method to target patients with severe seasonal AR. In the present study, we highlighted optimal discrimination cut-offs. This tool could be implemented in daily practice to identify severe patients that need a specialized intervention.

## Introduction

Allergic rhinitis (AR) affects up to 50% of some populations, especially in "westernized" countries and its prevalence, in France, tripled over the last 25 years and is around 31% [1,2].

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Current guidelines try to categorize patients by differentiating between those suffering from “mild” symptoms and those with “moderate to severe” forms of rhinitis [3–5]. There is not a unanimous way to define patients as simply “severe”, even though it seems important to highlight this specific group, because of the consistent burden associated to these patients, in terms of increased morbidity and therefore direct healthcare and indirect socio-economic cost [6,7].

ARIA guidelines look for duration and types of symptoms reported to the physician, and the new allergy diary App for smartphones questions patients on how they feel, through a visual analogue scale (VAS) [4,8]. Therefore, if on one hand, current classification is based on physician’s appreciation of the disease as presented by the patient, on the other hand, it highlights the importance of how the patient feels, regardless the items proposed by the guideline. The real goal, both in the “classical” ARIA classification and in the ARIA App for patients’ self-evaluation, is to assess the control of the disease, regardless its severity. In fact, AR control implies that patients do not present bothersome symptoms when exposed to allergens, while severe forms characterize patients who are not able to control their symptoms even if an appropriate high-dose treatment is prescribed and their compliance is good.

Several scores have been previously validated to assess AR control, such as the CARAT, the RCAT, the ARCT, and the VAS (both on a pencil-and-paper tool and through smartphones) [2,9]. At the same time, some scores, including symptoms scores and VAS, have been tested or even validated to assess patients’ severity and categorize patients [10–14]. A few authors proposed on the other hand to assess severe AR, by analyzing patients in clusters, and stratify them, based on the severity of their symptoms [15–17]. Therefore, in literature, severe forms may be identified through physicians’ questionnaire, self-assessment methods, or by analyzing the results of published cluster analysis. Besides identifying the best tool to stratify patients, it is debated whether physician’s or patient’s assessment would serve as the best guide to classify the patient’s severity.

The aim of the present paper was therefore to assess the best method to stratify patients suffering from seasonal AR and to then propose cut-offs able to determine which patients suffer from severe forms of rhinitis.

## Materials and methods

### Study design

In a multicenter French study, 36,397 adult patients with a previous medical diagnosis of seasonal AR and consulting a physician were included. All patients were consulting either a general practitioner or an ENT, or an allergist, or a dermatologist, or a pulmonologist. A total of 8,143 doctors distributed over the whole French territory participated to the study. The PollinAir study was approved in France in 2005. The approval by an ethic committee was declared as not applicable at that time. Instead of the study was approved by the National Committee for Information Management on medical research (Comité Consultatif sur le Traitement de l’Information en Matière de Recherche dans le domaine de la santé) and by the National Commission on informatics and health (CNIL, Commission Nationale Informatique et Liberté). Information was provided to included subjects or to their caregivers through a written document. Informed written consent to participate in the survey was obtained for all patients by the physicians. The CNIL approved in 2016 that all data acquired prior to 2016, without the previous need of an authorization of an Ethic Committee, could still be exploited. The survey and its methodology have been described in detail elsewhere [10,18].

### Collected data

Each doctor interviewed the patients after confirming the previous medical diagnosis of seasonal AR through a clinical visit, and answered 17 questions for each included patient; each

question focused on one item, and the physician was supposed to rate every symptom from 0 to 4 in a 5-point Likert scale (0: absent, 1: mild, 2: moderate, 3: severe, and 4: very severe). Evaluated symptoms were: 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, and sleep alteration. Other collected data included age, gender, location (rural / urban), disease onset (years before), duration of episode (days), reported history of asthma, conjunctivitis, atopic dermatitis, food allergy, or hives, results of skin-prick tests (SPTs) to respiratory allergens (positive / negative), positivity of serum specific IgE to respiratory allergens (positive / negative), previous or concomitant allergen immunotherapy (yes / no), and region (center, east, north-west, Paris agglomeration, south-east, south-west and west). On the day of the visit, patients completed a Visual Analogue Scale (VAS) on a paper, indicating, on a 10-cm line, how severe they believed their rhinitis was ("how bothersome are your allergic rhinitis symptoms?").

### Data and statistical analysis

Five approaches to classify patients according to AR severity were assessed:

1. **K-means clustering (KMC)** [19] was used as unsupervised classification on standardized variables to categorize AR patients. A group of three clusters were then selected for further analyses.
2. **Agglomerative hierarchical clustering (AHC)** [20] was used as unsupervised classification on standardized variables to categorize AR patients. A group of three clusters were then selected for further analyses.
3. **Allergic Rhinitis Physician Score (ARPhyS)**, previously described as "Global Symptomatic Score (GSS-20)" [10,18] was calculated, based on five physician-diagnosed symptoms. These symptoms were assessed by each doctor during the interview with the patients. To each nasal (nasal obstruction, rhinorrhea, sneezes and nasal pruritus) and ocular symptom (ocular pruritus), doctors attributed a severity score ranging from 0 to 4, as described above. This score could therefore possibly range from a minimum of 0 to a maximum of 20 points. The score was categorized into three terciles.
4. **Total Symptoms Score (TSS-17)** [21,22], which is the global score resulting from adding up the evaluation of the 17 items rated by physicians for each included patient. This score could therefore possibly range from a minimum of 0 to a maximum of 68 points. The score was categorized into three terciles.
5. **Visual Analogue Scale (VAS)** [11,12], which is a global self-assessment wellness score reported by each patient, and ranging from 0 (= no discomfort) to 100 (= maximal discomfort). The score was categorized into three terciles.

Classification in three groups had been chosen to follow current guidelines on AR severity and their adaptation [3,23,24]. For validation, K-means algorithm and agglomerative hierarchical clustering models were carried out 10 times by the leave-one-out method to ensure stability and repeatability of the models.

Classical statistical methods were used for the analysis [19–21,25–27]. Discrimination analyses was conducted with Fisher linear and quadratic discriminant analysis, along with non-parametric kernel density estimation methods [28] and allowed to evaluate miss-classification of the patients among the three categories on each of the five scales. Cross-validation check was used to assess the validity of each scale [29]. Reliability of the ARPhyS scale and of the

TSS-17 were evaluated through Cronbach's alpha coefficient. At last, Cohen's  $\kappa$  coefficient was computed to study the degree of agreement between the five scales.

All analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA). All *p-values* <0.05 were considered statistically significant.

## Results

### Patients' stratification

Out of the 36,397 subjects initially included in the trial, 8,288 were excluded from further analysis, because of missing data. The other 28,109 patients were then categorized in three classes, of "mild", "moderate", and "severe" AR, as shown in Table 1. Stratification by cluster analysis is shown in Fig 1. There were 10,617 patients in the mild, 9446 patients in the moderate and 8046 patients in the severe category based on the ARPhyS scale (Table 1).

### Discrimination and cross-validation

When considering all the five approaches, the best discrimination was offered by the ARPhyS scale, followed by the KMC, and then by the TSS-17 and by the AHC, while the VAS produced the worst results (Table 2). For validation, K-means algorithm and agglomerative hierarchical clustering models were carried out 10 times by the leave-one-out method to ensure stability and repeatability of the models. These methods showed 95.6 and 94.8% repeatability. The ARPhyS scale showed the best results in terms of error rates and cross-validation error rates, as highlighted in Table 2. Based on the ARPhyS stratification in mild, moderate and severe symptoms, the characteristics of the included patients are shown in Table 3. The duration of the rhinitis episode did not have a statistically significant impact on the ARPhyS scale, despite the large sample size. The proportion of rural population was significantly higher in the severe category compared to the mild category by approximately 3%; no statistically significant difference was noted in gender distributions across the categories (Table 3). The number of patients presenting with a history of conjunctivitis, asthma, atopic dermatitis, food allergy, and hives,

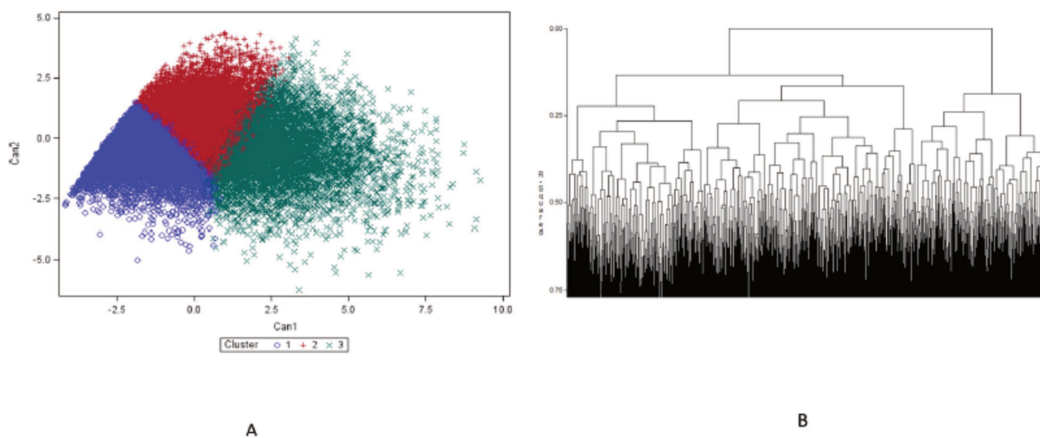
**Table 1. Distribution of mild, moderate, and severe patients, based on the five approaches used in the study.**

	Mild		Moderate		Severe	
	Included subjects, n (%)	Cumulated frequency (n)	Included subjects (n)	Cumulated frequency (n)	Included subjects (n)	Cumulated frequency (n)
		Cumulated Percentage (%)		Cumulated Percentage (%)		Cumulated Percentage (%)
KMC	11358 (40.41)	11358	10163 (36.16)	21521	6588 (23.44)	28109
		40.41		76.56		100.00
AHC	8021 (28.54)	8021	12403 (44.12)	20424	7685 (27.34)	28109
		25.54		72.66		100.00
ARPhyS	10617 (37.77)	10617	9446 (33.60)	20063	8046 (28.62)	28109
		37.77		71.38		100.00
TSS-17	9579 (34.08)	9579	9177 (32.65)	18756	9353 (33.27)	28109
		34.08		66.73		100.00
VAS	9247 (32.90)	9247	9689 (34.47)	18936	9173 (32.63)	28109
		32.90		67.37		100.00

The difference in terciles group is due to the TIES = Low option (default): ties are assigned to lower categories.

CV: cross-validation; KD: kernel density; KMC: k-means clustering; AHC: agglomerative hierarchical clustering; ARPhyS: Allergic Rhinitis Physician Score; TSS-17: Total Symptom Score with 17 items; VAS: Visual Analogue Scale (0–100).

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**Fig 1. Cluster analysis through two methods (all variables standardized).** (A) K-means clustering, non-hierarchical clustering approach;  $k = 3$  (Cluster 1 = 'mild' allergic rhinitis; Cluster 2 = 'moderate' allergic rhinitis; Cluster 3 = 'severe' allergic rhinitis). (B) Agglomerating hierarchical clustering dendrogram, with y-axis that shows the  $R^2$  as the distance measure ( $R^2 = 16.5\%$ ).

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and with positive SPT or specific IgE or with a previous or concomitant allergen immunotherapy significantly increased with severity.

### Reliability, agreement and stratification

Score reliability, assessed through Cronbach's  $\alpha$  coefficient, was acceptable (0.626, computed on the original raw scores) for the ARPhyS scale, and excellent for the TSS-17 (0.864). Maximum variability was observed in the first canonical component direction explaining 99.8% of the total variability for the ARPhyS scale. As for agreement between scores, VAS showed the lowest agreement if compared with all the other scores, as shown in Table 4.

In order to choose cut-offs able to properly stratify patients, based on the ARPhyS scale, we identified those values that would be best associated to equivalent previously highlighted

**Table 2. Overall error (misclassification) rates and cross-validation error rates according to the approaches and the different discrimination methods.**

Discrimination methods	KMC		AHC		ARPhyS		TSS-17		VAS	
	Error rates (%)	CV error rates (%)	Error rates (%)	CV error rates (%)	Error rates (%)	CV error rates (%)	Error rates (%)	CV error rates (%)	Error rates (%)	CV error rates (%)
Linear	4.30	4.40	22.39	22.48	3.08	3.18	8.31	8.36	43.93	44.06
Quadratic	10.96	11.20	23.36	23.58	2.89	3.06	9.34	9.48	45.43	45.95
KD with equal bandwidth	0.04	11.50	0.67	15.62	0.00	7.92	0.00	11.43	1.85	48.53
KD with unequal bandwidth	0.99	15.43	5.62	23.97	0.12	8.11	2.43	16.18	8.07	50.87

CV: cross-validation; KD: kernel density; KMC: k-means clustering; AHC: agglomerative hierarchical clustering; ARPhyS: Allergic Rhinitis Physician Score; TSS-17: Total Symptom Score with 17 items; VAS: Visual Analogue Scale (0–100).

Smoothing parameter for hierarchical clusters was varied from 0.4 to 1.0 for sensitivity analysis. A moderate smoothing bandwidth (0.8) showed the best results for all analyses. Linear discrimination was better than quadratic discrimination for all analysis. ARPhyS, TSS-17 and VAS are divided into tertiles; KMC and AHC are grouped into 3 clusters.

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**Table 3. Characteristics of the patients according to allergic rhinitis severity as assessed with the ARPhyS Scale.**

Characteristics	Mild (N = 10,617)		Moderate (N = 9,446)		Severe (N = 8,046)		p-value <sup>1</sup>
	Mean	SE	Mean	SE	Mean	SE	
Age (years)	35.12	0.15	34.30	0.15	33.32	0.16	< 0.001
Onset (years ago)	6.85	0.07	7.38	0.07	7.91	0.08	< 0.001
Duration of episode (days)	19.64	0.22	19.23	0.23	19.70	0.26	0.500
Loss of appetite	0.22	0.00	0.42	0.01	0.69	0.01	< 0.001
Nasal congestion	2.18	0.01	2.63	0.01	3.02	0.01	< 0.001
Daily activity disturbed	0.80	0.01	1.16	0.01	1.54	0.01	< 0.001
Sneezing	1.68	0.01	2.52	0.01	3.17	0.01	< 0.001
Tiredness	0.83	0.01	1.20	0.01	1.63	0.01	< 0.001
Painful throat	0.55	0.01	0.76	0.01	1.11	0.01	< 0.001
Irritability	0.46	0.01	0.78	0.01	1.16	0.01	< 0.001
Lacrimation	0.95	0.01	1.54	0.01	2.27	0.01	< 0.001
Earache	0.14	0.01	0.22	0.01	0.38	0.01	< 0.001
Nasal obstruction	0.94	0.01	1.58	0.01	2.25	0.01	< 0.001
Ears/Throat itching	0.45	0.01	0.82	0.01	1.33	0.01	< 0.001
Nasal itching	1.12	0.01	1.97	0.01	2.79	0.01	< 0.001
Ocular itching	0.60	0.01	1.32	0.01	2.29	0.01	< 0.001
Rhinorrhoea	1.87	0.01	2.56	0.01	3.13	0.01	< 0.001
Sleep disturbed	0.87	0.01	1.25	0.01	1.64	0.01	< 0.001
Headache	0.60	0.01	0.88	0.01	1.20	0.01	< 0.001
Cough	0.73	0.01	1.00	0.01	1.27	0.01	< 0.001
	N (%)	SE	N, %	SE	N, %	SE	
Female	5,550 (52.27)	0.48	4,933 (52.22)	0.51	4,191 (52.09)	0.56	0.970
Rural	4,332 (40.80)	0.48	4,013 (42.48)	0.51	3,532 (43.90)	0.55	< 0.001
History of conjunctivitis	6,349 (59.80)	0.49	6,762 (71.59)	0.48	6,679 (83.01)	0.43	< 0.001
History of asthma	2,227 (20.98)	0.41	2,402 (25.43)	0.47	2,404 (29.88)	0.53	< 0.001
History of atopic dermatitis	1,472 (13.86)	0.35	1,554 (16.45)	0.40	1,521 (18.91)	0.46	< 0.001
History of food allergy	647 (6.09)	0.24	662 (7.01)	0.28	691 (8.59)	0.33	< 0.001
History of hives	1,766 (16.63)	0.38	1,780 (18.84)	0.42	1,761 (21.89)	0.48	< 0.001
Positive SPT	2,064 (19.44)	0.44	1,962 (20.77)	0.47	2,052 (25.52)	0.55	< 0.001
Positive specific IgE	1,042 (9.81)	0.32	1,104 (11.69)	0.37	1,153 (14.33)	0.43	< 0.001
Previous or concomitant AIT	813 (7.66)	0.26	660 (6.99)	0.27	721 (8.96)	0.33	< 0.001
Region							
- Centre	755 (7.11)	0.25	706 (7.47)	0.27	585 (7.27)	0.29	< 0.001
- East	1,232 (11.60)	0.31	1,210 (12.81)	0.34	1,068 (13.27)	0.38	
- North-west	1,518 (14.30)	0.34	1,317 (13.94)	0.36	1,022 (12.70)	0.37	
- Paris agglomeration	2,020 (19.03)	0.38	1,643 (17.39)	0.39	1,442 (17.92)	0.43	
- South-east	2,068 (19.48)	0.38	1,975 (20.91)	0.42	1,766 (21.95)	0.46	
- South-west	1,615 (15.21)	0.35	1,410 (14.93)	0.37	1,245 (15.47)	0.40	
- West	1,409 (13.27)	0.33	1,185 (12.54)	0.34	918 (11.41)	0.35	

SPT: skin prick tests; AIT: Allergen Immunotherapy; SE: Standard Error.

<sup>1</sup> Kruskal-Wallis test for continuous or ordinal variables, and  $\chi^2$ -test for categorical variables.

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terciles: we propose therefore cut-offs at a score of 8–9 for mild to moderate symptoms and of 11–12 for moderate to severe symptoms. To summarize, patients were classified as presenting with “mild” symptoms if they scored 0 to 8 with the ARPhyS scale; they had “moderate” symptoms if they scored 9 to 11; they should be considered as “severe” whenever they scored 12 to 20 (Table 5).



**Table 4. Cohen's  $\kappa$  matrix showing agreement between the different methods of classification.**

	KMC	AHC	ARPhyS	TSS-17	VAS
KMC	1	0.49	0.41	0.67	0.28
AHC	0.49	1	0.33	0.54	0.24
ARPhyS	0.41	0.33	1	0.45	0.25
TSS-17	0.67	0.54	0.45	1	0.32
VAS	0.28	0.24	0.25	0.32	1

KMC: k-means clustering; AHC: agglomerative hierarchical clustering; ARPhyS: Allergic Rhinitis Physician Score; TSS-17: Total Symptom Score with 17 items; VAS: Visual Analogue Scale (0–100). ARPhyS, TSS-17 and VAS are divided into tertiles; KMC and AHC are grouped into 3 clusters.

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### Missing data analysis

When analyzing data from the 8,288 patients excluded from the cohort, because of missing data, no significant statistical difference was highlighted when considering sex, age, history of conjunctivitis, asthma, atopic dermatitis, food allergy, hives, and positive SPT. Significant difference was on the contrary pointed out when evaluating other items: proportion of rural population included in the analysis was significantly higher than those who were not included due to missing data (43.4% vs. 39.9%;  $p < 0.001$ ); same considerations as for positive specific IgE (11.9% vs. 11.0%;  $p = 0.036$ ); at last, the included population underwent previous or concomitant allergen immunotherapy almost significantly more than the excluded group (7.9% vs. 7.3%;  $p = 0.048$ ).

### Discussion

When dealing with patients suffering from allergic rhinitis, physicians should be able to easily detect those presenting severe forms. In fact, severe AR patients may often suffer from comorbidities, may need more drugs to control their symptoms, and may present an impaired quality of life, besides being at risk for an increased loss of productivity and absenteeism [2]. The cost

**Table 5. The ARPhyS score, with cut-offs level to identify patient's severity.**

ARPhyS							
Please, rate the severity of each of the following symptoms as presented in this moment by your patient:							
		0	1	2	3	4	Score
A	Nasal obstruction	0	1	2	3	4	
		Absent	Mild	Moderate	Severe	Very severe	
B	Rhinorrhea	0	1	2	3	4	
		Absent	Mild	Moderate	Severe	Very severe	
C	Sneezes	0	1	2	3	4	
		Absent	Mild	Moderate	Severe	Very severe	
D	Nasal pruritus	0	1	2	3	4	
		Absent	Mild	Moderate	Severe	Very severe	
E	Ocular pruritus	0	1	2	3	4	
		Absent	Mild	Moderate	Severe	Very severe	
						Total Score	
If total score is 8 or less, then your patient presents <b>mild</b> symptoms							
If total score is between 9 and 11, then your patient presents <b>moderate</b> symptoms							
If total score is 12 or more, then your patient presents <b>severe</b> symptoms							

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of AR is therefore elevated when considering severe patients; in a recent study by Colás et al., the authors estimated that the cost of severe AR is of 2.965,28 € per year, including direct and indirect costs [2]. Therefore, it seems important to be able to promptly recognize severe forms to provide patients proper efficient treatments.

In recent years, cluster analysis has become more and more common to identify subgroups of patients: it consists in applying unsupervised statistical methods to a population with a wide distribution of related symptoms, and then identifying possible homogeneous phenotypes, with minimum overlap between each other [15]. In a work by Burte et al., the authors highlight three different clusters of rhinitis (allergic and non-allergic), from a population of 983 adults, but they do not differentiate them based on severity [17]. In a work by Bousquet PJ et al., on the contrary, the authors identified clusters of severe AR, in a population of 990 patients, and then compared them with the ARIA classification [15]. They found that, in *real-life*, physicians prescribe a therapy, with no regard to nasal symptoms severity [15], and therefore current guidelines and proposed cluster do not help general practitioners in stratifying the severity of patients presenting with AR. We identified three clusters, through two different methods, in a population of 28,109 patients. Clusters showed no overlap between each other. After evaluation through Fisher linear and quadratic discriminant analysis, and non-parametric kernel density estimation methods, we found that cluster analysis does not provide the best results in terms of discrimination, error rate and cross-validation, if compared to other assessed methods (Table 2).

Visual Analogue Scales, on the other hand, have been used for several diseases in recent years. They have been tested and validated for AR, even on smartphones screens [9]. This approach, advised by the novel ARIA guidelines, is useful to assess symptoms control and quality of life impairment, but also severity in patients suffering from AR [8,12]. In fact, a recent paper by Del Cuvillo et al. showed in a population of 3,572 patients that a VAS greater than 7 cm is a reliable score to identify severe patients (Negative Predictive Value, NPV, of a VAS above 7: 98.6%; Positive Predictive Value, PPV, at 7: 20.4%) [12]. A previous paper by Bousquet PJ et al., on a cohort of 3,052 patients, proposed a 5-cm cut-off for mild forms, while moderate to severe patients were to be considered for a VAS of over 6 cm (with a NPV of 56.5% and a PPV of 94.3%) [11]. The two papers found two different cut-offs, but in the study by Bousquet PJ et al., the authors only differentiated "mild" patients from "moderate/severe", while the study by del Cuvillo categorized patients into three severity groups (mild, moderate, and severe). On the other hand, in a paper by Rouve et al., it seemed that categorizing AR severity in patients through VAS brought to an exaggerated inclusion in the severe group [10]. In the present paper, we found that VAS proved the worst results in terms of discrimination and cross-validation (Table 2), and the least agreement in terms of results if compared with the other 4 tested methods (Table 4). Considering our findings from a very large cohort of patients, we may speculate that VAS is a useful tool for diagnosis and assessment of disease control, for both patients and physicians, but not the best tool for classifying patients according to severity by physicians. Another possible explanation of the discrepancy between our results and those from del Cuvillo and Bousquet PJ is that we only included patients suffering from seasonal AR, while the previous authors did not use such selection criterion.

In contrast with the ARIA guidelines, we found that the duration of the disease does not have a significant impact on the severity of symptoms, and such result confirms what had been previously stated by Bousquet PJ et al. [15]. Rather than differentiating the disease between intermittent and persistent, attention should be focused on nasal and ocular symptoms, based on our findings. In a study by Valero et al., the authors evaluated a TSS-4 to stratify AR patients, based on the clinical items proposed by the ARIA guidelines [14], and in a following study the authors validated the TSS-4 as a tool to assess severe forms [13]. Through these

papers, Valero et al. underlined that total symptoms scores seem to be practical methods for physicians to target severe patients, following current ARIA guidelines. Based on such considerations, in our study, even though the ARPhyS scale showed a Cronbach's alpha-coefficient inferior to the TSS-17, we chose the first questionnaire because, besides being superior as a discriminating method, it is also quicker and easier to use in everyday clinical practice. Also, the ARPhyS scale (Table 5) allowed us to identify tertiles that maximally correlated in the first canonical dimension and therefore to propose simple cut-offs to categorize AR into "mild", "moderate", and "severe". [11]. On the other hand, we really wanted to highlight the importance of identifying severe patients, since mild ones usually do not even consult their general practitioner for rhinitis symptoms, while severe may need a specialized approach in order to control their symptoms and comorbidities.

A possible limit of the study is that patients visiting physicians were only evaluated during spring and summer seasons, which might limit the generalizability of our results to patients visiting during autumn and winter seasons. However, the large sample size provides robustness in the results and we were able to propose a practical tool for physicians, which is fast and obtained from a *real-life* study.

The ARIA classification of AR severity is useful, especially to differentiate mild patients from the others. Several tools have been developed for physicians to assess severity and control in recent years. Such tools need to be easy-to-use and efficient, and, so far, only a few of them have been validated. Through the present study, we evaluated two different tools to assess AR severity: one composed by 17 questions and the other one, the ARPhyS scale, by 5 questions. When comparing our tool to the other tested methods, we found that the ARPhyS scale is the best in terms of discrimination and cross-validation. Also, it is an easy tool for physicians and we found some cut-off values able to differentiate mild patients from moderate, and from severe ones. Such tool could therefore be implemented in daily practice to identify severe patients that need a specialized intervention or anyway a more important therapeutic treatment.

### Author Contributions

**Conceptualization:** Isabella Annesi-Maesano.

**Data curation:** Davide Caimmi, Nour Baiz, Soutrik Banerjee.

**Formal analysis:** Davide Caimmi.

**Methodology:** Davide Caimmi, Shreosi Sanyal, Soutrik Banerjee.

**Project administration:** Isabella Annesi-Maesano.

**Supervision:** Nour Baiz, Pascal Demoly, Isabella Annesi-Maesano.

**Validation:** Pascal Demoly, Isabella Annesi-Maesano.

**Writing – original draft:** Davide Caimmi.

**Writing – review & editing:** Shreosi Sanyal, Pascal Demoly.

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## **Contribution de bases de données en vie réelle de patients adultes souffrant de rhinite allergique**

Résumé : La prévalence de la rhinite allergique (RA) est en augmentation dans le monde entier. Malheureusement, cette maladie est souvent considérée comme triviale, et les patients ont une tendance à ne pas consulter un médecin, malgré le fait que la RA a un impact très important sur leur qualité de vie. Les recommandations ARIA conseillent d'évaluer la sévérité de la maladie avant traitement et le contrôle des symptômes au cours du suivi pour optimiser le traitement, améliorer la qualité de vie des patients, et diminuer le coût de la RA. En analysant des bases de données en vie réelle, nous avons détecté un score simple et pratique qui permet aux médecins d'évaluer la sévérité de la RA et nous avons validé un système pour vérifier le contrôle des symptômes par *visual analogue scale* (VAS) sur l'écran des smartphones. Cette validation se base sur les données recueillies par l'application pour smartphones « MASK-Air® » et a été réalisé selon les recommandations COSMIN, avec évaluation, de la cohérence interne, de la fiabilité, de la sensibilité, et de l'acceptabilité. Le score pour évaluer la sévérité se base sur les résultats de l'étude Pollin'Air, après comparaison de 5 méthodes de classification des patients (deux types d'analyses en cluster, un score à 17 questions, le score ARPhyS à 5 questions et le VAS). L'évaluation de la sévérité et du contrôle de la RA sont essentielles pour bien gérer les patients, leurs symptômes et leur qualité de vie. Grâce à l'analyse de bases de données en vie réelle, nous avons validé des outils faciles à utiliser et à comprendre, et rapides à compléter, et qui peuvent donc être vraiment utilisés dans la pratique clinique.

Mots clés : ARPhyS ; bases de données ; contrôle ; rhinite allergique ; sévérité ; VAS.

## **Contribution of real-life databases of adult patients suffering from allergic rhinitis**

Abstract: The prevalence of allergic rhinitis (AR) is increasing worldwide. Unfortunately, this disease is often considered as trivial, and patients tend not to consult their physician, and even less a specialist, even though AR has a very significant impact on the quality of life of patients, which translates into a risk of absenteeism and impaired presenteeism. ARIA guidelines recommend evaluating the severity of the disease before treatment and the control of symptoms during follow-up to optimize treatment, improve patients' quality of life, and reduce the direct and indirect cost of AR. By analyzing real-life databases, we detected a simple and practical score that allows physicians to assess AR severity and we validated a system to verify the control of symptoms by a visual analogue scale (VAS) on smartphone screens. This last validation was based on data collected by the "Allergy Diary / MASK-Air®" application for smartphones of the MASK study. It was carried out according to COSMIN criteria, with an evaluation, among other things, of internal consistency, reliability, sensitivity, and acceptability. The score to assess AR severity is based on the results of the Pollin'Air study, after comparison of 5 methods for patients' classification (two types of cluster analyses, a 17-question score, the 5-question ARPhyS score and the VAS). Assessing both severity and control in AR is essential to properly manage patients, their symptoms and quality of life. Through the analysis of real-life databases, we validated tools that are easy to use and understand, and quick to complete, therefore meet the essential characteristics to be truly used in clinical practice.

Keywords : allergic rhinitis ; ARPhyS ; control ; databases ; severity ; VAS.