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# Rhinitis phenotypes and multimorbidities in the general population: the CONSTANCES cohort

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Shareable abstract (@ERSpublications)

**For the first time in a general adult population, this study shows novel rhinitis phenotypes based on allergic rhinitis and non-allergic rhinitis multimorbidities, and that participants with asthma and conjunctivitis had more severe rhinitis** <https://bit.ly/3ReCsoN>

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## Abstract

**Background** Scarce epidemiological studies have characterised allergic rhinitis (AR) and non-allergic rhinitis (NAR) in adults. In a population-based cohort, our aims were to 1) describe rhinitis, AR and NAR, and 2) explore how asthma and conjunctivitis may lead to the identification of novel rhinitis phenotypes.

**Methods** In this cross-sectional analysis, current rhinitis was defined as present in the last 12 months using a questionnaire from the French CONSTANCES cohort. Participants with current rhinitis reporting nasal allergies were considered as AR, otherwise as NAR. We described AR and NAR phenotypes, and their phenotypes including co-occurrence with ever-asthma and ever-conjunctivitis.

**Results** Among the 20 772 participants included in this analysis (mean±SD age 52.6±12.6 years; 55.2% female), crude prevalences of AR and NAR were 28.0% and 10.9%. AR participants more frequently reported persistent rhinitis (31.6% *versus* 25.1%) and moderate-to-severe rhinitis (40.1% *versus* 24.2%) than NAR participants. Among AR or NAR participants, those with ever-asthma reported more moderate-to-severe rhinitis. Participants with AR, ever-asthma and ever-conjunctivitis had an earlier age of rhinitis onset, more severe rhinitis and higher eosinophil counts than participants in other groups. Results were replicated in another cohort.

**Conclusions** In this large population-based cohort, 40% reported current rhinitis, with a lower prevalence of moderate-to-severe rhinitis than in clinical practice. For the first time in a general adult population, we showed that AR and NAR alone or in combination with asthma or in combination with asthma and conjunctivitis are different phenotypes. These results provide new insights on how best to manage rhinitis and its multimorbidities.

## Introduction

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

Behind the apparent simplicity of its clinical definition, rhinitis is a complex and heterogeneous disease characterised by several phenotypes. After excluding acute infectious rhinitis, rhinitis can be divided into two major phenotypes: allergic rhinitis (AR) and non-allergic rhinitis (NAR). AR is caused by



IgE-mediated reactions to inhaled allergens and NAR is a heterogeneous group of nasal conditions [4]. However, allergic and non-allergic mechanisms are often intertwined. AR and NAR even share some common symptoms (nasal congestion and rhinorrhoea), but they have different clinical features and treatments [5]. AR usually starts in childhood, whereas NAR often appears later. Many patients with AR have a seasonal exacerbation of symptoms, mainly due to aeroallergen exposure, and AR is characterised by the presence of the full spectrum of nasal symptoms, which are frequently associated with eye symptoms [5]. Most NAR patients have symptoms triggered by non-allergenic exposures and ocular symptoms appear to be uncommon [5]. However, most of this knowledge on rhinitis is derived from clinical practice, and there are few epidemiological studies in the general adult population that have assessed the prevalence and characteristics of phenotypes of rhinitis. Furthermore, few of them have assessed NAR [3, 6, 7].

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

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

## Methods

### *Study design*

A cross-sectional study was carried out with the data from the 2014 annual follow-up of CONSTANCES. CONSTANCES is a population-based cohort of almost 220 000 adults aged 18–69 years at inclusion, randomly selected from social security affiliates in France (<https://www.constances.fr>). The participants were enrolled from 2012 to 2020 in 20 administrative districts (supplementary figure S1). At inclusion, participants completed standardised questionnaires and had a complete medical examination [11–13]. Annual follow-ups were done by questionnaire.

All participants who were included until the end of 2013 received the 2014 questionnaire that included two pages of detailed, validated and standardised questions on rhinitis (supplementary material).

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

### *Definitions*

#### *Rhinitis*

We defined current and ever-rhinitis using the standardised questions proposed in the International Study of Asthma and Allergies in Childhood (ISAAC) [14], as recommended by Allergic Rhinitis and its Impact on Asthma (ARIA) [15]. Participants were considered as having ever-rhinitis if they answered yes to “During your lifetime, have you ever had a problem with sneezing, or a runny, or a blocked nose when you did not have a cold or the flu?”, otherwise participants who answered no were classified as never having rhinitis. Among those with ever-rhinitis, participants were classified as having current rhinitis if they answered yes to “Have you had these problems in the last 12 months?”, otherwise participants who answered no were classified as having non-current rhinitis.

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

Definitions of rhinitis duration, rhinitis severity and reported symptoms are described in the supplementary material.

### Asthma

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

### Conjunctivitis

Participants were considered as having ever-conjunctivitis if they answered yes at the 2014 annual follow-up questionnaire to “During your lifetime, have you ever had allergic conjunctivitis?”.

### Statistical methods

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

The Chi-squared test for categorical variables and the t-test (when comparing two groups) or ANOVA comparison of variances (when comparing more than two groups) for continuous variables were used. We also conducted sensitivity analyses using alternative definitions to distinguish AR from NAR: one definition based on the triggers of nasal symptoms and one definition based on the classification tree obtained by BURTE *et al.* [18] with an unsupervised approach to identify AR and NAR (supplementary material).

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

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

### Replication study

To validate our findings, we replicated some analyses in the case-control EGEEA study. We used a rhinitis definition based on very similar questions. EGEEA participants also had biomarkers and tests of allergic sensitisation (total IgE and skin prick tests (SPTs) to 12 allergens) (supplementary material).

## Results

### Demographic characteristics of the participants

The 2014 annual follow-up questionnaire was sent to 26 737 participants included by 2013 and was completed by 21 507 (80%) of them. Participants with missing data regarding the definitions of rhinitis ( $n=497$ ) or nasal allergies ( $n=238$ ) were excluded from the analyses (supplementary figure S2). Non-included participants were on average more often male, younger, smokers, with a lower level of education and a higher body mass index, and reported more ever-asthma than included participants (supplementary table S1).

There were 20 772 participants included in the main analyses (mean $\pm$ SD age 52.6 $\pm$ 12.6 years; 55.2% female). Among them, 13.5% were current smokers, 12.7% reported ever-asthma and 29.2% reported ever-conjunctivitis (table 1).

### AR and NAR

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

The characteristics of the participants according to their rhinitis status (never, non-current or current) are presented in table 1. Participants with current rhinitis were more often female, younger, with a higher education level, had higher eosinophil counts, and had more ever-asthma, ever-conjunctivitis and ever-eczema than participants with never-rhinitis or with non-current rhinitis.

Participants with current AR reported significantly more often ever-asthma, ever-conjunctivitis and ever-eczema than those with NAR (table 2). The age of rhinitis onset was on average 10 years earlier for AR compared with NAR. AR participants reported more nasal symptoms than NAR participants; the

TABLE 1 Characteristics of participants according to their rhinitis status

	All (n=20 772)	Never-rhinitis (n=9674)	Non-current rhinitis (n=3029)	Current rhinitis (n=8069)	p-value
<b>Sex</b>					<0.0001
Male	9297 (44.8)	4358 (45.0)	1459 (48.2)	3480 (43.1)	
Female	11 475 (55.2)	5316 (55.0)	1570 (51.8)	4589 (56.9)	
<b>Age, years</b>					<0.0001
<30	1057 (5.1)	470 (4.9)	123 (4.1)	464 (5.8)	
[30–45[	4924 (44.1)	2181 (22.5)	645 (21.3)	2098 (26.0)	
[45–60[	7648 (36.8)	3659 (37.8)	1184 (39.1)	2805 (34.8)	
≥60	7143 (34.4)	3364 (34.8)	1077 (35.6)	2702 (33.5)	
<b>Tobacco status</b>					0.063
Never-smoker	9164 (46.4)	4353 (47.3)	1323 (46.0)	3488 (45.5)	
Ex-smoker	7904 (40.0)	3588 (39.0)	1157 (40.2)	3159 (41.2)	
Current smoker	2675 (13.5)	1259 (13.7)	398 (13.8)	1018 (13.3)	
<b>Educational level</b>					<0.0001
Less than high school	1938 (9.4)	927 (9.7)	316 (10.6)	695 (8.7)	
High school	6755 (32.9)	3321 (34.7)	1036 (34.8)	2398 (30.1)	
University	11 825 (57.6)	5316 (55.6)	1625 (54.6)	4884 (61.2)	
<b>Body mass index, kg·m<sup>-2</sup></b>					0.019
<18.5	460 (2.3)	222 (2.3)	66 (2.2)	172 (2.2)	
[18.5–25[	11 510 (56.5)	5327 (56.2)	1610 (54.1)	4573 (57.9)	
[25–30[	6283 (30.9)	2970 (31.3)	966 (32.5)	2347 (29.7)	
≥30	2104 (10.3)	968 (10.2)	332 (11.2)	804 (10.2)	
<b>Asthma</b>					<0.0001
Never-asthma	17 793 (87.3)	8948 (94.2)	2485 (83.8)	6360 (80.4)	
Ever-asthma	2579 (12.7)	549 (5.8)	481 (16.2)	1549 (19.6)	
<b>Conjunctivitis</b>					<0.0001
Never-conjunctivitis	13 354 (70.8)	7582 (85.3)	1803 (65.9)	3969 (54.8)	
Ever-conjunctivitis	5509 (29.2)	1308 (14.7)	931 (34.1)	3270 (45.2)	
<b>Eczema</b>					<0.0001
Never-eczema	13 631 (71.9)	7166 (79.4)	1883 (68.7)	4582 (63.7)	
Ever-eczema	5337 (28.1)	1863 (20.6)	858 (31.3)	2616 (36.3)	
<b>Blood eosinophil count, cells·mm<sup>-3</sup></b>	185.5±126.2	172.0±112.2	189.7±125.5	199.8±139.7	<0.0001
<b>Age of onset of rhinitis, years</b>	26.3±16.1	NA	25.2±15.1	26.7±16.5	0.0002

Data are presented as n (%) or mean±SD, unless otherwise stated. NA: not applicable.

highest differences between the two groups were observed for associated eye symptoms (68.8% versus 35.3%) and nasal itching (67.0% versus 39.7%). AR participants reported more persistent symptoms (31.6% versus 25.1%) and more moderate-to-severe rhinitis (40.1% versus 24.2%) than NAR participants. Triggers of rhinitis symptoms differed between AR and NAR: the largest differences were observed for pollens (52.3% versus 10.2%), dust mites/house dust (33.4% versus 10.4%) and unknown triggers (27.1% versus 48.6%). Treatments by oral antihistamines and intranasal corticosteroids were reported by 32.0% of AR participants and 6.0% of NAR participants.

The seasonality of symptoms differed between AR and NAR: AR participants reported symptoms mainly during the spring, whereas NAR participants reported symptoms mainly during the winter (figure 1).

Using alternative definitions of rhinitis, the crude prevalence of current AR varied from 20.3% to 28.4% and that of current NAR varied from 10.0% to 18.6% (supplementary table S2). The  $\kappa$  concordance coefficient between the main definition and the alternative definitions was the highest for the alternative definition based on the classification tree adaptation ( $\kappa=0.96$ ) and the lowest for the alternative definition based on the symptom triggers ( $\kappa=0.37$ ). Similar differences between AR and NAR were found with the main and alternative definitions in terms of multimorbidities, reported symptoms, triggers, seasonality and treatments (supplementary table S3 and supplementary figures S3 and S4).

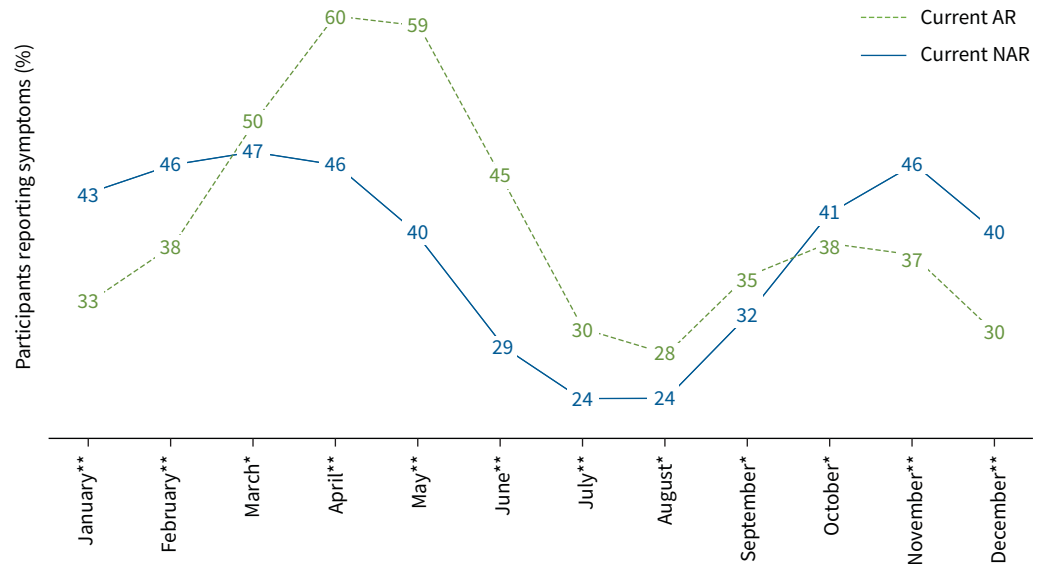
#### *Rhinitis phenotypes including ever-asthma and ever-conjunctivitis status*

Among AR participants, 1383 reported ever-asthma (24.3%). Among NAR participants, 166 reported ever-asthma (7.5%) (table 3). Among both AR and NAR participants, those who reported ever-asthma had

**TABLE 2** Characteristics of participants with current rhinitis, current allergic rhinitis (AR) or current non-allergic rhinitis (NAR)

	All current rhinitis (n=8069)	AR (n=5806)	NAR (n=2263)	p-value
<b>Sex</b>				0.072
Male	3480 (43.1)	2468 (42.5)	1012 (44.7)	
Female	4589 (56.9)	3338 (57.5)	1251 (55.3)	
<b>Age, years</b>	51.9±12.9	51.7±12.8	52.4±13.3	0.036
<b>Tobacco status</b>				0.0044
Never-smoker	3488 (45.5)	2534 (46.0)	954 (44.3)	
Ex-smoker	3159 (41.2)	2289 (41.5)	870 (40.4)	
Current smoker	1018 (13.3)	688 (12.5)	330 (15.3)	
<b>Educational level</b>				0.77
Less than high school	695 (8.7)	495 (8.6)	200 (8.9)	
High school	2398 (30.1)	1717 (29.9)	681 (30.4)	
University	4884 (61.2)	3528 (61.5)	1356 (60.6)	
<b>Body mass index, kg·m<sup>-2</sup></b>				0.34
<18.5	172 (2.2)	124 (2.2)	48 (2.2)	
[18.5–25[	4573 (57.9)	3264 (57.5)	1309 (59.0)	
[25–30[	2347 (29.7)	1690 (29.8)	657 (29.6)	
≥30	804 (10.2)	599 (10.6)	205 (9.2)	
<b>Asthma</b>				<0.0001
Never-asthma	6360 (80.4)	4304 (75.7)	2056 (92.5)	
Ever-asthma	1549 (19.6)	1383 (24.3)	166 (7.5)	
<b>Conjunctivitis</b>				<0.0001
Never-conjunctivitis	3969 (54.8)	2317 (44.7)	1652 (80.4)	
Ever-conjunctivitis	3270 (45.2)	2868 (55.3)	402 (19.6)	
<b>Eczema</b>				<0.0001
Never-eczema	4582 (63.7)	3021 (59.2)	1561 (74.5)	
Ever-eczema	2616 (36.3)	2081 (40.8)	535 (25.5)	
<b>Blood eosinophil count, cells·mm<sup>-3</sup></b>	199.8±139.7	208.6±146.4	177.3±117.9	<0.0001
<b>Age of onset of rhinitis, years</b>	26.7±16.5	24.3±15.3	34.6±17.5	<0.0001
<b>Reported triggers of rhinitis symptoms<sup>#</sup></b>				
Dust mites or house dust	2172 (26.9)	1937 (33.4)	235 (10.4)	<0.0001
Animals	732 (9.1)	677 (11.7)	55 (2.4)	<0.0001
Air pollution	1847 (22.9)	1560 (26.9)	287 (12.7)	<0.0001
Change in weather	2278 (28.2)	1677 (28.9)	601 (26.6)	0.037
Tobacco	452 (5.6)	359 (6.2)	93 (4.1)	0.0003
Pollens	3266 (40.5)	3035 (52.3)	231 (10.2)	<0.0001
Cold air	2050 (25.4)	1423 (24.5)	627 (27.7)	0.0030
Other	1017 (12.6)	735 (12.7)	282 (12.5)	0.81
Unknown	2673 (33.1)	1573 (27.1)	1100 (48.6)	<0.0001
<b>Reported symptoms<sup>#</sup></b>				
Rhinorrhoea	5266 (70.7)	4051 (75.1)	1215 (59.0)	<0.0001
Nasal congestion/obstruction	5257 (72.4)	4000 (76.3)	1257 (62.1)	<0.0001
Nasal itching	4212 (59.5)	3445 (67.0)	767 (39.7)	<0.0001
Sneezing	5128 (69.4)	4073 (75.9)	1055 (52.2)	<0.0001
Associated eye symptoms	4391 (59.8)	3693 (68.8)	698 (35.3)	<0.0001
<b>Reported symptoms, n</b>	3.2±1.4	3.6±1.3	2.3±1.3	<0.0001
<b>Rhinitis severity</b>				<0.0001
Mild	4253 (64.3)	2862 (59.9)	1391 (75.8)	
Moderate-to-severe	2358 (35.7)	1913 (40.1)	445 (24.2)	
<b>Rhinitis duration</b>				<0.0001
Intermittent	5422 (70.2)	3798 (68.4)	1624 (74.9)	
Persistent	2302 (29.8)	1758 (31.6)	544 (25.1)	
<b>Rhinitis treatment</b>				<0.0001
Neither OA nor INCS	3507 (45.1)	1911 (34.1)	1596 (73.5)	
OA only	1322 (17.0)	1204 (21.5)	118 (5.4)	
INCS only	1025 (13.2)	700 (12.5)	325 (15.0)	
OA and INCS	1925 (24.7)	1794 (32.0)	131 (6.0)	

Data are presented as n (%) or mean±SD, unless otherwise stated. OA: oral antihistamine; INCS: intranasal corticosteroid. #: several possible answers.



**FIGURE 1** Percentage of current allergic rhinitis (AR) and current non-allergic rhinitis (NAR) participants reporting symptoms by month. \*:  $p < 0.05$ ; \*\*:  $p < 0.0001$ .

higher eosinophil counts, an earlier age of rhinitis onset and more moderate-to-severe rhinitis than those without asthma. Participants with AR and ever-asthma also reported more ever-conjunctivitis and ever-eczema than those with AR only. These differences were not significant for participants with NAR, even if the tendency was the same.

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

In CONSTANCES, the characteristics of AR participants with and without ever-asthma and ever-conjunctivitis ( $n=1855$  AR only,  $n=1958$  AR plus ever-conjunctivitis,  $n=418$  AR plus ever-asthma and  $n=848$  AR plus ever-conjunctivitis plus ever-asthma) are shown in table 4. Statistically significant differences were observed for almost all the characteristics. In particular, participants with AR plus ever-conjunctivitis plus ever-asthma had an earlier age of rhinitis onset, more moderate-to-severe rhinitis, reported more comedication (intranasal corticosteroids and antihistamines) and had higher blood eosinophil counts than participants from all other groups.

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

## Discussion

In a large population-based study, four out of 10 adults reported current rhinitis and 30% of them reported moderate-to-severe rhinitis. We found the well-known characteristics of AR and NAR with questionnaire-based definitions. We showed that AR and NAR alone or with asthma or with asthma and conjunctivitis are different phenotypes.

## Strengths and limitations

CONSTANCES is the largest French population-based epidemiological study in adults. CONSTANCES is, however, not fully representative of the French adult population as 1) participants were randomly selected from the beneficiaries of the National Health Insurance Fund (“Caisse Nationale d’Assurance Maladie”

TABLE 3 Characteristics of participants with current allergic rhinitis (AR) or current non-allergic rhinitis (NAR) including ever-asthma status

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

Data are presented as n (%) or mean±sd, unless otherwise stated. OA: oral antihistamine; INCS: intranasal corticosteroid. #: several possible answers.



**TABLE 4** Characteristics of participants with current allergic rhinitis (AR) including ever-asthma (A) and ever-conjunctivitis (C) status

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

Data are presented as n (%) or mean±SD, unless otherwise stated. OA: oral antihistamine; INCS: intranasal corticosteroid. #: several possible answers.

(CNAM)) that covered ~85% of the French population and 2) some geographical areas of France were not included. This may lead to a misestimation of the actual rhinitis prevalence. Furthermore, the 2014 population is even more selected, mainly regarding age, with few participants <30 years old. This may have slightly impacted the characterisation and identification of our phenotypes. Recall bias is possible, more likely for ever-asthma than for current rhinitis as the questions on current rhinitis characteristics covered the last 12 months, limiting memory issues.

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

We defined ever-asthma based on a validated and standardised question used in ECRHS [16], and recently published in CONSTANCES [19, 20].

### *Interpretation of results*

The prevalence of current rhinitis in our population was 40%. This result is difficult to compare with the literature as the definition of rhinitis varies greatly between studies and ranges from <10% to >50% [1]. According to ARIA 2008 [1], the prevalence of AR was estimated to be ~25% of the general European population, which is consistent with our findings. Three studies conducted in Belgium, Sweden and Italy found very similar prevalences of NAR, between 9.6% and 12.0% [21–23]. Recently, a study in the Netherlands found a prevalence of NAR of 26% [7]. The actual prevalence of rhinitis may be underestimated because most studies had only considered AR. Studies considering both AR and NAR are needed to obtain an overall prevalence of rhinitis and to confirm our results.

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

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

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

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

For the first time in adults from a population-based study, we described phenotypes of AR and NAR accounting for ever-asthma status. We observed contrasting characteristics across the groups. Our results showed that compared with AR participants without ever-asthma, those with ever-asthma reported 1) earlier onset of the disease, 2) more frequent moderate-to-severe rhinitis, 3) more conjunctivitis and eczema multimorbidities, 4) a higher level of blood eosinophils, and 5) more comedication. This latter finding suggests a more severe AR [30]. We validated these results by finding similar characteristics for all groups in the EGEA study. Moreover, allergen sensitisation is available in EGEA and there was an increased number of sensitisations in AR with asthma [10]. It therefore appears that rhinitis alone and rhinitis and asthma represent two different diseases as found in real-life [31, 32] and genetic studies: rhinitis alone being associated with Toll-like receptors, and rhinitis and asthma multimorbidity with interleukin (IL)-5 (associated with eosinophilia) and IL-33 [33]. However, biological pathways that are involved in rhinitis alone *versus* rhinitis with asthma are only partly understood and further studies are needed to understand the underlying biological mechanisms involved in the aetiology of these phenotypes.

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

#### *Implications of all the available evidence*

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

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

#### *Conclusions*

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

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