Received: 31 August 2021 | Revised: 1 December 2021 | Accepted: 21 December 2021

DOI: 10.1111/all.15223

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

ORIGINAL ARTICLE

Rhinitis, Sinusitis and Upper Airway Disease

The prevalence of non-allergic rhinitis phenotypes in the general population: A cross-sectional study

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Abstract

Background: Non-allergic rhinitis (NAR) can be subdivided into several phenotypes: rhinorrhea of the elderly, rhinitis medicamentosa, smokers', occupational, hormonal, drug-induced, gustatory, and idiopathic rhinitis. There are two pathophysiological endotypes of NAR: inflammatory and neurogenic. Phenotypes may serve as an indicator of an underlying endotype and, therefore, help to guide the treatment. The prevalence of each phenotype in the general population is currently unknown.

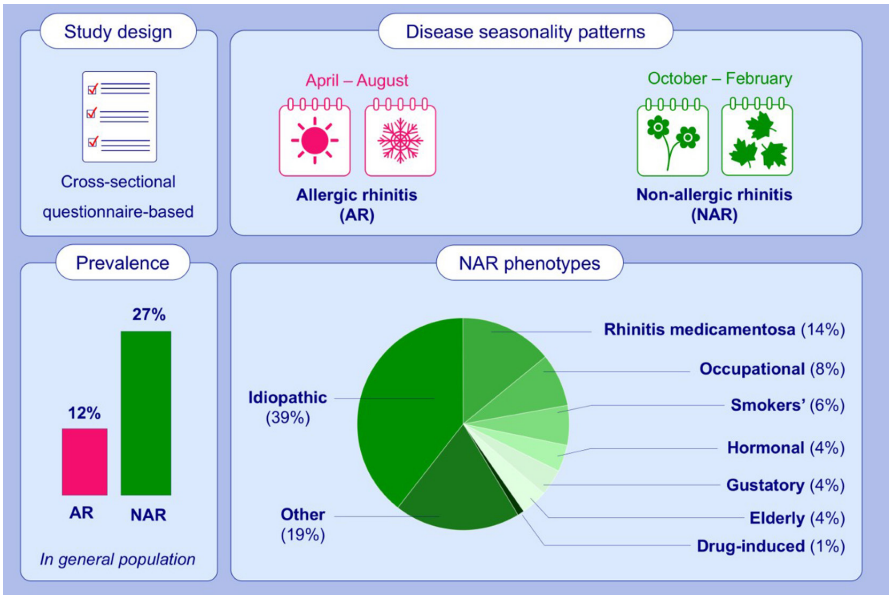
Methodology/Principal: Cross-sectional questionnaire-based study in the general population of the Netherlands.

Results: The prevalence of chronic rhinitis in the general population was 40% ($N = 558$, of those, 65% had NAR and 28% AR, in 7% allergy status is unknown). Individuals with NAR ($N = 363$) had significantly more complaints in October–February. Those with AR ($N = 159$) had significantly more complaints in April–August. The most common NAR phenotypes were idiopathic (39%) and rhinitis medicamentosa (14%), followed by occupational (8%), smokers' (6%), hormonal (4%), gustatory (4%), and rhinorrhea of the elderly (4%). The least prevalent phenotype was drug induced (1%). Nineteen percent of the NAR group could not be classified into any of the phenotypes.

Conclusions: This is the first study to describe the prevalences of NAR phenotypes in the general population. AR and NAR have a distinct seasonality pattern with NAR being more prevalent in autumn/winter and AR in spring/summer. Our data on the prevalence of phenotypes may help clinicians to anticipate the type of patients at their clinic and help guide a tailored treatment approach. The high prevalence of rhinitis medicamentosa is alarming, since this is a potentially preventable phenotype.

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

Abbreviations: AR, Allergic rhinitis; CR, Chronic rhinitis; CRSwNP, Chronic rhinosinusitis with nasal polyps; DR, Drug-induced rhinitis; HR, Hormonal rhinitis; IR, Idiopathic rhinitis; LAR, Local allergic rhinitis; MWU, Mann-Whitney U; NAR, Non-allergic rhinitis; NARES, Non-allergic rhinitis with eosinophilia syndrome; ND, Nasal decongestant; NERD, NSAID-exacerbated respiratory disease; NSAID, Non-steroid anti-inflammatory drug; OCP, Oral contraceptive pill; OR, Occupational rhinitis; PDE5, Phosphodiesterase 5; RM, Rhinitis medicamentosa; RoE, Rhinorrhea of the elderly; SR, Smokers rhinitis; URTI, Upper respiratory tract infection; VAS, Visual analogue scale; WHO, World health organization.



GRAPHICAL ABSTRACT

The prevalence of NAR and AR in general population: 27% and 12%. AR symptoms get worse in spring/ summer, NAR symptoms in autumn/ winter. The prevalences of NAR phenotypes: idiopathic 39%, rhinitis medicamentosa 14%, occupational 8%, smokers' 6%, hormonal 4%, rhinorrhoea of the elderly 4%, gustatory 4% and drug-induced 1%. Nineteen percent could not be defined in neither of the phenotypes. Abbreviations: AR, allergic rhinitis; NAR, non-allergic rhinitis

1 | INTRODUCTION

Non-allergic rhinitis (NAR) is a form of chronic rhinitis (CR) that is characterized by rhinorrhea, blocked nose, sneezing, and/or itchy nose without clinical signs of infection or allergy.[1,2] NAR decreases the quality of life[3] and has a substantial financial impact.[4] We have recently suggested that CR (and, consequently, NAR) should be defined in epidemiological studies as the presence of at least one nasal symptom for more than 21 days per year.[5] When this definition was applied to the general population, the prevalence of CR was 40% (65% NAR, 28% allergic rhinitis (AR), and in 7% allergy status was unknown).[5]

NAR is an umbrella term that covers a heterogeneous group of patients whose complaints have different phenotypes and endotypes and, therefore, require different treatment strategies. To choose the best treatment for each patient, it is necessary to understand the underlying endotype. While in clinical practice, determination of endotype in each patient is not technically feasible, and phenotypes may serve as a predictor[1] and, therefore, may help to tailor the treatment. Additionally, understanding the (prevalence of the) phenotypes of NAR may help clinicians to expect what kind of NAR patients they will most often encounter. The phenotypes of NAR defined/mentioned in the EAACI taskforce paper include rhinitis (rhinorrhea) of the elderly, *rhinitis medicamentosa*, smokers', occupational, hormonal, drug-induced, gustatory, and idiopathic rhinitis. Rhinitis medicamentosa is a subtype of drug-induced rhinitis, which we propose to distinguish as a separate phenotype due to a different route of the drug administration and the underlying mechanism.

The term "idiopathic rhinitis" is used when a patient does not fit into any of the aforementioned phenotypes and suffers from NHR. NHR is the stimulation of one or more nasal symptoms upon encounter of unspecific environmental stimuli, such as temperature or humidity changes, strong odors, or smoke[1] and is objectively confirmed by cold-dry air provocation.[6] NHR is a common phenomenon in rhinitis and rhinosinusitis.[7-9]

The most important endotypes of NAR are inflammatory and neurogenic (Figure 1).[1]

Some NAR phenotypes clearly belong to one endotype: idiopathic,[10] rhinorrhea of the elderly, and gustatory rhinitis are of the neurogenic endotype.[11] Other phenotypes, for example, occupational rhinitis, may belong to both inflammatory and neurogenic, depending on the agent that has led to the development of the symptoms.[1] Mechanisms behind several phenotypes, for example, hormonal, are not completely understood.[11,12]

Apart from the obvious subtypes of AR and NAR, some potential intermediate phenotypes, both with an inflammatory endotype,[1] exist: local allergic rhinitis (LAR) and non-allergic rhinitis with eosinophilia syndrome (NARES). LAR is characterized by local production of specific IgE during nasal exposure to aeroallergens[13-16] in the absence of systemic atopy.[17] Whether LAR should be considered a subtype of AR, NAR, or an independent entity is a subject of debate.[18] On the one hand, LAR is similar to AR in terms of pulmonary comorbidities,[17] sensitizations to aeroallergens tested by nasal provocation testing,[13] and treatment strategies.[19,20] On the other hand, LAR does not evolve into systematic atopy over time.[17] Besides, LAR and AR may co-exist in a form of

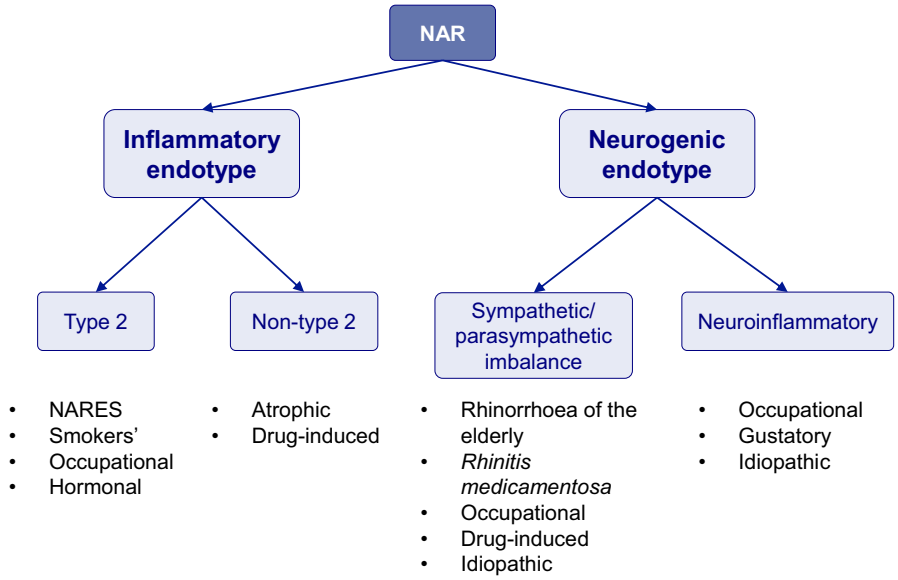


FIGURE 1 Endotype and phenotype of NAR

so-called dual-allergic rhinitis.[21,22] NARES is characterized by the presence of eosinophils in nasal mucosa in patients with NAR.[23] Seeing that local eosinophilia is present in both conditions[24] and the fact that studies describing NARES did not perform intranasal allergen provocations nor measurement of nasal IgE,[25,26] LAR is possibly a subtype of NARES. On the other hand, some studies claim that these are two independent subtypes[11]: in the study by Meng et al., NARES was characterized by high eosinophil cationic protein, whereas LAR was characterized by high histamine.[24] Another study demonstrated the absence of allergen-specific IgE in NARES,[12] which is characteristic of LAR. For this study, we consider LAR to be a form of AR because it cannot be discriminated with a questionnaire only from AR.

We found a prevalence of NAR of 28% in general population.[5] To the best of our knowledge, the prevalence of the different phenotypes of NAR is currently unknown. Seeing that phenotypes may serve as an indicator of an underlying endotype, knowledge about their prevalence may help clinicians to expect the phenotypes they will most often encounter in daily practice and to choose tailored treatment strategies. The aim of this study was to determine the prevalence of NAR phenotypes in the general population.

2 | METHODS

We performed a cross-sectional, questionnaire-based study in a random sample of participants representing the general population of the Netherlands. Informed consent was obtained from all participants. The same subset of participants was used for an early published paper on the definition of CR.[5] The questionnaire (Attachment 1) included questions intended to define each of the phenotypes.

2.1 | Definitions used

2.1.1 | Chronic rhinitis

CR was defined as the presence of nasal complaints about at least 21 days/year or a history of a positive allergy test and nasal medication use (outside of periods with common cold), irrespective of duration of the complaints.

2.1.2 | AR and NAR

When the participants fulfilled the CR criteria and answered affirmatively on the question whether they had allergic rhinitis or hay fever, they were considered as having (self-reported) AR. When the answer was negative, they were considered as having NAR, unless they had only eye symptoms ($N = 14$). Every patient who missed the question "Do you have allergic rhinitis" was excluded from this analysis.

2.1.3 | Nasal complaints

We asked participants which of the nasal complaints they had for at least one hour per day on most days of the week (hereinafter termed "regular nasal complaints"). Additionally, we asked them which of the aforementioned complaints they were experiencing at the time of filling in the questionnaire (hereinafter "current nasal complaints").

2.1.4 | Definitions of phenotypes

The phenotypes were defined according to EAACI position paper on NAR.[1] The algorithm used for phenotypes definitions is

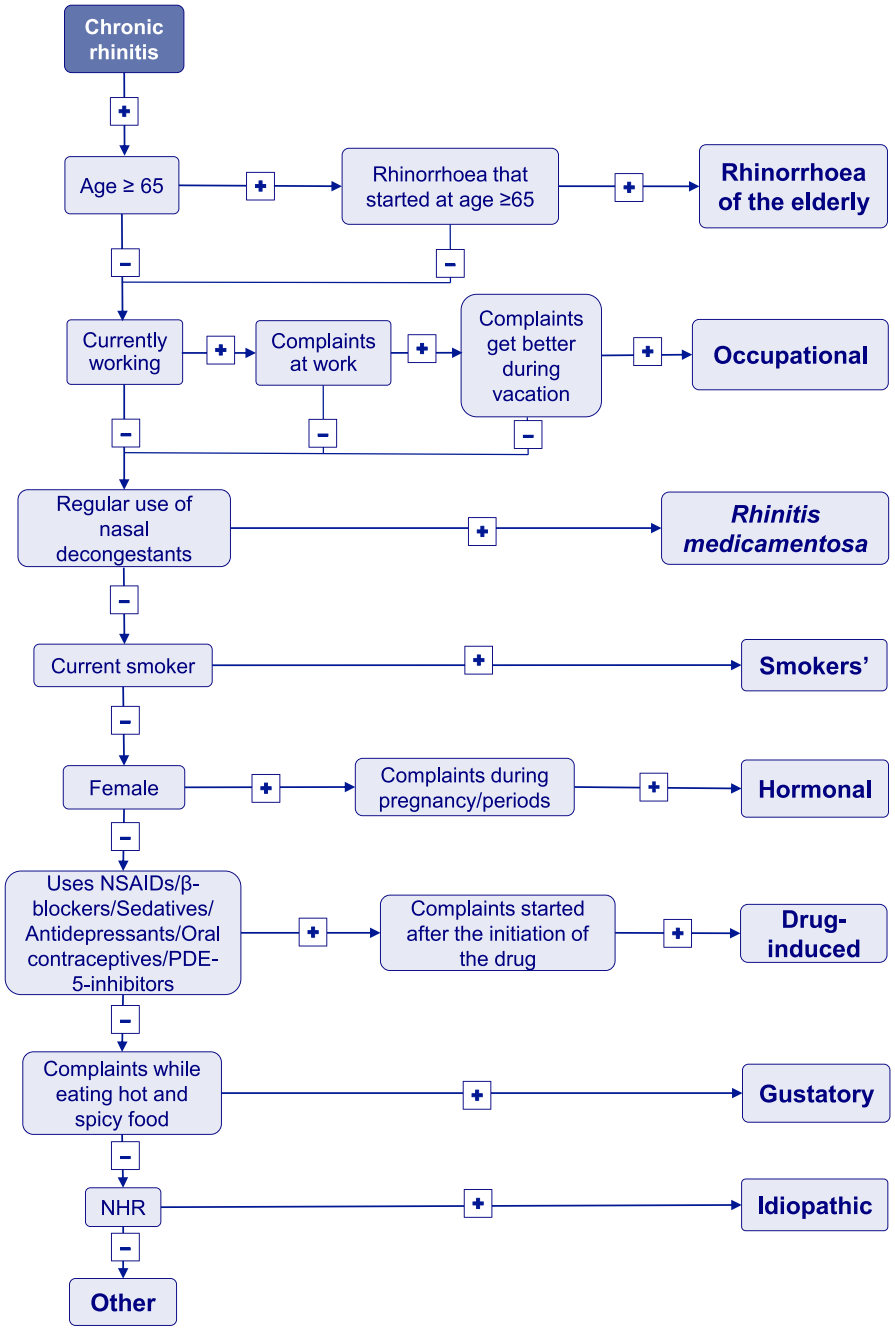


FIGURE 2 Algorithm behind definitions of NAR phenotypes. Green arrows with a "+" sign represent "Yes," and red arrows with a "−" sign represent "No." NHR − nasal hyperreactivity

presented in Figure 2. Based on the algorithm, each subject was assigned exclusively to one phenotype. If a participant was not defined as having rhinorrhea of the elderly (ROE), occupational rhinitis (OR), rhinitis medicamentosa (RM), smokers' rhinitis (SR), hormonal rhinitis (HR), drug-induced rhinitis (DR), or gustatory rhinitis (GR) and had CR and NHR, he/she was classified in idiopathic rhinitis (IR) group. If NHR was absent, he/she was classified into the "other" group.

2.2 | Statistical analysis

Data are summarized as frequencies, means and standard deviations, medians, and interquartile ranges. To detect the differences between the groups, we used an unpaired sample *t*-test for normally distributed numerical variables (age), and an independent-sample Mann-Whitney U-test (MWU-test) for non-normally distributed numerical variables (VAS score) (SPSS).

3 | RESULTS

In December 2019, five thousand questionnaires were sent out to the residents of one municipality in the Netherlands. One thousand thirty-three participants filled in the questionnaire (response rate 27%).

3.1 | Common cold

In the whole study group, the median number of common colds was 2 (IQR 1–3). The median number of total days with common colds was 10 (IQR 4–20).

3.2 | AR and NAR

There were 363 participants with NAR, 159 with AR, and 790 controls. Twenty-two participants who did not answer the question "Do you have allergic rhinitis" were excluded from this analysis. Figure 3 shows the distribution of months with worst complaints for AR and NAR. Individuals with NAR had significantly more complaints in October–February, (chi-square, $p < .001$). Those with AR had significantly more complaints in April–August (chi-square, $p < .05$).

3.3 | NAR phenotypes

The prevalence of NAR phenotypes is presented in Figure 4. The most prevalent phenotype was IR (39% of NAR group). A comparison of baseline characteristics of NAR phenotypes is presented in Table 1. Nasal obstruction, rhinorrhea, and postnasal drip were the most common regular complaints (Figure 5).

3.4 | Rhinorrhea of the elderly

- In the general population, participants with rhinorrhea as the only regular complaint were significantly older compared to the rest (64 ± 15 vs 59 ± 17 years, $p = .028$). In NAR, the same trend was observed, though not statistically significant (61 ± 16 vs 58 ± 18).
- In NAR, participants with rhinorrhea as the most bothering complaint were older than the rest (62 ± 19 vs 56 ± 18, *T*-test $p = .026$, MWU-test $p = .008$).
- Regardless of the age cut off used, the prevalence of RoE was around 10% for the corresponding age-group (Attachment 2). The remaining 90% of participants of the same age had other phenotypes of NAR (with the same prevalence of each phenotype as for the whole NAR group).

3.5 | Occupational rhinitis

The majority of working participants in the NAR group reported having nasal complaints at work (Attachment 2), but only a third of them reported an improvement during weekend/vacation.

From all the participants defined as having OR ($N = 30$), only one had nasal complaints related to work-specific triggers. In the majority of participants ($N = 11$), nasal complaints were attributable to hyperreactivity to non-specific triggers encountered at work (such as air conditioning, dust, and dry air). Seven participants thought that their complaints were caused by HDM or other allergies, and in eleven participants, the trigger was unknown.

3.6 | Rhinitis medicamentosa

- Sixty-one participants in the NAR group (17%) and 42 controls (5%) reported regular use of nasal decongestants (ND) (Attachment 2).

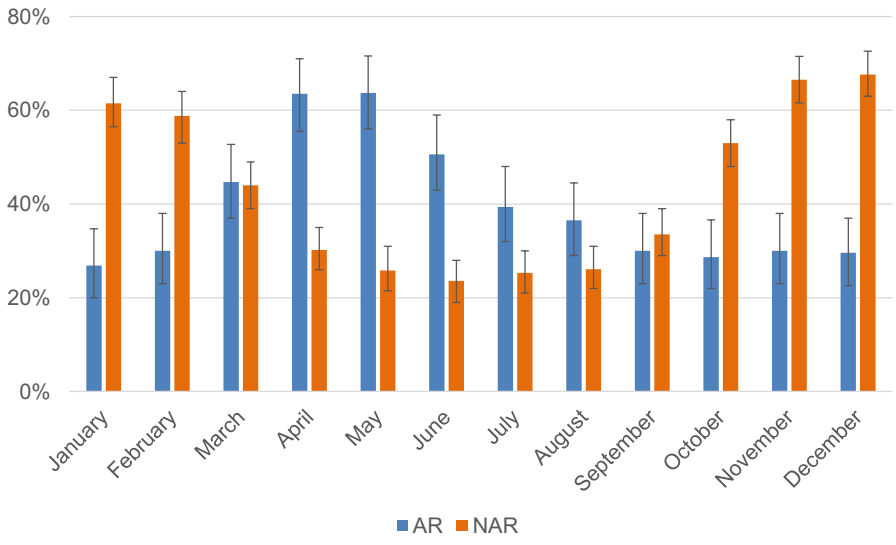


FIGURE 3 Percentages of individuals with worst nasal complaints per month of the year, for AR and NAR. Vertical bars represent 95% CI. The differences were statistically more significant in January, February, April, May, June, July, August, October, November, and December

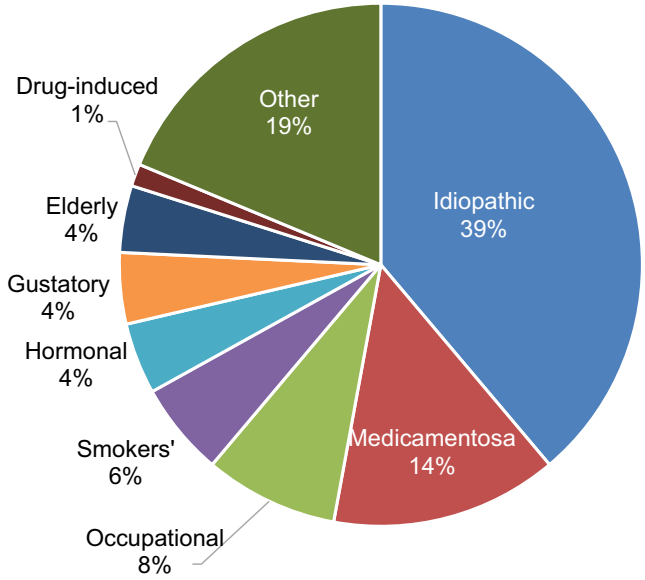


FIGURE 4 The prevalence of NAR phenotypes (NAR group, $N = 363$)

Fifty-one participants with NAR were defined as having *rhinitis medicamentosa* (RM), and ten participants classified into the OR group (Figure 2).

- Within participants who reported the regular use of ND, those with NAR had a significantly higher VAS compared to those from the control group (45 ± 26 vs 19 ± 24, *t*-test $p < .001$; MWU test $p < .001$). Similarly, there were significantly more moderate/severe cases (ARIA) among ND users from the NAR group (84% vs 36%, chi-square $p < .001$).

3.7 | Smokers' rhinitis

3.7.1 | Current smokers

- Current smokers were significantly more likely to have NAR compared to non-smokers (chi-square $p = .034$, OR 1.7 (1.04–2.8); RR 1.6 (1.004–2.6)).
- Current smokers in the NAR group had significantly more pack-years of smoking compared to currently smoking controls (32 ± 29 vs 14 ± 14; *t*-test $p = .014$; MWU test $p = .04$).

3.7.2 | Former smokers

- Former smokers had the same probability of having NAR compared with those who never smoked.
- Pack/year of smoking for former smokers was not different between NAR and controls.

3.8 | Hormonal rhinitis

Sixteen women were classified as having HR. Two of them had nasal complaints during both pregnancy and menstruation, eight during pregnancy only, and six during menstruation only.

3.9 | Drug-induced rhinitis

- There were significantly more medication users in NAR compared to the controls (chi-square $p = .008$, OR 1.4 95% CI 1.1–1.8, RR 1.2 95% CI 1.1–1.5).
- The proportions of users of painkillers (including paracetamol and NSAIDs), β-blockers, antidepressants, sedatives, and "other" medications were not significantly different between NAR and controls. There was also no difference in medication intolerance.
- Thirty-six participants have developed their nasal symptoms after initiation of a medication. Of those, in six participants nasal complaints have started the same year as they have started using the medication. Of the whole group of participants who developed symptoms after initiation of a medication, five were using medication enlisted in EAACI position paper and were defined as having DR. The medications that they reported (could be more than one per subject) were NSAIDs ($N = 1$), β-blockers ($N = 3$), antidepressants ($N = 2$), and "other" ($N = 4$).
- The majority of NAR population used medications classified as "other": anticoagulants, calcium channel blockers, ACE inhibitors, statins, glucose-lowering medications, thiazide diuretics, PPI inhibitors, P2Y12 inhibitors, etc.

3.10 | Gustatory rhinitis

- Sixteen participants (4% of NAR) were defined as having GR.
- In the GR group, rhinorrhea was the most prevalent regular and current complaint ($N = 10$, 63%, for both). The most bothering complaints were rhinorrhea ($N = 7$, 44%) and nasal obstruction ($N = 6$, 38%).
- The majority ($N = 11$, 69%) of the GR group reported NHR.

3.11 | Idiopathic rhinitis

- One hundred and forty-one participants (39% of NAR) were classified as having IR.

3.12 | Other

- Sixty-eight participants (19% of NAR) could not be classified into any of the phenotypes.

TABLE 1 Characteristics of NAR phenotypes*

		Rhinorrhea of the elderly	Occupational	Medicamentosa	Smokers'	Hormonal	Gustatory	Idiopathic	Other	Controls
N (% of the NAR group)		15 (4%)	30 (8%)	51 (14%)	21 (6%)	16 (4%)	16 (4%)	141 (39%)	68 (19%)	790
Demographic characteristics										
Age	Mean ± SD	78 ± 6.3	52 ± 13	60 ± 17	61 ± 15	45 ± 18	52 ± 19	57 ± 18	63 ± 17	60 ± 16
	Median (IQR)	77 (73; 82)	54 (43.5; 64)	65 (53.5; 73)	62 (55.5; 69.5)	47.5 (30; 57.25)	60 (35.25; 66.75)	59 (48.5; 70)	68 (54; 75)	63 (51; 72)
Gender: Female *N* (%)		5 (33%)	18 (60%)	26 (51%)	9 (43%)	16 (100%)	8 (50%)	62 (44%)	24 (35%)	427 (54%)
Current smoker		0	4 (13%)	5 (10%)	21 (100%)	-	-	-	-	38 (5%)
Former smoker		7 (47%)	15 (50%)	24 (47%)	-	3 (19%)	3 (19%)	76 (54%)	37 (54%)	337 (43%)
Self-reported asthma		0	5 (17%)	6 (12%)	0	0	0	7 (5%)	4 (6%)	26 (3%)
Other pulmonary complaints (cough, dyspnea, shortness of breath, and wheezing)		6 (40%)	13 (43%)	20 (39%)	12 (57%)	8 (50%)	6 (38%)	39 (28%)	15 (22%)	91 (11%)
Number of common colds per year	Mean ± SD	11 ± 27	6 ± 20	6 ± 9	3 ± 5	4 ± 4	5 ± 8	5 ± 9	2 ± 3	2 ± 4
	Median (IQR)	3 (1; 7)	3 (2; 4)	3 (2; 5)	2 (1; 3)	2.5 (1; 10)	2 (1; 5)	2 (1; 4)	2 (1; 2)	1 (1;2)
Nasal medication use										
Regular use of nasal decongestants		0	10 (33%)	51	-	-	-	-	-	42 (5%)
Regular use of nasal medication		2 (13%)	8 (27%)	16 (31%)	5 (24%)	2 (13%)	0	24 (17%)	6 (9%)	28 (4%)
Systemic antihistamines		0	1 (3%)	0	1 (5%)	0	0	1 (1%)	0	6 (1%)
Topical steroids and/or antihistamines		1	4 (13%)	11 (22%)	0	0	0	12 (9%)	5 (7%)	9 (1%)
Saline nasal spray/rinse		0	2 (7%)	1 (2%)	1 (5%)	1 (6%)	0	8 (6%)	0	8 (1%)
Other/unknown		1	3 (10%)	6 (12%)	3 (14%)	1 (6%)	0	7 (5%)	1 (1%)	9 (1%)
Nasal complaints										
The number of regular nasal complaints	Mean ± SD	2.6 ± 1.5	2.4 ± 1.6	2.3 ± 1.6	2.3 ± 1.3	2.4 ± 1.3	2.2 ± 1.5	1.9 ± 1.6	1.5 ± 1.1	0.3 ± 0.8
	Median (IQR)	3 (1; 4)	2.0 (1.0; 4.0)	2 (1; 3)	2 (1;3)	2 (1.25; 3.75)	2 (1; 3.75)	2 (1; 3)	1 (1; 2)	0 (0; 0)
The number of current nasal complaints	Mean ± SD	2.4 ± 1.2	2.4 ± 1.6	2.3 ± 1.5	1.6 ± 1.3	2 ± 0.8	2.1 ± 1.3	2 ± 1.4	1.8 ± 1.2	0.4 ± 1.0
	Median (IQR)	2 (1; 3)	1.6 (1; 4)	2 (1; 3)	1 (1; 2.5)	2 (1; 2.75)	2 (1; 3)	2 (1; 3)	1 (1; 2)	0 (0; 0)

(Continues)

TABLE 1 (Continued)

		Rhinorrhea of the elderly	Occupational	Medicamentosa	Smokers'	Hormonal	Gustatory	Idiopathic	Other	Controls
Duration of nasal complaints per day	<1 h per day	4 (27%)	8 (27%)	20 (39%)	9 (43%)	6 (38%)	6 (38%)	54 (38%)	29 (43%)	84 (11%)
	≥1 h per day	9 (60%)	22 (73%)	25 (49%)	12 (57%)	10 (63%)	9 (56%)	80 (57%)	31 (46%)	55 (7%)
	No nasal complaints/ Unknown	2 (1%)	0	2 (4%)	0	0	1 (6%)	3 (2%)	8 (12%)	440 (56%)
Duration of nasal complaints per year (days per year)	Mean ± SD	228 ± 129	180 ± 129	177 ± 127.45	218 ± 121	268 ± 111	239 ± 117	224 ± 131	219 ± 133	17 ± 47
	Median (IQR)	250 (100; 365)	110 (63.75; 300)	150 (50; 300)	200 (100; 365)	325 (150; 365)	300 (112.5; 348.75)	200 (100; 365)	200 (100; 365)	8 (0; 14)
Years with nasal complaints	Mean ± SD	6 ± 4	15 ± 13	17 ± 17	15 ± 9	24 ± 18	12.5 ± 16	18 ± 17	16 ± 17	14 ± 19
	Median (IQR)	5 (4;9)	11 (4.75; 20.25)	10 (4.5; 22.5)	17 (5.5; 20)	21 (11; 38)	5 (1; 15)	12.5 (5; 21.75)	10 (3; 20)	5 (1; 20)
ARIA										
Severity	Mild	1 (7%)	3 (10%)	8 (16%)	8 (38%)	5 (31%)	3 (19%)	35 (25%)	29 (43%)	333 (42%)
	Moderate/severe	11 (73%)	26 (87%)	42 (82%)	11 (52%)	9 (56%)	12 (75)	94 (67%)	36 (52%)	119 (15%)
	Unknown	3 (20%)	1 (3%)	1 (2%)	2 (10%)	2 (13%)	1 (6%)	12 (9%)	3 (4%)	319 (41%)
Duration	Intermittent	3 (20%)	15 (50%)	25 (49%)	9 (43%)	3 (19%)	7 (44%)	59 (42%)	32 (47%)	266 (34%)
	Persistent	12 (80%)	15 (50%)	24 (47%)	12 (57%)	13 (81%)	8 (50%)	79 (56%)	33 (49%)	22 (3%)
	Unknown	0	0	2 (4%)	0	0	1 (6%)	3 (2%)	3 (4%)	502 (64%)
VAS nasal complaints (0–100, mm)	Mean ± SD	49 ± 23	44 ± 25	43 ± 27	34 ± 29	45 ± 28	45 ± 24	38 ± 26	30 ± 27	10 ± 17
	Median (IQR)	52 (31; 68)	53 (19.5; 54.5)	41.5 (19.75; 65)	29 (7.25; 58.75)	35.5 (21.5; 73.75)	49.5 (19.75; 54.75)	31.5 (17; 60.75)	22 (7; 48)	2 (0; 12)

Abbreviations: DR, drug-induced rhinitis; GR, gustatory rhinitis; HR, hormonal rhinitis; NAR, non-allergic rhinitis; OR, occupational rhinitis; RM, rhinitis medicamentosa; RoE, rhinorrhea of the elderly; SR, smokers' rhinitis.

*Drug-induced rhinitis ($N = 5$) is not presented due to a small size.

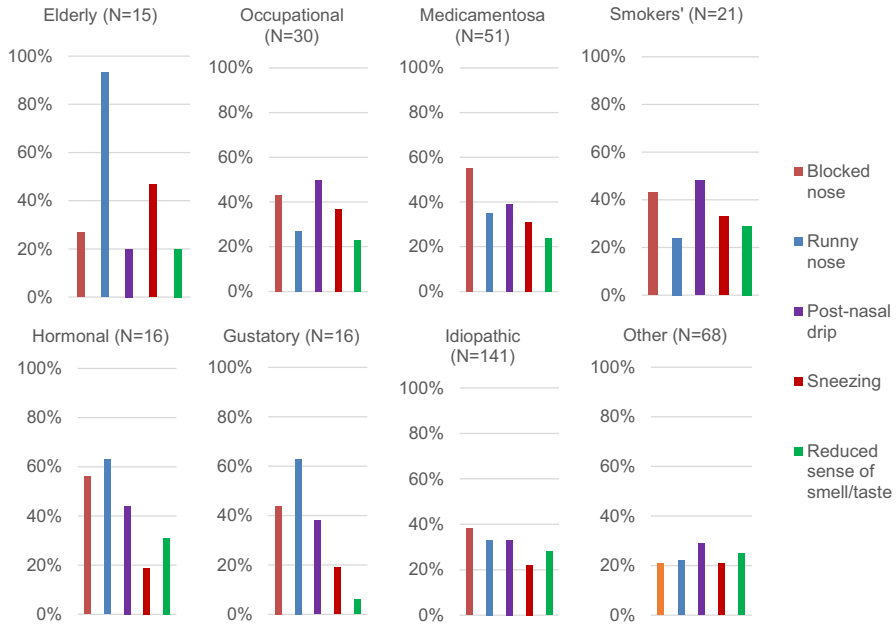


FIGURE 5 The prevalence of regular nasal complaints per phenotype in NAR group ($N = 363$). Drug-induced rhinitis and occupational rhinitis are not presented due to small group sizes

- This group was mostly represented by participants with milder complaints in terms of the number of complaints, VAS score, and the proportion of mild cases (ARIA) (Table 1).

4 | DISCUSSION

This is the first paper that describes the prevalence of NAR phenotypes in the general population. Though some data on prevalence of individual phenotypes in particular populations are available (such as HR in pregnancy,[27] SR[28,29] and OR in bakers[30]), the distribution of each phenotype (as described by EAACI position paper[1]) in the general population has not been previously reported. Phenotyping of NAR is essential for choosing the best treatment option. For example, IR is effectively treated with capsaicin,[31] which is totally different from the treatment of RoE with ipratropium bromide[32] or the treatment of RM by discontinuing the ND abuse.

For studies on prevalence of diseases, data from the general population are mandatory. In this study, we found a prevalence of CR of 40% what is comparable to other European studies.[33-35] Ideally, some form of allergy testing should be used for the differentiation between AR and NAR in studies, but that is not always feasible. However, Savouré et al. have shown that the question "Have you ever had allergic rhinitis?" or "Have you ever had hay fever?" has a positive predictive value of 0.71 (0.64–0.78) and a negative predictive value of 0.77 (0.71–0.84) in never asthmatics.[36] We expect that our study where we used not only the question about allergic rhinitis/hay fever but also whether the patient was tested for allergies will have at least comparable results. Our studies showed 70% of the subjects with CR to have NAR. This is higher than in a study by Bachert et al., where the prevalences of AR and NAR had a proportion of 3:1,[35] or the study of Bozek et al., where the proportion was 1:1,[13] and is comparable with the study by Jessen and Janzon, where the proportion was 1:4.[37] One of the reasons for this discrepancy could be that we only evaluated subjects with CR. It is possible that more subjects with NAR than AR have symptoms for more than 21 days per year. Furthermore, we do not expect that AR/NAR proportion would influence the results of NAR phenotype analysis. In this study, as far as we know, for the first time we show the difference between two distinct seasonality patterns between the AR and the NAR, with AR complaints being more prevalent during pollen season[38] and NAR during winter, when viral infections and factors that may correspond to NHR are more apparent (e.g., dry air and temperature differences between inside and outside). Possibly, a proportion of NAR patients is represented by unconfirmed mono-sensitized HDM allergy, though mono-sensitization to HDM is quite rare.[38] Therefore, only a minority of NAR group could have been wrongly assigned because of an unrecognized mono-sensitization to HDM.

To further phenotype NAR, we used definitions as proposed by the EAACI position paper.[1] Some subjects (7% of NAR group) can be phenotyped in different categories. For example, out of 31 currently smoking participants, 24 were classified as SR and seven as RM, though the latter seven participants most likely have a combination of SR and RM. For this study, we have chosen to exclusively include subjects in the most likely category and used an algorithm as described in this manuscript (Figure 2). Our definition, therefore, did not account for possible overlaps and the interactions between the provoking factors, what is more likely in reality. Hence, the reader should keep in mind that these data are an oversimplification of the truth. On the other hand, our approach to use NHR as a criterion for IR is a valid attempt to separate rhinitis patients from those with other diagnoses, which is reflected by a lower disease burden in the "other" group.

There are still many gaps in knowledge about NAR phenotypes. To facilitate further research in the field, robust definitions for each

phenotype should be developed (e.g., what duration and frequency of a medication use lead to the development of drug-induced rhinitis; after what age do we consider nasal discharge a RoE, etc.). Moreover, although there is increasing information about the relation between phenotypes and endotypes in NAR with the consequences for therapy, the picture is far from complete. In Figure 1, we propose underlying endotypes like neurogenic and inflammatory for the different phenotypes. We do realize, however, that significant overlap can be found (e.g., OR and DR can be inflammatory or neurogenic), of which it is unclear whether that is present in all subjects. Additionally, RM, apart from having a neurogenic component, also has a vascular one. In order to systematically fill in those gaps and to refine existing definitions and classification, and due to a shortage of effective NAR treatment options, we suggest that a new EAACI taskforce addresses these issues.

Van Rijswijk hypothesized that IR accounts for about 50% of NAR.[39] Our findings confirm this hypothesis: IR was the most prevalent phenotype (39% of NAR group). IR is a purely neurogenic phenotype, and the recognition of the disease with NHR as the most prominent symptom[40] has significant implications for the treatment.[31,40-42]

Twenty percent of the NAR group could not be classified into any of the phenotypes. We were not able to identify a pattern that would explain the nature of nasal complaints in this group. If NHR was not used as a defining factor for IR, these patients would have been classified as having IR. Possibly, this group includes participants with anatomical reasons for nasal symptoms like a septal deviation and/or inferior turbinate hypertrophy and/or some (yet) unrecognized phenotypes.[43]

The second most common phenotype was RM (17% of NAR). Strictly speaking, RM is a subtype of DR,[1] though we have analyzed them separately due to the fact that RM is caused by a very specific medication that acts locally, has a different pathophysiological mechanism,[11] and is associated with psychiatric conditions, such as anxiety[44] or opioid use disorders.[45] Mehuys et al. have also demonstrated an alarmingly high rates of ND (ab)use: about a half of individuals with persistent rhinitis purchasing over-the-counter medication for their nasal complaints were overusing ND, even though the majority was educated about the limit on duration of use.[46] A high prevalence of RM is a major concern, seeing that this is a preventable phenotype, and warrants attention in our daily practice because it is something often not spontaneously mentioned by our patients.

Interestingly, the pattern of complaints does not predict phenotype nor endotype (Figure 5) (except for ROE, which was defined by the presence of rhinorrhea). As such, OR, RM, and SR have a similar pattern with nasal obstruction and post-nasal drip being the most prominent complaints, but they all belong to different endotypes (inflammatory or neurogenic, neurogenic, and inflammatory, respectively). Likewise, HR and GR are similar in terms of rhinorrhea and nasal obstruction but, then again, belong to different endotypes (inflammatory and neurogenic, respectively). This could be explained by the presence of (sub)endotypes or gaps in knowledge regarding the pathophysiology of the endotypes.

Our study has a number of limitations that were described earlier and in our previous publication,[5] such as inability to objectively exclude NARES, LAR, septal deviations, or CRS. Though due to the low prevalence of CRS (~4% of general population when confirmed objectively[47-49]) and NARES (2% in Dutch primary care patients with recurrent nasal symptoms[25]), we expect that only a minority of the NAR group was represented by these conditions. Seeing that the severity of septal deviation does not correlate with subjective complaints[50] and that CR was defined by the presence of nasal symptoms, we do not expect that inability to exclude this anatomical feature would influence the results.

Another major limitation is the lack of a more thorough medical history, which may be necessary for accurate phenotyping. For example, we assigned all subjects that developed nasal symptoms after starting medication that can induce DR[1] into this phenotype. But subjects might have had other reasons for their symptoms not related to the use of medication, and we were not able to stop medication to prove the relation. Additionally, none of the participants reported the use of phosphodiestherase-5 inhibitors, probably because they do not consider it as a "medication," though it may cause DR.[51]

Moreover, the limited size of some of our groups made further subgroup analyses impossible. Finally, seasonality patterns described for AR and NAR should be validated for other climate zones.

It was previously hypothesized that up to 50%–70% of AR may be represented by mixed rhinitis.[52] Unfortunately, the design of the questionnaire did not allow for the differentiation of this group.

5 | CONCLUSIONS

This is the first study to describe the prevalence of NAR phenotypes in general population. AR and NAR have distinct seasonality patterns with NAR being more prevalent in autumn/winter and AR in spring/summer. Idiopathic rhinitis is the most common phenotype of NAR, followed by rhinitis medicamentosa. The high prevalence of rhinitis medicamentosa is alarming. A new EAACI taskforce should systematically fill in gaps in knowledge about NAR phenotypes.

ACKNOWLEDGMENTS

The authors thank I. Bruins and Y. te Winkel for their assistance in digitalization of the questionnaires.

CONFLICT OF INTEREST

None.

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SUPPORTING INFORMATION

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How to cite this article: Avdeeva KS, Fokkens WJ, Segboer CL, Reitsma S. The prevalence of non-allergic rhinitis phenotypes in the general population: A cross-sectional study. *Allergy*. 2022;77:2163–2174. doi:10.1111/all.15223