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To the Editor,

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

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We therefore compared questionnaire-based versus SPT-based definition for AR and for NAR in adults from the first follow-up of the French Epidemiological case-control and family study on the Genetics and Environment of Asthma (EGEA) (<https://egeanet.vjf.inserm.fr/index.php/en/>; see Online Supplementary 1 for details).

Current rhinitis was defined by a positive response to: *"Have you had problems with sneezing, runny nose or stuffy nose when you didn't have a cold or flu in the last 12 months?"*. Among the participants with current rhinitis, two definitions of AR and NAR were used: one based on SPTs and one on questionnaire. Participants who had at least one positive SPT were classified as SPT-based AR (AR-SPT), otherwise as SPT-based NAR (NAR-SPT). Participants who responded positively to *"Have you ever had allergic rhinitis?"* or *"Have you ever had hay fever?"* were classified as questionnaire-based AR (AR-Q), otherwise as questionnaire-based NAR (NAR-Q). Due to the EGEA design, analyses were separately conducted among never-asthmatics and ever-asthmatics. Characteristics of AR or NAR were compared between SPTs and questionnaire definitions using a marginal logistic model to account for matched pair data.

Among the 696 participants included in the analyses (mean 42 years), 53.6% were women, 51.4% non-smokers, and 57.5% ever-asthmatics. Agreement measures between SPTs and questionnaire definitions were satisfactory for never-asthmatics. For ever-asthmatics, sensitivity and Positive Predictive Value were high but specificity, Negative Predictive Value, Youden's index and Cohen's Kappa coefficient were rather low (Table 1). Among never-asthmatics, differences in participants' characteristics between questionnaire and SPTs were observed for age for both AR and NAR, and for age of onset and one trigger for AR (Table 2). Among ever-asthmatics, differences were observed for age, sex, smoking and IgE level for both AR and NAR; for age of onset and one trigger for AR, and for ever allergic conjunctivitis, associated eye-symptoms and two triggers for NAR. AR-Q participants reported more symptoms during the spring than AR-SPT participants and this being even significant for ever-asthmatic participants, conversely to what is observed for NAR (Online Supplementary 2).

In epidemiological studies, when allergy tests are lacking, a simple and easily available definition of AR and NAR is needed. We acknowledge that the best possible diagnosis of AR and NAR is achieved with a specific clinical diagnosis: anamnesis and SPTs/specific IgE, by a specialized

health professional. As we did not have anamnesis, our definition of current rhinitis is based on the ISAAC definition (2) as suggested by the ARIA (3). To distinguish AR from NAR by questionnaire, we used an adaptation of the ECRHS definition(4). Although SPTs are the gold-standard for distinguishing AR from NAR, SPT positivity is not systematically associated with nasal symptoms(5). Indeed, among EGEA participants with never-rhinitis, 29% of those with never-asthma and 67% of those with ever-asthma had at least one positive SPT(6). Also, SPT negativity does not systematically reflect NAR, as observed for local allergic rhinitis (7). The questionnaire approach has the advantage of relying on what participants directly identify as nasal allergies, and could therefore consider the forms of local allergic rhinitis that the SPTs approach does not. This could partly explain the higher reports of pollen trigger, associated eye-symptoms and symptoms in spring we observed in the NAR group with the SPT-based definition compared to the questionnaire-based definition. Based on this, the moderate agreement we observed between SPTs and questionnaire would not necessarily reflect a false classification of AR/NAR by questionnaire.

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

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J. Bousquet reports personal fees from Chiesi, Cipla, Hikma, Menarini, Mundipharma, Mylan, Novartis, Purina, Sanofi-Aventis, Takeda, Teva, Uriach, other from KYomed-Innov, outside the submitted work.

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Tables

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

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

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

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

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

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

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

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