Symptom control and health-related quality of life in allergic rhinitis with and without comorbid asthma: a multicentre European study

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Abstract

Background: Allergic rhinitis (AR) is a major non-communicable disease that affects the health-related quality of life (HRQoL) of patients. AR is significantly related to asthma also affecting HRQoL. However, data on HRQoL and symptom control in AR patients with comorbid asthma are lacking. **Objective:** To assess the differences of symptom control and HRQoL in AR patients with and without comorbid asthma. **Methods:** In this multicentre, cross-sectional study, patients with AR were screened and administered questionnaires of demographic characteristics and health conditions (symptoms/diagnosis of AR and asthma, disease severity level, and allergic conditions). HRQoL was assessed using a modified version of the RHINASTHMA questionnaire and symptom control was evaluated by a modified version of the Control of Allergic Rhinitis/Asthma Test (CARAT). **Results:** Out of 643 patients with AR, 500 (78%) had asthma as a comorbidity, and 54% had moderate-severe intermittent AR, followed by moderate-severe persistent AR (34%). Patients with both AR and asthma had significantly higher RHINASTHMA scores than the patients with AR alone (e.g., median RHINASTHMA-total score 84 vs. 48.5, respectively). Conversely, CARAT scores were significantly lower in AR with comorbid asthma than in the patients with AR alone (median CARAT-total score 16.5 vs. 23, respectively). Upon stratifying asthma based on severity, AR patients with severe persistent asthma had worse HRQoL and control than AR patients with mild persistent asthma. **Conclusions:** Our observation of poorer HRQoL and symptoms control in AR patients with comorbid asthma supports the importance of a comprehensive approach for the management of AR in case of a comorbid allergic condition.

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Running head: HRQoL and control in allergic rhinitis with asthma

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ABSTRACT

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Objective: To assess the differences of symptom control and HRQoL in AR patients with and without comorbid asthma.

Methods: In this multicentre, cross-sectional study, patients with AR were screened and administered questionnaires of demographic characteristics and health conditions (symptoms/diagnosis of AR and asthma, disease severity level, and allergic conditions). HRQoL was assessed using a modified version of the RHINASTHMA questionnaire and symptom control was evaluated by a modified version of the Control of Allergic Rhinitis/Asthma Test (CARAT).

Results: Out of 643 patients with AR, 500 (78%) had asthma as a comorbidity, and 54% had moderate-severe intermittent AR, followed by moderate-severe persistent AR (34%). Patients with both AR and asthma had significantly higher RHINASTHMA scores than the patients with AR alone (e.g., median RHINASTHMA-total score 84 vs. 48.5, respectively). Conversely, CARAT scores were significantly lower in AR with comorbid asthma than in the patients with AR alone (median CARAT-total score 16.5 vs. 23, respectively). Upon stratifying asthma based on severity, AR patients with severe persistent asthma had worse HRQoL and control than AR patients with mild persistent asthma.

Conclusions: Our observation of poorer HRQoL and symptoms control in AR patients with comorbid asthma supports the importance of a comprehensive approach for the management of AR in case of a comorbid allergic condition.

KEYWORDS : allergy treatment, food allergy, pollen, rhinitis, vaccines

INTRODUCTION

Allergic rhinitis (AR) is a type-2 chronic inflammatory disease affecting the nasal mucosa and characterized by nasal symptoms such as sneezing, rhinorrhoea (nasal discharge), pruritus, and nasal congestion[1-3]. It is one of the most common non-communicable chronic diseases in the world, affecting over 400 million people of all ages, particularly the paediatric population[1-6]. While the prevalence of physician-diagnosed AR in the United States has been observed as high as 15% and 30%, based on self-reported nasal symptoms[7,8], the prevalence was as high as up to 50% in many European countries[9]. According to the Allergic Rhinitis and its Impact on Asthma (ARIA) and the Global Alliance against Chronic Respiratory Diseases (GARD) statements, severe, refractory, or mixed forms of AR are significantly increasing across the globe and have contributed substantially to the socio-economic burden of the disease[10-12].

AR often coexists with other conditions, such as atopic dermatitis, rhinosinusitis, rhino-conjunctivitis, and particularly asthma – a coherent feature often referred to as 'the atopic march' due to common systemic inflammatory processes[2,4]. 40-50% of patients with AR also have asthma whereas the prevalence of AR as a comorbidity in asthmatic patients is even higher, i.e., 70-90%[13]. Several reports described that the patients suffering from AR show a poorer quality of life (QoL), being affected by impaired sleep pattern, increased amount of fatigue, depression, risk of driving accident, and altered physical and social functions[8,14-16]. Often, a poor perception of AR symptoms is associated with poor control of AR[17]. However, studies assessing health-related quality of life (HRQoL) and symptoms control in AR patients with concomitant asthma are lacking.

The Aerobiological Information Systems and allergic respiratory disease management (AIS Life +) study focused on this aspect, by using specifically designed and validated questionnaires on quality of life and control for AR with comorbid asthma.

METHODS

Study design and participants

In the international multi-centre (Austria, France, and Italy) cross-sectional AIS Life + study, conducted between 2013 and 2014, we enrolled participants suffering from nasal allergy. A convenient sample of indi-

viduals with an active condition of pollen-induced AR was selected from pre-existing epidemiological study databases or through web advertisement (Pisa, Italy), clinics of general practitioners (Paris, France) or public health database and pulmonary clinics (Vienna, Austria) and invited to participate in this epidemiological survey. All potential participants were administered a screening questionnaire through a telephone interview to check whether they were eligible for the study. We included individuals who: 1) were adults ([?] 18 years of either sex); 2) reported allergic rhinitis diagnosis/symptoms or positive clinical tests to pollen in the last 12 months; 3) spent most of the week (at least 5 days/week) living, studying, or working in the areas where this study was conducted; and 4) were not treated with allergen immunotherapy over the previous 6 years.

The study was approved by the ethics committees of the participating centres in Italy (Ethics Committee of University-Hospital of Pisa; Protocol No. 14248) and in Austria (Berlin Charite University Ethics: EA1/119/12), and signed informed consents were obtained from all the participants before recruitment. In France, the approval by an external ethic committee was declared as not applicable at that time: instead, the study was approved by the Hospital ethic committee, by the National Committee for Information Management on Medical Research (*Comite' Consultatif sur le Traitement de l'Information en Matiere de Recherche dans le domaine de la sante'*) and by the National Commission on Informatics and Health (CNIL, *Commission Nationale Informatique et Liberte'*). In France, 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 utilized. In any case, patients were seen in the frame of routine care ("*soins courants* "). The AIS study was conducted according to the Declaration of Helsinki and reported as per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[18].

Instruments and variables

A standardized health questionnaire was administered to all eligible individuals in order to obtain information on their demographic characteristics (age, gender, body mass index [BMI], level of education), and potential risk factors (smoking status, exposure to second-hand smoke, and drug consumption), on symptoms/diagnosis of AR and asthma, disease severity level, as well as on previous clinical tests (spirometry, skin prick test and serum level of immunoglobulin E [IgE]).

The health-related quality of life (HRQoL) of the participants was assessed using a modified version of the validated RHINASTHMA questionnaire (the higher the score, the lower the HRQoL), i.e., the only available instrument that allows evaluating the concomitant impact of AR and asthma on HRQoL[19]. This 30-item questionnaire provides individual scores for upper airways, lower airways, respiratory allergy impact, and a composite score (the Global Summary [GS] score, which indicates the overall impact of the disease). The details of the instrument and the scoring system can be found elsewhere[19]. Patients used a five-point Likert scale ('not at all', 'a little', 'fairly', 'much', 'very much') to indicate the extent to which they were bothered by each AR and asthma during the year preceding the completion of the questionnaire. These responses are then converted into scores, from 0 to 100, with larger scores corresponding to worse HRQoL. A RHINASTHMA-GS score from 0 to 20, indicating minimal or absent disease impact on patient life, was considered reflective of optimal HRQoL.

The control of AR and asthma was evaluated by a modified version of the Control of Allergic Rhinitis/Asthma Test (CARAT) (the higher the score, the higher the disease control)[20,21]. CARAT is a 10-item questionnaire containing information about the frequency of symptoms, sleep impairment, activities limitation, and need for more medication: the response options for all the questions follow a 4-point Likert scale (range 0-3). The range of CARAT score is 0–30, 0 being the complete absence of control: the minimal clinically important difference (MCID) is 3.5[22]. The Global Initiative for Asthma (GINA) classification 2017[23] and ARIA (2008)[6] were used to classify asthma according to its severity.

Statistical analyses

Data were described as frequency (%), mean (standard deviation [SD]), or median (interquartile range [IQR]) for categorical, continuous, and ordinal variables, respectively. To test the association among quality of life and control (RHINASTHMA and CARAT – total and subdomains) scores, and AR-asthma (independent variable), we first used a bivariate analysis using Wilcoxon rank-sum test. Then, we constructed univariable (unadjusted) and multivariable (adjusted) regression models among the independent variable and HRQoL and control scores using a mixed effect Poisson regression model. As potential confounders, we tested fixed factors (age, sex, BMI, smoking status, exposure to smoke, education, ARIA grade, sensitivity to allergens, and drugs taken in the last 12 months) and a random factor (the country). To include confounders in the regression models, we used *a priori* evidence criteria, i.e., covariates were considered as confounders if were found consistent in previous literature. However, confounders were retained in the model if they modified the estimates of the remaining variables by more than 10%. We checked the collinearity of the confounders using the variance inflation factor (VIF). The parsimony of the models was confirmed by Akaike's information criteria (AIC).

We also performed two secondary analyses. Firstly, we tested if there was any effect modification by obesity on the association between AR-asthma, and the HRQoL and control scores. Secondly, we performed meta-analyses to determine if there were any heterogeneity in the HRQoL and control (total) scores between the participating countries. All analyses were conducted using a complete case approach in Stata V.16 (StataCorp, College Station, TX, USA), and a p-value < 0.05 was considered statistically significant.

RESULTS

Demographic and clinical characteristics of all the participants, stratified by country, are presented in Table 1. Of all participants, nearly 40% were males with a mean age of 44 (standard deviation, SD: 14) years, 15% of the participants were obese, 47% were smokers and nearly 33% reported exposure to smoke, 78% of the participants had asthma as a comorbidity, 54% had moderate-severe intermittent AR and 34% had moderate-severe persistent AR. As for allergic sensitization, pollens were the most prevalent allergen (89%) among the participants, followed by house dust mites (57%). Concerning the HRQoL parameters, the participants had a median (IQR) RHINASTHMA-total score of 76 (53, 91) and CARAT-total score of 18 (14, 22). In the bivariate analysis, we found that participants with both AR and asthma had significantly higher RHINASTHMA (total and subdomain) scores than the participants with AR alone (**Figure 1**). Moreover, CARAT (total and subdomain) scores were significantly lower in AR with comorbid asthma than in AR alone (**Figure 2**).

Table 1

Figure 1 & 2

In the multivariable analysis, we observed that, compared to AR alone, AR with comorbid asthma was significantly associated with poorer quality of life (regression coefficient [β] φορ PHINAΣTHMA-τοταλ σϲορε: 0.22· 95% ϲονφιδενϲε ιντεραλ [ˆI]: 0.19, 0.25). Τηε ασϲοϲιατιον ωας περϲιϲτεντ ιν PHINAΣTHMA ϲυβδομαιν ϲϲορες· ηοωεερ, τηε μαγνιτυδε οφ τηε εϲτιματες ωας διφφερεντ, βεινγ τηε ηιγηεϲτ φορ λοωερ αιρωαψϲ (0.36· 0.31, 0.41) ανδ τηε λοωεϲτ φορ υππερ αιρωαψϲ (0.09· 0.04, 0.14). Υπον ϲτρατιφψινγ αϲτημα, βαϲεδ ον τηε 2017 ΓΙΝΑ γραδες, τηε μαγνιτυδε οφ τηε ασϲοϲιατιον ωας τηε ηιγηεϲτ ιν AP πατιεντϲ ωιτη ϲεερε περϲιϲτεντ αϲτημα (β for RHINASTHMA-total score: 0.25; 95%CI: 0.22, 0.29), and the lowest in AR patients with mild persistent asthma (0.15; 0.10, 0.20) (**Figure 3 and Supplementary Table 1**). We did not find any multicollinearity between the covariates (VIF<3).

Figure 3

We observed a poorer control of symptoms in AR patients with asthma comorbidity than in patients with AR alone (β for CARAT-total score: -0.20; 95%CI: -0.25, -0.15); the lower airway symptoms were more

poorly controlled (-0.23; -0.29, -0.17) than the upper airway symptoms (-0.11; -0.20, -0.01). Upon stratifying asthma according to GINA grade, AR patients with severe persistent asthma had the poorest control (β for CARAT-total score: -0.25; 95%CI: -0.31, -0.19) than those with mild persistent asthma (-0.06; -0.14, 0.03) (**Figure 4 and Supplementary Table 2**).

Figure 4

In the sensitivity analysis for effect modification by obesity (**Supplementary Table 3**), we found that the association between AR+asthma and RHINASTHMA-total score was marginally higher among non-obese participants (β: 0.23; 95%CI: 0.19, 0.26) than obese ones (0.16; 0.07, 0.25) (*p-value* for interaction = 0.09). The difference was more pronounced for upper airways, the association being significantly higher among non-obese participants (β for RHINASTHMA-upper: 0.10; 0.05, 0.15) than obese ones (0.01; -0.13, 0.15) (*p-value* for interaction = 0.04). However, we did not observe significant differences in other subdomains. We did not observe any effect modification by obesity for CARAT scores (**Supplementary Table 4**).

The association of AR+asthma with RHINASTHMA-total score was highly heterogeneous (I^2: 87%; p-value for heterogeneity = <0.001) across the participating countries (**Figure 5A**). While the association was the highest in Austria (β: 0.29; 95%CI: 0.24, 0.34), it tended towards null in France (0.07, -0.06, 0.19). Similar heterogeneity was observed for CARAT-total score (I^2: 79%, p = 0.008) (**Figure 5B**). However, the overall estimates from the meta-analyses for the association between AR+asthma, and RHINASTHMA-total and CARAT-total scores were similar to the ones reported in the main analysis.

Figure 5

DISCUSSION

In our study, we found a significantly worse quality of life (RHINASTHMA total and subdomain scores) and symptoms control (CARAT total and subdomain scores) in AR patients with comorbid asthma than in patients with AR alone. Such associations were not influenced by any physiological variables. However, we found that the association was significantly higher among non-obese participants compared to obese ones, when assessed through RHINASTHMA-upper symptoms score but not with CARAT. We also observed country-specific variations in the RHINASTHMA and CARAT total scores. Although one previous study compared the individual/social burden of disease between asthmatics and asthmatics with concomitant AR, unlike ours, that study did not compare the difference of disease control and HRQoL between the two groups of patients[24].

It is well-known that several triggers such as seasonal meteorological changes, pollen season, air pollution, or even occupational exposures may lead to poor quality of life of asthmatic patients with or without AR [8,25-27]. It has also been observed that AR patients are often reported to have poor control over their symptoms if persistent comorbid asthma is present[28-31]. Although no direct comparative study on the control and HRQoL of AR and AR with asthma has been reported yet, our findings well reciprocate the previous results. Asthma and AR share eight common genes (*CLC, EMR4P, IL5RA, FRRS1, HRH4, SLC29A1, SIGLEC8, IL1RL1*) that are presumed to describe the link for multimorbidity[32]. They also share common risk factors such as atopic genetic background (for the allergic endotypes), environmental exposures (allergens, moulds, indoor and outdoor air pollution, some respiratory viruses, etc.), type of occupation, and active tobacco smoking.

Our findings add important clinical knowledge to the existing strategies for the management of AR with concomitant asthma. Although AR and asthma are two different diseases with distinct clinical features, when AR persists with asthma, either condition is often overlooked[31,33] due to the lack of a combined tool for monitoring control and HRQoL of both diseases at the same time. Despite the well-established guidelines of ARIA and GARD for a new management protocol for AR and asthma together[10,12,34-37], reports adopting

these guidelines in the management of AR with persistent asthma are still lacking. Our findings would help guide practitioners to use the appropriate assessment tools while treating such patients. Our findings underline the impact of respiratory hypersensitivity conditions in the quality of life of patients and call for prevention and public health strategies to diminish the burden of these conditions. Currently there are effective treatments for AR and asthma, several risk factors are known (*e.g.,* allergies, rhinitis, tobacco smoke) and tools to control the disease have been developed. However, we are still uncertain how to prevent AR patients from developing asthma, allergen immunotherapy being the current only attempt. Preventive measures should be able to change the natural history of the disorder, avoiding asthma development in patients with AR and/or evolution through providing its control[38].

Our study has some limitations. Firstly, considering that subjective symptom-rating scales may not be entirely accurate, the risk for potential bias could not be completely avoided. However, we used standardized instruments, and therefore the possibility of such bias was marginal. Secondly, the considered period might be insufficient to evaluate the quality of life and the control appropriately. Thirdly, other comorbidities might have modified the patients' responses. Despite these limitations, our findings are derived from incident patients drawn from the general population of three European countries in which AR and asthma diagnoses were made by a doctor. However, due to the small sample size, it is not possible to indicate whether these results may be generalized. Further studies, after controlling for potential confounders and biases in larger populations, are therefore warranted.

CONCLUSION

In summary, using combined assessment tools for AR and asthma, we found that AR patients with comorbid asthma have a poorer quality of life and symptoms control than those with AR alone. This finding highlights the importance of a comprehensive approach for the management of AR in case of a comorbid allergic condition for optimum care, and such strategies would be the gateway for reducing the global burden of these diseases.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception and design of or acquisition of data or analysis and interpretation of data. All authors gave input to the manuscript and revised the manuscript critically for important intellectual content. All authors gave final approval of the version to be published. Sandra Baldacci, Maria Prentovic, and Isabella Annesi-Maesano were principal investigators of their respective centres. Subhabrata Moitra was responsible for statistical analyses.

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Table 1: Descriptive statistics of the study patients overall and by country

	All (N=643)	**IT (N=245)**	**FR (N=212)**	**AT (N=186)**
Sex (male), n (%)	249 (38.9)	89 (36.3)	104 (49.5)	56 (30.1)
Age (years), mean (SD)	44.1 (14.4)	47.4 (14.2)	41.6 (15.3)	42.3 (12.5)
BMI, n (%)				
Underweight	31 (4.9)	6 (2.5)	21 (10.1)	4 (2.2)
Normal weight	358 (56.4)	144 (59.0)	118 (56.5)	96 (52.8)
Overweight	154 (24.3)	61 (25.0)	40 (19.1)	53 (29.1)

	All (N=643)	**IT (N=245)**	**FR (N=212)**	**AT (N=186)**
Obese	92 (14.5)	33 (13.5)	30 (14.4)	29 (15.9)
Smokers, n (%)	302 (47)	103 (42)	104 (49)	95 (51)
Exposure to smoke, n (%)	209 (32.6)	63 (25.8)	97 (45.8)	49 (26.3)
Education, n (%)				
Maximum 8 years	166 (25.9)	56 (22.9)	69 (32.9)	41 (22.0)
9-13 years	231 (36.0)	115 (46.9)	67 (31.9)	49 (26.3)
>13 years	244 (38.1)	74 (30.2)	74 (35.2)	96 (51.6)
GINA grade, n (%)				
No asthma	141 (22.0)	88 (35.9)	3 (1.4)	50 (26.9)
Intermittent	190 (29.6)	63 (25.7)	58 (27.6)	69 (37.1)
Mild persistent	36 (5.6)	13 (5.3)	13 (6.2)	10 (5.4)
Moderate persistent	60 (9.4)	20 (8.2)	27 (12.9)	13 (7.0)
Severe persistent	214 (33.4)	61 (24.9)	109 (51.9)	44 (23.7)
ARIA grade, n (%)				
Mild intermittent	60 (9.7)	40 (17.3)	7 (3.3)	13 (7.3)
Mild persistent	11 (1.8)	7 (3.0)	1 (0.5)	3 (1.7)
Moderate-severe intermittent	336 (54.3)	111 (48.1)	149 (71.0)	76 (42.7)
Moderate-severe persistent	212 (34.3)	73 (31.6)	53 (25.2)	86 (48.3)
Sensitivity to allergens, n (%)				
Sensitivity to at least one allergen	579 (90)	199 (81.1)	212 (100)	168 (90.3)
House dust mite	357 (56.9)	152 (64.1)	112 (53.1)	93 (51.7)
Moulds	123 (19.6)	32 (13.5)	51 (24.2)	40 (22.2)
Pollen	561 (89.2)	186 (78.5)	212 (100.0)	163 (90.6)
Dog	143 (22.8)	68 (28.7)	21 (10.0)	54 (30.0)
Cat	284 (45.2)	90 (38.0)	102 (48.3)	92 (51.1)
Birch	225 (35.8)	39 (16.5)	50 (23.7)	136 (75.6)
Cypress	110 (17.5)	38 (16.0)	57 (27.0)	15 (8.3)
Grass	275 (43.8)	149 (62.9)	53 (25.1)	73 (40.6)
Artemisia	82 (13.1)	6 (2.5)	47 (22.3)	29 (16.1)
Olive tree	173 (27.6)	78 (32.9)	57 (27.0)	38 (21.1)
Parietaria sp.	127 (20.2)	63 (26.6)	56 (26.5)	8 (4.4)
Platanus sp.	100 (15.9)	20 (8.4)	60 (28.4)	20 (11.1)
Ambrosia sp.	87 (13.9)	8 (3.4)	20 (9.5)	59 (32.8)
Drugs taken in the last 12 months, n (%)	464 (72.2)	190 (77.6)	100 (47.2)	174 (93.6)
RHINASTHMA score, median (IQR)				
RHIN-total (30 not at all – 150 very much)	76 (53, 91)	52 (43, 67)	91 (85, 95)	70 (59, 91)

	All (N=643)	**IT (N=245)**	**FR (N=212)**	**AT (N=186)**
RHIN - upper respiratory (9 not at all – 45 very much)	25 (20, 29)	20 (16, 25)	27 (24, 30)	27 (21, 34)
RHIN - lower respiratory (13 not at all – 65 very much)	30 (21, 39)	20 (16, 26)	39 (36, 43)	28 (22, 36)
RHIN - respiratory allergy impact (8 not at all – 40 very much)	17 (12, 24)	12 (10, 15)	24 (22, 27)	16 (12, 21)
CARAT score, median (IQR)				
CARAT-total (0 worst – 30 best)	18 (14, 22)	22 (18, 25)	15 (13, 18)	16 (12, 20)
CARAT- upper respiratory (0 worst – 12 best)	6 (4, 8)	7 (4, 8)	6 (5, 8)	4 (1, 6)
CARAT- lower respiratory (0 worst – 18 best)	12 (9, 16)	16 (13, 17)	9 (7, 11)	12 (9, 15)

Data presented as mean (SD) for continuous variables, median (interquartile range [IQR]) for ordinal variables, and frequency (%) for categorical variables.

Abbreviations: ARIA: Allergic Rhinitis Impact on Asthma guidelines; BMI: Body Mass Index; CARAT: Control of Allergic Rhinitis and Asthma Test; GINA: Global Initiative for Asthma; FR: France; IT: Italy; AT: Austria

Figure Legends:

Figure 1: Differences of RHINASTHMA-Total and subdomain scores between patients with AR alone and AR with asthma.

Data presented as median (solid line) and interquartile range [IQR] (dashed line) unless otherwise stated. P-values were calculated from Wilcoxon-ranked sum test.

Figure 2: Differences of CARAT-Total and subdomain scores between patients with AR alone and AR with asthma.

Data presented as median (solid line) and interquartile range [IQR] (dashed line) unless otherwise stated. P-values were calculated from Wilcoxon-ranked sum test.

Figure 3: Adjusted association between AR+asthma and RHINASTHMA-Total and subdomain scores.

Data presented as regression coefficient (β) (symbol) and 95% confidence interval [CI] (horizontal bar) unless otherwise stated. Models were adjusted for age, sex, BMI, smoking status, exposure to smoke, education, ARIA grade, sensitivity to allergens, and drugs taken in the last 12 months as fixed factors, and country as a random factor.

Figure 4: Adjusted association between AR+asthma and CARAT-Total and subdomain scores.

Data presented as regression coefficient (β) (symbol) and 95% confidence interval [CI] (horizontal bar) unless otherwise stated. Models were adjusted for age, sex, BMI, smoking status, exposure to smoke, education, ARIA grade, sensitivity to allergens, and drugs taken in the last 12 months as fixed factors, and country as a random factor.

Figure 5: Meta-analysis results of the association between AR+asthma and (A) RHIN-Total score and (B) CARAT-Total score, stratified by countries.

Models were adjusted for sex, age, smoking status, exposure to smoke, education, ARIA grade, sensitivity to allergens, and drugs taken in the last 12 months as fixed factors. I-squared, variation in estimated effect attributable to heterogeneity.

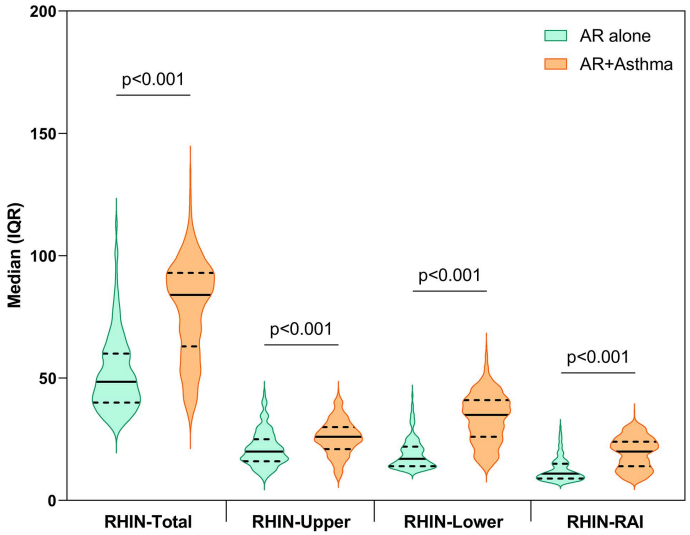

Figure 1_Moitra et al.

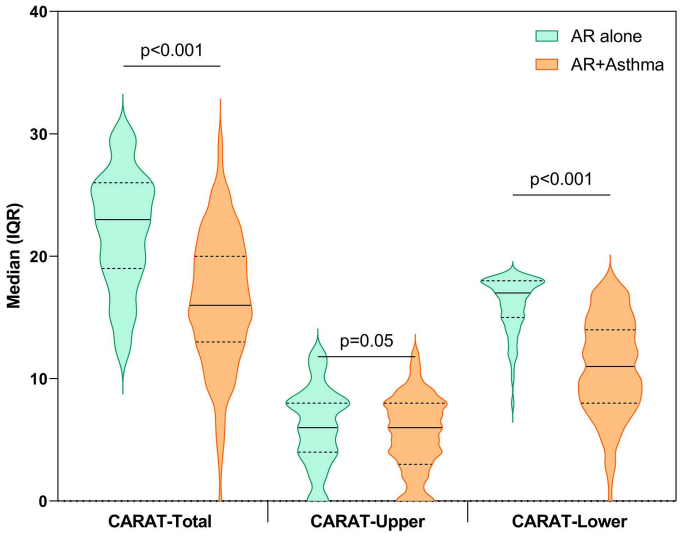

Figure 2_Moitra et al.

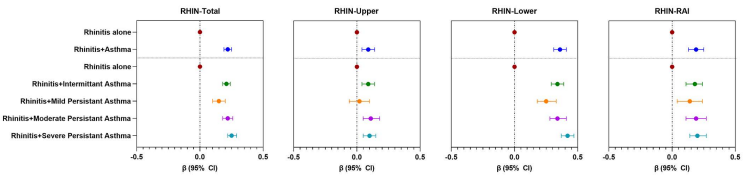

Figure 3_Moitra et al.

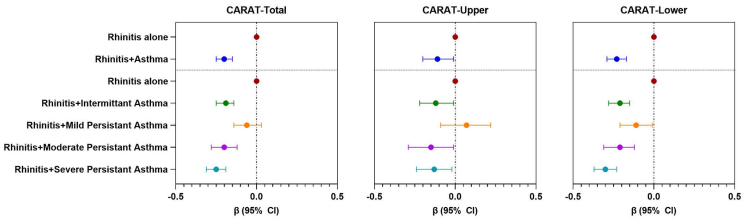

Figure 4_Moitra et al.

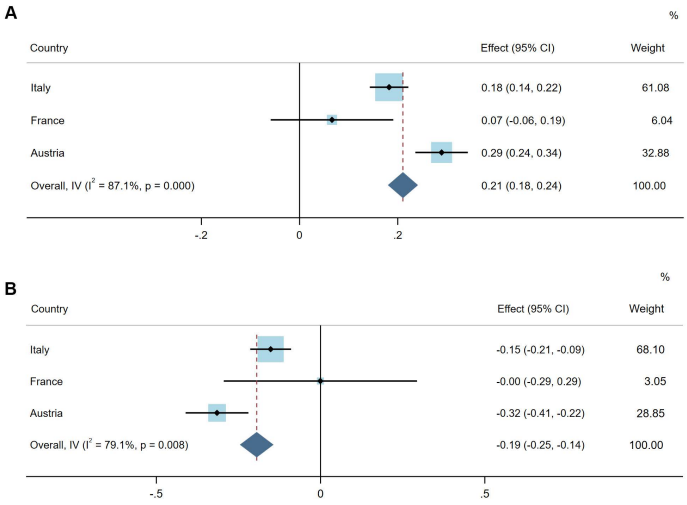

Figure 5_Moitra et al.