Anxiety and depression risk in patients with allergic rhinitis: a systematic review and meta-analysis*

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Rhinology 59: 4, 360 - 373, 2021

https://doi.org/10.4193/Rhin21.087

***Received for publication:**

March 7, 2021

Accepted: May 26, 2021

Abstract

Background: Allergic diseases appear to be associated with mood disorders. However, particularly regarding allergic rhinitis (AR), such association has not been adequately systematically reviewed. Therefore, we conducted a systematic review and meta-analysis to quantify the association between AR and depression and anxiety.

Methodology: We performed an electronic search of PubMed, Web of Science and Scopus for observational studies assessing the association between AR and depression and anxiety. Such association was quantified by means of random-effects meta-analysis, with estimation of pooled odds ratio (OR). Sources of heterogeneity were explored by subgroup analysis.

Results: We included a total of 24 primary studies, of which 23 assessed depression and 11 assessed anxiety. Of these, 12 studies presented OR from multivariable regression models and were included in our meta-analysis. AR was associated with higher odds of depression and anxiety.

Conclusions: AR appears to be associated with high risk of depression and anxiety. While our results point to the importance of mental comorbidities among patients with AR, longitudinal studies are needed adopting uniform definitions and presenting results stratified by AR severity.

Key words: allergic rhinitis, allergy, anxiety, depression, mental health

Introduction

Allergic rhinitis (AR) affects more than 400 million people worldwide[1]. In Europe, its prevalence is approximately 25%, being even higher in urban areas[1,2]. Allergic rhinitis and its comorbidities are often overlooked, underdiagnosed and undertreated[3]. In fact, despite not being a life-threatening disease, AR has important consequences on health and well-being, being associated with disruption of sleeping patterns[4], cognitive and performance impairment[5,6] and decrease in quality of life[7] and work and school performance[5,8]. In addition, AR may also be associated with higher risk for psychiatric disease - mental illness was found to be associated with several chronic diseases, including chronic respiratory diseases. An association between allergic disorders (asthma, rhinitis and dermatitis) and mental illness has been identified, especially in mood disorders such as depression and anxiety[9,10]. Furthermore, depressive symptoms have also been correlated with seasonality and severity of allergy[11]. Asthma is the allergic disorder for which there have been more studies establishing an association with the development of mental illness. In fact, a previous systematic review

has found that asthmatic patients have a risk 2.1 times higher of developing depression and a risk 1.8 times higher of developing anxiety when compared to those without asthma[12]. Although it is possible that a similar association with mood disorders can also be found in AR, such association has not been systematically reviewed in a fully dedicated study to this research question. The aim of this study is to systematically review the literature to assess and quantify the association between AR and depression and anxiety. In addition, we aimed to identify variables potentially explaining heterogeneity across studies.

Materials and methods

Eligibility criteria and search strategy

This review was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement and with the Cochrane Handbook for Systematic Reviews[13,14]. We included observational studies comparing patients with diagnosed AR versus those without AR on the frequency of depression and/or anxiety. Case reports, reviews and editorials were excluded.

Our search was performed in three electronic databases – PubMed, Web of Science and Scopus –, in March 2020. Research on electronic databases was complemented with manual review of the references in the included primary studies. No date or language restrictions were applied.

Study selection and data extraction

After duplicates removal, two authors (JR and FFP) independently screened all titles and abstracts of the studies obtained from database searches. Subsequently, the full texts of selected studies were retrieved and independently read by two authors (JR and FFP), who extracted data on the year of publication, country of study, study design, average age, percentage of female subjects, frequency of asthma and atopic dermatitis, percentage of urban dwellers, AR definition and method of assessment, depression/anxiety definition and method of assessment, number of subjects with and without AR, frequency of depression and anxiety in each group and adjusted effect size measures.

Countries where the study was performed were grouped into three regions - Europe, USA and Far East. Concerning AR assessment, studies were classified into those in which AR 1) was clinically diagnosed when the study was being performed, 2) had been previously registered by a healthcare professional (i.e., information on AR was obtained by consulting patients' clinical files), or 3) was simply reported by the patient. We also classified primary studies according to the method of outcome assessment (either depression or anxiety), into those in which 1) a previous diagnosis had been registered by a healthcare professional (i.e., information on depression/anxiety was obtained by consulting participants' clinical files); 2) validated questionnaires were applied, or 3) symptoms or a previous diagnosis had simply been reported by the patient without the use of validated questionnaires. We used a purposely-built form to extract data. We developed a pilot version which was modified after assessment of the first 10 studies.

Any disagreement between authors was solved by consensus and, if not reached, by discussion with a third author (BSP). Data missing from the primary studies was requested by contacting the authors. Duplicate or overlapping reports were identified, privileging the ones with more complete results.

Quality assessment

An adapted version of The National Health Institute (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies was used to evaluate the included primary studies[15]. The tool consists of 14 items with "Yes/No" answers. Question number 8, inquiring if the study examines different exposure levels and their relation with the outcome, was not answered for any study due to the dichotomous format of the data retrieved. For cross-sectional studies, no answers were registered for questions 6, 7, 10, 12 and 13, as such questions would not be applicable. The two authors (JR and FFP) independently assessed the quality of each study, with any disagreement being solved by consensus.

Data analysis

As our main analysis, we performed meta-analysis assessing the associations between AR and anxiety and depression, based on adjusted odds ratios (ORs) (i.e., OR obtained with multivariable regression models) retrieved from included primary studies. Whenever primary studies applied more than one multivariable model, we retrieved the results obtained with the model adjusting for the largest number of independent variables. In order to assess results consistency, we also performed meta-analysis for the crude associations between AR and anxiety/depression, by pooling raw data retrieved from included primary studies. For those studies only providing effect size measures and the respective confidence intervals, raw data was estimated using the methods described by Di Pietrantonj and using estimraw interactive tool[16,17].

Pooled ORs were estimated by means of random-effects meta-analysis, with weighting by the restricted maximum likelihood approach. In each meta-analysis, we only included primary studies with the same design (i.e., we did not include cross-sectional and cohort studies in the same analyses). Between-study heterogeneity was assessed using the I^2 statistic and the Cochran Q statistic. An I^2>50% and a Cochran Q statistic P value <0.1 were considered to represent substantial heterogeneity.

In order to identify variables that could explain such differences across primary studies' results, we performed subgroup analyses. Subgroup analyses were based on the types of covariates included in multivariable models, as well as on the study region,

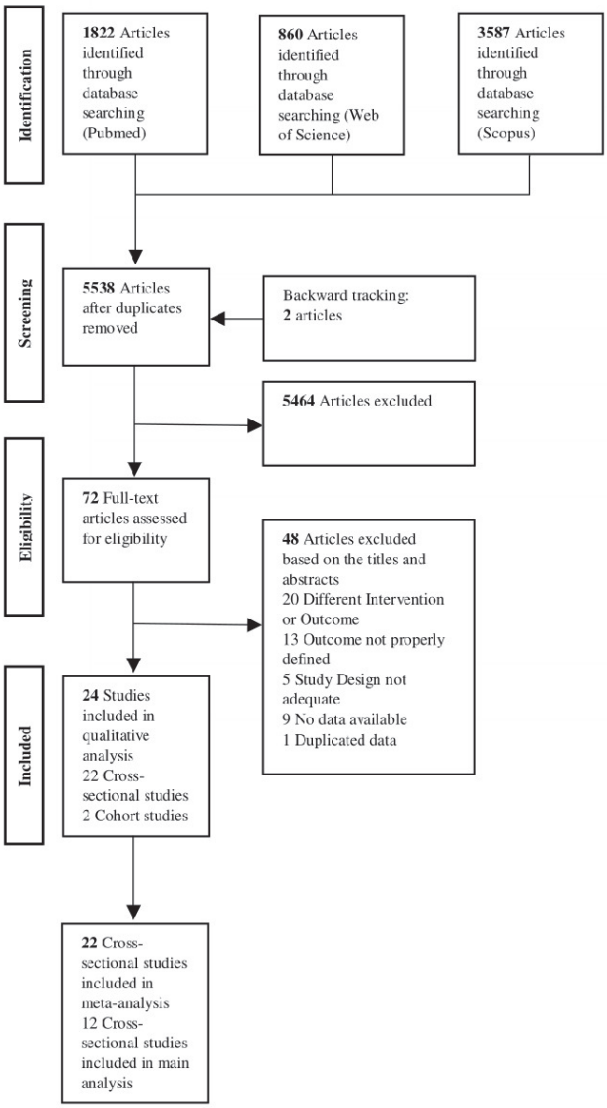

Figure 1. PRISMA Flow Diagram showing search strategy and studies selection.

participants' age group and methods of exposure and outcome assessment (as defined in the Data Extraction section). Meta-regression was not performed within our main analyses on account of the insufficient number of included primary studies in the analysis for which substantial heterogeneity was found, but was performed in the ancillary analyses using raw data. Publication bias was assessed by observation of funnel plots and trim-and-fill analysis for each outcome. Data analysis was performed using software R (version 4.0), with use of the metafor package.

Results

Study selection

The study selection process is illustrated in Figure 1. We retrieved a total of 6269 citations from electronic databases and 2 additional citations from reference consultation of included primary studies. After duplicates removal and initial title and abstract screening, 72 studies were identified for full-text review. Of these, we were not able to assess 8 studies, as full papers were not available even after contacting the authors (n=6), or no information in English was provided after contacting the authors (n=2). Forty studies were further excluded after full-text reading, leaving 24 primary studies included in the systematic review[18-41]. Among the included papers, 13 studies solely reported results on depression[19,21-23,28-32,36,37,39,41], one study solely reported results on anxiety[35] and 10 studies presented results on both depression and anxiety[18,20,24-27,33,34,38,40]. Of these 24 primary studies, 12 studies[20,26-30,34-36,38,39,41] presented OR from multivariable regression models and were included in our main analyses – 11 studies[20,26-30,34,36,38,39,41] provided results from multivariable models assessing the association between AR and depression, while 6 studies[20,26,27,34,35,38] provided results from multivariable models assessing the association between AR and anxiety (5 studies[20,26,27,34,38] provided information on both depression and anxiety).

Studies characteristics

Table 1 summarizes the characteristics of the 23 included primary studies assessing the association between AR and depression[18-34,36-41]. These studies were published between 1991 and 2019 and their sample sizes ranged from 88 to 240 million participants, resulting in a total of more than 243 million participants. Twenty-one studies had a cross-sectional design[18-21,23-33,36-41], while two consisted of cohort studies[22,34]. Eleven studies were conducted in America[19-21,24-27,29,35,36,41], 7 in Europe[18,28,32,33,37,38,40] and 5 in Asia[22,23,30,31,39]. Thirteen studies included only adults [18,20,21,27-30,33,35-37,39-41], 6 included only children/adolescents[19,22,23,26,31,34] and 4 included participants of both age groups[24,25,32,38]. Allergic rhinitis diagnosis was performed by a physician at the time of assessment in 6 studies[18-20,28,34,40], obtained by consulting the clinical file in 4 studies[22,24,37,38] and reported by the patient in 13 studies[21,23,25-27,29-33,36,39,41]. Depression was evaluated by a validated questionnaire in 12 studies[18-21,27-29,32-34,36,38], self-reported in 7 studies[23,25,26,30,31,39,41] and assessed by consulting clinical files in 4 studies[22,24,37,38]. In our main meta-analysis, we included a total of 19,220,087 participants with AR and depression was identified in 3,939,572 of them, corresponding to a frequency of 20.5% (range 0.6–38.7%). These studies also included a total of 222,648,239 participants without AR, of whom 36,941,336 had depression, corresponding to a frequency of 16.6% (range 0.2–16.7%).

Table 2 presents details of the 11 studies examining the possible association between AR and anxiety[18,20,24-27,33-35,38,40]. These studies were published between 1999 and 2019 and their sample sizes ranged from 88 to 1,750,000, resulting in a total of more than 2 million of participants included in this analysis.

Table 1. Characteristics of primary studies assessing depression in patients with allergic rhinitis (AR).

Studies	Year	Country	Study design	Age group (mean)	Women (%)	AR assessment method	Depression assessment method	N Participants	Participants with AR		Participants without AR		Adjusted OR (CI)
									Total	Participants with depression – N (%)	Total	Participants with depression – N (%)	
Addolorato G[18]	1999	Italy	Cross-Sectional	Adults (32.8)	100	Clinical diagnosis	Zung self-rating depression scale	88	24	5 (20.8)	64	7 (10.9)	[b]
Bahreinian S[19]	2011	Canada	Cross-Sectional	Children/adolescents (12.5)	44	Clinical diagnosis	CDI-S	431	131	38 (29.0)	300	91 (30.3)	[b]
Bedolla-Barajas M[20]	2017	Mexico	Cross-Sectional	Adults (28.3)	57.5	Clinical diagnosis	BDI-II	207	111	43 (38.7)	96	16 (16.7)	2.5 (1.3-5.0)
Bell IR[21]	1991	USA	Cross-Sectional	Adults (20.1)	58.4	Self-report	Questionnaire (not specified)	372	99	9 (9.1)	273	8 (2.9)	[b]
Chen MH[22]	2013	Taiwan	Cohort	Children/adolescents (13.1)	44.3	ICD-9-CM	ICD-9-CM	8365	1673	41 (2.5)	6692	81 (1.2)	[b]
Chun YH[23]	2015	South Korea	Cross-Sectional	Children/adolescents (15)	46.3	Self-report physician diagnosis	Self-report physician diagnosis	3192	1046	104 (9.9)	2146	225 (10.5)	[b]
Cuffel B[24]	1999	USA	Cross-Sectional	Children/adolescents and Adults (NA)	61.1	Previous clinical diagnosis	ICD-9-CM	641205	85298	10276 (12.0)	555907	42799 (7.7)	[b]
Derebery J[25]	2008	USA	Cross-Sectional	Children/adolescents and Adults (47.4)	5.1	Self-report	Self-report	7024	3831	659 (17.2)	3193	265 (8.3)	[b]
Garg N[26]	2014	USA	Cross-Sectional	Children/adolescents (2.5)	48.3	Self-report physician diagnosis	Self-report physician diagnosis	16616	2519	15 (0.6)	14097	31 (0.2)	7.6 (2.3-25.0)
Goodwin RD[27]	2002	USA	Cross-Sectional	Adults (46.9)	51.6	Self-report	MIDUS	2612	416	79 (19.0)	2196	294 (13.4)	1.3 (0.9-1.7)
Grosso A[28]	2019	Italy		Adults (49.7)	50.1	Clinical diagnosis	PHQ-2	1699	972	116 (11.9)	727	37 (5.1)	3.1 (2.3-4.2)
Hurwitz EL[29]	1999	USA	Cross-Sectional	Adults (NA	50.7	Self-report physician diagnosis	DIS	6574	583	53 (9.1)	5991	313 (5.2)	2.0 (1.3-3.2)
Kim DH[30]	2016	South Korea	Cross-Sectional	Adults (45.7)	50.2	Self-report physician diagnosis	Self-report physician diagnosis	11154	1467	63 (4.3)	9687	387 (4.0)	1.3 (0.9-1.8)
Kim SY[31]	2019	South Korea	Cross-Sectional	Children/adolescents (15)	46.7	Self-report physician diagnosis	Self-report	408737	102113	34187 (33.5)	306624	94796 (30.9)	[b]
Kovacs M[32]	2003	Hungary	Cross-Sectional	Children/adolescents and Adults (32.4)	58.1	Self-report	BDI	12449	304	27 (8.9)	12145	1008 (8.3)	[b]

Studies	Year	Country	Study design	Age group (mean)	Women (%)	AR assessment method	Depression assessment method	N Participants	Participants with AR		Participants without AR		Adjusted OR (CI)
									Total	Participants with depression – N (%)	Total	Participants with depression – N (%)	
Lind N[33]	2014	Sweden	Cross-Sectional	Adults (51.5)	55.1	Self-report physician diagnosis	HADS	3066	190	12 (6.3)	2876	127 (4.4)	[b]
Nanda MK[34]	2016	USA	Cohort	Children/adolescents (6.9)	45.2	Clinical diagnosis	BASC-2	546	119	22 (18.5)	427	37 (8.7)	1.9 (1.0-3.9)
Roxbury CR[36]	2019	USA	Cross-Sectional	Adults (45.7)	49.4	Self-report	PHQ-9	3572	699	31 (4.4)	2873	132 (4.6)	0.9 (0.7-1.2)
Sato Y[37] [a]	2018	Sweden	Cohort	Adults (NA)	(NA)	ICD-8	Previous clinical diagnosis	201090	9727	745 (7.7)	191363	13080 (6.8)	[b]
Schmitt J[38]	2016	Germany	Cross-Sectional	Children/adolescents and Adults (45.3)	54.1	ICD-10	ICD-10	1811094	111394	4456 (4.0)	1699700	49291 (2.9)	1.6 (1.6-1.7)
Shin JH[39]	2018	South Korea	Cross-Sectional	Adults (46.4)	51.5	Self-report physician diagnosis	Self-report physician diagnosis	14252	1807	94 (5.2)	12445	498 (4.0)	1.7 (1.1-2.7)
Tas HI[40]	2019	Turkey	Cross-Sectional	Adults (31.4)	61.1	Clinical diagnosis	BDI	175	101	24 (23.8)	74	8 (10.8)	[b]
Zhou S[41]	2017	USA	Cross-Sectional	Adults (47)	48.2	Self-report	Self-report	240000000	19100000	3934600 (20.6)	220900000	36890300 (16.7)	1.3 (1.1-1.5)

Abbreviations: BASC-2, Behaviour Assessment System for Children, Second Edition; BDI, Beck Depression Inventory; BDI-II, Beck Depression Inventory-II; CDI-S, Children's Depression Inventory Short Form; DIS, Diagnostic Interview Schedule; HADS, Hospital Anxiety and Depression Scale; ICD-8, International Classification of Diseases, Eight Revision; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10, International Classification of Diseases, Tenth Revision; MIDUS, Midlife Development in the United States; NA – not available; PHQ-2, Patient Health Questionnaire-2; PHQ-9, Patient Health Questionnaire-9; [a] Cohort study considered as cross-sectional despite being a cohort due to the format of the available data; [b] Adjusted OR not presented in primary study.

Table 2. Characteristics of primary studies assessing anxiety in patients with allergic rhinitis (AR).

Studies	Year	Country	Study design	Age group (mean age - years)	AR assessment method	Anxiety assessment method	Women (%)	N Participants	Participants with AR		Participants without AR		Adjusted OR (CI)
									Total	Participants with anxiety – N (%)	Total	Participants without anxiety – N (%)	
Addolorato G[18]	1999	Italy	Cross-Sectional	Adults (32.8)	Clinical diagnosis	STAI	100	88	24	16 (66.7)	64	11 (17.2)	[a]
Bedolla-Barajas M[20]	2017	Mexico	Cross-Sectional	Adults (28.3)	Clinical diagnosis	BAI	57.5	207	111	51 (45.9)	96	10 (10.4)	5.9 (2.7-13.0)
Cuffel B[24]	1999	USA	Cross-Sectional	Children/adolescents and Adults (NA)	Previous clinical diagnosis	ICD-9-CM	61.1	641205	85298	1261 (1.5)	555907	6871 (1.2)	[a]
Derebery J[25]	2008	USA	Cross-Sectional	Children/adolescents and Adults (47.4)	Self-report	Self-report	5.1	7024	3831	356 (9.3)	3193	125 (3.9)	[a]
Garg N[26]	2014	USA	Cross-Sectional	Children/adolescents (2.5)	Self-report physician diagnosis	Self-report physician diagnosis	48.3	27556	2519	60 (2.4)	14097	128 (0.9)	4.6 (1.8-11.6)
Goodwin RD[27]	2002	USA	Cross-Sectional	Adults (46.9)	Self-report	MIDUS	51.6	2632	416	17 (4.1)	2196	53 (2.4)	1.2 (0.7-2.2)
Lind N[33]	2014	Sweden	Cross-Sectional	Adults (51.5)	Self-report physician diagnosis	HADS	55.1	3066	190	5 (2.6)	2876	20 (0.7)	[a]
Nanda MK[34]	2016	USA	Cohort	Children/adolescents (6.9)	Clinical diagnosis	BASC-2	45.2	546	119	25 (21.0)	427	58 (13.6)	1.4 (0.7-2.6)
Oh H[35]	2018	USA	Cross-Sectional	Adults (NA)	Self-report	DSM-IV	52.7	10334	4096	1783 (43.5)	6238	2032 (32.6)	1.4 (1.3-1.6)
Schmitt J[38]	2016	Germany	Cross-Sectional	Children/adolescents and Adults (45.3)	ICD-10	ICD-10	54.1	1750949	111394	11362 (10.2)	1699700	103682 (6.1)	1.5 (1.5-1.6)
Tas HI[40]	2019	Turkey	Cross-Sectional	Adults (31.4)	Clinical diagnosis	BAI	61.1	175	101	15 (14.9)	74	2 (2.7)	[a]

Abbreviations: BAI, Beck Anxiety Inventory; BASC-2, Behaviour Assessment System for Children, Second Edition; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; HADS, Hospital Anxiety and Depression Scale; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10, International Classification of Diseases, Tenth Revision; MIDUS, Midlife Development in the United States; NA – not available; STAI, State and Trait Anxiety Inventory; [a] Adjusted OR not presented in primary study.

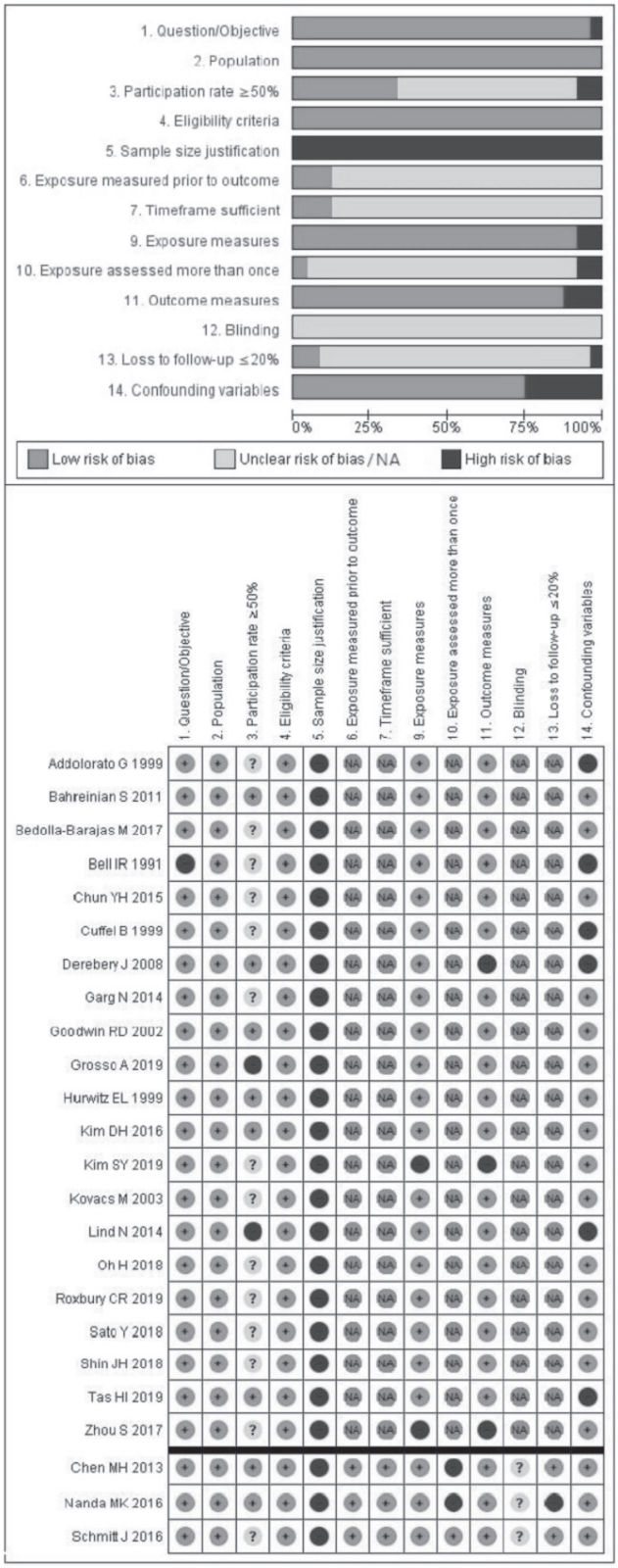

Figure 2. Risk of bias graph and risk of bias summary.

Ten studies had a cross-sectional design[18,20,24-27,33,35,38,41], with the other one consisting of a cohort study[34]. Seven studies were conducted in America[20,24-27,34,35] and 4 in Europe[18,33,38,41]. Six studies included only adults[18,20,27,33,35,41], 2 included only children[26,34] and 3 included both age groups[24,25,38]. Allergic rhinitis diagnosis was performed by a physician in 4 studies[18,20,34,41], previously registered by a in the clinical files in 2 studies[24,38] and self-reported in the remaining 5 studies[25-27,33,35]. Anxiety was previously registered by in clinical files in 3 studies[24,35,38], determined by questionnaire in 6 studies[18,20,27,33,34,41] and self-reported in 2 studies[25,26]. In our main meta-analysis, we included a total of 118,655 participants with AR and anxiety was identified in 13,298 of them, corresponding to a frequency of 11.2% (range 2.4-45.9%). On the other hand, anxiety was detected in only 105,963 of the 1,722,754 participants without AR, corresponding to a frequency of 6.2% (range 0.9-32.6%).

Quality assessment

No studies complied with all quality items in the NIH Quality Assessment Tool. Two cohort studies[22,34] complied with 10 and one[38] with 9 items out of 13. The cross-sectional studies complied with between 4 and 7 quality items out of 8 (median of 6 items). None of the studies presented a sample size justification, four did not adjust for confounding and three did not have clearly defined outcome measures (Figure 2).

Meta-analytic association between AR and Depression

We performed a random-effects meta-analysis on the association between AR and depression, including the 11 primary studies with a cross-sectional design and with available adjusted OR (Figure 3). The number of cohort studies was too small for meta-analytical evaluation. We found that patients with AR presented with a higher chance of depression when compared to healthy controls (pooled meta-analytical OR=1.61; 95%CI=1.32-1.96; P<0.001; I^2=0% Q-Cochran p-value=0.34) (Table 3). Consistent results were observed in subgroup analysis, with all except two analyses resulting in significant positive associations between AR and depression, with low-moderate heterogeneity. In particular, in subgroup analyses according to the method of AR assessment, we identified similar associations between AR diagnosed by self-report or clinical diagnosis, with low heterogeneity (OR=1.40; 95%CI=1.04-1.89; P<0.026; I^2=0% vs OR=1.95; 95%CI=1.32-2.87; P<0.001; I^2=23%). This association was also similar among the different methods of depression diagnosis (self-report: OR=1.86; 95%CI=1.10-3.13; P<0.020; I^2=37%; questionnaire: OR=1.48; 95%CI=1.04-2.09; P<0.028; I^2=0%; previous clinical diagnosis: (OR=1.61; 95%CI=1.20-2.15; P<0.001).
We also performed a sensitivity analysis excluding the largest included study (Zhou et al.)[41], which had also important methodological limitations (namely the assessment of AR and anxiety/depression by self-reporting) – we observed a pooled OR=1.66 (95%CI=1.34-2.04; P<0.001), with no detectable heterogeneity (I^2=0% Q-Cochran p-value=0.30) (Supplementary Table 1). Meta-analytical evaluation of the raw data retrieved from inclu-

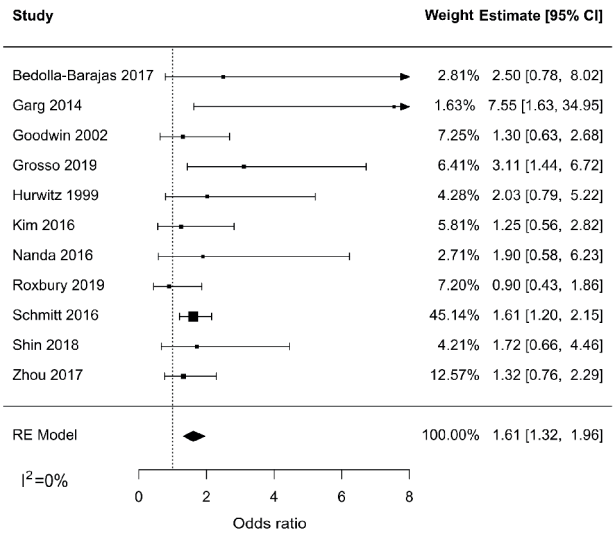

Figure 3. Forest Plot showing the meta-analytic estimate for the association between allergic rhinitis and depression.

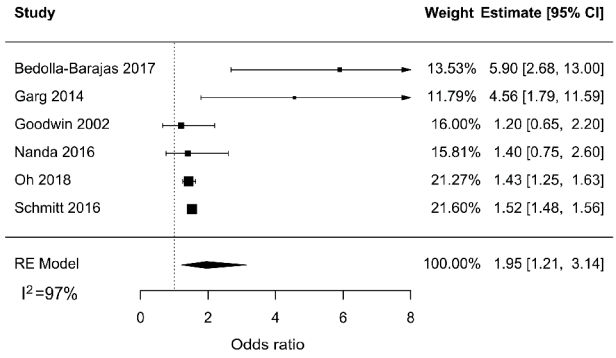

Figure 4. Forest Plot showing the meta-analytic estimate for the association between allergic rhinitis and anxiety.

ded primary studies supported higher chance of depression in patients with AR when compared to healthy controls (pooled meta-analytical OR=1.40; 95%CI=1.30-1.52), although severe heterogeneity was detected (I^2=98%, P<0.001) (Table 4).

Meta-analytic association between AR and anxiety

The meta-analysis on the association between AR and anxiety included 6 cross-sectional primary studies with available adjusted OR (Figure 4). We found that AR was associated with higher frequency of anxiety, although severe heterogeneity was detected (pooled OR=1.91; 95%CI=1.21-3.02; P=0.005; I^2=97%). However, no heterogeneity was detected in subgroup analysis of studies whose models included demographic variables (OR=1.52; 95%CI=1.48-1.55; P<0.001; I^2=0%), for those which adjusted simultaneously for demographic and socioeconomic variables and comorbidities/habits (OR=1.45; 95%CI=1.28-1.64; P<0.001; I^2=0%) (Table 5). In subgroup analyses performed by the method of AR assessment, we identified similar associations between AR diagnosed by self-report or clinical diagnosis (OR=1.78; 95%CI=0.91-3.49; P<0.092; I^2=79% vs OR=2.19; 95%CI=0.94-5.12; P<0.069; I^2=89%). This association was also similar among the different methods of anxiety diagnosis (self-report: OR=2.15; 95%CI=0.90-5.16; P<0.085; I^2=89%; questionnaire: OR=2.23; 95%CI=0.60-8.21; P<0.229; I^2=82%; previous clinical diagnosis: (OR=1.52; 95%CI=1.48-1.56; P<0.001). Meta-analysis of the raw data retrieved from included primary studies sustained higher chance of anxiety in patients with AR when compared to healthy controls (pooled meta-analytical OR=2.10; 95%CI=1.73-2.56; P<0.001; I^2=95%), although severe heterogeneity was detected (I^2=98%, P<0.001) (Table 4).

Analysis of publication bias

The funnel plots (Figure 5) displayed an asymmetrical pattern, being suggestive of publication bias in favour of studies reporting positive associations between AR and depression/anxiety. The trim-and-fill analysis estimated three missing studies for the association between AR and depression – if those studies were included in the meta-analysis, a pooled OR of 1.45 would have been observed (95%CI=1.15-1.82; p=0.002; I^2=17%). No missing studies were estimated in trim-and-fill analysis for the association between AR and anxiety.

Discussion

In this systematic review, we assessed the association between AR and the presence of depression and anxiety, two common mental disorders. We observed, by means of meta-analysis, that patients with AR have 1.6 times more chances to present depression and 1.9 times to more chances to present anxiety. We performed a meta-analytic evaluation including studies with adjusted ORs and we found a statistically significant association between AR and depression, comparing with healthy controls, with no heterogeneity being detected. Concerning anxiety, adjusted ORs obtained with multivariable regression models also demonstrated a positive association between AR and anxiety, with no heterogeneity being detected in subgroup analyses of studies adjusting for a larger set of covariates.

Our results are compatible to those of a recent systematic review that demonstrated higher risk of depression in allergic patients[42]. While in that study the authors performed a subgroup analysis on AR (identifying a positive link between AR and depression), such analysis included only 5 studies, it did not assess anxiety as an outcome variable and was not undertaken as a primary aim of the study and all the involving analysis we perform in this study.

The pathophysiologic mechanisms underlying the association between depression/anxiety and AR may be similar to those observed in asthma, which has also been associated with increased risk of depression[12,43]. Such mechanisms include increased

Table 3. Meta-analytical results and results of the subgroup analyses on the association between allergic rhinitis and depression.

	N studies	Subgroup analysis	
		OR (95%CI) [p-value]	Heterogeneity – I^2; p-value
All studies	11	1.61 (1.32-1.96) [<0.001]	0%; 0.341
Variables adjusted for in multivariable models [a]			
Demographic variables	10	1.58 (1.30-1.94) [<0.001]	0%; 0.300
Demographic and socioeconomic variables	7	1.73 (1.25-2.40) [0.001]	11%; 0.238
Demographic variables and comorbidities/habits	7	1.69 (1.11-2.57) [0.014]	35%; 0.127
Demographic and socioeconomic variables and comorbidities/habits	5	1.95 (1.20-3.18) [0.007]	33%; 0.148
Region			
USA	6	1.43 (1.03-1.98) [0.033]	0%; 0.222
Europe	2	2.02 (1.09-3.73) [0.025]	59%; 0.118
Far East	2	1.43 (0.77-2.65) [0.255]	0%; 0.620
Age group			
Children and adolescents	3	1.52 (1.15-2.02) [0.031]	4%; 0.423
Adults	3	2.15 (1.05-4.42) [0.035]	45%; 0.149
Method of rhinitis assessment			
Self-report	7	1.40 (1.04-1.89) [0.026]	0%; 0.322
Clinical diagnosis	4	1.95 (1.32-2.87) [0.001]	23%; 0.423
Method of depression assessment			
Self-report	5	1.86 (1.10-3.13) [0.020]	37%; 0.216
Questionnaire	5	1.48 (1.04-2.09) [0.028]	0%; 0.298
Previous clinical diagnosis	1	1.61 (1.20-2.15) [0.001]	-[b]

CI=Confidence interval; OR=Odds Ratio; [a] One study did not specify the variables for which adjustments were performed in multivariable models. Adjusting for demographic variables implies adjusting for at least one of the following: sex, age, ethnicity, marital status or region; adjusting for socioeconomic variables implies adjusting for at least one of the following: education, parental education, employment status or income; adjusting for comorbidities/habits implies adjusting for at least one of the following: comorbidities, body mass index, smoking habits, alcohol consumption or exercise habits. [b] No heterogeneity computed, as there is one single study in this subgroup.

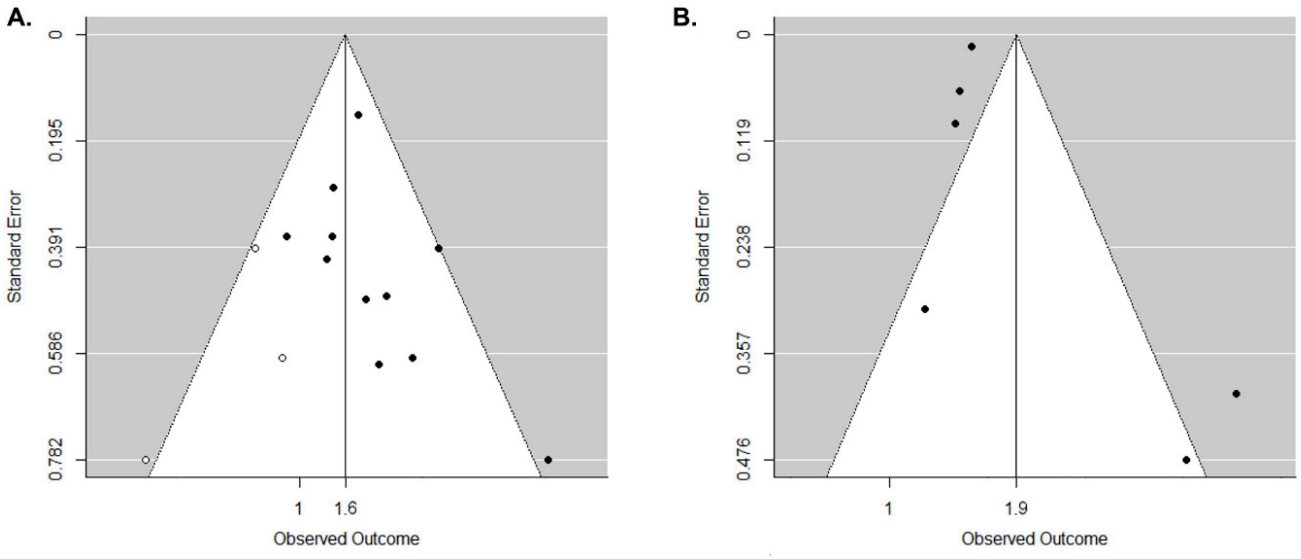

Figure 5. Funnel plots for assessment of publication bias among studies included in the meta-analysis of the association between: A) RA and the risk of depression; B) RA and risk of anxiety.

levels of pro-inflammatory cytokines, disturbance in cholinergic regulation or excessive histamine production[10,44,45]. In fact, high systemic levels of inflammatory mediators produced in the allergic process appears to have an important contribution in limbic system deregulation and depression pathogenesis[46]. On the other hand, there is a robust body of evidence showing altered circulating levels of immune cells and inflammatory mediators in patients with mental disorders. Our results are also compa-

Table 4a. Results of the subgroup and meta-regression analyses on the association between allergic rhinitis and depression and anxiety.

	DEPRESSION				
		Subgroup analysis		Meta-regression	
	N studies	OR (95%CI) [p-value]	Heterogeneity – I^2; p-value	Univariable meta-regression – OR (95%CI) [p-value]	Multivariable meta-regression – OR (95%CI) [p-value]‡
All studies	21	1.40 (1.30, 1.52) [<0.001]	98%; <0.001		
Year of publication	21	-†		0.98 (0.98-0.99) [<0.001]	0.99 (0.98-1.00) [0.159]
Mean age	18	-†		1.01 (1.00-1.01) [0.025]	
Age group					
Children and adolescents	4	1.15 (0.89, 1.48) [0.290]	71%; 0.01	0.75 (0.60-0.94) [0.014]	0.78 (0.61-1.00) [0.054]
Adults	13	1.41 (1.25, 1.59) [<0.001]	75%; <0.001	1.07 (0.84-1.35) [0.606]	
Adults and children	4	1.62 (1.40, 1.88) [<0.001]	97%; <0.001	1.25 (1.08-1.46) [0.004]	1.21 (0.93-1.58) [0.161]
Percentage of females	21			1.00 (1.00-1.00) [0.955]	
Region					
Europe	7	1.42 (1.18-1.70) [<0.001]	85%; <0.001	0.98 (0.82-1.18) [0.858]	
North America	10	1.63 (1.40-1.89) [<0.001]	98%; <0.001	1.29 (1.06-1.56) [0.012]	
Far East	4	1.12 (1.03-1.22) [0.007]	24%; 0.267	0.73 (0.59-0.89) [0.002]	
Percentage of asthmatics	10	-†		0.99 (0.97-1.02) [0.631]	
Percentage of patients with atopic dermatitis	8	-†		1.00 (0.99-1.00) [0.272]	
Percentage of urban dwellers	5	-†		0.99 (0.98-1.00) [0.012]	
Method of rhinitis assessment					
Self-report	13	1.35 (1.24, 1.48) [<0.001]	97%; <0.001	0.92 (0.79-1.08) [0.304]	1.18 (0.92-1.52) [0.187]
Clinical diagnosis	5	2.04 (1.20, 3.46) [0.009]	72%; 0.006	1.41 (1.05-1.89) [0.021]	1.80 (1.22-2.64) [0.003]
Previous clinical diagnosis	3	1.38 (1.17, 1.63) [<0.001]	98%; <0.001	0.98 (0.84-1.15) [0.823]	
Method of depression assessment					
Self-report	7	1.33 (1.20, 1.48) [<0.001]	66%; 0.001	0.92 (0.79-1.07) [0.263]	
Questionnaire	11	1.63 (1.27, 2.09) [<0.001]	69%; <0.001	1.15 (0.96-1.39) [0.122]	
Previous clinical diagnosis	3	1.38 (1.17, 1.63) [<0.001]	98%; <0.001	0.98 (0.84-1.15) [0.823]	
Number of good quality items	21	-†		0.99 (0.91-1.07) [0.785]	

CI=Confidence interval; OR=Odds Ratio; † Subgroup analysis not performed, as this is a continuous variable; ‡ Residual heterogeneity: 69.8%, Omnibus p-value<0.001.

tible to those of meta-analyses linking chronic diseases with mood disorders. In fact, regarding depression, we found that patients with AR had 1.6 times more odds to develop depression, compared to healthy controls. This result is not dissimilar from those previously described for the association between depression and asthma (such as the meta-analysis by Lu et al., which identified a relative risk of 1.6 and the meta-analysis by Gao et al., which identified a relative risk of 1.2)[42,47], as well as between depression and hypertension, cardiac disease, diabetes or chronic lung disease (meta-analytical ORs ranging from 1.3 and 2.1)[48]. Patients with these chronic diseases tend to be older on average than those with AR, which hints at the important impact of AR in young patients, also suggested by the impact of AR in work productivity[8]. Concerning anxiety, we found that patients with AR have 1.9 higher odds of developing anxiety compared to controls, similar to what has been previously described for the association between anxiety and asthma (OR=1.8)[12] or between anxiety and other chronic diseases, such as hypertension[49], cardiac disease[50], diabetes[51] or chronic lung disease[52] (OR ranging from 1.2 and 1.9).

In this systematic review, we included studies with different methods of assessing AR, depression and anxiety. Presence of AR was identified by self-report in 7 studies[26,27,29,30,36,39,41] and in these studies we need to consider the possibility of an incorrect diagnosis by a mistake with other naso-sinusal diseases such as sinusitis or non-allergic rhinitis. Some studies used a survey designed to estimate the prevalence of various health issues and which also included questions about whether AR has been diagnosed by a doctor, possibly leading to an underestimation of AR frequency[26,27,29,30,39]. Regarding the outcome assessment, depression was mainly detected by questionnaires or self-report, constituting an important limitation that may result in an overestimation – Kim et al. and Zhou et al. assessed depression inquiring "Have you been diagnosed with depression by a doc-

Table 4b. Results of the subgroup and meta-regression analyses on the association between allergic rhinitis and depression and anxiety.

	ANXIETY				
		Subgroup analysis		Meta-regression	
	N studies	OR (95%CI) [p-value]	Heterogeneity – I^2; p-value	Univariable meta-regression – OR (95%CI) [p-value]	Multivariable meta-regression – OR (95%CI) [p-value]‡
All studies	10	2.10 (1.73-2.56) [<0.001]	95%; <0.001		
Year of publication	10	-†		1.02 (0.99-1.04) [0.205]	
Mean age	8	-†		0.99 (0.97-1.01) [0.407]	
Age group					
Children and adolescents	1	2.66 (1.95-3.63) [<0.001]	-Ψ	1.31 (0.72-2.37) [0.379]	
Adults	6	3.61 (1.87, 6.98) [<0.001]	84%; <0.001	1.48 (0.93-2.37) [0.098]	
Adults and children	3	1.70 (1.25, 2.32) [<0.001]	99%; <0.001	0.62 (0.39-0.98) [0.042]	
Percentage of females	10	-†		1.00 (0.99-1.01) [0.862]	
Region					
Europe	4	3.99 (1.57-10.17) [0.004]	80%; <0.001	1.42 (0.79-2.53) [0.237]	
North America	6	2.06 (1.55-2.75) [<0.001]	95%; <0.001	0.71 (0.40-1.26) [0.237]	
Percentage of asthmatics	3	-†		1.02 (0.95-1.11) [0.529]	
Percentage of patients with atopic dermatitis	3	-†		1.04 (0.97-1.11) [0.309]	
Method of rhinitis assessment					
Self-report	5	2.17 (1.59, 2.95) [<0.001]	84%; <0.001	0.97 (0.61-1.54) [0.892]	
Clinical diagnosis	3	7.74 (4.38, 13.69) [<0.001]	0%; 0.88	4.23 (2.18-8.21) [<0.001]	
Previous clinical diagnosis	2	1.45 (1.00, 2.10) [<0.001]	99%; <0.001	0.54 (0.33-0.87) [0.012]	
Method of depression assessment					
Self-report	2	2.53 (2.13, 3.01) [<0.001]	0%; 0.69	1.33 (0.87-2.05) [0.193]	
Questionnaire	6	3.61 (1.87, 6.98) [<0.001]	84%; <0.001	1.48 (0.93-2.37) [0.098]	
Previous clinical diagnosis	2	1.45 (1.00, 2.10) [0.05]	99%; <0.001	0.54 (0.33-0.87) [0.012]	
Number of good quality items	10	-†		0.98 (0.71-1.37) [0.923]	

CI=Confidence interval; OR=Odds Ratio; † Subgroup analysis not performed, as this is a continuous variable; ‡ Residual heterogeneity: 69.8%, Omnibus p-value<0.001; Ψ No heterogeneity computed, as there is one single study in this subgroup.

tor?" and "How often feel depressed?", which do not constitute the best way to establish the diagnosis by possible misinterpretation of a reactive depression situation. However, in our review, sub-group analyses did not reveal differences according to the various assessment methods of AR and depression and anxiety. Particular attention must be given to the study performed by Zhou et al, the largest study included in our review. Besides being by far the study contributing with most participants, it uses a database that was designed and populated using a probability sample survey to potentially represent the entire USA population (posing even the risk of double inclusion of participants who are also assessed in other primary studies). Therefore, we performed sensitivity analysis removing the study of Zhou et al., observing similar results, with low heterogeneity. This systematic review has some limitations worth discussing. Firstly, the studies included in our meta-analyses are cross-sectional. Meta-analytical evidence on the association between other depression/anxiety and other chronic diseases (such as diabetes and hypertension) has also largely comprised cross-sectional studies as their primary studies. This hinders the establishment of a temporal relationship (and, subsequently, of causality) between exposure and outcome. Longitudinal studies investigating the association between AR and risk of depression/anxiety are scarce (we were only able to identify two of them), limiting the possibility of assessing whether AR associates with increased risk of developing depression/anxiety. However, the cohort studies identified by us are in accordance with the results of our meta-analysis, with both identifying a significant increase in risk of depression and anxiety in patients with AR. Further well-designed cohort studies are needed in the future. Furthermore, only three studies included in this review stratified AR according to the severity or length of exposure to rhinitis symptoms[20,30,36]. Although there may be some association between the duration of symptoms and the risk of depression or anxiety, as shown by Kim et al., the underlying evidence is still scarce and not robust[30].

In addition, no primary study complied with all items of methodological quality. None of the studies presented a sample size

Table 5. Meta-analytical results and results of the subgroup analyses on the association between allergic rhinitis and anxiety.

	N studies	Subgroup analysis	
		OR (95%CI) [p-value]	Heterogeneity – I^2; p-value
All studies	6	1.91 (1.21-3.02) [0.005]	97%; 0.002
Variables adjusted for in multivariable models [a]			
Demographic variables	5	1.52 (1.48-1.55) [<0.001]	0%; 0.114
Demographic and socioeconomic variables and comorbidities/habits	4	1.45 (1.28-1.64) [<0.001]	0%; 0.101
Region			
USA	4	1.45 (1.28-1.64) [<0.001]	0%; 0.101
Age group			
Children and adolescents	3	1.87 (1.06-3.29) [0.031]	71%; 0.068
Adults	4	1.84 (1.01-3.34) [0.044]	98%; 0.005
Method of rhinitis assessment			
Self-report	3	1.78 (0.91-3.49) [0.092]	79%; 0.045
Clinical diagnosis	3	2.19 (0.94-5.12) [0.069]	89%; 0.003
Method of depression assessment			
Self-report	3	2.15 (0.90-5.16) [0.085]	89%; 0.002
Questionnaire	2	2.23 (0.60-8.21) [0.229]	82%; 0.019
Previous clinical diagnosis	1	1.52 (1.48-1.56) [<0.001]	-[b]

CI=Confidence interval; OR=Odds Ratio; [a] One study did not specify the variables for which adjustments were performed in multivariable models. Adjusting for demographic variables implies adjusting for at least one of the following: sex, age, ethnicity, marital status or region; adjusting for socio-economic variables implies adjusting for at least one of the following: education, parental education or income; adjusting for comorbidities/habits implies adjusting for at least one of the following: comorbidities, body mass index, smoking habits. [b] No heterogeneity computed, as there is one single study in this subgroup.

justification and some studies did not adjust for confounding or have valid, reliable and clearly defined outcome measures. Such methodological concerns are not unexpected findings since many of the studies were based on data collected not for the specific purpose of evaluating this association.

Another limitation concerns the heterogeneity observed in the analysis assessing the association between AR and anxiety, which can be explained, among others, by differences in the exposure and outcomes assessment methods, the use of broad definitions of depression and anxiety (rather than clinical definitions) in some primary studies and differences in participants' demographic characteristics (e.g., regarding their age). Nevertheless, no heterogeneity was observed in sugbroup analyses restricted to studies reporting results of multivariable models adjusting for a larger set of variables.

Finally, publication bias is probably present. The predominance of studies with a positive association between AR and mood disorders (as portrayed in the asymmetry of the funnel plots), suggests an overestimation of our pooled Odds Ratio. Thus, the real association between AR and depression/anxiety is probably weaker than the one obtained in this meta-analysis, as suggested by trim-and-fill analysis for the association between AR and depression (although significant associations were still observed in such analysis).

This study has also several strengths. To the best of our knowledge, this study is the first to perform a systematic review and meta-analysis focused on the association between AR and depression and/or anxiety. Previous studies focused on atopy or the overall effect of allergic disorders without evaluating the specific effect of AR in mental health. Furthermore, our analysis comprises a profound and extensive literature research, assessing data on over 222 million participants in the AR-depression association and on over 1.7 million participants in AR-anxiety link. In an attempt to minimize the impact of publication bias, we searched three different electronic databases and complemented with search on primary studies' references. We also did not apply exclusion criteria based on the date or language of publication. Finally, we explored sources of heterogeneity through subgroup analyses and meta-regression, allowing for the identification of variables explaining across-studies differences.

Conclusion

In summary, this review supports the hypothesis that allergic diseases, probably due to a common mechanism, are associated with mental illness. In particular, our results suggest that patients with AR have higher chance of mood disorders, such as depression and anxiety. This points to the importance of enhancing awareness among clinicians on the mental comorbidities of AR, which should allow earlier diagnosis and possibly referral

for psychiatric evaluation. The cross-sectional nature of included primary studies (along with the fact that some studies assessed AR and anxiety/depression by self-reporting), however, does not allow for inferring on any causal relation, nor on the directionality for the association between AR and anxiety/depression. In fact, the scarcity of longitudinal studies assessing this question is a relevant limitation - therefore, to allow the assessment of temporal associations and to diminish the impact of confounding variables, longitudinal studies are needed, preferably with a prospective design, adopting uniform definitions (with on-site AR and depression/anxiety assessment based on validated questionnaires and/or clinical diagnosis) and presenting results stratified by AR severity. In a more distant future, experimental studies may even be designed to assess whether a more adequate control of the AR also results in better control of comorbidities and increased patient well-being.

Authorship contribution

Data collection was a long process performed by JR, FFP and KR. Meta-analysis required the essential specialized work of BSP. The revision of the manuscript and important clinical correlations were performed by two renowned authors in the areas of ENT and Allergy, respectively, RV and JB.

Conflict of interest

The authors declare that they have no relevant conflicts of interest.

Financial disclosure

This is an unfunded project.

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This manuscript contains online supplementary material

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Meta-analytical results and results of the subgroup analyses on the association between allergic rhinitis and depression excluding the study performed by Zhou et al.

	N studies	Subgroup analysis	
		OR (95%CI) [p-value]	Heterogeneity – I^2; p-value
All studies	10	1.66 (1.34-2.04) [<0.001]	0%; 0.300
Variables adjusted for in multivariable models [a]			
Demographic variables	9	1.63 (1.32-2.02) [<0.001]	0%; 0.254
Demographic and socioeconomic variables	6	1.93 (1.30-2.87) [0.001]	16%; 0.236
Demographic variables and comorbidities/habits	7	1.69 (1.11-2.57) [0.014]	35%; 0.127
Demographic and socioeconomic variables and comorbidities/habits	5	1.95 (1.20-3.18) [0.007]	33%; 0.148
Region			
USA	5	1.61 (0.96-2.71) [0.073]	34%; 0.143
Europe	2	2.02 (1.09-3.73) [0.025]	59%; 0.118
Far East	2	1.43 (0.77-2.65) [0.255]	0%; 0.620
Age group			
Children and adolescents	3	1.52 (1.15-2.02) [0.031]	4%; 0.423
Adults	7	1.61 (1.13-2.29) [0.009]	19%; 0.347
Method of rhinitis assessment			
Self-report	6	1.44 (1.01-2.05) [0.044]	0%; 0.226
Clinical diagnosis	4	1.95 (1.32-2.87) [0.001]	23%; 0.423
Method of depression assessment			
Self-report	4	1.59 (1.02-2.49) [0.043]	0%; 0.201
Questionnaire	5	1.48 (1.04-2.09) [0.028]	0%; 0.298
Previous clinical diagnosis	1	1.61 (1.20-2.15) [0.001]	-[b]

CI=Confidence interval; OR=Odds Ratio; [a] One study did not specify the variables for which adjustments were performed in multivariable models. Adjusting for demographic variables implies adjusting for at least one of the following: sex, age, ethnicity, marital status or region; adjusting for socioeconomic variables implies adjusting for at least one of the following: education, parental education, employment status or income; adjusting for comorbidities/habits implies adjusting for at least one of the following: comorbidities, body mass index, smoking habits, alcohol consumption or exercise habits. [b] No heterogeneity computed, as there is one single study in this subgroup.