

# Allergic disorders and risk of depression: A systematic review and meta-analysis of 51 large-scale studies



Zhiyu Lu, BS <sup>\*,†</sup>; Lina Chen, BS <sup>\*</sup>; Suling Xu, MS <sup>‡</sup>; Qingyi Bao, BS <sup>†</sup>; Yongyan Ma, BS <sup>\*</sup>; Lili Guo, BS <sup>\*</sup>; Shuaishuai Zhang, BS <sup>\*</sup>; Xiaoping Huang, BS <sup>\*</sup>; Chao Cao, PhD <sup>\*</sup>; Liemin Ruan, MS <sup>§</sup>

<sup>\*</sup> Department of Respiratory Medicine, Ningbo First Hospital, Ningbo, China

<sup>†</sup> Ningbo University School of Medicine, Ningbo, China

<sup>‡</sup> Department of Dermatology, Affiliated Hospital of Medical College, Ningbo University, Ningbo, China

<sup>§</sup> Department of Mental Health, Ningbo First Hospital, Ningbo, China

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## ABSTRACT

**Background:** Previous studies have suggested that allergic disorders are associated with an increased risk of depression. However, the results are conflicting.

**Objective:** To determine the association between allergic disorders and depression based on large-scale studies.

**Methods:** We reviewed relevant articles obtained from PubMed and Embase. Studies were eligible if they reported an association between allergic disorders and depression and provided available data. Study selection, data extraction, and analyses were undertaken. Pooled relative risks (RRs) with 95% confidence intervals (CIs) were calculated.

**Results:** Of 1,827 studies identified, 51 including more than 2.5 million participants met our inclusion criteria. Overall, the results showed that allergic disorders were associated with a significant increased risk of depression (pooled RR 1.59, 95% CI 1.48–1.71). A higher risk of depression also was observed in patients with asthma (RR 1.59, 95% CI 1.46–1.74) and those with allergic rhinitis (RR 1.57, 95% CI 1.27–1.93). Subgroup analyses were conducted based on sex and age. Children (RR 1.66, 95% CI 1.41–1.96) and adults (RR 1.58, 95% CI 1.44–1.74) with allergic disorders had a higher risk of depression than controls. However, no significant association was found between allergic disorders and risk of depression in male subjects (RR 1.37, 95% CI 0.98–1.91), but a positive association was detected in female subjects (RR 1.65, 95% CI 1.44–1.89).

**Conclusion:** The results from our study showed that allergic disorders significantly increased the risk of depression.

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## Introduction

Allergic disorders have become major worldwide public health issues, causing severe social and economic burdens and significant quality-of-life impairment.<sup>1</sup> Moreover, the prevalence of allergic disorders, such as asthma and allergic rhinitis, which are estimated to affect 300 million and 400 million people, respectively, around the world, has continued to escalate over time.<sup>2</sup> Equally detrimental is depression, another major global public health issue. As one of the major psychiatric diseases, depression severely affects

patients and society. In total 4% to 20% of the population around the world have had major depression during their lifetime, and it is forecast to be the second leading cause of disability by 2020.<sup>3</sup> Therefore, depression, allergic disorders, and especially their association have become worldwide subjects of current research and clinical interest.

An association between allergic disorders and risk of depression has been hotly debated, but the relation is inconsistent rather than conclusive. A large population-based epidemiologic study reported an association between allergic disorders and a significantly higher risk of depression.<sup>4</sup> Further, the temporal association in adolescents in Taiwan suggested the atopic cohort had an increased risk of major depression compared with the nonatopic cohort after a 10-year duration.<sup>5</sup> However, Brunner et al<sup>6</sup> found no significant association between allergic disorders and risk of depression in a prospective study.

Therefore, we carried out this systematic review and meta-analysis based on large-scale studies to examine the association between allergic disorders and risk of depression.

Drs Ruan and Cao contributed equally to this article.

**Reprints:** Liemin Ruan, MS, Department of Mental Health, Ningbo First Hospital, 59 Liuting Road, Ningbo, 315010, China; E-mail: [lmruan@tom.com](mailto:lmruan@tom.com).

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## Methods

### Search Strategy

We selected relevant studies by searching PubMed and Embase from inception until November 2016. Allergic disorders were identified using the following search terms: *asthma*, *allergic rhinitis*, *hay fever*, and *allergy* or *atopy*. The search terms *depression* or *depressive disorders* were used to identify citations relevant to depression. The search was limited to articles published in the English language and conducted in humans. Case reports, reviews, editorials, comments, practice guidelines, historical articles, news, and meta-analyses were excluded.

### Study Selection

We screened titles and abstracts against the inclusion criteria to identify potential relevance, and then the full-text copies of potentially relevant articles were retrieved and reviewed to confirm eligibility. To enhance the reliability of the results, we specified a minimum sample of 100 participants for all epidemiologic studies. In cohort studies, the exposure was allergic disorders and the end point was depression. In cross-sectional studies, we selected articles or abstracts that assessed the prevalence of depression in patients with allergic disorders compared with a nonallergic group. Studies were eligible if they reported odds ratios (ORs) or relative risks (RRs) or raw data from which we could derive RRs with 95% confidence intervals (CIs) for the potential effect of allergic disorders on risk of depression.

### Data Extraction

We extracted the surname of the first author, year of publication, country of study origin, participants' characteristics including age group (children or adults), sex and number of participants, types of allergic disorders, criteria of allergic disorders and depression diagnosis, duration of follow-up (for cohort studies), and risk estimates from enrolled studies. When studies reported ORs or RRs with different degrees of adjustment for several risk factors, we used the maximum adjusted estimate. For studies presenting with several categories, the highest vs lowest category was used to calculate the pooled RR. For studies with different criteria of allergic disorder

diagnosis (such as the association between self-reported asthma and risk of depression or between register-based asthma and risk of depression), we selected the RRs for the best diagnosis method (register-based asthma). For cohort studies, if studies reported depression at several intervals, we selected the longest period for this meta-analysis.

### Data Analysis

The RRs and corresponding 95% CIs were used to assess the association between allergic disorders and risk of depression. We extracted dichotomous data from studies reporting the number of patients with events and total participants and pooled them to calculate RRs and 95% CIs. In addition, subgroup analyses by sex, age, and diseases (asthma and allergic rhinitis) were performed. In analyses, we assessed heterogeneity with the Cochran Q statistic, with a *P* value less than .10 suggesting evidence of heterogeneity. Then, the magnitude of heterogeneity was measured using the  $I^2$  statistic, with values of 25% to 49% representing low heterogeneity, values of 50% to 75% representing moderate heterogeneity, and values greater than 75% representing high heterogeneity.<sup>7</sup> The funnel plot was used to evaluate the possibility of publication bias. We used the Begg test and Egger test to test for the asymmetry of funnel plots. All statistical analyses were conducted with Review Manager 5.3 (Cochrane Collaboration, London, United Kingdom) and STATA 12 (StataCorp, College Station, Texas). Statistical results were deemed significant if the 2-sided *P* value was less than .05.

## Results

### Study Selection

Figure 1 shows the flow diagram of study identification and selection. We identified 721 articles from the PubMed database and 3,335 articles from the Embase database. After removing duplicates, we identified 1,827 unique citations from the electronic database. After initial screening, based on titles and abstracts, 81 articles or abstracts remained for further assessments. After detailed evaluation, 30 more articles were excluded according to our inclusion criteria. Therefore, 51 studies were included in our systematic review and meta-analysis.<sup>4–6,8–55</sup>

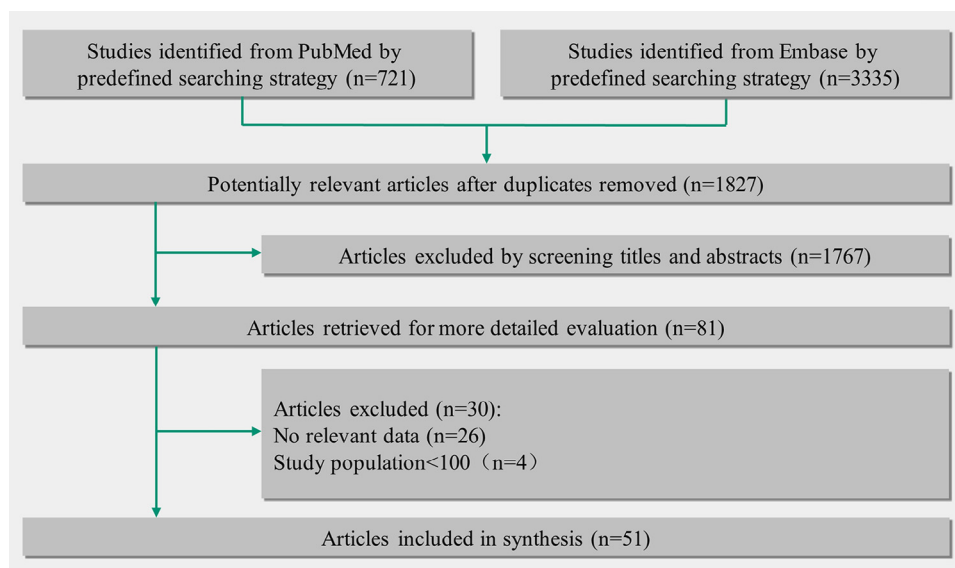


**Figure 1.** Details of literature search and study selection.

### Study Characteristics

The included 51 studies (Table 1) included more than 2.5 million participants, with individual study samples ranging from 100 to 1,811,094. Twenty-two studies were from North America,<sup>6,9–15,23,24,26,29,31,33,38–40,49,50,53–55</sup> 14 were from Europe,<sup>21,25,28,30,32,34,37,42,45–48,51,52</sup> 12 were from Asia,<sup>5,8,16–20,27,36,41,43,44</sup> 2 were from Australia,<sup>4,22</sup> and 1 included subjects from 5 continents (Europe, Australia, South America, Asia, and Africa).<sup>35</sup> Twenty-nine studies included adults ( $\geq 18$  years old),<sup>4,6,9,12,13,15,20,21,25–27,29–31,34,35,38,41,43,44,46–53,55</sup> 15 included children ( $< 18$  years),<sup>5,8,10,11,16–19,23,33,39,40,42,54</sup> and 5 included adults and children.<sup>22,24,28,32,36,45</sup> In defining depression, 4 studies used a clinical diagnostic interview,<sup>5,9,12,48</sup> 46 studies used self-report questionnaires,<sup>4,6,8,10,11,13–37,39–47,49–55</sup> and 1 did not report on the method used.<sup>38</sup> For criteria of allergic disorders, physician diagnosis was used in 23 studies,<sup>4,5,10–12,15–20,23,24,26,30,31,34,36,41,44,50,51,53</sup> and another 22 studies applied self-report questionnaires or telephone interview.<sup>6,8,9,13,21,22,25,27–29,32,33,35,39,42,43,45–47,49,52,55</sup> In addition, 1 study used parent or guardian assessment<sup>54</sup> and 1 study applied clinical tests.<sup>48</sup> Only 4 studies did not report on the relevant information.<sup>14,37,38,40</sup>

### Allergic Disorders and Risk of Depression

Fifty-one studies concerning the association between allergic disorders and risk of depression contributed 67 available data and more than 2.5 million participants to this meta-analysis. Most outcome data showed positive associations and most were statistically significant. However, some studies reported inconsistent findings, suggesting no association in their studies. In our quantitative analysis, allergic disorders significantly increased the risk of depression compared with that in the nonallergic group (pooled RR 1.59, 95% CI 1.48–1.71; eFigure 1). This finding suggested that patients with allergic diseases have a 1.59-fold risk of depression compared with controls.

### Subgroup Analyses

Based on the specific types of allergic disorders, we conducted subgroup analysis. In the analysis of the asthma group, the pooled RR of subjects with vs without asthma was 1.59 (95% CI 1.46–1.74; Fig 2 and Table 2) with high heterogeneity observed ( $I^2 = 86.1\%$ ). For allergic rhinitis, the RR was 1.57 (95% CI 1.27–1.93; Fig 3 and Table 2) with moderate heterogeneity ( $I^2 = 45.2\%$ ). Therefore, patients with asthma or allergic rhinitis were more likely to develop depression compared with the nonallergic group.

Further, we carried out subgroup analyses to detect a potential association in different age groups. Results indicated a positive association between allergic disorders and risk of depression in children (RR 1.66, 95% CI 1.41–1.96; Fig 4 and Table 2) and adults (RR 1.58, 95% CI 1.44–1.74; Fig 5 and Table 2). The analyses provided valid evidence that an association between allergic disorder and risk of depression exists in children and adults. Significant heterogeneity was present in the 2 group analyses ( $I^2 = 88.4\%$  for adults;  $I^2 = 74.0\%$  for children).

In addition, we performed subgroup analysis based on sex. Interestingly, no association was found in male subjects (pooled RR 1.37, 95% CI 0.98–1.91; eFigure 2 and Table 2). In contrast, we detected a far more significant association in female subjects (combined RR 1.65, 95% CI 1.44–1.89; eFigure 3 and Table 2), which was much higher than that in male subjects. Evidence of high heterogeneity was found in the 2 analyses ( $I^2 = 90.3\%$  in male subjects;  $I^2 = 61.1\%$  in female subjects).

### Analysis of Publication Bias

Visual inspection of the funnel plot of the overall analysis did not show asymmetry, indicating no evidence of publication bias. Moreover, we used the Egger test to confirm the asymmetry of the funnel plot, and the result for publication bias was significant ( $P = .498$ ).

### Discussion

This systematic review and meta-analysis examined the association between allergic disorders and risk of depression from 51 studies involving more than 2.5 million participants worldwide. Our principal finding was that allergic disorders were significantly associated with risk of depression. Furthermore, our subgroup analysis based on different types of allergic disorders showed that asthma and allergic rhinitis increased the risk of depression. Similarly, children and adults with allergic disorders had a higher risk of depression. However, in different sex groups, female subjects with allergic disorders were much more likely to be depressed, whereas no association was detected in male subjects.

A previous prospective systematic review and meta-analysis<sup>56</sup> reported the robust association between psychosocial factors and atopic disorders; however, that meta-analysis lacked studies that specifically addressed the relation between allergic disorders and risk of depression. Recently, a meta-analysis of prospective studies<sup>57</sup> suggested that the risk of developing depression was higher in subjects with asthma than in healthy controls (RR 1.23, 95% CI 0.72–2.10,  $P = 0.45$ ), but presented no such relation for asthma predicting depression. The result might not explain the temporal association between asthma and risk of depression because of the limited studies and participants. Another meta-analysis conducted in 2014<sup>58</sup> based on epidemiologic studies examined the association between allergic disorders and risk of depression. Results showed that the prevalence of depression in subjects with asthma was much higher (OR 1.52, 95% CI 1.30–1.79). However, only 3 studies with available data involving approximately 30,000 participants were included in this meta-analysis, which indicated low statistical power. Further, the 3 studies were not in accord with our inclusion criteria of study selection owing to the broader inclusion criteria of Jiang et al.<sup>58</sup> Such evidence should be interpreted with caution. Thus far, the relation between allergic disorders and risk of depression has not been systematically examined overall.

There is evidence that psychological health might somehow be linked to control of and recovery from allergic disorders.<sup>59</sup> However, there are few studies, especially large, well-conducted, and randomized trials, evaluating the effectiveness of psychotherapeutic intervention in patients with allergic disorders. Therefore, firm conclusions could not be drawn because of the low quality of the few available studies.

### Strength of Our Meta-Analysis

To date, this systematic review and meta-analysis is the most comprehensive to evaluate whether allergic disorders increase the risk of depression compared with previous systematic review and meta-analysis.<sup>56–58</sup> The important difference and strength between previous meta-analyses and the present meta-analysis has several aspects. First, the types of included studies and the number of studies and participants differed between previous meta-analyses and the present meta-analysis. In this meta-analysis, we included 51 studies, which is much larger than the 2 prospective studies included in the meta-analysis of Gao et al.<sup>57</sup> and the 10 epidemiologic studies with available data in 3 studies included in the meta-analysis of Jiang et al.<sup>58</sup> In addition, we analyzed more than 2.5 million participants worldwide. The large-scale sample significantly increased the

**Table 1**  
Characteristics of 51 Studies Included in Present Study

| Study source                             | Study population | Adults, children  | Male/female     | Participants, N | Types of allergic disorders                  | Criteria of depression                     | Criteria of allergic disorders | Follow-up (y) |
|------------------------------------------|------------------|-------------------|-----------------|-----------------|----------------------------------------------|--------------------------------------------|--------------------------------|---------------|
| Ahmadiyafshar et al, 2016 <sup>8</sup>   | Iran             | children          | NA              | 1,500           | asthma                                       | BDI                                        | questionnaire                  |               |
| Becerra et al, 2016 <sup>12</sup>        | USA              | adults            | 18,200/2,381    | 20,581          | asthma                                       | physician diagnosis                        | physician diagnosis            |               |
| Ferro et al, 2016 <sup>22</sup>          | Australia        | adults + children | 2,409/2,328     | 4,767           | asthma                                       | DSM-oriented scales                        | YSR/YASR                       | 21            |
| van den Bemt et al, 2016 <sup>51</sup>   | Netherlands      | adults            | 978/1,407       | 2,385           | asthma                                       | DSM-IV                                     | physician diagnosis            | 23            |
| Chung et al, 2016 <sup>20</sup>          | Korea            | adults            | 102,694/126,050 | 228,744         | asthma                                       | CIDI-SF                                    | physician diagnosis            |               |
| Wei et al, 2016 <sup>5</sup>             | China Taiwan     | children          | 25,126/24,678   | 49,804          | atopic disorders                             | physician diagnosis                        | physician diagnosis            | 10            |
| Schmitt et al, 2016 <sup>45</sup>        | Germany          | adults + children | 834,923/979,171 | 1,811,094       | allergic rhinitis                            | HADS                                       | ICD-10                         | 7             |
| Tedner et al, 2016 <sup>46</sup>         | Sweden           | adults            | 10,905/13,780   | 24,685          | asthma                                       | DSM-IV, 11-Item Iowa Short Version ≥8      | ICD                            |               |
| Whiteley et al, 2016 <sup>53</sup>       | USA              | adults            | 36,289/38,711   | 75,000          | atopic dermatitis                            | MCS                                        | physician diagnosis            |               |
| Yu, 2016 <sup>55</sup>                   | USA              | adults            | NA              | 5,555/34,613    | atopic dermatitis                            | DSM-IV                                     | PHQ                            |               |
| Jonsson et al, 2016 <sup>32</sup>        | Sweden           | adults + children | NA              | 2,939           | asthma                                       | questionnaire                              | questionnaire                  | 16.5          |
| Chun et al, 2015 <sup>19</sup>           | Korea            | children          | 1,710/1,482     | 3,192           | asthma                                       | questionnaire                              | physician diagnosis            |               |
| Arias et al, 2015 <sup>9</sup>           | USA              | adults            | 89,093/117,900  | 206–993         | asthma                                       | physician diagnosis                        | NSDUH                          |               |
| Han et al, 2016 <sup>29</sup>            | USA              | adults            | 10,056/10,216   | 20,272          | asthma                                       | PHQ-9                                      | NHANES                         |               |
| Nanda et al, 2016 <sup>39</sup>          | USA              | children          | 299/247         | 546             | allergic rhinitis + atopic dermatitis        | BASC-2                                     | ISAAC                          | 7             |
| Garg and Silverberg, 2014 <sup>23</sup>  | USA              | children          | 13,308/12,470   | 25,778          | asthma, hay fever food allergy, eczema       | questionnaire                              | physician diagnosis            |               |
| Trojan et al, 2014 <sup>49</sup>         | USA              | adults            | 8,831/3,513     | 12,344          | asthma                                       | 10-item CES-D score ≥10                    | questionnaire                  | 12            |
| Brunner et al, 2014 <sup>6</sup>         | USA              | adults            | 1,396/1,620     | 3,016           | asthma                                       | 20-item CES-D score ≥16                    | questionnaire                  | 25            |
| Sanna et al, 2014 <sup>4</sup>           | Australia        | adults            | 942/1,085       | 2,027           | asthma hay fever                             | DSM-IV-TR research version                 | physician diagnosis            |               |
| Chen et al, 2014 <sup>17</sup>           | Taiwan           | children          | 5,824/2,215     | 8,039           | asthma                                       | ICD-9-CM                                   | physician diagnosis            | 7             |
| Chen et al, 2014 <sup>18</sup>           | Taiwan           | children          | 4,225/3,040     | 7,265           | asthma                                       | ICD-9-CM                                   | physician diagnosis            | 11            |
| Lind et al, 2014 <sup>34</sup>           | Sweden           | adults            | 1,460/1,814     | 3,274           | asthma, allergic rhinitis, atopic dermatitis | HADS                                       | physician diagnosis            |               |
| Lu et al, 2014 <sup>36</sup>             | Singapore        | adults + children | NA              | 365             | asthma                                       | Revised Child Anxiety and Depression Scale | physician diagnosis            |               |
| Nanda et al, 2014 <sup>40</sup>          | USA              | children          | NA              | 576             | allergic rhinitis                            | BASC-2                                     | NA                             | 3             |
| Chen et al, 2013 <sup>16</sup>           | China Taiwan     | children          | 4,460/3,905     | 8,365           | allergic rhinitis                            | ICD-9-CM                                   | physician diagnosis            | 11            |
| Yaghmaie et al, 2013 <sup>54</sup>       | USA              | children          | NA              | 79,667          | atopic dermatitis                            | 2007 National Survey of Children's Health  | parent or guardian assessment  |               |
| Muni et al, 2013 <sup>38</sup>           | USA              | adults            | NA              | 843             | asthma                                       | NA                                         | NA                             |               |
| Goodwin et al, 2012 <sup>25</sup>        | Germany          | adults            | 1,913/2,268     | 4,181           | allergy                                      | DSM-IV                                     | physician diagnosis            |               |
| Goral et al, 2012 <sup>27</sup>          | Israel           | adults            | 3,931/5,340     | 9,271           | asthma                                       | MHI-5                                      | INHS-1                         |               |
| Trojan et al, 2012 <sup>50</sup>         | USA              | adults            | NA              | 12,944          | asthma                                       | 10-item CES-D score ≥10                    | physician diagnosis            | NA            |
| Borse et al, 2012 <sup>14</sup>          | USA              | NA                | NA              | 29,282          | asthma                                       | MEPS                                       | NA                             |               |
| Mekov et al, 2012 <sup>37</sup>          | Bulgaria         | NA                | NA              | 322             | asthma                                       | 20-item CES-D                              | NA                             |               |
| Brunner et al, 2012 <sup>15</sup>        | USA              | adults            | NA              | 2,977           | asthma                                       | 20-item CES-D ≥ 16                         | physician diagnosis            | 15            |
| Park et al, 2013 <sup>43</sup>           | Korea            | adults            | 1,849/2,596     | 4,445           | asthma                                       | 4th KNHANES                                | questionnaire                  |               |
| Loerbroks et al, 2012 <sup>35</sup>      | 57 countries     | adults            | NA              | 245,727         | asthma                                       | DSM-IV                                     | questionnaire                  |               |
| Walters et al, 2011 <sup>52</sup>        | UK               | adults            | 9,697/12,853    | 22,550          | asthma                                       | Read/OXMIS codes                           | Read/OXMIS codes               | 10            |
| Bahreianian et al, 2011 <sup>11</sup>    | Canada           | children          | 243/188         | 431             | asthma atopy                                 | 10-Item CDI-S score ≥2                     | physician diagnosis            |               |
| de Miguel Diez et al, 2011 <sup>21</sup> | Spain            | adults            | 14,208/14,758   | 28,966          | asthma                                       | questionnaire                              | questionnaire                  |               |
| Ryu et al, 2010 <sup>44</sup>            | Korea            | adults            | 49/61           | 110             | asthma                                       | 20-item BDI score ≥16                      | physician diagnosis            |               |
| Bahreianian et al, 2010 <sup>10</sup>    | Canada           | children          | NA              | 485             | asthma atopy                                 | CDI-S score ≥2                             | physician diagnosis            |               |
| Otten et al, 2009 <sup>42</sup>          | Netherlands      | children          | 2,770/3,057     | 5,827           | asthma                                       | 6-item Depressive Mood List                | ISAAC                          | 2             |
| Katon et al, 2007 <sup>33</sup>          | USA              | children          | 699/652         | 1,351           | asthma                                       | C-DISC-4.0, DSM-IV                         | questionnaire                  |               |
| Ng et al, 2007 <sup>41</sup>             | Singapore        | adults            | NA              | 300             | asthma                                       | GMS, DSM-IV                                | physician diagnosis            |               |
| Bloch, 2007 <sup>13</sup>                | USA              | adults            | 431/595         | 1,026           | allergy                                      | questionnaires                             | questionnaire                  |               |
| Haarasilta et al, 2005 <sup>28</sup>     | Finland          | adults + children | NA              | 942             | respiratory allergy                          | UM-CIDI-SF, DSM-III-R                      | questionnaire                  |               |
| Goodwin et al, 2004 <sup>24</sup>        | USA              | adults + children | NA              | 1,025           | asthma                                       | CIDI                                       | physician diagnosis            | 21            |
| Goodwin et al, 2003 <sup>26</sup>        | USA              | adults            | 250/748         | 998             | asthma                                       | DSM-IV                                     | physician diagnosis            |               |
| Timonen et al, 2002 <sup>48</sup>        | Finland          | adults            | 2,721/2,707     | 5,428           | allergic symptom atopy                       | physician diagnosis                        | skin prick tests               | 31            |
| Timonen et al, 2001 <sup>47</sup>        | Finland          | adults            | 5,297/5,190     | 10,487          | atopic disorders                             | DSM-III-R                                  | ICD-9                          | 31            |
| Hurwitz et al, 1999 <sup>31</sup>        | USA              | adults            | 3,111/3,725     | 6,836           | asthma hay fever                             | DSM                                        | physician diagnosis            |               |
| Ho and Jones, 1999 <sup>30</sup>         | South Wales      | adults            | NA              | 2,755           | asthma                                       | questionnaire                              | physician diagnosis            |               |

Abbreviations: BASC-2, Behavior Assessment System for Children, Second Edition; BDI, Beck Depression Inventory; CDI-S, Children's Depression Inventory Self-Esteem; C-DISC-4.0, National Institute of Mental Health Diagnostic Interview Schedule for Children, Version 4; CES-D, Center for Epidemiological Studies Depression Scale; CIDI, World Health Organization World Mental Health Composite International Diagnostic Interview; CIDI-SF, World Health Organization World Mental Health Composite International Diagnostic Interview, Short Form; DSM, *DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*; GMS, Geriatric Mental State Schedule; HADS, Hospital Anxiety and Depression Scale; ICD, *International Classification of Diseases*; ICD-9-CM, *International Classification of Diseases, Ninth Revision, Clinical Modification*; ICD-10, *International Classification of Diseases, Tenth Revision*; INHS-1, First Israeli National Health Interview Survey; ISAAC, International Study of Asthma and Allergies in Childhood; KNHANES, Korea National Health and Nutrition Examination Survey; MCS, Mental Health Component Score; MEPS, Medical Expenditure Panel Survey; MHI-5, 5-item Mental Health Inventory; NA, not available; NHANES, US National Health and Nutrition Examination Survey; NSDUH, National Survey on Drug Use and Health; OXMIS, Oxford Medical Information System; PHQ-9, Patient Health Questionnaire; UM-CIDI-SF, University of Michigan Composite International Diagnostic Interview Short Form; YASR, Young Adult Self-Report Obsessive-Compulsive Scale; YSR, Youth Self-Report.

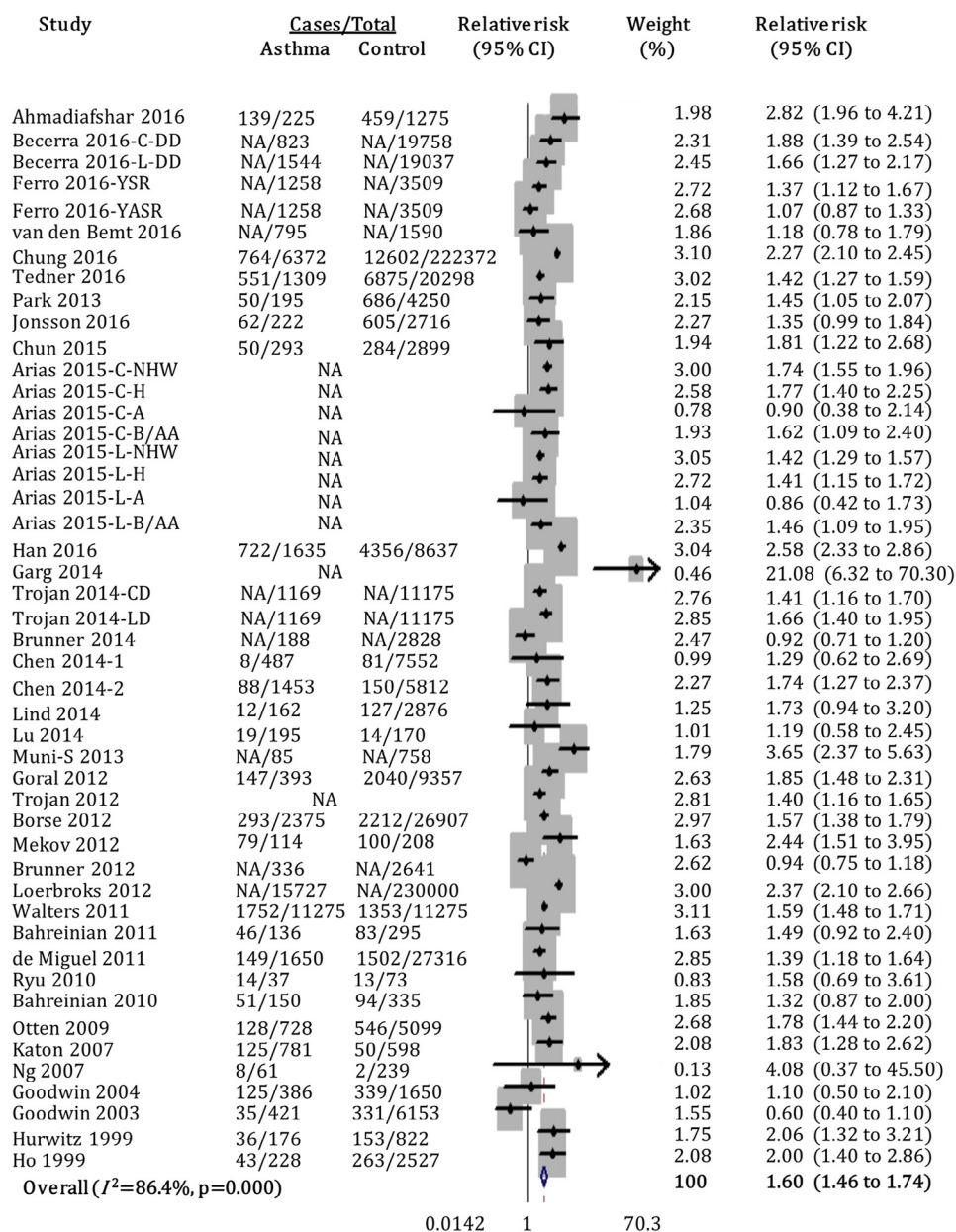


**Figure 2.** Forest plot of association between asthma and depression. Horizontal lines indicate 95% confidence intervals (CIs). The dotted vertical line represents the pooled relative risk and the solid vertical line represents the null effect. The size of the squares is proportional to the weight of the studies. NA, not available.

statistical power to detect potential associations. In contrast, in the studies by Gao et al and Jiang et al, the study samples were only 25,566 and 28,564, respectively, which were smaller than our study sample. Moreover, validity of the meta-analysis largely depends on

**Table 2**  
Subgroup Analysis of Depression in Patients With Allergic Disorders

|                             | Studies, n | Participants, n | RR (95% CI)      | $I^2$ , % |
|-----------------------------|------------|-----------------|------------------|-----------|
| Types of allergic disorders |            |                 |                  |           |
| Asthma                      | 32         | NA              | 1.59 (1.45–1.75) | 89.7      |
| Allergic rhinitis           | 5          | 1,823,440       | 1.57 (1.27–1.93) | 45.2      |
| Age groups                  |            |                 |                  |           |
| Children                    | 15         | 197,593         | 1.66 (1.40–1.96) | 73.1      |
| Adults                      | 29         | 513,088         | 1.58 (1.43–1.75) | 91.8      |
| Sex                         |            |                 |                  |           |
| Male                        | 8          | NA              | 1.37 (0.98–1.91) | 90.3      |
| Female                      | 9          | NA              | 1.65 (1.44–1.89) | 61.1      |

Abbreviations: CI, confidence interval; NA, ??; RR, relative risk.

the quality of the included studies. Second, most previous studies focused on 1 or 2 types of allergic disorders (eg, asthma and allergic rhinitis). This review and meta-analysis combined all the evidence from numerous studies evaluating the various allergic disorders into 1 review and meta-analysis to examine the overall effect of allergic disorders on risk of depression. Third, the fully adjusted estimates were selected from the included studies to weaken the influence of confounding factors. Fourth, this meta-analysis examined a more specific association between allergic disorders and risk of depression based on specific allergic disorders (asthma and allergic rhinitis), sex difference (male vs female), and age difference (adults vs children).

#### Limitation of Our Meta-Analysis

Several limitations of this meta-analysis should be acknowledged. First, some studies with small samples (<100 participants)

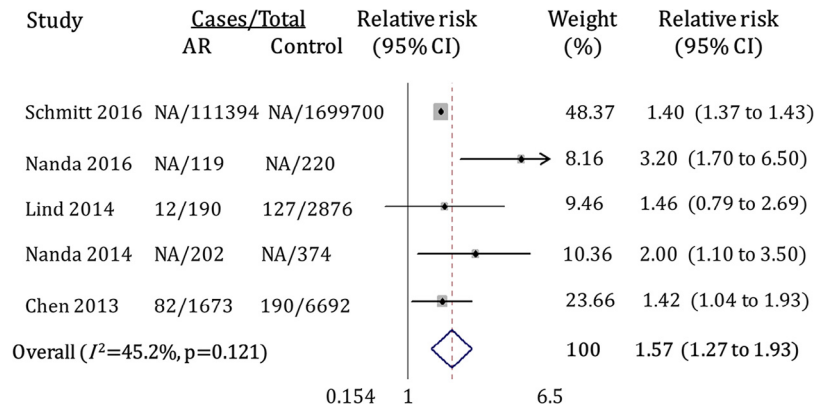


**Figure 3.** Forest plot of association between allergic rhinitis (AR) and depression. Horizontal lines indicate 95% confidence intervals (CIs). The dotted vertical line represents the pooled relative risk and the solid vertical line represents the null effect. The size of the squares is proportional to the weight of the studies. NA, not available.

were excluded from our analyses, which might result in residual confounding or other biases. Second, although fully adjusted estimates were used, different levels of adjustment for potential confounders limited our meta-analysis, allowing for the possibility that confounding factors (body mass index, smoking, socioeconomic covariates, medical adherence, etc) might have affected the final conclusion. Third, it is noteworthy that use of medications such as corticosteroid could be a potential cause of depression in patients with allergic disorders.<sup>60</sup> However, the detailed description of medication use in patients with allergic disorders was sparsely available in the included studies. Thus, we could not determine the role of medication use, poor quality of life, difficulties with employment, and other psychosocial issues in poorly controlled allergic disorders. In addition, hospitalization, emergency department visits, fragmentation of family life, and caregiver stress can contribute to depression. Further researches are urgently required to investigate these potential factors. Furthermore, the diagnosis of depression and allergic disorders (some were diagnosed by physicians or psychiatrists, whereas some were measured by different questionnaires) varied among

these included studies and could lead to some misclassification bias.

#### Future Practice and Research

This meta-analysis provided valid evidence that allergic disorders have a strong effect on depression, which implies that clinicians should pay more attention to the psychologic status of patients with allergic disorders. More psychological and psychotherapeutic interventions might be required in clinical treatment. Future research should report the effect of depression on the possible exacerbation of allergic disorders and the association between psychological or psychotherapeutic intervention and the outcome of allergic disorders. Further, large, well-conducted, and randomized trials that evaluate the effectiveness of psychotherapeutic intervention in patients with allergic disorders are warranted. In addition, experimental studies examining the underlying mechanisms linking allergic disorders and risk of depression are warranted.

In summary, this systematic review and meta-analysis provided the most complete picture to date of evidence in humans showing

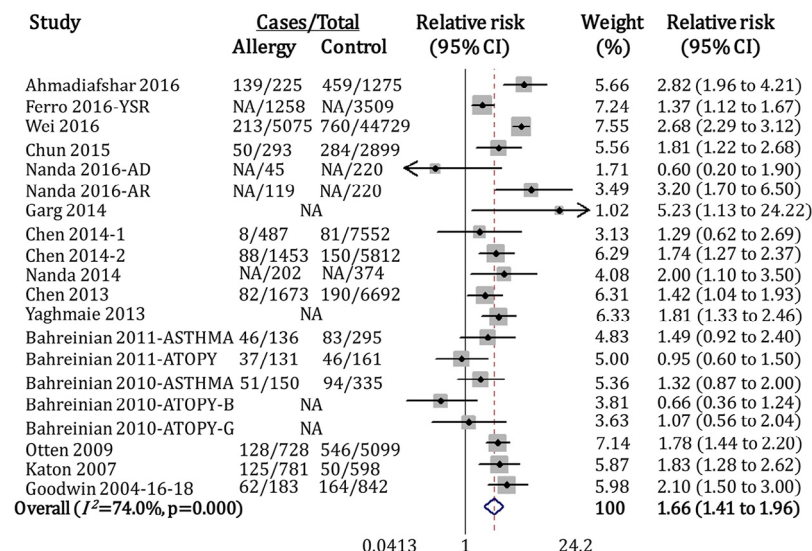


**Figure 4.** Forest plot of association between allergic disorders and depression in children. Horizontal lines indicate 95% confidence intervals (CIs). The dotted vertical line represents the pooled relative risk and the solid vertical line represents the null effect. The size of the squares is proportional to the weight of the studies. NA, not available.

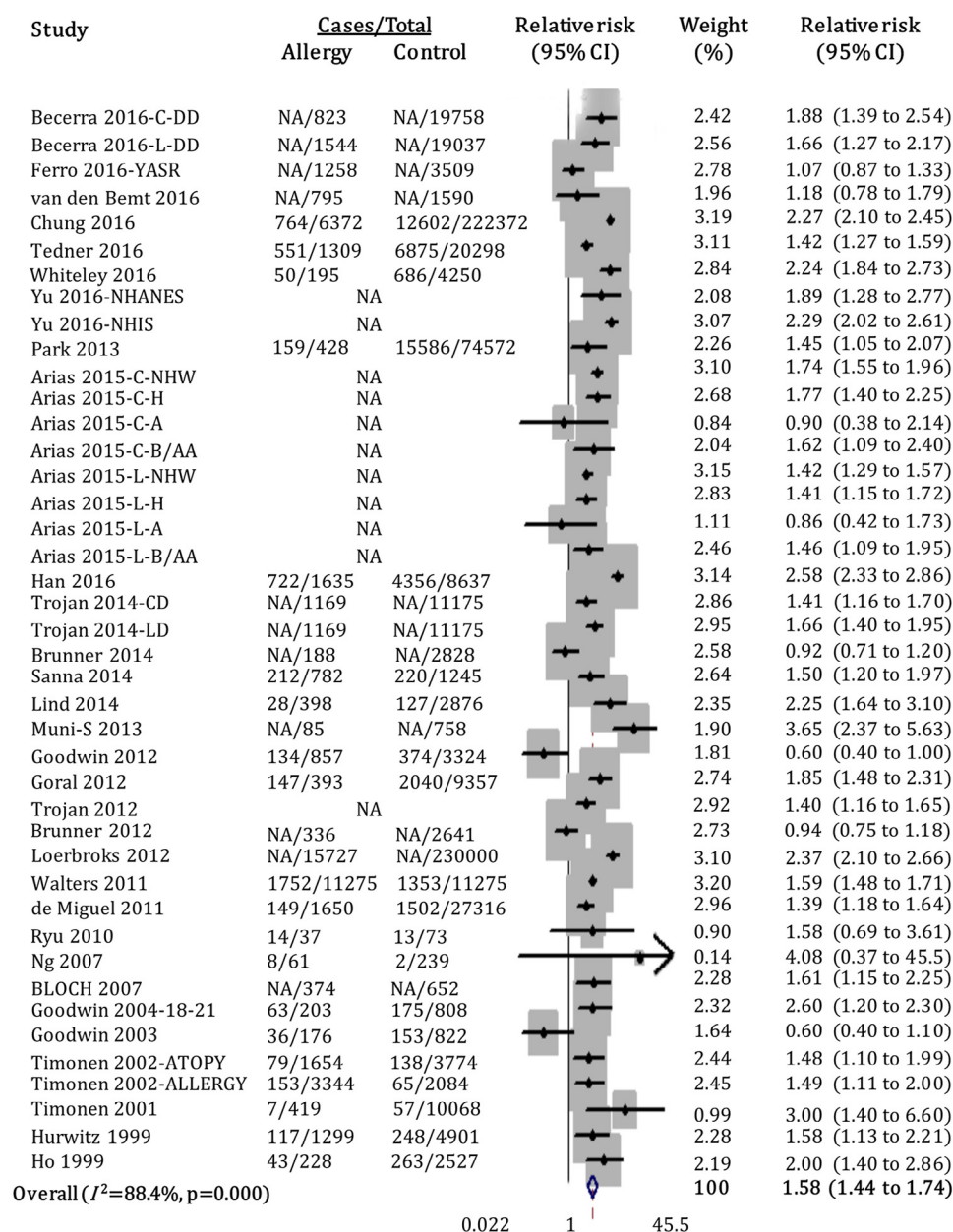


**Figure 5.** Forest plot of association between allergic disorders and depression in adults. Horizontal lines indicate 95% confidence intervals (CIs). The dotted vertical line represents the pooled relative risk and the solid vertical line represents the null effect. The size of the squares is proportional to the weight of the studies. NA, not available.

that patients with allergic disorders are 1.59 times more likely to have a comorbidity of depression compared with controls without allergic disorders. A higher risk of depression also was observed in patients with asthma and with allergic rhinitis. Similar results were observed in children and adults with allergic diseases. However, no significant association was found between allergic disorders and depression in male subjects, whereas a positive association was detected in female subjects.

### Supplementary Data

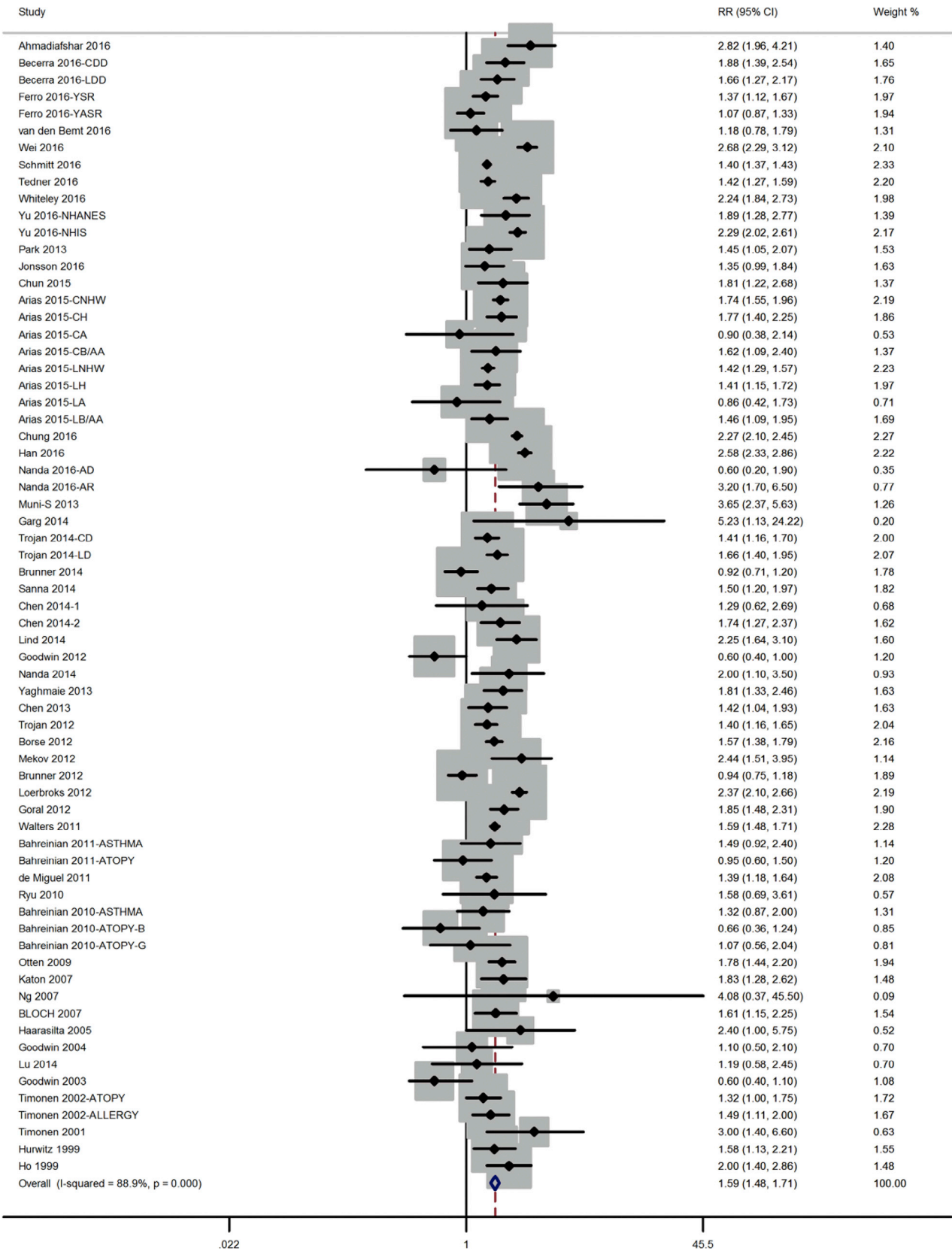
Supplementary data related to this article can be found at <https://doi.org/10.1016/j.anai.2017.12.011>.

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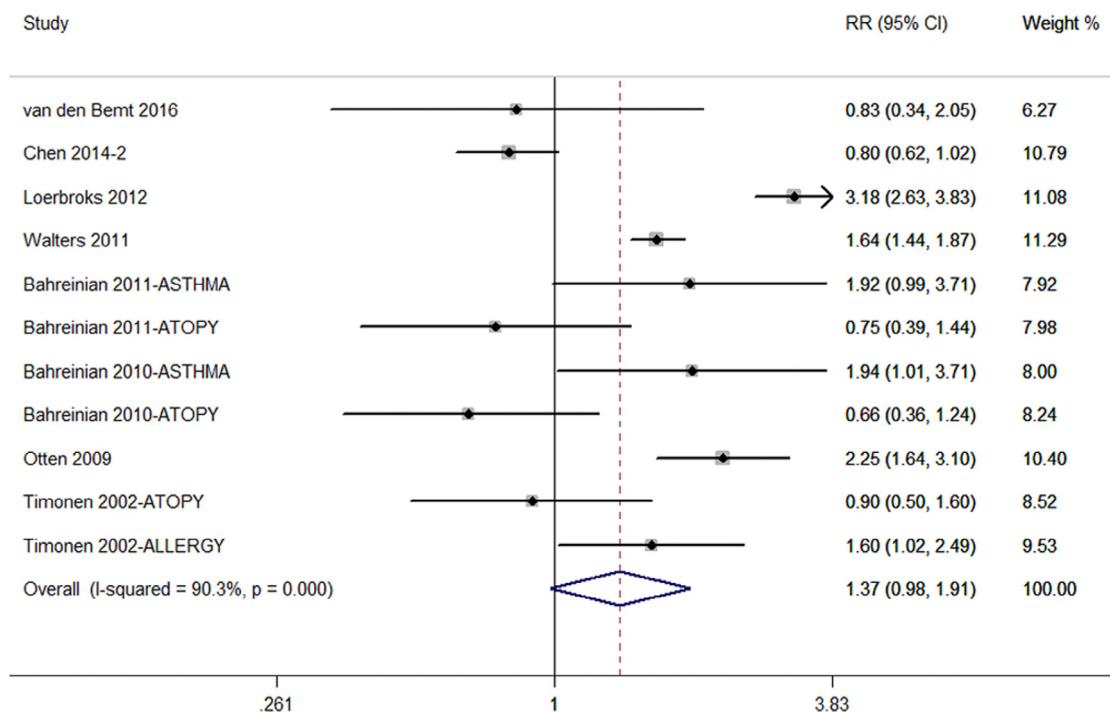
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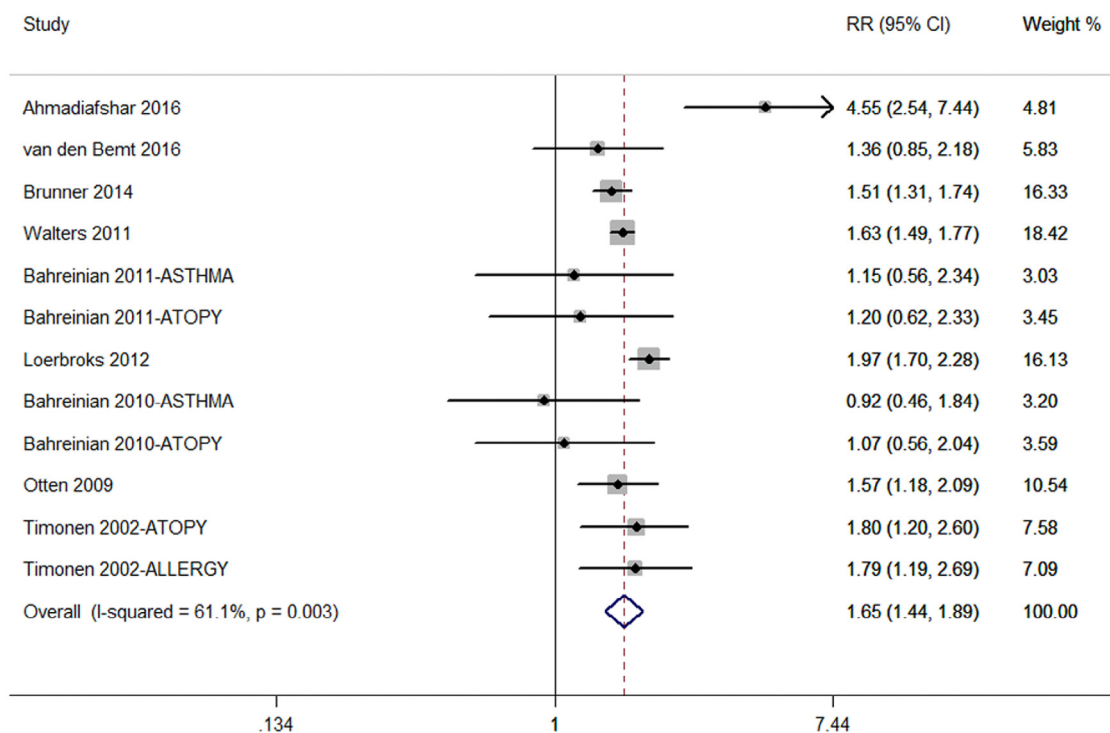
Supplementary Data



**eFigure 1.** Forest plot of overall association between allergic disorders and depression. Horizontal lines indicate 95% confidence intervals (CIs). The dotted vertical line represents the pooled relative risk (RR) and the solid vertical line represents the null effect. The size of the squares is proportional to the weight of the studies.



**eFigure 2.** Forest plot of association between allergic disorders and depression in male subjects. Horizontal lines indicate 95% confidence intervals (CIs). The dotted vertical line represents the pooled relative risk (RR) and the solid vertical line represents the null effect. The size of the squares is proportional to the weight of the studies.



**eFigure 3.** Forest plot of association between allergic disorders and depression in female subjects. Horizontal lines indicate 95% confidence intervals (CIs). The dotted vertical line represents the pooled relative risk (RR) and the solid vertical line represents the null effect. The size of the squares is proportional to the weight of the studies.