Allergies in Children with Autism Spectrum Disorder: a Systematic Review and Meta-analysis

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Abstract The presentation of allergic diseases in children with autism spectrum disorder (ASD) was evaluated systematically through a literature search using MEDLINE, EMBASE, Cochrane Library, and CINAHL databases. Any comparative studies on children with ASD and allergic diseases were evaluated for eligibility followed by risk of bias assessment, data synthesis, and meta-analysis. No randomized clinical trials were identified but 10 eligible observational studies were found, all of low methodological quality. A high estimated prevalence of asthma (OR 1.69, 95 % CI 1.11 to 2.59; 2,191 ASD children) and atopic rhinitis (OR 1.66, 95 % CI 1.49 to 1.85; 1,973 ASD children) were indicated. Rates of food allergy did not show significant differences between groups. Currently, clinical evidence was not found to draw any specific clinical implication.

Keywords Allergy · Autism spectrum disorder · Asthma · Atopic dermatitis · Atopic rhinitis · Food allergy

Introduction

Autism spectrum disorder (ASD) comprises a wide spectrum of developmental and functional impairment in the brain, and the prognosis varies depending on the symptom severity manifested in the individual (Fernell et al. 2013; Howlin et al. 2004; Levy and Perry 2011). ASD is characterized by a deficit of social interaction and personal skills, impairment in verbal and non-verbal communication, repetitive patterns of behavior, and notable consuming interests (American Psychiatric Association 2013). The diagnostic assessment for autism requires an elaborate screening process, which involves substantial consultations with many specialists and other physicians (Myers and Johnson 2007). The global prevalence of autism is estimated to be one in 160 people, and many studies have reported that the combination of genetic and environmental factors implicate a strong association in some aspects of ASD (Bailey et al. 1995; Campbell et al. 2006; Elsabbagh et al. 2012; Hallmayer et al. 2011); however, the development of ASD continues to be largely unclear.

Recently, a concern about the comorbidity of autism with allergy symptoms has been increasing along with rates of allergy among school children worldwide (Pawankar et al. 2013). Several studies have suggested a heightened prevalence of immune abnormalities and allergic diseases, including atopic dermatitis, asthma, allergic rhinitis, and food allergies, in children with ASD (Noriega and Savelkoul 2014; Jyonouchi 2010; Jung 2015; Altarac 2008). The collective opinions from these studies are difficult to define due to inconsistent findings on the association between ASD and allergic diseases; therefore, more perspective on evaluating these

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mixed findings are required. On the basis of these inconsistent reports, we speculate that children with ASD could be susceptible to specific types of allergic disease.

Allergic disease is caused by an acute immunological response that involves mast cells, basophils, and eosinophil activation by allergens cross-linking with immunoglobulin E (IgE) (Gould et al. 2003). This allergic cascade subsequently triggers the immediate hypersensitivity response with the release of histamine and other inflammatory mediators such as cytokines or the eosinophil response (Corry and Kheradmand 1999). Some studies have demonstrated that the imbalance between inflammatory mediators and their counter-regulatory molecules could affect the central nervous system homeostasis, which can result in neurological disorders or possible ASD development in the affected child (Wei et al. 2011; Goyal and Miyan 2014; Ashwood et al. 2006). Other studies have also proposed that allergy can induce stress, which could also indirectly instigate ASD development (Dave et al. 2011; Liezmann et al. 2011; Fine et al. 2014). Based on these implications, several evidence-based reviews have evaluated ASD core behavior interventions involving immune system modulation, but the evidence did not support the effectiveness of the interventions (Millward et al. 2008; Williams et al. 2013; Williams et al. 2012). Meanwhile, a review on food allergen avoidance trials showed some behavioral improvement in children with ASD (Neggers 2011).

In this context, evaluating the association between ASD and allergic diseases is necessary to clarify the conflicting findings and to uncover more precise potential risk or confounding factors. This systematic review thus attempts to examine the association between ASD and different allergic diseases in children by compiling and summarizing available evidence both qualitatively and quantitatively.

Methods

Search Strategy and Selection Criteria

The methods used to conduct this review were in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* and MOOSE guidelines (Higgins and Green 2011; Stroup et al. 2000). A comprehensive database search was conducted on May 17, 2014 using MEDLINE, EMBASE, the Cochrane Library and CINAHL, three prerequisite databases, and a topic-specific database. The search approach was to combine synonyms and related terms and identify pertinent English language articles using thesaurus search terms (Higgins and Green 2011). Terms used included “child development disorders, pervasive,” “attention deficit disorder,” “learning disorder,” “autism,” and “hypersensitivity,” with the application of the “explode” function to include all appropriate narrower terms (e.g., autism, asthma, etc.), in all

potentially relevant combinations (see search strategy in [Appendix Table 2](#)). The reference list retrieved from the database searches was reviewed by five authors in consultation with experts in the field as needed. EndNote version X6 software (Thomson Reuters, New York, NY, USA) was used to store and manage the retrieved citations for screening.

All comparative study designs that at least incorporated a control group, such as randomized clinical trials, non-randomized trials or cohorts with a control group comparison, and case-control and cross-sectional studies, were reviewed for potential inclusion. For observational studies (e.g., cohort studies with a control group or case-control studies), we included in the review only those in which the ASD group and control group were identified within the same time period with a clear indication that no overlap between the two groups was permitted. Inclusion criteria were set in compliance with standard Cochrane review protocols and with reference to the Non-Randomised Studies Methods Group (NRSMG) of the Cochrane Collaboration (Higgins and Green 2011).

Regarding population of interest, studies that included children up to 18 years of age who were clinically diagnosed with ASD (including autistic disorder, Asperger’s syndrome, and pervasive developmental disorder not otherwise specified) and with an exposure of allergies or immune hypersensitivity were eligible for this review. The criteria for considering children with ASD in this review were developed from both the established *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR) and the current DSM-V (American Psychiatric Association 2000, 2013). The primary study factors included common allergic symptoms in children indicated by clinical diagnosis criteria (e.g., atopic dermatitis, asthma, rhinitis, and food allergies). Immune reactivity response in relation to serum IgE level, eosinophil count level, autoinflammatory response, and immune-related biochemical marker expression were examined as secondary study factors.

On the other hand, studies in which participants were clinically diagnosed with a comorbidity in another category of developmental disorders (e.g., attention deficit hyperactivity disorder, specific learning disabilities) or with a neurological disorder such as epilepsy were excluded. Studies of animal models, systematic reviews, single case reports, and articles that did not provide relevant or original full data were also excluded from this review (see excluded studies in [Appendix Table 3](#)).

Selection of Studies and Data Assessment

Three authors in one group and two authors in another group independently screened all titles and abstracts of publications identified by the search in order to assess their eligibility. After identifying potential titles and abstracts from the search, two groups of authors ensured that judgments were reproducible

by comparing the selection results. When authors disagreed on the inclusion of a study, all authors resolved the issue by discussion. Studies that did not meet the criteria were excluded from this initial stage. The primary focus was to select papers focusing on children with ASD *without* other developmental disorder comorbidities that might obscure the exposure of the study population. Two authors then obtained the full-text articles of identified eligible studies for independent assessment to decide which studies fulfilled the inclusion criteria. When studies referred to related, previously published protocols or studies, the referenced studies were assessed for criteria eligibility as well. Any disagreement at this stage was resolved by discussion between all reviewers based on their expert opinions, including referral to other literature sources if necessary. Two authors independently performed risk of bias assessment and data extraction for included studies using a modified data collection form recommended by the *Cochrane Handbook* (Higgins and Green 2011). To assess risk of bias for non-randomized studies or observational studies, the validated Risk of Bias Assessment Tool for Non-randomized Studies (RoBANS) was used (Kim et al. 2013). In addition, the Cochrane Risk of Bias Assessment Tool for Non-Randomized Studies of Interventions (ACROBAT-NRSI) guideline was used to support judgment of study quality (Sterne et al. 2014). Critical assessments were conducted using the domain-based evaluation form linked to the risk of bias tool. Each component was categorized as low risk, unclear risk, or high risk according to the RoBANS tool (Kim et al. 2013). The Cochrane Collaboration's summary assessments of risk of bias were followed in reference to response options for an overall RoB judgment and consisted of the following: (1) low: low risk of bias for all key domains, (2) unclear: unclear risk of bias for one or more key domains, and (3) high: high risk of bias for one or more key domains. Overall risk of bias across studies consisted of the following: (1) overall low risk of bias across studies, where most data from studies was classified as low risk of bias for all major domains; (2) overall unclear risk of bias across studies, where most data from studies was classified as low or unclear risk of bias; and (3) overall high risk of bias across studies, where the proportion of data from studies at high risk of bias was enough to influence the interpretation of the results (Higgins and Green 2011). Study characteristics and results were entered into Review Manager (RevMan) 5.3 software for data synthesis (Cochrane 2014).

Data Synthesis and Analysis

Studies with similar design characteristics were combined for meta-analysis. When outcome measures data were amenable to synthesis, they were entered into RevMan 5.3 software for pair-wise comparison. The prevalence effect sizes between ASD and control groups were calculated in the form of odds

ratios (OR) and 95 % confidence intervals. Unless otherwise indicated, a p value cut-off point of 0.05 indicated statistical significance. A random-effects model was used to yield the summary quantification of the pool effect across the studies by each outcome. If the included studies were diverse in methodology or estimated with a significant inconsistency, both random-effects and fixed-effect models were applied to observe the estimation effect trend. Statistical heterogeneity between trials was evaluated by the Chi^2 statistic method with the significance set at p value <0.10 and I^2 tests were used to determine inconsistency for the combined studies. For continuous outcome data, the inverse-variance random effects method was used to summarize differences in the levels of biomarkers, while the standardized mean difference (SMD) and 95 % confidence interval with significance set at 0.05 were used to report the summary statistics. A sensitivity analysis was also conducted to examine the overall effect estimation and confidence interval variation by combining all initial included studies in the meta-analysis. The same meta-analysis was then repeated only for those studies that strongly complied with the inclusion criteria.

Results

The search yielded 240 citations after duplications were removed. A flow diagram of included and excluded studies is shown in Fig. 1. All studies identified were observational comparative studies; high-quality study designs such as clinical randomized trials were not found to meet the objective of this review. After screening the titles and abstracts of studies initially identified as including an ASD population and allergy diseases, 16 articles were identified for full-text eligibility assessment. From the 16 selected articles, six studies were excluded based on reasons detailed in Appendix Table 3. A total of 10 studies were finally included in the meta-analysis. When meta-analysis was not possible for some outcome measures, available data were narratively described. Out of the 10 included studies, seven were case-control studies (Renzoni et al. 1995; Mrozek-Budzyn et al. 2013; Mostafa et al. 2008a, b, 2010; Magalhaes et al. 2009; Jyonouchi et al. 2008) and one was a cross-sectional study (Mostafa and Al-Ayadhi 2013). The remaining two were a population-based cross-sectional cohort study (Shibata et al. 2013) and a retrospective study (Chen et al. 2013). The included studies were conducted in the USA, Brazil, Egypt, Poland, Italy, Japan, and Taiwan.

A total of 10,380 children participated in the included studies, and 2,234 were children with ASD clinically diagnosed by DSM-III-R, DSM-IV, DSM-IV-TR, the Autism Diagnostic Interview-Revised (ADI-R), the Autism Diagnostic Observation Schedule (ADOS), or International Classification of Disease (ICD) code criteria. A summary of the characteristics of included studies is shown in Table 1. For

Fig. 1 Flow diagram of study selection

reverse correlation comparison in population-based cross-sectional cohort studies, autistic traits were measured using the Japanese version of the Autism Screening Questionnaire (ASQ). Among the eligible studies, allergy diseases such as atopic dermatitis, asthma, allergic rhinitis, and food allergies, or intolerances were identified and categorized as the primary risk factors of interest. Autoimmune-related diseases such as ulcerative colitis, Crohn's disease, type 1 diabetes, autoimmune thyroid disease, and Kawasaki disease were also found to be reported in some of the studies but were considered as secondary risk factors of interest in this review. These studies are presented in [Appendix Table 4b](#).

Diagnoses of the allergy diseases in these included studies were based on clinical standardized diagnostic criteria using questionnaires, the ICD-9, or skin prick tests. Immune response measures were evaluated by clinical laboratory analysis of inflammatory cytokines, serum IgE, and eosinophil in children's serum samples. Further details on measurements used and key results for all included studies are presented in [Appendix Table 4b](#). These observational studies shared similar characteristics in terms of their objectives, methods, and participants, but the studies could not meet the quality equivalent of randomized trial studies. Overall, methodological quality of the included studies was assessed as almost uniformly low across all parameters based. Six studies were considered as unclear risk of bias (Chen et al. 2013; Magalhaes

et al. 2009; Mostafa and Al-Ayadhi 2013; Mostafa et al. 2008b; Mrozek-Budzyn et al. 2013; Shibata et al. 2013) and four studies were of high risk of bias (Jyonouchi et al. 2008; Mostafa et al. 2008a, 2010; Renzoni et al. 1995). A table of risk of bias for each study is presented in [Appendix Table 5a](#) and a summary of overall risk of bias for outcomes across studies is presented in [Appendix Table 5a](#).

Atopic Dermatitis

Five studies reported rates of atopic dermatitis symptoms in children with ASD compared with controls. Two were case-control studies (Mostafa et al. 2010; Jyonouchi et al. 2008), one was a cross-sectional study (Mostafa and Al-Ayadhi 2013), one was a population-based cross-sectional cohort study (Shibata et al. 2013), and one was a retrospective cohort study (Chen et al. 2013). The total number of participants for these four combined studies was 9,717, of whom 1,990 children were diagnosed with ASD (Fig. 2a). Meta-analysis of data from these studies showed a slight trend toward higher dermatitis rates in ASD compared to control groups (OR 1.30, 95 % CI 0.97 to 1.75; 1,990 ASD children, five studies, $I^2 = 36\%$), though the effect estimate did not reach a statistical significance ($p = 0.08$). There was no evidence of inconsistency or significant heterogeneity across the studies. After excluding studies with high risk of bias, the result did not show

Table 1 Summary of study characteristics

Study ID	Country	Study design	Number of participants (N=total) (observation period)	Age range in years/ (median range)	Allergy diseases and autoimmune diseases	Data sources
Chen et al. 2013	Taiwan	Retrospective cohort	N=7990 ASD: n=1598; control: n=6392 (January 1, 1996–December 31, 2010)	17.51 (11.34)	Asthma, allergic rhinitis, atopic dermatitis, urticaria, Crohn's disease, ulcerative colitis, type 1 diabetes, autoimmune thyroid disease, Kawasaki disease	The National Health Insurance Research Database (NHIRD); ICD-9th Revision-Clinical Modification codes
Jyonouchi et al. 2008	USA	Case-control	N=238 ASDs with frequent infection: n=26; controls: (ASDs without frequent infection: n=107; CRS/ROM: n=38; food allergies: n=24; normal: n=43)	2.5 (1.0–13.7) to 7.6 (2.3–13.4)	Allergic rhinitis, allergic conjunctivitis, atopic dermatitis, asthma, food allergy, primary immunodeficiency, and innate immune response	DMS-IV; ADI-R; ADOS; skin prick test, NIH guideline criteria; enzyme-linked immunosorbent assay (ELISA)
Magalhaes et al. 2009	Brazil	Case-control	N=45 Asperger's syndrome: n=15; control: (with atopic: n=15; without atopic: n=15)	10–12	Atopic: allergic rhinitis, rhinitis with dermatitis, allergic rhinitis with asthma, and asthma. Eosinophils and serum IgE	DSM-IV-TR; WISC-III assessment; nephelometry assay using BN-PROSPEC; eosinophil count with SYSMEXXT1800i; skin prick tests
Mostafa and Al-Ayadhi 2013	Egypt	Cross-sectional	N=84 Autism: n=42; healthy children control: n=42	6–11	Asthma, atopic dermatitis and allergic rhinitis. Serum levels of anti-myelin basic protein and anti-myelin-associated glycoprotein auto-antibodies	DSM-IV, Childhood Autism Rating Scale (CARS); peak expiratory flow rate; objective Scoring Allergic Dermatitis index system (obj-SCORAD); ELISA; quantitative sandwich-type enzyme immune-assay
Mostafa et al. 2010	Egypt	Case-control	N=60 Autism: n=30; healthy children control: n=30	4–12	Asthma, atopic dermatitis and allergic rhinitis. CD4 ⁺ CD25 ^{high} T cell count	DSM-IV; CARS, peak expiratory flow rate, obj-SCORAD, Coulter-Epics-XL flow cytometer
Mostafa et al. 2008a	Egypt	Case-control	N=80 Autism: n=40; healthy children control: n=40	3–12	Asthma, atopic dermatitis and allergic rhinitis. Serum IgE and serum serotonin	DSM-IV, CARS, sleep-deprived interictal EEG, Stanford Binet test, Mini-Wright peak expiratory flow rate; obj-SCORAD, ELISA, competitive serotonin enzyme immune assay kit
Mostafa et al. 2008b	Egypt	Case-control	N=100 Autism: n=50; healthy children control: n=50	4–16	Asthma, atopic dermatitis and allergic rhinitis. Serum IgE	DSM-IV, CARS, sleep-deprived interictal EEG, Stanford Binet test, peak expiratory flow rate, obj-SCORAD, ELISA
Mrozek-Budzyn et al. 2013	Poland	Case-control	N=288 Autism: n=96; control n=192 children	Up to 14	Asthma and allergy	ASD (ICD-10 code), interview with child's mother, skin prick test
Renzone et al. 1995	Italy	Case-control	N=86 Autism: n=43; mental retardation of various kind control: n=43	3–18	Food allergy	DMS-III-R; Autism Behavior Checklist; prick tests; IgE Fluoroimmuno Assay-Pharmacia CAP system; Coulter-counter for eosinophils count
Shibata et al. 2013	Japan	Population-based cross-sectional	N=1409 (kindergarten n=1073, nursery school n=333, response rate 59.7%) (September to November 2009)	3–5	Allergic disease: asthma, nasal allergy, Japanese cedar pollinosis, eczema	Japanese version Autism Screening Questionnaire; allergic disease questionnaire diagnosis by medical doctor

Fig. 2 Forest plots of prevalence estimates summary for (a) atopic dermatitis, (b) asthma, (c) atopic rhinitis, and (d) food allergy mediated by IgE compared between the ASD group and control group

(a) Atopic dermatitis

(b) Asthma

(c) Atopic rhinitis

(d) Food allergy mediated by IgE

any significant change to the effect estimate (OR 1.28, 95 % CI 0.91 to 1.81, $I^2=59\%$, $p=0.15$).

Asthma

Nine studies reported rates of asthma in children with ASD compared with controls. The studies comprised six case-control studies (Mrozek-Budzyn et al. 2013; Mostafa et al. 2008a, b, 2010; Magalhaes et al. 2009; Jyonouchi et al. 2008), one cross-sectional study (Mostafa and Al-Ayadhi 2013), one population-based cross-sectional cohort (Shibata et al. 2013), and one retrospective cohort study (Chen et al. 2013). The total number of participants from the nine studies was 10,215, of whom 2,191 children were identified as having ASD (Fig. 2b). The analysis showed that ASD children were

more likely to have asthma compared to the control group (OR 1.69, 95 % CI 1.11 to 2.59; 2,191 ASD children, nine studies, $I^2=49\%$) with a statistical significance of ($p=0.02$). Heterogeneity was, however, detected among these studies ($p=0.05$). After eliminating studies with high risk of bias, the effect estimate did not differ significantly (OR 1.66, 95 % CI 1.12 to 2.46, $I^2=41\%$, $p=0.01$).

Atopic Rhinitis

Of five studies reporting on atopic rhinitis rates in ASD children compared to controls, two were case-control studies (Magalhaes et al. 2009; Jyonouchi et al. 2008), one was a cross-sectional study (Mostafa and Al-Ayadhi 2013), one was a population-based cross-section cohort study (Shibata

et al. 2013), and one was a retrospective cohort study (Chen et al. 2013). The total number of participants in the five studies was 9,685, of whom 1,973 children were identified as having ASD (Fig. 2c). Pooled analyses showed that children with ASD were more likely to have atopic rhinitis compared to their controls (OR 1.66, 95 % CI 1.49 to 1.85, 1,973 ASD children, five studies, $I^2=0\%$). The effect estimate showed a statistical significance of $p<0.00001$ and there was no evidence of inconsistency and heterogeneity among the studies. Even after the high risk of bias study was excluded, the result did not show any significant change to the effect estimate (OR 1.68, 95 % CI 1.41 to 1.99, $I^2=9\%$, $p<0.00001$).

Food Allergy Mediated by IgE

Three case-control studies reported on rates of IgE-mediated food allergy among ASD children compared with controls (Renzoni et al. 1995; Mrozek-Budzyn et al. 2013; Jyonouchi et al. 2008). The total number of participants from these studies was 550, of whom 272 children were identified as having ASD (Fig. 2d). The standard mean estimate odds ratio for food allergy in ASD children compared to controls did not imply statistical significance ($p=0.40$), though there seemed a slightly higher susceptibility with ASD (OR 1.23, 95 % CI 0.76 to 2.01, 272 ASD children, three studies, $I^2=0\%$). No evidence of heterogeneity and inconsistency among the studies was detected. After excluding studies with high risk of bias, only one study was indicated (OR 1.25, 95 % CI 0.73 to 2.13, $p=0.41$) and there was no significant difference in the overall effect estimate.

Total Serum IgE Level and Eosinophil Count

Three case-control studies reported on total serum IgE levels in children with ASD relative to those without (Renzoni et al. 1995; Mostafa et al. 2008b; Magalhaes et al. 2009). Since one of the three studies used a different standard of measurement, geometric mean (kU/L), and standardized mean (IU/L) in reporting the outcome (Renzoni et al. 1995), only two studies could be combined in the meta-analysis. The total number of participants from the two studies in the meta-analysis was 130, of whom 65 children were identified as having ASD (Fig. 3). Based on the pooled results, total serum IgE levels were higher in children with ASD relative to the control group (SMD 0.67, 95 % CI -0.03 to 1.36; 65 ASD children, two studies, $I^2=65\%$), but the difference did not reach a statistical significance ($p=0.06$). Moderate heterogeneity was evident across the studies. Likewise, the study that was not included in the meta-analysis (Renzoni et al. 1995) did not show a statistically significant difference in the total serum IgE expression between children with ASD (geometric mean 66, 95 % CI 48 to 90 kU/L) and controls (geometric mean 65, 95 % CI 44 to 96 kU/L).

Additionally, two studies reported eosinophil counts in children with ASD relative to those without (Renzoni et al. 1995; Magalhaes et al. 2009). Both studies reported significantly higher eosinophil counts in the serum samples of the ASD group compared to the control group. One study (Magalhaes et al. 2009) with a total of 45 children, of whom 15 were specified as having Asperger's syndrome, reported a higher geometric mean in eosinophil percentages in children with Asperger's syndrome compared to that in the control group ($p<0.001$). In contrast, the second study (Renzoni et al. 1995), in which 43 of 86 children had autism, reported that children with ASD had higher eosinophil absolute counts than controls (259.1 ± 27 vs. 193.4 ± 18 cells/cmm; $p<0.05$).

Discussion

In this review, significantly elevated rates of both asthma ($p=0.02$) and allergic rhinitis ($p<0.00001$) were reported in children with ASD relative to those without. Specifically, children with ASD were 69 % more likely to have asthma than were those in the control groups, and, similarly, allergic rhinitis was 66 % more common in the ASD group than in the control group. One explanation for such high rates of allergic diseases in the ASD group could relate to immune sensitivity corresponding to intrinsic stress factors and/or psychosocial stress commonly found in children with ASD (Watling et al. 2001; Scifo et al. 1996; Liezmann et al. 2011; Fine et al. 2014; Corbett et al. 2009). In addition, some research has suggested that stress could aid in releasing neurogenic inflammatory agents, which is also identified in bronchial mucosa or immune cells, and conversely, that the immune system could also modulate the central nervous system function via various molecules, including cytokines (Fine et al. 2014; Dave et al. 2011; Akhondzadeh and Asadabadi 2012). Based on these speculations, the bidirectional mechanism process could also possibly account for the findings of the population-based cross-sectional cohort study carried out by Shibata et al. (2013), in which children with asthma or rhinitis had higher scores on the Japanese version of the ASQ than controls the children in the control group. The meta-analysis for the combined studies did not reflect the diagnostic period of ASD; however, findings supported the presence of the association between ASD and allergic diseases, particularly asthma and allergic rhinitis. Thus, additional research in determining this association during early detection periods of ASD is needed. This review did not, however, find significantly different rates of atopic dermatitis in the ASD group relative to controls, thereby implying that children with ASD could be more susceptible to a particular type of allergy rather than allergies in general.

Total serum level IgE (IU/ml)

Fig. 3 Forest plot of summary-standardized mean differences (SMD) of total serum IgE levels between the ASD group and control group. The original measurement unit for the total serum IgE in mean $\pm$ standard error

was adjusted to mean and standard deviation for meta-analysis (IU/ml) (see [Appendix Table 4b](#) for original data units)

Findings from this review did not support a significant association between ASD and IgE-mediated food allergy. The slightly higher rates in the ASD group than in the control group could be reflected by the high risk of bias of studies and the fact that allergen-specific IgE levels could change in association with the ability to tolerate food which attribute to false results from allergen testing (Panel 2010). As for the total serum IgE levels in children with ASD, the difference did not reach a statistical significance for the two combined studies, even though serum IgE level appeared higher in the ASD group. The natural history or typical progression of allergic diseases that begins early in a child's life and the tendency for spontaneous remission of allergic diseases with age, known as "allergic march," could also play a role in the association (Wahn 2000). However, more studies are necessary to clarify the differences between food allergies and food intolerance, as food intolerance is not the result of immediate allergic reactivity (Panel 2010). The meta-analysis result for total serum IgE levels was an expression of the pool estimate for SMD rather than the original units of measurement; therefore, more studies are required to investigate substantial difference estimates (Higgins and Green 2011).

Taken from the studies together, higher eosinophil counts were reported in children with ASD compared to the control group, which could be linked to the fact that production of IgE is regulated by a specific type of cytokine produced from Th2 cells, and the regulation process subsequently induces eosinophil activation (Woszczek et al. 2002; Sannohe et al. 2003; Busse 1996). In addition, Chen et al. (2013) identified Crohn's disease (OR 1.44, 95 % CI 0.89 to 2.33) and type 1 diabetes (OR 4.01, 95 % CI 1.00 to 16.04) as having associations with ASD, which is also consistent with higher odds of an abnormal inflammatory response (see [Appendix Table 4b](#) for the summary of outcome measure results). Imbalances in proinflammatory markers like interleukin-23 (IL-23) or T-cell regulator CD4 cells, anti-myelin basic protein, and serotonin were also reported to be associated with ASD in the reviewed studies, but pooling of data for these immune symptoms was not possible due to the involvement of various cytokine and inflammatory response pathways. Other

research suggests that an immune response and inflammation of the central nervous system could contribute to the pathogenesis of autism, which supports a possible mechanism for these observed associations (Wei et al. 2011; Ashwood et al. 2006). A consistent pattern of high rates of immune dysregulation is evident in children with ASD, although the differences in reporting across studies limited further data synthesis of this point.

A key strength of this review is its examination of rates of different types of allergic diseases in children with ASD by using a standardized estimate for consistent comparison. The findings from this review could facilitate in the advancement of coherent design and study for the comorbidity of ASD and allergic diseases, as well as intervention development. In referencing to the current DSM-5 diagnostic criteria, which has encompassed separate autistic disorders into a single diagnostic category, the inclusion criteria of participants were more consistent and refined. In addition, the manual also included diagnostic criteria for developmental disorders comorbidities such as attention-deficit/hyperactivity disorder, which in recent years also gained attention for high prevalence of allergies (Marshall 1989; Moffitt and Melchior 2007). This could set an opportunity for elucidating the specific subset of children with the comorbidity of ASD and other developmental disorders in association with allergic diseases in the future.

It is important to mention that all studies identified in the present review were observational studies, which are prone to unclear risk of bias in the selection of participants and blinding of outcome assessments across studies and yielded low overall quality of evidence. In each study, the most common drawback was small sample size and the inability to infer causal relationships between the exposure and outcome variable. Data retrieved from population-based cross-sectional studies or national databases provided preliminary association estimates; however, most cases of ASD could not be identified in a neutral setting, which may lead to a potentially skewed population due to the selection and diagnosis process. Another limitation of this systematic review is the different diagnostic criteria used in each study (e.g., ADOS, DSM-III, DSM-IV-TR, DSM-5, or ICD-10) such as the DSM-IV-TR diagnostic

criteria, which did not include comorbidities of other developmental disorders as opposed to the current version, the DSM-5 diagnostic criteria. However, the core clinical concepts of ASD and ADHD have not been changed in the ADOS, DSM-IV-TR, DSM-5, or ICD-10, and hence, this current evaluation would unlikely be influenced by differences in criteria or versions (Worley and Matson 2012; Volkmar et al. 1992). Considering this limitation, the population of children with ASD is relatively sparse compared to the general population; therefore, the findings should be interpreted with caution in light of the risk of over-estimating the true power of significance from possible subtypes of the ASD population. As for allergic diseases, the optimal estimate for each type of allergic disease was limited by the different outcome measurements used among the studies. This could be partly due to the prevalence of allergens in the environment resulting in allergy testing variations in different countries. Future studies should consider these confounders and include a larger number of participants to strengthen statistical power. Publication bias was not investigated due to variations in study design and population size across studies. Given the lack of randomized controlled trials from the literature search at this time, there is a high possibility of confounding factors, such as genetic status of children, psychological stress, medication status, or comorbidity of different types of developmental disorders or allergic disease that could not be ruled out. Psychological stress in children could possibly be one of the key confounding factors between ASD and allergy although further investigations and more detailed analyses, such as meta-regressions, are needed.

The findings presented in this review only allowed for prevalence-based conclusions to be drawn from the available evidence. There is no clinical base of evidence at this point to support an etiological association between autism and allergy; however, children with ASD posed a high risk of specific asthma and atopic rhinitis, but not food allergy.

Compliance with Ethical Standards

Funding All phases of this study were supported by a National Center for Child Health and Development Grant (26A-5) and a Health Labour Sciences Research Grant (No. 13800128) from the Ministry of Health, Labour, and Welfare, Japan. None of these sources participated in any part of the performance of the study.

Conflict of Interest The authors declare that they have no competing interests.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Appendix

Table 2 Search strategy

MEDLINE	
May 17, 2014	
ID	Search terms
1	exp *Child Development Disorders, Pervasive
2	exp *"Attention Deficit and Disruptive Behavior Disorders"
3	exp *Learning Disorders
4	or/1–3
5	exp *Hypersensitivity
6	4 and 5
7	Remove duplicates from 6
8	Limit 7 to humans
9	Limit 8 to (comment or congresses or editorial or historical article or interactive tutorial or introductory journal article or lectures or legal cases or letter or news or newspaper article or overall or patient education handout)
10	8 not 9
EMBASE	
May 17, 2014	
No.	Search terms
#1	"autism"/exp/mj
#2	"attention deficit disorder"/mj
#3	"learning disorder"/exp/mj
#4	#1 OR #2 OR #3
#5	"hypersensitivity"/exp/mj
#6	#4 AND #5
#7	#6 AND [humans]/lim AND [embase]/lim NOT [medline]/lim
The Cochrane Library	
May 17, 2014	
Cochrane DARE	
ID	Search terms
#1	MeSH descriptor: [child development disorders, pervasive] explode all trees
#2	MeSH descriptor: [attention deficit and disruptive behavior disorders] explode all trees
#3	MeSH descriptor: [learning disorders] explode all trees
#4	#1 or #2 or #3
#5	MeSH descriptor: [hypersensitivity] explode all trees
#6	#4 and #5
May 17 2014	
Cochrane CDSR	
ID	Search terms
#1	MeSH descriptor: [child development disorders, pervasive] explode all trees
#2	MeSH descriptor: [attention deficit and disruptive behavior disorders] explode all trees
#3	MeSH descriptor: [learning disorders] explode all trees
#4	#1 or #2 or #3

Table 2 (continued)

#5	MeSH descriptor: [hypersensitivity] explode all trees
#6	#4 and #5
Cochrane CCTR	
ID	Search terms
#1	MeSH descriptor: [child development disorders, pervasive] explode all trees
#2	MeSH descriptor: [attention deficit and disruptive behavior disorders] explode all trees
#3	MeSH descriptor: [learning disorders] explode all trees
#4	#1 or #2 or #3
#5	MeSH descriptor: [hypersensitivity] explode all trees
#6	#4 and #5
CINAHL	
May 17, 2014	
ID	Search terms
S1	(MM “Child Development Disorders, Pervasive+”)
S2	(MM “Attention Deficit Hyperactivity Disorder”)
S3	(MM “Learning Disorders+”)
S4	S1 or S2 or S3
S5	(MM “Hypersensitivity+”)
S6	S4 and S5

Table 3 Excluded studies with reasons

Number	Studies	Reasons for exclusion	Country
1	Bakkaloglu (2008) Bakkaloglu B, Anlar B, Anlar FY, Oktem F, Pehlivanurk B, Unal F, et al. Atopic features in early childhood autism. <i>European Journal of Paediatric Neurology (EJPN): Official Journal of the European Paediatric Neurology Society.</i> 2008;12(6):476–9.	There was no information on whether controls were screened for autism and the selection of controls included febrile convulsion, mild to moderate development delay, or epilepsy. Serum IgE was not measured in the control group.	Turkey
2	Boris (2004) Boris M, Goldblatt A. Pollen exposure as a cause for the deterioration of neurobehavioral function in children with autism and attention deficit hyperactive disorder. <i>Journal of Nutritional & Environmental Medicine.</i> 2004;14(1):39–45	Study observing both ASD and ADHD behavior regression without control group comparison. The comparison was between both ASD and ADHD.	USA

Table 3 (continued)

Number	Studies	Reasons for exclusion	Country
3	Ohya (2013) Ohya Y, Narita M, Futamura M, Hamaguchi M, Yamamoto K, Tsumura Y, et al. Association between childhood asthma and autism spectrum disorders. <i>Allergy: European Journal of Allergy and Clinical Immunology.</i> 2013;68 (Ohya Y.; Narita M.; Futamura M.; Hamaguchi M.; Yamamoto K.; Tsumura Y.; Nomura I.; Kitazawa H.; Morita K.; Kawaguchi T.; Yomase M.; Saito H.) National Center for Child Health and Development, Division of Allergy, Tokyo, Japan):451	The study did not identify the control group.	Japan
4	Rao (2010) Rao AN, Koch M, Ghosh S, Suresh Kumar V. Food allergy investigations and its significance in autism spectrum disorders. <i>International Journal of Pharma and Bio Sciences.</i> 2010;1(4).	This is a cross-sectional study including ADHD in the population with no control group.	Bangalore
5	Tsai (2014) Tsai PH, Chen MH, Su TP, Chen YS, Hsu JW, Huang KL, et al. Increased risk of autism spectrum disorder among early life asthma patients: an 8-year nationwide population-based prospective study. <i>Research in Autism Spectrum Disorders.</i> 2014;8(4):381–6.	A multiple report study on the same population selection (national database 2002–2010) during the time frame of 1996–2010 (Chen et al. 2013). A high risk of overlapping population selection with the included study of Chen et al. (2013).	Taiwan
6	Black (2002) Black C, Kaye JA, Jick H. Relation of childhood gastrointestinal disorders to autism: nested case-control study using data from the UK General Practice Research Database. <i>BMJ.</i> 2002;325(7361):419–421.	It specified on gastrointestinal symptoms and not allergic symptoms.	UK

Table 4 A summary report for the assessment method used, result data presented by each study, and adjusted odds ratios for each outcome

Table 4a. A summary for the estimate prevalence of allergy diseases in ASD groups in comparison to control group							
Study ID	Definition of ASDs symptoms	Measurement of allergic symptoms	Main results	Prevalence estimate in adjusted odds ratio (M–H, random, 95 % CI)			
				Atopic dermatitis	Asthma	Atopic rhinitis	Food allergy
Chen et al. 2013	ASD (ICD9-CM code)	ICD-9-CM codes	A total of 1596 patients with ASDs were identified and were found to have a significantly higher prevalence of allergic and autoimmune diseases than the control group.	OR 1.45 (1.25, 1.68)	OR 1.69 (1.47, 1.93)	OR 1.66 (1.48, 1.86)	
Jyonouchi et al. 2008	DSM-IV criteria; Autism Diagnostic Interview-Revised; Autism Diagnostic Observational Schedules	NIH guideline criteria for asthma; skin prick test; patient self reporting GI symptoms	Atopy is not closely associated with clinical features of the ASDs test group. Compared to ASDs and normal case controls.	OR 1.22 (0.24, 6.28)	OR 0.71 (0.28, 1.83)	OR 1.20 (0.49, 2.93)	OR 5.57 (0.31, 101.08)
Magalhaes et al. 2009	DSM-VI-TR, WISC-III assessment clinically	Clinically evaluated in accordance with the literature and skin prick tests	In the Asperger group, 12 of 15 had allergic clinical features and 11 of the 15 patients were positive with dermatophagoides pteronyssinus. Higher incidence of atopy was observed in the Asperger group, which was 86.6 % compared to 7 % in the healthy controls	OR 1.00 (0.06, 17.62)	OR 7.43 (1.23, 45.01)	–	–
Mostafa and Al-Ayadhi 2013	DSM-IV, history from caregivers, and neuropsychiatric assessment with CARS	Physician diagnosis based on clinical symptoms and serum assay	Patients with severe autism had a significantly higher frequency of allergic manifestations (61.5 %; 16/26) than children with mild to moderate autism (25 %; 4/16), $p=0.02$	OR 7.53 (0.38, 150.47)	OR 17.96 (0.99, 325.45)	OR 5.52 (0.26, 118.61)	–
Mostafa et al. 2010	DSM-IV, history from caregivers, and neuropsychiatric assessment with CARS	Immunologist evaluation on clinical symptoms and questionnaire	Autistic patients with allergic manifestations (40 %) had a lower frequency of CD4 ⁺ CD25 ^{high} regulatory T cells than those without. Among the 12 autistic patients with allergies, 4 had mild to moderate autism and 8 had severe autism	OR 7.76 (0.38, 157.14)	OR 16.18 (0.87, 301.62)	–	–
Mostafa et al. 2008a	DSM-IV, history from caregivers, and neuropsychiatric assessment with CARS	Clinical assessment and standardized diagnostic criteria and serum assay	45 % of autistic children (18/40) had one allergic disease or more. The frequency of allergic manifestations was significantly higher in autistic children than control subjects $\chi^2=10.6$, $p<0.01$	–	OR 4.75 (0.94, 23.98)	–	–
Mostafa et al. 2008b	DSM-IV, history from caregivers, and neuropsychiatric assessment with CARS	Clinical assessment and standardized diagnostic criteria and serum assay	Frequency of allergic manifestations was significantly higher in autistic children $p<0.001$. Of the autistic children, 52 % (26/50) had one or more allergic diseases compared to 10 % (5/50) of control subjects	–	OR 7.58 (1.60, 35.93)	–	–
	ICD 10 by psychiatrist			OR 1.12 (0.36, 3.43)	–	–	OR 1.25 (0.73, 2.13)

Study ID	Study Design	Study Population	Exposure	Outcome	Results	Conclusions
Mrozek-Budzyn et al. 2013	Case-control	Children with autism and controls	Food allergy	Frequency of asthma and allergic diseases in both children with autism and the control group was not significant. Food allergy was more frequent in allergic children with autism	OR 0.78 (0.19, 3.13)	
Renzoni et al. 1995	Case-control	Autistic children with clinical aspects	Food allergy	Autistic children with clinical aspects suggestive of allergy were 67.4 % (29/43). Data on allergic symptoms were not available for controls	OR 1.02 (0.74, 1.41)	
Shibata et al. 2013	Case-control	Autistic children with clinical aspects	Food allergy	Multiple logistic analysis demonstrated gender, birth order, maternal smoking, and nasal allergy to be significantly positively related to higher ASD score	OR 1.25 (0.79, 1.95)	
Table 4b. A summary for immune reactivity response between ASD group and control group from each study					OR 1.60 (1.08, 2.36)	
Study ID	Study Design	Study Population	Exposure	Outcome	Results	Conclusions
Chen et al. 2013	Case-control	Children with autism and controls	Food allergy	Immune reactivity measurement results and adjusted odds ratio (M-H, random, 95 % CI)	OR 1.46 (0.90, 2.35)	
Jyonouchi et al. 2008	Case-control	Children with autism and controls	Food allergy	Immune reactivity measurement results and adjusted odds ratio (M-H, random, 95 % CI)	OR 4.01 (1.00, 16.04)	
Magalhaes et al. 2009	Case-control	Children with autism and controls	Food allergy	Immune reactivity measurement results and adjusted odds ratio (M-H, random, 95 % CI)	OR 332.05 (19.25, 5393.4)	
Mostafa and Al-Ayadhi 2013	Case-control	Children with autism and controls	Food allergy	Immune reactivity measurement results and adjusted odds ratio (M-H, random, 95 % CI)	OR 1.60 (1.08, 2.36)	

Table 4 (continued)

Mostafa et al. 2010	Children with autism and a family history of autoimmune disease (53.3 %) had a significantly lower frequency of CD4 ⁺ CD25 ^{high} regulatory T cells than those without	—	—	anti-MAG (mean±SEM) in autism group (2468.9±644.4) compared to healthy group (1285.9±435.1) $p<0.001$ Lower amount of CD4 ⁺ CD25 ^{high} frequency (median IQR, %) in autism group; (0.14, 0.15) compared to control group; (0.57, 0.41) $p<0.001$ Higher serum serotonin level (median (IQR)) in autism group (78.5 (50.5)) compared to control group (42 (39.5)) $p<0.001$
Mostafa et al. 2008a	Autistic children had significantly higher serum serotonin levels than controls. There was significant positive correlation between serum serotonin and total IgE levels in autistic patients ($r=0.835$, $p<0.001$)	—	—	
Mostafa et al. 2008b	Autistic children had significantly higher serum total IgE levels than healthy control ($p<0.01$). Serum total IgE levels is associated with autistic severity ($p<0.05$)	—	—	A significance of difference of (mean±SD) between autism group (204±186.3) and control (70.3±57.2) $p<0.001$
Mrozek-Budzyn et al. 2013	All skin prick tests performed in autistic children were positive, while in the control group, two children had negative test outcomes.	—	—	
Renzoni et al. 1995	There is no statistical significance in the mean value of total IgE serum between autistic patients and control. Eosinophilia was shown to occur with a significantly higher prevalence in autistic children ($p=0.012$)	—	—	A significance of difference of (mean±SEM): absolute count (cells/cmm) between autistic group (259.14±27) and control group (193.4±18) $p<0.05$
Shibata et al. 2013	—	—	—	—

Table 5 Risk of bias tables

Table 5a. Risk of bias was assessed using the Risk of Bias Assessment Tool for Non-randomized Studies (RoBANS). The Cochrane Risk of Bias Assessment Tool for Non-Randomized Studies of Interventions (ACROBAT-NRSI) was used to support judgment of study quality.

Chen 2013 (retrospective cohort study)

Bias assessment		Support for Judgment
Selection of participants	Low	Selected from the same baseline population from National Health Insurance Research Database.
Confounding variables	Low	Confounding domains were adjusted for by matching age and gender, and logistic regression statistic analyses were used.
Measurement of exposure	Unclear	Patient records from clinician reports were retrieved from the National Health Insurance database. There was no mention whether it identified all the spectrum of ASD base on ICD classification.
Blinding of outcome assessments	Low	Blinded due to diagnostic records from database.
Incomplete outcome data	Low	There was no missing data according to the intended investigation across all groups.
Selective outcome reporting	Low	All reported results corresponded to the objective of the cohort study.

Table 5 (continued)

Jyonouchi 2008 (case-control study)		
Bias assessment	Judgment	Support for Judgment
Selection of participants	Low	All ASD with allergy, referred to the Pediatric Allergy and Immunology clinic within the institution, controls were selected independently of their exposure from same clinic and also General Pediatrics Clinic.
Confounding variables	Low	Confounding domains were adjusted for by matching and with clarified exclusion criteria.
Measurement of exposure	Low	Laboratory tests and clinical diagnoses were conducted according to established protocols by clinicians.
Blinding of outcome assessments	Unclear	Not performed. Minimal influence by knowledge of the study participants but did not mention if the patient identity on the blood sample were coded to avoid bias for testing.
Incomplete outcome data	Low	There was no missing data according to the intended investigation across all groups.
Selective outcome reporting	High	Frequency difference between normal control with ASD-control and ASD-test group in innate immune responses to TLR agonists was not shown in some figures due to probable insignificance.

Table 5 (continued)

Magalhaes 2009 (case-control study)		
Bias assessment	Judgment	Support for Judgment
Selection of participants	Unclear	Cases and two control groups were selected from the same Neurology Outpatient Clinic of Instituto Fernandes Figueira. Not clear whether the Neurology Outpatients ward, Pediatric/Adolescent Follow-up ward and Allergy Outpatient ward used referrals systems.
Confounding variables	Low	Confounding domains were adjusted by matching. Medication records from the participants were evaluated for exclusion.
Measurement of exposure	Low	Clinical test and diagnoses were done according to established standardized protocols by clinicians.
Blinding of outcome assessments	Low	Not performed. Minimal influence by knowledge of the study participants.
Incomplete outcome data	Low	Data outcomes were sufficiently reported according to the intended investigation.
Selective outcome reporting	Unclear	Eosinophil data was only reported in p-value and not in standard measurement value.

Table 5 (continued)

Mostafa 2013 (cross-sectional study)		
Bias assessment	Judgment	Support for Judgment
Selection of participants	Low	ASD group was selected from the Neuropsychiatric Clinic and a control group was selected from the Outpatient Clinic at the same hospital.
Confounding variables	Low	Confounding domains were adjusted for by matching, and the exclusion criteria were clarified.
Measurement of exposure	Low	Clinical tests and neuropsychiatric assessment conducted by clinicians were based on standardized established protocols.
Blinding of outcome assessments	Unclear	Not performed. Minimal influence by knowledge of the study participants but did not mention if patient identity recorded on the blood sample was coded to avoid bias for testing.
Incomplete outcome data	Low	Missing data was not detected according to the intended investigation.
Selective outcome reporting	Unclear	Most results were reported but it was not clearly mentioned how many patients had high anti-MAG or how many had high anti-MBP; instead, the total number of the two groups was indicated.

Table 5 (continued)

Mostafa 2010 (case-control study)		
Bias assessment	Judgment	Support for Judgment
Selection of participants	Unclear	Cases and controls were selected from the same hospital, and controls were selected from the General Outpatients Clinic. Not clear if they were at the same ward as the Neuropsychiatric Clinic.
Confounding variables	Low	Confounding domains were adjusted for by matching age and sex, and exclusion criteria were clarified.
Measurement of exposure	Low	Clinical serum tests and neuropsychiatric assessment conducted by clinicians were based on standardized established protocols.
Blinding of outcome assessments	Unclear	Not performed. Minimal influence by knowledge of the study participants but did not mention if the patient identity on the blood samples were coded to avoid bias for testing.
Incomplete outcome data	High	There was no indication whether the missing number in Table 1 for the control means that patients were not identified or clinical tests were not conducted.
Selective outcome reporting	Unclear	Most of the results were reported but the Figure 1 was not in color; therefore, it was not appropriate to show the data in a scatter plot that requires color, but a line plot should be included as well.

Table 5 (continued)

Mostafa 2008a (case-control study)		
Bias assessment	Judgment	Support for Judgment
Selection of participants	Unclear	Cases and controls were selected from the same hospital, and controls were selected from the General Outpatients Clinic. Not clear whether they are at the same ward as the Neuropsychiatric Clinic.
Confounding variables	Low	Confounding domains that were adjusted for by matching age and sex, and stratified in logistic regression.
Measurement of exposure	Low	Clinical neuropsychiatric evaluation and laboratory assessment conducted by clinicians were based on standardized established protocols at the time of the study.
Blinding of outcome assessments	Unclear	Not performed. Minimal influence by knowledge of the study participants, but it was not mentioned if patient identity on the blood sample was coded to avoid bias for testing, or if the test was done by another independent laboratory.
Incomplete outcome data	Low	All data were collected from all participants and reported.
Selective outcome reporting	High	The correlation between serum serotonin and IgE% in the control group was not reported, only the case group was shown.

Table 5 (continued)

Mostafa 2008b (case –control study)		
Bias assessment	Judgment	Support for Judgment
Selection of participants	Unclear	Cases and controls were selected from the same hospital, and controls were selected from the General Outpatients Clinic. Not clear if they are at the same ward as the Neuropsychiatric Clinic.
Confounding variables	Low	Confounding domains were adjusted by matching age and sex, and exclusion criteria were clarified.
Measurement of exposure	Low	Clinical evaluation was done with special emphasis on neuropsychiatric assessment and clinical manifestations of allergy.
Blinding of outcome assessments	Unclear	Not performed. Minimal influence by knowledge of the study participants, but it was not mentioned if patient identity on the blood sample was coded to avoid bias for testing, or if the test was done by another independent laboratory.
Incomplete outcome data	Low	All data were collected from all participants and reported.
Selective outcome reporting	Low	No indication of selective outcome reporting.

Table 5 (continued)

Mrozek-Budzyn 2013 (case-control study)		
Bias assessment	Judgment	Support for Judgment
Selection of participants	Low	Control group was clinically examined for any sign of autism by nurse interview before comparison with the intervention group. The case control was selected from a previous vaccine cohort study.
Confounding variables	Low	Confounding domains were adjusted for by matching birth and gender, and by logistic regression.
Measurement of exposure	Low	Psychiatrist assessed clinical evaluation; questionnaire and skin prick test were conducted for allergic assessment.
Blinding of outcome assessments	Low	Not performed. May have some recall bias for family history of allergy evaluation, but this does not affect laboratory assessment outcome. Control and case group result assessment were done independently.
Incomplete outcome data	Unclear	There was attrition in the skin-prick test administration for the control (19%) and autistic (66.7%) groups, but children who did not take the test were diagnosed by clinical symptoms and were compared.
Selective outcome reporting	Low	There was no indication of selective outcome reporting base by their intended analyses.

Table 5 (continued)

Renzoni 1995 (case-control study)		
Bias assessment	Judgment	Support for Judgment
Selection of participants	Unclear	The control group was recruited from the same population that gave rise to the case group and was clearly defined to have no autism.
Confounding variables	Low	Confounding domains were adjusted for by matching age and sex.
Measurement of exposure	Low	Neurologist and psychiatrist assessed clinical evaluation and laboratory tests.
Blinding of outcome assessments	Low	Only one other clinician was blinded for clinical assessment, but the participants and other investigators were not blinded. Minimal influence by knowledge of the study participants.
Incomplete outcome data	High	Skin prick test could only be conducted in the autistic group, not in the controls group; however, immune markers were measured.
Selective outcome reporting	High	The intended analysis and results were reported but there was missing skin prick test results for the control group.

Table 5 (continued)

Shibata 2013 (population-based cross-sectional cohort study)		
Bias assessment	Judgment	Support for Judgment
Selection of participants	Unclear	Selected from different schools in Kanazawa city, Japan, but it was not clear if all schools were subjected to a standardized enrollment process or similar by curriculum.
Confounding variables	Low	Confounding domains that were adjusted for by conditional logistic regression.
Measurement of exposure	Low	Medical doctor assessment using autism behavior rating questionnaires.
Blinding of outcome assessments	Unclear	The outcome assessors were unaware of the questionnaires received, but the participants may have likely been influenced by the knowledge of the study.
Incomplete outcome data	Low	All outcome data were reported and the attrition was very low, only two participants dropped out (0.14%), but unlikely to affect the analysis.
Selective outcome reporting	Low	All reported results were corresponded to all intended analyses.

Table 5 (continued)**Table 5b.** A summary of overall risk of bias for outcomes across studies

	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcome assessments	Incomplete outcome data (attrition bias)	Selective outcome reporting
Chen 2013	+	+	?	+	+	+
Jyonouchi 2008	+	+	+	?	+	+
Magalhaes 2009	?	+	+	+	+	?
Mostafa 2008a	?	+	+	?	+	+
Mostafa 2008b	?	+	+	?	+	+
Mostafa 2010	?	+	+	?	+	?
Mostafa 2013	+	+	+	?	+	?
Mrozek-Budzyn 2013	+	+	+	+	?	+
Renzone 1995	?	+	+	+	+	+
Shibata 2013	?	+	+	?	+	+

Table 5 (continued)

Study ID	Study design	Risk of bias	*Overall risk of bias	Exposed population	Not exposed population	Relative effect (95% CI)	Absolute effect (95% CI)
Atopic dermatitis							
Chen 2013	retrospective cohort	Unclear	Unclear	417/1990 (21.0%)	13.00%	OR 1.30 (0.97 to 1.75)	33 more per 1000 (from 3 fewer to 77 more)
Jyonouchi 2008	case-control	High					
Mostafa 2010	case-control	High					
Mostafa 2013	cross-sectional	Unclear					
Shibata 2013	cross-sectional cohort	Unclear					
Asthma							
Chen 2013	retrospective cohort	Unclear	Unclear	456/2191 (20.8%)	18.60%	OR 1.69 (1.11 to 2.59)	93 more per 1000 (from 16 more to 186 more)
Jyonouchi 2008	case-control	High					
Magalhaes 2009	case-control	Unclear					
Mostafa 2008a	case-control	High					
Mostafa 2008b	case-control	Unclear					
Mostafa 2010	case-control	High					
Mostafa 2013	cross-sectional	Unclear					
Mrozek-Budzyn 2013	case-control	Unclear					
Shibata 2013	cross-sectional cohort	Unclear					

Table 5 (continued)

Atopic rhinitis							
Chen 2013	retrospective cohort	Unclear	Unclear	686/1973 (34.8%)	13.80%	OR 1.66 (1.49 to 1.85)	72 more per 1000 (from 55 more to 90 more)
Jyonouchi 2008	case-control	High					
Magalhaes 2009	case-control	Unclear					
Mostafa 2013	cross-sectional	Unclear					
Shibata 2013	cross-sectional cohort	Unclear					
Food allergy mediated by IgE							
Jyonouchi 2008	case-control	High	High	43/272 (15.8%)	11.60%	OR 1.23 (0.76 to 2.01)	23 more per 1000 (from 25 fewer to 93 more)
Mrozek 2013	case-control	Unclear					
Renzoni 1995	case-control	High					
Total serum level IgE							
Magalhaes 2009	case-control	Unclear	Unclear	65	65		SMD 0.67 higher (0.03 lower to 1.36 higher)
Mostafa 2008b	case-control	Unclear					
SMD: standardized mean difference; OR: odds ratio.							
- Low: low risk of bias for all key domains (*overall low: most information is form studies at low risk of bias)							
- Unclear: unclear risk of bias for one or more key domains (*overall unclear: most information is from studies at low or unclear risk of bias)							
- High: high risk of bias for one or more key domains (*overall high: the proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results.)							
*: the overall risk of bias judgements were supported by The Cochrane Collaboration’s summary assessments of risk of bias.							

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