



Association of food hypersensitivity in children with the risk of autism spectrum disorder: a meta-analysis

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Abstract

This meta-analysis was performed to clarify the association between food hypersensitivity in children and autism spectrum disorder (ASD) in detail. Relevant studies published in 8 databases before March 2020 were retrieved and screened according to established inclusion criteria. The odds ratio (OR) with the 95% confidence interval (CI) was pooled to estimate the effect. Subgroup analyses were performed in terms of publication year, study design, location, sample size, definition of food hypersensitivity, definition of ASD, and study quality score. Furthermore, we stratified studies by participant sex and age to perform a more detailed analysis. This meta-analysis included 12 published articles with 434,809 subjects. A significant association was observed between food hypersensitivity and the risk of ASD (OR = 2.792, 95% CI: 2.081–3.746). The risk of ASD among girls and subjects younger than 12 with food hypersensitivity may be greater than that among boys and those older than 12. The results of sensitivity analysis and publication bias analysis show that the association is relatively stable.

Conclusion: Our results showed a positive association between food hypersensitivity and autism spectrum disorder, and girls and subjects younger than 12 may be more sensitive to this association. The role of food hypersensitivity in the onset of ASD deserves more attention.

What is Known:

- Food hypersensitivity is a term used to describe food allergies and food intolerance.
- ASD is a group of neurodevelopmental disorders that are characterized by deficits in social interaction, repetitive or stereotypic behavior, and verbal communication disorder.

What is New:

- In this work, we reviewed and analyzed the available data and studies and found a positive association between food hypersensitivity and ASD.
- Girls and children younger than 12 may be more sensitive to have ASD than boys and children older than 12.

Keywords Food hypersensitivity · Food allergy · Food intolerance · Autism spectrum disorder · Meta-analysis

Hong Li and Haixia Liu contributed equally to this work.

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Abbreviations

AHRQ	Agency for Healthcare Research and Quality
ABC	Autism Behavior Checklist
ADI	Autism Diagnostic Interview
ADI-R	Autism Diagnostic Interview-Revised
ADOS	Autism Diagnostic Observation Schedule
ASD	Autism spectrum disorder
CARS	Childhood Autism Rating Scale
CBM	China Biology Medicine disc/Sinomed
CNKI	China National Knowledge Infrastructure
CCMD	Chinese diagnostic criteria for mental disorders
CIs	Confidence intervals
DSM	Diagnostic and Statistical Manual of Mental Disorders
FEM	Fixed effects model
HRs	Hazard ratios
IL	Interleukin
ICD	International Statistical Classification of Diseases
NHIS	National Health Interview Survey
NOS	Newcastle-Ottawa Scale
ORs	Odds ratios
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analyses
PRs	Prevalence ratios
REM	Random effects model
RRs	Relative risks
TNF	Tumor necrosis factor

Introduction

Autism spectrum disorder (ASD) is a group of neurodevelopmental disorders characterized by deficits in social interaction, repetitive or stereotypic behavior, and verbal communication disorder [1]. Researchers have found evidence of sex differences in ASD; that is, ASD is more common in boys than in girls [2, 3]. Most children with ASD go to the doctor for speech dysplasia or delay [4], which could be diagnosed as early as 3 years of age [5]. A systematic review demonstrated that the global incidence of ASD in 2010 was 7.6‰ and there was little regional variation in the prevalence of ASD worldwide [6]. A long-term autism monitoring study conducted in the USA found that the prevalence of ASD was increasing annually (children aged 4 years: 1.34% in 2010, 1.53% in 2012, and 1.70% in 2014 [7]; children aged 3 to 17 years: 2.24% in 2014, 2.41% in 2015, and 2.76% in 2016 [8]; children aged 8 years: 1.85% in 2016 [3]). The prevalence of ever-diagnosed ASD in the USA has state-level differences, which varied from 1.54% in Texas to 4.88% in Florida in 2016 [9]. A study conducted in Spain revealed an ASD prevalence of 1.23% in 2017 with geographical differences, and the ASD incidence increased from 0.07% in 2009 to 0.23% in 2017 [10]. In addition, the economic burden of supporting a

child with ASD was estimated to be 1.4 million dollars both in the USA and UK [11] because of no cure, and the economic burden of ASD in the USA, combining annual direct medical, direct nonmedical, and productivity costs, was forecasted to range from \$162–\$367 billion (0.884–2.009% of GDP) in 2015 and \$276–\$1011 billion (0.982–3.600% of GDP) in 2025 [12]. The cause of ASD is widely believed to be a combination of genetics and environment [13, 14]. Currently, several studies have shown that immune diseases and allergies are closely related to ASD [15–17], especially in terms of food [15]. Food hypersensitivity is a common medical condition of the immune system, which may be one of the factors related to ASD [15]. Food hypersensitivity is a term used to describe food allergies and food intolerance [18]. According to a study from Russia, a high frequency of hypersensitivity to cereal and dairy products was found in children with ASD [19]. Based on data from the National Health Interview Survey (NHIS) collected between 1997 and 2016 in the USA, it was reported that the weighted prevalence of food allergies was higher in children with ASD (11.25%) than in children without ASD (4.25%) [15]. A recent review also supported the relationship between food and ASD, which found that maternal diet during gestation and the diet of children with ASD were modifiable risk factors for the development or worsening of symptoms of ASD [20]. Harumi Jyonouchi's studies revealed that food allergies may account for some gastrointestinal symptoms observed in children with ASDs [21]. The pathogenesis is more likely that mast cells (primarily in the hypothalamus and participate in the regulation of behavior and language [22]) activated by allergens [22, 23] release pro-inflammatory and neurotoxic molecules [23], which disrupt the gut-blood-brain barriers [24] (the effect of the gut-microbiota-brain axis [25]) and stimulate microglia [26], thus contributing to brain focal inflammation and ASD [22–25]. However, the findings of previous studies on whether individuals with ASD have abnormal immunoglobulin (Ig) levels are slightly different, including increased IgG4 [27] and the absence of elevated IgE [28]. Growing studies show that early intervention plays an important role in the prognosis of ASD [29, 30]. Given the high prevalence and high economic burden of ASD, food, as an easily implemented and accepted intervention, caught our attention. Our meta-analysis aimed to clarify the association between food hypersensitivity in children and ASD in detail.

Methods

This meta-analysis was performed with reference to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines.

Literature search

Before 8 March 2020, relevant available articles were identified by literature searching from the following databases: (1) PubMed; (2) Cochrane Library; (3) Science Direct; (4) Web of Science; (5) China National Knowledge Infrastructure (CNKI); (6) Sinomed (CBM); (7) Wanfang Data; and (8) Chinese VIP Database. The systematic retrieval strategy was as follows: (Food Hypersensitivity OR Food Hypersensitivities OR Food Allergy OR Food Allergies OR Food intolerance OR Food Anaphylaxis) and (Autism OR Autism Spectrum Disorder OR Autism Spectrum Disorders OR Asperger Syndrome OR Autistic Disorder OR ASD). Additionally, we reviewed the references from the relevant articles to identify additional eligible studies.

Study selection

The following inclusion criteria were applied: (1) a study that focused on the association between food hypersensitivity and autism spectrum disorder, in which food hypersensitivity and autism spectrum disorder have clear definitions; (2) an observational study published as an original study; and (3) studies that provided odds ratios (ORs) and 95% confidence intervals (CIs) or data to calculate them. The exclusion criteria were as follows: (1) studies for which the full text was unavailable or only the abstract was available; (2) reviews, case reports, comments, or letters to the editor; (3) studies for which data on effect size were unavailable or not adequate to analyze; and (4) duplicate studies. The most recent and complete data were included if studies were the same or progressive. Two authors (H Liu and H Li) independently performed the eligibility assessment, and discrepancies were resolved through discussion (k , number of studies [31, 32] = 12, Kappa coefficient [33] = 0.856).

Determination of exposure and outcome

Food hypersensitivity was clearly defined based on parental reports or clinical diagnosis or abnormal immune indicators. ASD was defined clearly in articles by clinical diagnosis or more detailed diagnostic criteria/abnormal assessment scale scores. The studies that did not clearly distinguish between allergic diseases and food hypersensitivity, and the studies that did not confirm that this population was ASD (such as children with a low score on one scale may be diagnosed with ASD in the future) were not considered.

Data extraction

The following information was extracted according to a predesigned extraction form by two independent authors: first author's name, publication year, location where the study was

carried out, sample size, study design, definition of food hypersensitivity, definition of ASD, and study quality score. The extracted data included relative risks (RRs), odds ratios (ORs), prevalence ratios (PRs) or hazard ratios (HRs) and 95% confidence intervals (CIs), of which indexes adjusted for the most confounders were preferred. If the above effect indexes were not available, the raw unadjusted data (such as the number of exposed and unexposed persons in the case group and control group or the number of patients and nonpatients in the exposed group and unexposed group) in the original studies could be extracted. If the data on the total population was missing, the subgroup results in the article could be combined to represent the total results. If the data on effect size in one article were all missing, the article would not be considered.

Study quality assessment

According to the Agency for Healthcare Research and Quality (AHRQ), the Newcastle-Ottawa Scale (NOS) and 11-item Prevalence Study Quality checklist were recommended to assess the quality of the included case-control studies, cohort studies, and cross-sectional studies [34]. For NOS, studies that scored 0–3 points, 4–6 points, and 7–9 points were classified as low, moderate, and high quality in turn, respectively. For the 11-item checklist, the quality of the studies was assessed as follows: low quality = 0–3; moderate quality = 4–7; and high quality = 8–11.

Statistical analysis

The strength of the association between food hypersensitivity and autism spectrum disorder was evaluated by calculating the pooled effect estimates and their 95% CIs. To explore the sources of heterogeneity, we performed subgroup analysis in terms of publication year, location, sample size, study design, definition of food hypersensitivity, definition of ASD, and study quality score. Furthermore, eligible studies were stratified by sex and age. Heterogeneity analysis among studies was performed using Cochran's Q chi-square test and I^2 analysis [31]. $I^2 \geq 50\%$ indicated the existence of significant heterogeneity, and the random effects model (REM) was used as the pooling method; otherwise, the fixed effects model (FEM) was used. Sensitivity analysis was performed to assess the stability of the results [35]. Funnel plot asymmetry, Begg's tests, and Egger's tests were used to assess publication bias qualitatively and quantitatively [36, 37]. All statistical analyses were performed using Stata (version 14.0; Stata Corp, College Station, TX) software. Differences were deemed statistically significant when $P < 0.05$.

Results

Study selection and characteristics of studies

A total of 1254 records were initially retrieved from 8 databases. After study selection, our meta-analysis finally included only 12 published articles [14, 15, 38–47]. The flowchart of the literature search is shown in Fig. 1. This meta-analysis included 434,809 subjects, including participants from 4 cross-sectional studies, 7 case-control studies, and only 1 cohort study. Among these studies, 6 studies were performed in the USA, 3 in China, 1 in Italy, 1 in Norway, and 1 in Iran. Study quality assessment indicated that all included studies were of moderate or high quality, and all included case-

control studies were of high quality. The characteristics of the eligible studies are summarized in Table 1.

Quantitative synthesis

In general, we extracted raw unadjusted data from 7 studies [14, 38, 43, 44–47] and adjusted ORs from 5 studies [15, 39, 40–42] to pool the result of this meta-analysis (Bresnahan et al.'s study [41] was the only cohort study we included, which reported an OR value; thus we pooled using OR finally). The pooled OR from the random effects model was 2.792 (95% CI: 2.081–3.746; $I^2 = 75.2\%$), which indicated a statistically significant association between food hypersensitivity and autism spectrum disorder. The main result is shown in Fig. 2.

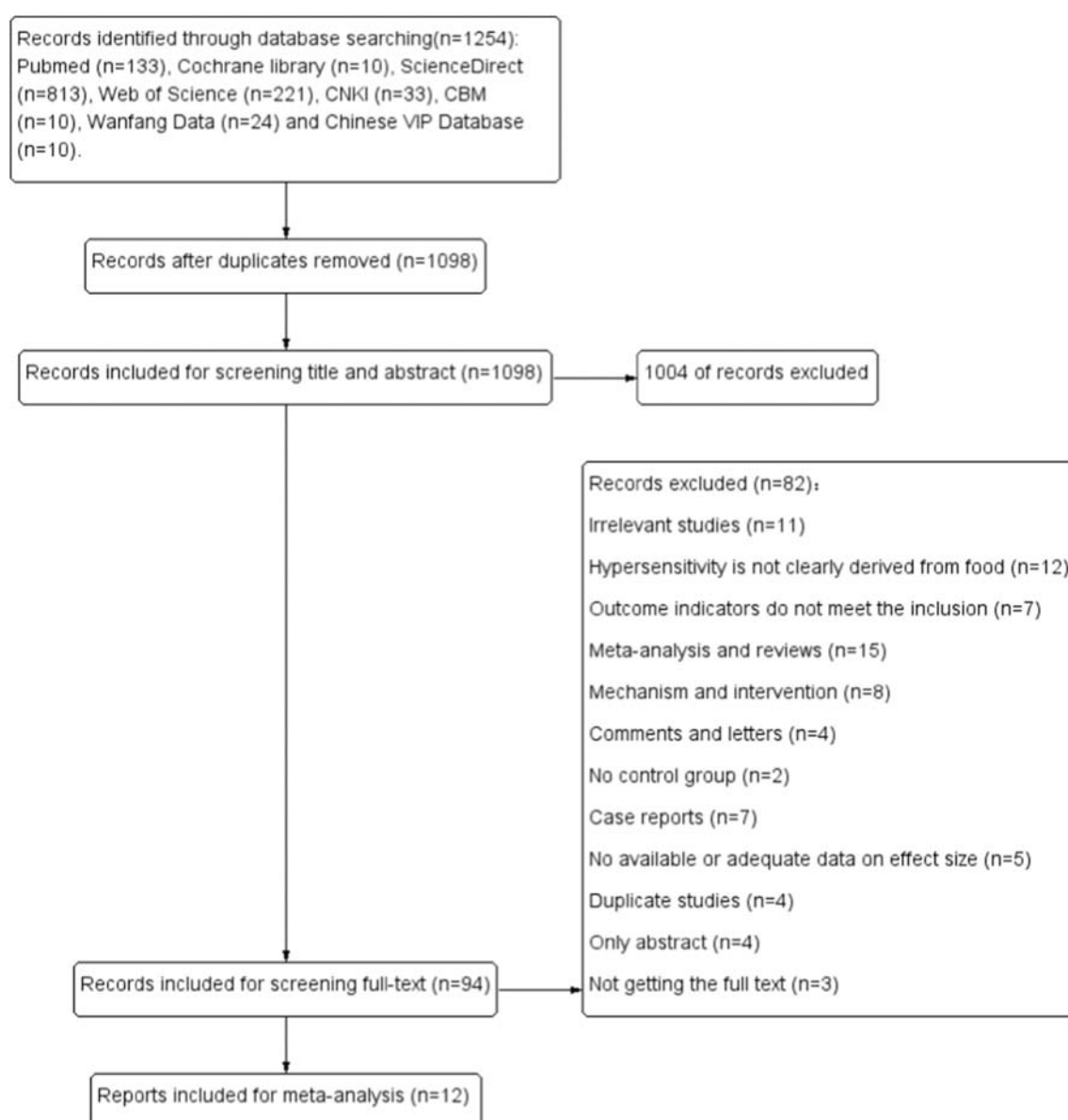


Fig. 1 Flow diagram of the study search and selection process

Table 1 Characteristics of studies included in the meta-analysis

First author's name	Publication year	Location	Sample size	Study design	Definition of exposure	Definition of case	Study quality score
Renzoni E [38]	1995	Italy	86	Case-control	Total serum IgE ≥ 200 kU/L	DSM-III-R and ABC	8
Gurney JG [39]	2006	USA	85,272	Cross-sectional	Parental report	Clinical diagnosis	6
Geng X [45]	2010	China	102	Case-control	sIgG(+)	CCMD-3 and CARS	7
Garg N [40]	2014	USA	16,610	Cross-sectional	Clinical diagnosis	Clinical diagnosis	7
Li S [46]	2014	China	60	Case-control	Fasting blood test ≥ 50 U/mL	ICD-10 (2 diagnosis) and ABC	7
Bresnahan M [41]	2015	Norway	45,126	Cohort	Parental report	DSM-IV-TR and ICD-10	6
Lyll K [42]	2015	USA	951	Case-control	Parental report	ADOS and ADI-R	7
Zerbo O [43]	2015	USA	33,390	Case-control	ICD-9 (2 diagnosis)	ICD-9-CM (2 diagnosis)	8
Hu, Q [47]	2017	China	100	Case-control	IgG ≥ 50 U/mL	DSM-V, CARS and ABC	7
Xu G [15]	2018	USA	199,520	Cross-sectional	Parental report	Clinical diagnosis	5
Malek A [14]	2019	Iran	227	Case-control	Mother's report	ADI and DSM-IV-TR	7
Tan Y [44]	2019	USA	53,365	Cross-sectional	Parental report	Clinical diagnosis	7

DSM, Diagnostic and Statistical Manual of Mental Disorders; ABC, Autism Behavior Checklist; CCMD, Chinese diagnostic criteria for mental disorders; CARS, Childhood Autism Rating Scale; ICD, International Statistical Classification of Diseases; ADOS, Autism Diagnostic Observation Schedule; ADI (ADI-R), Autism Diagnostic Interview (Autism Diagnostic Interview-Revised)

Then, subgroup analysis was performed based on the characteristics of 12 studies. When grouping by publication year, the pooled OR of the studies published before 2017 (OR = 2.685, $I^2 = 78.3\%$) was lower than those of studies published after 2017 (OR = 2.985, $I^2 = 74.2\%$) and the heterogeneity was higher; these differences were both statistically significant. Regarding study design, the reported result of the only cohort study [41] (OR = 1.800, 95% CI: 1.006–3.220) was lower than that of cross-sectional studies (OR = 2.803; 95% CI: 2.151–3.651; $I^2 = 62.3\%$) and may be much lower than that of case-control studies (OR = 3.459; 95% CI: 1.719–6.962; $I^2 = 82.1\%$). Compared with the studies conducted in the other locations, statistical significance was found in the studies conducted in the USA (OR = 2.467; 95% CI: 1.923–3.163; $I^2 = 67.6\%$) and in China (OR = 11.746; 95% CI: 5.869–23.510; $I^2 = 4.4\%$). The pooled OR of studies with more than 30,000 participants was 2.408 (95% CI: 1.833–3.163; $I^2 = 75.5\%$), which may be lower than that of studies with fewer than 30,000 subjects (OR = 3.872; 95% CI: 1.779–8.429; $I^2 = 76.8\%$). Then, we reanalyzed the remaining 7 studies without studies of Malek et al. [14], Renzoni et al. [38], Geng et al. [45], Li et al. [46], and Hu [47] (which sample size is small) and found that the combined results (OR = 2.389, 95% CI: 1.898–3.008) are similar to the combined results of the total 12 studies (OR = 2.792, 95% CI: 2.081–3.746), which indicated that the sample size of including studies did not influence the correlation. Considering the definition of exposure, a significant relationship was found for food hypersensitivity reported by both diagnosis and assessment (OR = 3.861; 95% CI: 1.479–10.081; $I^2 = 85.0\%$) and parents 2.611

(95% CI: 2.109–3.232; $I^2 = 48.9\%$). Considering the case definition, a statistically significant correlation was found; the pooled OR was 3.070 (95% CI: 1.724–5.468; $I^2 = 79.4\%$) for studies that reported detailed ASD diagnostic criteria, which may be higher than those studies that reported no detailed ASD diagnostic criteria (OR = 2.803; 95% CI: 2.151–3.651; $I^2 = 62.3\%$). When grouping by study quality, the combined OR of high-quality studies (OR = 3.459; 95% CI: 1.719–6.962; $I^2 = 82.1\%$) was higher than that of moderate-quality studies (OR = 2.651; 95% CI: 2.072–3.391; $I^2 = 57.9\%$). The detailed results of the subgroup analysis are summarized in Table 2.

We only selected two studies (1 study [15] adjusted for the most confounders and 1 study with raw adjusted data [43]) with data about sex group and 6 studies (3 studies [15, 41, 42] adjusted for the most confounders and 3 studies with raw adjusted data [43, 45, 46]) with data about age group. A significant association was found between food hypersensitivity and ASD in both girls and boys, and the pooled OR was 2.470 (95% CI: 1.691–3.608; $I^2 = 0.0\%$) in girls, which was higher than the pooled OR in boys (OR = 1.894; 95% CI: 1.314–2.731; $I^2 = 68.1\%$). We found a significant association between food hypersensitivity and ASD whether or not subjects were younger than 12. The pooled OR was 2.494 (95% CI: 1.864–3.336; $I^2 = 48.7\%$) in those younger than 12, which may be higher than the pooled OR in those older than 12 (OR = 1.914; 95% CI: 1.023–3.581; $I^2 = 71.4\%$). The main results are summarized in Table 3.

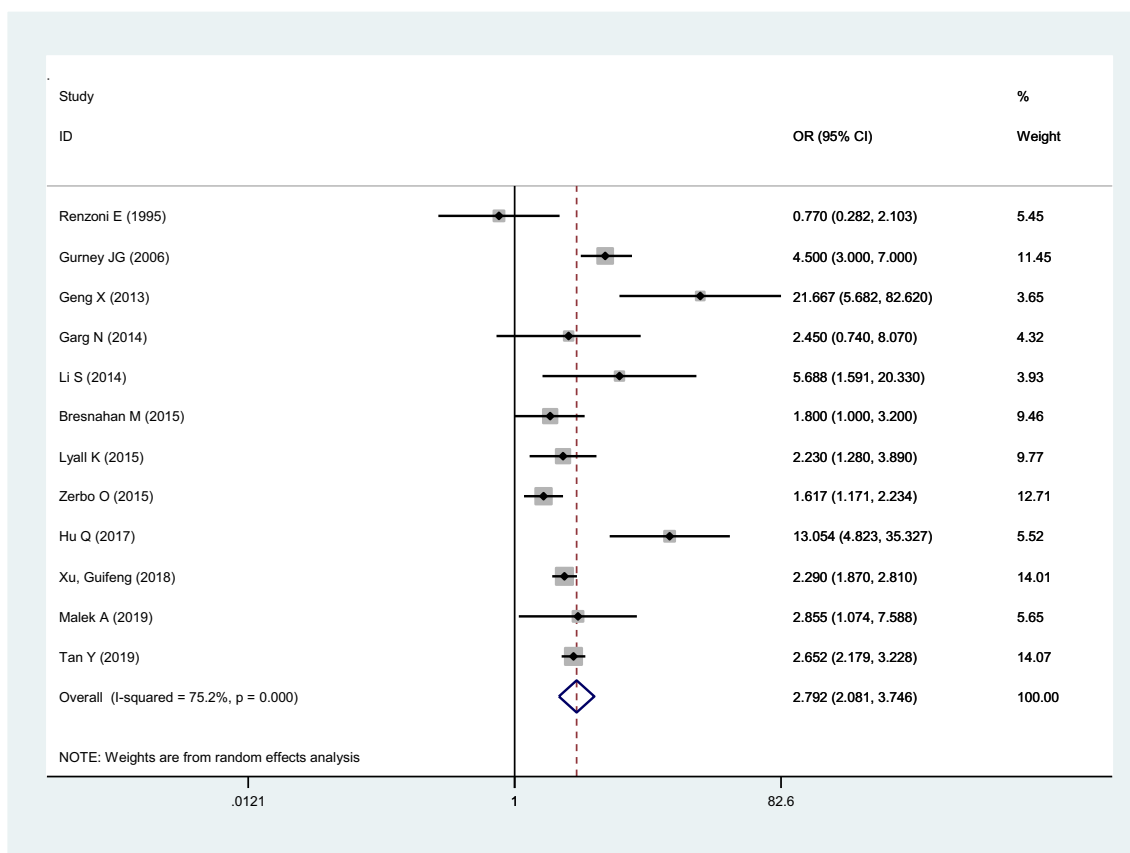


Fig. 2 Forest plot of the ORs with corresponding 95% CIs from 12 studies on food hypersensitivity with the risk of ASD

Sensitivity analysis and publication bias analysis

The results of sensitivity analysis conducted by omitting one study at a time were similar, without great fluctuation, suggesting that the pooled OR was relatively stable. The results of the roughly symmetrical funnel plot (Supplementary Fig. S3) and Begg's test ($P = 0.304$) and Egger's test ($P = 0.327$) showed no publication bias.

Discussion

Our meta-analysis concluded that food hypersensitivity was associated with an increased risk of ASD. Regardless of whether the study was published after 2017, the type of study design, the sample size, how food hypersensitivity was defined, how ASD was defined, and the quality of the study, the results demonstrated a correlation between food hypersensitivity and ASD, similar to the results of previous reviews [48–50]. The detailed relevant mechanism is most likely that mast cells activated by food hypersensitivity, release inflammatory and vasoactive mediators that increase blood-brain barrier permeability, and mast cells trigger corticotropin-releasing hormone secretion from the hypothalamus together with

peptide neurotensin and release interleukin (IL) and tumor necrosis factor (TNF), which in turn stimulate microglia proliferation and activation, leading to disruption of neuronal connectivity and aberrant immune response, thus contributing to focal inflammation and ASD [22–25, 51]. However, it is unclear whether there are abnormal immunoglobulin levels in patients with ASD, where a previous study reported increased IgG4 [27] and another study reported an absence of elevated IgE [28]. What's more, a recent review found that early impairments of visual behavior including oculomotor abilities, visual attention, and visual-motor integration may be involved in the onset of ASD [52]. Although there is currently no cure for ASD, many potential treatment approaches have been found to reduce symptoms and improve behavior, such as luteolin decreasing serum IL-6 and TNF levels and improving behavior [53], the combination of the flavonoids luteolin and quercetin reducing ASD symptoms [54], the natural flavonoids luteolin and tetramethoxyluteolin inhibiting inflammatory processes and having neuroprotective actions [55], methoxyluteolin inhibiting stimulation of mast cells a greater extent than luteolin or Torin1, and the novel flavonoid methoxyluteolin inhibiting mast cell stimulation entirely [56]. Moreover, a previous review suggested that a gluten-free and

Table 2 The pooled odds ratios of subgroup analysis for 12 studies between food hypersensitivity with ASD

Subgroups	No. of studies	OR (95% CI)	Z	P	Heterogeneity	
					I^2 (%)	P
All studies	12	2.792 (2.081–3.746)	6.84	0.000	75.2	0.000
Publication year						
< 2017	8	2.685 (1.619–4.451)	3.83	0.000	78.3	0.000
≥ 2017	4	2.985 (2.062–4.320)	5.80	0.000	74.2	0.009
Study design						
Cross-sectional study	4	2.803 (2.151–3.651)	7.64	0.000	62.3	0.047
Case-control study	7	3.459 (1.719–6.962)	3.48	0.001	82.1	0.000
Cohort study	1	1.800 (1.006–3.220)	1.98	0.048	NA	NA
Location						
USA	6	2.467 (1.923–3.163)	7.11	0.000	67.6	0.009
China	3	11.746 (5.869–23.510)	6.96	0.000	4.4	0.351
Other	3	1.633 (0.864–3.084)	1.51	0.131	42.9	0.174
Sample size						
≤ 30,000	7	3.872 (1.779–8.429)	3.41	0.001	76.8	0.000
> 30,000	5	2.408 (1.833–3.163)	6.31	0.000	75.5	0.003
Definition of exposure						
Parental report	6	2.611 (2.109–3.232)	8.81	0.000	48.9	0.082
Diagnosis/assessment	6	3.861 (1.479–10.081)	2.76	0.006	85.0	0.000
Definition of case						
Nondetailed diagnostic criteria	4	2.803 (2.151–3.651)	7.64	0.000	62.3	0.047
Detailed diagnostic criteria	8	3.070 (1.724–5.468)	3.81	0.000	79.4	0.000
Study quality						
High	7	3.459 (1.719–6.962)	3.48	0.001	82.1	0.000
Moderate	5	2.651 (2.072–3.391)	7.75	0.000	57.9	0.050

casein-free diet could be implemented when someone was diagnosed with an allergy or intolerance to nutritional gluten or casein [57]. Additionally, the use of folic acid and multivitamin supplements among women before and during pregnancy has been reported to reduce the risk of ASD in offspring [58].

While significant results were found in the studies conducted in the USA and China, no significant relationship was

found in the studies conducted in the other locations. In addition, studies conducted in China were all case-control studies with few subjects, which may exaggerate the relationship. In terms of sex and age, girls and subjects younger than 12 with food hypersensitivity may be more likely to have ASD than boys and those older than 12. This may be related to the high prevalence of immune diseases and low prevalence of ASD in girls [2, 59]. Differences in age may be because most children

Table 3 The pooled odds ratios of included studies stratified by different ages and sex

	No. of studies	OR (95% CI)	Z	P	Heterogeneity	
					I^2 (%)	P
Sex	2					
Boys	2	1.894 (1.314–2.731)	3.42	0.001	68.1	0.077
Girls	2	2.470 (1.691–3.608)	4.68	0.000	0.0	0.777
Age	6					
< 12	6	2.494 (1.864–3.336)	6.15	0.000	48.7	0.058
≥ 12	2	1.914 (1.023–3.581)	2.03	0.042	71.4	0.061

with ASD were diagnosed early at aged 3 [5], the capacity of visuospatial attention increases slightly with age and the reaction time to initiate an eye movement decreases until 14–15 years of age approximately [52]. Therefore, larger and well-designed studies are needed to confirm the differences in regard to sex and age.

This meta-analysis has several advantages. First, to our knowledge, this meta-analysis was the first to discuss the correlation between food hypersensitivity and ASD. Second, we performed detailed subgroup analyses, including by publication year, study design, location, sample size, definition of food hypersensitivity, definition of ASD, and study quality score. Third, we extracted data from different sex and age groups to explore sensitive populations. Finally, the adjusted ORs were preferentially extracted for pooling. In addition, sensitivity analysis and publication bias analysis showed that our conclusion was stable and convincing. However, our meta-analysis also has several limitations. First, the extracted data included unadjusted and adjusted data, and the adjustment factors were not the same in some studies. That may result in underestimating or exaggerating risk. Second, the heterogeneity of all studies ($I^2 = 75.2$, $P = 0.000$) was high, which may decrease reliability. The source of high heterogeneity may be the differences in the study quality, study design, study location, and ASD or food hypersensitivity definition of including studies. Finally, on account of the relatively small number of studies, our meta-analysis included only one cohort study and we know that the results of cohort studies are more reliable than those of cross-sectional studies. Therefore, more high-quality cohort studies are needed in the future.

Conclusion

In summary, our meta-analysis shows that food hypersensitivity is associated with ASD. This correlation was not influenced by the publication year, design type, sample size, definition of food hypersensitivity, definition of ASD, or the quality of included studies but may be affected by location where the study was carried out. The ASD risk among girls and subjects younger than 12 with food hypersensitivity may be greater than that among boys and those older than 12. Given the high prevalence of and lack of cure for ASD in the general population, the role of food hypersensitivity in the onset of ASD deserves more attention. Certainly, our finding requires more studies to be confirmed further.

Authors' Contributions Hong Li, Haixia Liu, and Yehuan Sun designed the research; Hong Li, Haixia Liu, and Xin Chen conducted the research; Hong Li, Haixia Liu, and Jian Zhang analyzed the data; Hong Li and

Haixia Liu, and Xin Chen wrote the paper. Yehuan Sun mainly reviewed the paper and Guanglei Tong assisted. Hong Li and Haixia Liu had primary responsibility for the final content. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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Supplementary Figure 3. Funnel plot of 12 studies. Each dot represents a different study.

