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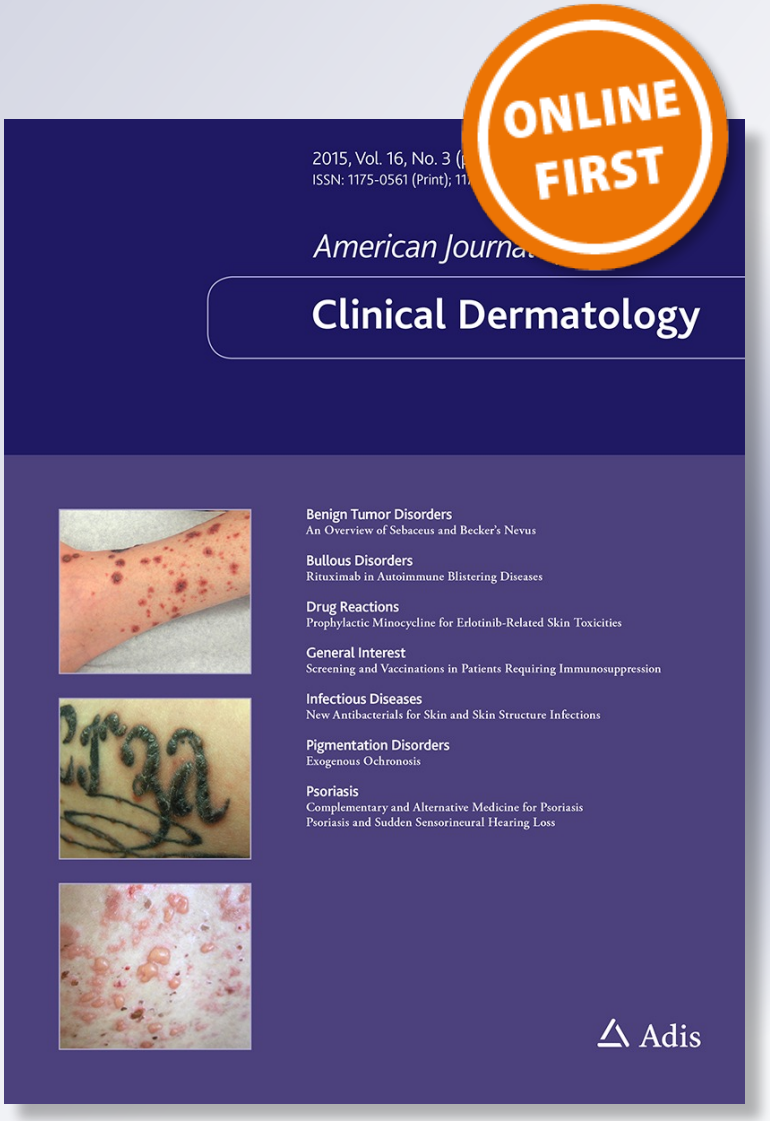


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SYSTEMATIC REVIEW

# Association Between Atopic Dermatitis and Autism Spectrum Disorders: A Systematic Review

**Lucia Billeci[1] · Alessandro Tonacci[1] · Gennaro Tartarisco[2] · Liliana Ruta[2,3] · Giovanni Pioggia[2] · Sebastiano Gangemi[4]**



**Abstract**

*Background* Atopic dermatitis (AD) is an allergic disorder caused by both immunological dysregulation and epidermal barrier defect. Several studies have investigated the association between AD and mental health disorders. Autism spectrum disorders (ASD) are a heterogeneous group of neurodevelopmental conditions characterized by impairments in social communication and restricted, stereotyped interests and behaviors. The concurrent increased prevalence of AD and ASD in the last decades has led many scientists to investigate the relationship between the two diseases.

*Objective* The aim of this systematic review was to examine the association between AD and ASD.

*Methods* A systematic review was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. PubMed and ScienceDirect were searched up to March 2015 for all reports examining the association between ASD and AD. Descriptive statistics of the studies are reported.

*Results* The review included 18 studies assessing the association between ASD and AD. Of these studies, two focused on ASD in relation to AD alone, 14 discussed ASD in relation to both AD and other atopic disorders, and two evaluated AD in parents of children with ASD. Most of these studies found a positive association between the two disorders, although there were some studies going in the opposite direction. The entity of the association is somewhat inconsistent among the different studies given that the frequencies of AD in ASD compared with a control group ranged from 7 to 64.2 %. In addition, odds ratios (ORs) or hazard ratios (HRs) gave different results as three studies found a weak association with an OR below 2 and a nonsignificant $p$ value, and three other studies found a moderate or strong association with an OR ranging from 1.52 to 7.17 and a significant $p$ value. When all atopic disorders were considered when evaluating the risk of ASD, the association was strong with an HR of 3.4 or an OR of 1.24 and $p < 0.001$.

*Conclusions* Overall, the results of this systematic review seem to reveal an association between ASD and AD, suggesting that subjects with ASD have an increased risk of presenting with AD compared with typically developing controls, and vice versa. This association is supported by clinical/epidemiological aspects, shared genetic background and common immunological and autoimmune processes. However, the variability in study population and design, and the presence of other risk factors acting as confounding factors, sometimes contribute to inconsistent results. Further studies are needed to clarify the underlying pathophysiologic mechanism explaining the association between ASD and AD and to explore the causal association between the two conditions.

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**Key Points**

The concurrent increased prevalence of atopic dermatitis (AD) and autism spectrum disorders (ASD) in the last decades has led to investigation of the relationship between the two diseases.

Overall, accumulating evidence seems to reveal an association between ASD and AD in the sense that subjects with ASD have an increased risk of presenting with AD compared with typically developing controls, and vice versa.

A better understanding of the association between the two conditions could be useful in investigating whether early targeted intervention directed to the shared genetic and biological factors would be effective in reducing the symptoms of ASD in later life.

## 1 Introduction

Autism spectrum disorders (ASD) are a heterogeneous group of neurodevelopmental conditions characterized by a dyad of early symptoms: impairments in social communication and restricted or stereotyped interests and behaviors [1]. ASD manifest during early childhood and in at least 30 % of cases children present a regression of development with loss of the skills previously acquired [2, 3]. The exact cause of ASD is still unknown [4], although a considerable genetic component to this condition has been proposed [5]. However, a clear genetic cause does not explain more than approximately 5 % of ASD, suggesting an interaction between genetic vulnerability and environmental factors [6].

The prevalence of ASD in the US has gradually increased in the last decade, from 1 in 88 in 2008 to 1 in 50 in 2011–2012 [7, 8].

Parallel to the rise in ASD prevalence, we have also seen a significant increase in the global prevalence estimates of 'atopic disease' (atopic dermatitis [AD], allergic rhinitis, allergic conjunctivitis and asthma), both in the developed and developing world [9]. According to the International Study of Asthma and Allergies in Childhood, from the 1990s to early 2000, the prevalence of asthma, allergic rhinitis, and AD among children in Australia rose significantly from 4.4, 3.7, and 10.1 % to 5.1, 4.5, and 13.8 %, respectively [10].

Narrowing the focus of interest to AD specifically, several epidemiological data worldwide have reported AD prevalence rates in both adulthood and childhood [11]. Recent studies have found that in the US, the prevalence of childhood AD rose from 7.4 % in 1997–1999 to 12.5 % in 2009–2011 [12], while in Norway an increase from 6.4 % in 1985 to 13.5 % in 2008 was observed [13].

The concurrent increase of atopic disease and ASD has, in recent years, induced many scientists to explore the possible etiological association between these two clinically distinct diseases. Among atopic diseases, AD (also known as atopic eczema) is a chronic inflammatory disease, which is characterized by dry and scaly skin lesions. It is usually referred to as 'atopic' even though it shows the typical atopic patterns of type I (immediate type) sensitization to environmental allergens in only a subset of individuals [14]. AD usually begins within the first year of life, preceding the other atopic diseases in 50 % of cases [15]. Children who have already experienced AD have an increased risk of developing one or more of the other atopic diseases, and for this reason AD is often considered as the beginning of the 'atopic march' [16, 17].

According to Darlenski et al. [18], AD can be viewed as an organ-specific manifestation of a systemic disorder. Both immunological dysregulation and epidermal barrier defects concur as pathophysiologic mechanisms to the disease development. A genetic predisposition [19] and triggering of environmental factors [20, 21] may also be involved in the development of disease.

The immunological mechanism underlying AD is characterized by immunoglobulin E (IgE)-mediated antigen presentation, stimulating Langerhans cells (LC), mast cells, and keratinocytes, resulting in increased populations of eosinophils and inflammatory dendritic epidermal cells, in turn capable of (in chronic AD) switching to the predominant T helper 2 (Th2) response [22, 23].

Overexpressed IgE receptors have been found on the surface of LC in both lesional and nonlesional skin of AD patients in comparison to healthy subjects [14].

Epidermal deficiency is characterized by a decrease in extracellular stratum corneum (SC) hydration, increased transepidermal water loss and specific structural deficits [23]. In 15–50 % of severe cases of AD, these epidermal defects are associated with mutations in the gene encoding for filaggrin, a structural protein of the cornified envelope of the SC [24].

AD is linked to several comorbidities, such as food allergy (FA), infections, skin disorders, ocular disorders, idiopathic nephritic syndrome, autoimmune disorders, gastrointestinal (GI) disorders, and metabolic syndrome [18, 25]. Furthermore, recent epidemiological studies have identified new comorbidities linked to AD, in particular several mental health conditions. The first evidence of an association between AD and emotional, mental state dates back to the early 1900s, when AD was termed 'neurodermatitis' [26]. Controlled studies beginning in the 1980s

confirmed that children with AD have a higher prevalence of psychological conditions compared with healthy controls [27, 28]. More recently, several studies have investigated the association between AD and more well-defined mental health disorders [25].

The aim of this systematic review was to examine the association between AD and ASD. To this purpose, we reviewed observational studies that investigated the prevalence of AD in ASD, and vice versa, as well as studies exploring the probability of developing ASD in children with familial AD.

## 2 Methods

### 2.1 Search Strategy

This systematic review was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [29]. Two databases (PubMed and ScienceDirect) were searched up to 9 March 2015, using five key terms related to ASDs ('ASD', 'autism', 'autistic disorder', 'asperger', and 'childhood schizophrenia') and five key terms related to AD ('atopic dermatitis', 'dermatitis', 'dermatology', 'eczema', and 'neurodermatitis'). The electronic search strategy used for Pubmed is described in Table 1.

We read the abstracts of those articles whose titles indicated that the association between ASD and AD may have been examined. The entire article was read if the abstract indicated that the article potentially met the inclusion criteria. References of the selected articles were also examined and those whose titles suggested that they could have examined the association between ASD and AD were hand searched to identify additional studies that met the inclusion criteria.

**Table 1** Search terms entered into the PubMed search engines for identification of the studies used in this systematic review

| Number | Search term |
|---|---|
| 1 | Autism [All fields] |
| 2 | Autistic disorder [All fields] |
| 3 | Asperger [All fields] |
| 4 | ASD [All fields] |
| 5 | Childhood schizophrenia [All fields] |
| 6 | Atopic dermatitis [All fields] |
| 7 | Eczema [All fields] |
| 8 | Neurodermatitis [All fields] |
| 9 | Dermatitis [All fields] |
| 10 | Dermatology [All fields] |
| 11 | English [Language] |
| 13 | 1 OR 2 OR 3 OR 4 OR 5 |
| 14 | 6 OR 7 OR 8 OR 9 OR 10 |
| 15 | 13 AND 14 AND 11 |

### 2.2 Study Selection

Articles were included in the present review according to the following inclusion criteria: (i) English language; (ii) publication in peer-reviewed journals; (iii) explicit reference to the evaluation of AD in subjects and not of atopy or atopic disorders in general; and (iv) quantitative information on the association between AD and ASD. Articles were excluded by title, abstract or full-text for irrelevance to the topic in question. Further exclusion criteria were (i) review articles, medical hypothesis and case reports; and (ii) articles with less than ten subjects.

### 2.3 Data Extraction

Two authors (LB, AT) performed the initial search and independently reviewed and selected the references based on the inclusion and exclusion criteria.

The data extracted included (i) study author names, (ii) publication dates, (iii) study designs (i.e. case-control, cross-sectional, longitudinal), (iv) sample sizes, (v) groups studied, (vi) clinical and biological variables, and (vii) outcomes of interest of the study. Any disagreement between the two co-authors over the eligibility of particular studies, given the inclusion/exclusion criteria mentioned, was discussed with a third reviewer (SG), independently.

Principal outcomes of interest included results from the univariate/multivariate analysis expressing the association between AD and ASD and, when available, the odds ratio (OR) or hazard ratio (HR) with confidence interval (CI) indicating the probability that a child with AD would develop ASD. When different clinical and biological measures were assessed within a study, only results related to AD were reported.

Given the considerable heterogeneity in the study designs and sample characteristics (mainly in terms of age and size), statistical methodologies and in the criteria to define AD as well as ASD symptoms, characteristics of study populations and protocols were summarized and study outcomes reported using descriptive statistics without conducting any meta-analyses.

## 3 Results

### 3.1 Study Characteristics

Figure 1 depicts the flow of articles retrieved for the review. The search of PubMed and ScienceDirect provided a total of 394 citations, and after adjusting for duplicates,

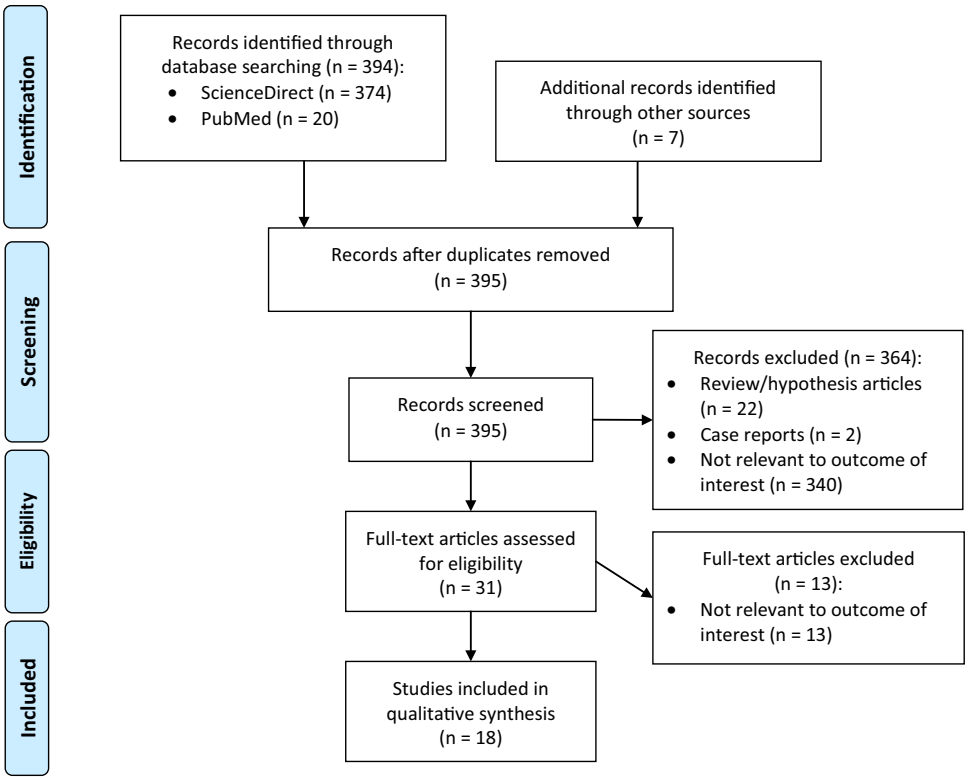


**Fig. 1** Systematic review process used in this study

388 citations remained. An additional group of seven studies meeting the inclusion criteria were identified by checking the references of selected papers. A total of 395 records were screened. Of these, 24 studies were excluded by title because they did not meet the criteria as they were reviews or hypothesis articles ($n$ = 22) or case studies ($n$ = 2). The majority of articles ($n$ = 340) were excluded as their title or abstract were not relevant to the outcome of interest for this review. The full text of the remaining 31 citations was examined in more detail.

A total of 18 studies, assessing the association between ASD and AD, met the inclusion criteria and were included in the systematic review. In particular, 2 articles focused on ASD in relation to AD alone, 14 studies discussed ASD in relation to both AD and other atopic (allergic) disorders, and 2 studies evaluated AD in the parents of children with ASD.

Table 2 summarizes the studies selected, in particular highlighting the number of subjects enrolled, study design, principal outcomes and the quantitative measures used to report the association between ASD and AD.

### 3.2 Association between Autism Spectrum Disorder (ASD) and Atopic Dermatitis (AD) Separately from Other Atopic Diseases

Only two studies have focused specifically on the association between ASD and AD; contradictory results were observed.

In the first study [30], data from the 2007 National Survey of Children's Health (NSCH), which was designed to estimate the prevalence of various child health issues, were used. The presence and severity of AD in the previous year was assessed in relation to mental health disorders, including ASD. The prevalence of ASD was found to be significantly increased in children with AD (2.19 vs. 0.89 % in the group without AD; $p < 0.0001$). A strong association between AD and ASD was found (OR 2.73, 95 % CI 1.94–3.84). The authors also found an increased prevalence of other atopic diseases and FA in the AD population. The adjusted OR (aOR) values of ASD in children according to AD severity after adjusting for potential confounders were 1.78 (95 % CI 1.14–2.77; $p$ = 0.0159) for mild AD, 3.25 (95 % CI 1.79–5.90; $p$ = 0.0003) for moderate AD, and 7.41 (95 % CI 3.82–14.36; $p < 0.0001$) for severe AD.

In a poster abstract, Adil et al. [31] presented results of a retrospective chart reviewing a cohort of children with AD assessed at the Cardinal Glennon Children's Hospital Dermatology Clinics (Missouri, USA). The cohort of children involved in the study featured a prevalence of severe AD higher than another previously published AD cohort (45.8 %). However, the authors reported that eight children (12 % of patients) had mental health conditions, including depression, anxiety, attention-deficit hyperactivity disorder (ADHD) and ASD, without specifying the number of children having each disorder, and concluded

**Table 2** Studies exploring the association between atopic dermatitis and autism spectrum disorders

| Study, country | Participants (Age in years) | Design | Variables | Main outcome | Prevalence and ORs/HRs |
|---|---|---|---|---|---|
| Yaghmaie et al. [30], USA | *N* = 79,667 (0–17) | National survey | AD, mental health disease, other atopic diseases, FA | Increased prevalence of ASD in patients with AD | 0.89 % ASD in the group without AD and 2.19 % in the group with AD<br>OR 2.73, 95 % CI 1.94–3.84, $p < 0.0001$ |
| Adil et al. [31], USA | *N* = 72 (3–10) | Retrospective chart review | AD, mental health disease, other atopic diseases, immunodeficiency, sleep disturbance, vitamin D | No association between AD and mental health disease, including autism | ASD in 12 % of AD subjects |
| Molloy et al. [32], USA | *N* = 20 ASD<br>*N* = 20 TD<br>(3–11) | Case-control study | Atopic history, cytokine levels | No differences in AD and other atopic disorders between ASD and TD | AD in 15 % ASD and in 10 % TD |
| Jyonouchi et al. [33], USA | *N* = 75 ASD GI(+)<br>(1.8–10.6)<br>*N* = 34 GI(−)<br>(2.1–10.2)<br>*N* = 15 NFH<br>(1.3–7.8)<br>*N* = 19 healthy controls<br>(1.0–9.0) | Case-control study | Atopic disorders, GI, cytokine level | No differences between ASD and TD in atopic disorders | AD in 6.7 % GI + ASD and in 8.8 % GI−ASD |
| Jyonouchi et al. [34], USA | *N* = 26 ASD test<br>(2.3–13.4)<br>*N* = 107 ASD control<br>(1.5–17.3)<br>*N* = 38 CRS/ROM<br>(1.0–17.8)<br>*N* = 24 FA<br>(1.0–13.7)<br>*N* = 43 healthy controls<br>(1.0–13.8) | Case-control study | Atopic diseases, immunodeficiency, FA, CRS/ROM | No differences in AD and other atopic disorders between groups | AD in 3.8 % ASD test, 5.6 % ASD control, 8.3 % FA, 0 % CRS/ROM and 4.7 % healthy controls |
| Mostafa et al. [35], Egypt | *N* = 50 ASD<br>*N* = 50 TD<br>(4–16) | Case-control study | Atopic diseases, GI and neurological manifestations, EEG abnormalities and IgE level | Increased prevalence of AD and other atopic disease in ASD, correlation with ASD severity, GI and neurological manifestation, IgE level and EEG abnormalities | AD alone in 16 % ASD and 0 % TD; AD + allergic rhinitis in 6 % ASD and 2 % TD; AD + asthma in 4 % ASD and 4 % TD |
| Mostafa et al. [36], Egypt | *N* = 40 ASD<br>*N* = 40 TD<br>(3–12) | Case-control study | Atopic diseases, IgE level, EEG abnormalities and serum serotonin level | Increased prevalence of AD and other atopic disease in ASD, higher hyperserotonemia in allergic ASD subjects than in nonallergic ASD subjects | AD alone in 7.5 % ASD and 0 % TD; AD + allergic rhinitis in 7.5 % ASD and 2.5 % TD; AD + asthma in 2.5 % ASD and 2.5 % TD; AD + allergic rhinitis + asthma in 2.5 % ASD and 0 % TD |

**Table 2** continued

| Study, country | Participants (Age in years) | Design | Variables | Main outcome | Prevalence and ORs/HRs |
|---|---|---|---|---|---|
| Mostafa and Al-Ayadhi [37], Egypt | *N* = 42 ASD<br>*N* = 42 TD<br>(6–11) | Case-control study | Allergic manifestation (ASD only), autoantibodies | High rates of allergic manifestations in ASD, higher serum level of autoantibodies in allergic ASD subjects than in nonallergic ASD subjects | AD alone in 7 % ASD, AD + allergic rhinitis in 3 % ASD, and AD + asthma in 9.5 % ASD |
| Magalhães et al. [38], Brazil | *N* = 15 ASD<br>*N* = 15 nonatopic TD<br>*N* = 15 atopic TD<br>(7–18) | Case-control study | Atopic disorders, atopic history, IgE level | Increased prevalence of atopic disorders, atopic history, IgE level in Asperger group | AD + allergic rhinitis in 13.3 % ASD and 0 % TD |
| Zerbo et al. [39], USA | *N* = 5565 ASD<br>*N* = 27,825 TD<br>(3–26) | Population study | Immune-mediated conditions (asthma, AD, rhinitis, food allergies, others) and autoimmune diseases | Increased prevalence of allergic conditions and autoimmune diseases in ASD group. No significance for AD | AD in 7.3 % ASD and 6.9 % TD; OR 1.07, 95 % CI 0.95–1.20 |
| Garg and Silverberg [40], USA | *N* = 27,566<br>(0–5) | National survey | Atopic history and mental health disease | AD strongly associated with autism, association with injuries | AD in 27.3 % ASD and 15.8 % TD; aOR 7.17, 95 % CI 2.56–20.04 |
| Schieve et al. [41], USA | *N* = 41,244<br>(3–17) | National survey | Atopic diseases, developmental disabilities, other medical conditions | Increased prevalence of allergic diseases and medical conditions in ASD | AD in 15.6 % ASD and 10.2 % TD; aOR 1.7, 95 % CI 1.2–2.5 |
| Shibata et al. [42], Japan | *N* = 1409 ASD<br>(3–5) | Population survey | Atopic diseases, environmental factors, ASD subscales | High prevalence of AD associated with ASD subscales | AD in 64.2 % ASD; OR 1.00, 95 % CI 0.71–1.41, $p = 0.986$ |
| Chen et al. [43], Taiwan | *N* = 1,000,000 | Nationwide study | Diagnosis of ASD, presence of allergic and autoimmune diseases | Increased prevalence of AD in ASD group compared with TD group | AD in 17.8 % ASD and 13 % TD; OR 1.52, 95 % CI 1.30–1.78, $p < 0.001$ |
| Chen et al. [44], Taiwan | *N* = 21,756<br>(0–3 at any atopy) | Longitudinal follow-up nationwide study | Allergic diseases, ASD and ADHD | Prevalence of ASD increased in the atopic cohort, early prevalence of atopic diseases in early childhood increased the risk of developing ASD | HR 3.40, 95 % CI 1.95–5.93, $p < 0.001$ (atopic disorders) |
| Lin et al. [45], Taiwan | *N* = 578 ASD<br>*N* = 458 ASD/ADHD<br>*N* = 5386 ADHD<br>*N* = 25,688 TD<br>(0–18) | Nationwide study | Allergic diseases, ASD, ADHD and ASD/ADHD | Increased prevalence of allergic diseases, including AD, in pathological groups and ASD/ADHD had the highest incidence | AD in 17.3 % ASD, 17.9 % ASD/ADHD and 11.3 % TD<br>ASD: OR 1.24, 95 % CI 1.04–1.48<br>ASD/ADHD: OR 2.26, 95 % CI 1.83–2.79, $p < 0.001$ (atopic disorders) |
| Croen et al. [46], USA | *N* = 407 ASD<br>*N* = 2095 TD<br>(3–7) | Nested case-control study | Evaluation of maternal autoimmune and allergic disease of children with ASD identified by a clinical database | AD prevalence increased in mothers of children with ASD compared with controls | AD in 3.7 % of mothers of ASD and 2.2 % of mothers of controls ($p = 0.04$) |

**Table 2** continued

| Study, country | Participants (Age in years) | Design | Variables | Main outcome | Prevalence and ORs/HRs |
|---|---|---|---|---|---|
| Larsson et al. [47], Sweden | *N* = 4779 (1–3; follow-up 6–8) | Longitudinal follow-up population study | Questionnaire for the evaluation of ASD, AD and exposure to environmental factors | Significant association between maternal AD and ASD in the child, no significant association between AD at baseline and ASD at follow-up | 2.5 % of mothers with AD and 1.4 % of mothers without AD, $p = 0.023$<br>aOR 1.60, 95 % CI 0.96–2.67, $p = 0.08$ |

*AD* atopic dermatitis, *ADHD* attention-deficit hyperactivity disorders, *aOR* adjusted odds ratio, *ASD* autism spectrum disorders, *CI* confidence interval, *CRS/ROM* chronic rhinosinusitis/recurrent otitis media, *FA* food allergy, *GI* gastrointestinal symptoms, *HR* hazard ratio, *IgE* immunoglobulin E, *NFH* nonallergic food hypersensitivity, *OR* odds ratio, *TD* typically developing

that there was no association between AD and mental health disease. Moreover, AD was found to be associated with other atopic diseases and vitamin D deficiency.

### 3.3 Association between ASD and AD in Connection with Other Atopic Diseases

Fourteen studies explored the association between ASD and AD, considering AD in connection with other atopic diseases. Contradictory results were observed. While the majority of studies found an association between ASD and atopic diseases, three studies did not find any link [32–34].

Molloy et al. [32] focused on cytokine level as an indicator of immune system functionality, and evaluated the history of atopic features (allergy, asthma and AD) in children with ASD and in typically developing (TD) children. Despite a higher level of cytokines in the ASD group, none of the atopic disorders were significantly different between the two groups. In particular, the prevalence of AD was 15 % in the ASD group compared with 10 % in the TD group.

In the case-control study by Jyonouchi et al. [33], atopic disorders were evaluated in association with GI symptoms. No significant between-group differences for any of the atopic disorders were found in the ASD with GI (GI+) group compared with the ASD without GI (GI−) group. Although atopic disorders were not evaluated in healthy controls, the authors found that the ASD group showed similar prevalence rates to those reported in the general population (25.3 % in GI− ASD and 35.3 % in GI+ ASD). AD was diagnosed in 6.7 % of GI+ ASD children and in 8.8 % of GI− ASD children. The authors pointed out an association between AD and FA, observing that ASD with atopy, especially AD, had an increase in interleukin (IL)-5 production consequent to casein intake.

In another study [34], the same research group explored the association between clinical features and atopy, asthma, FA, primary immunodeficiency or innate immune responses in a subgroup of children with ASD characterized by frequent infections accompanied by worsening of behavioral symptoms and/or loss/decrease in acquired development, social skills. This test group was compared with an ASD control group as well as with three control groups (FA, chronic rhinosinusitis/recurrent otitis media [CRS/ROM], and healthy controls). The authors did not find significant between-group differences in the prevalence of AD and all other atopic diseases (ASD test: 3.8 %; ASD control: 5.6 %; FA: 8.3 %; CRS/ROM: 0; healthy controls: 4.7 %), concluding that atopy was not closely associated with clinical features of the ASD test group.

Among the 11 studies that found an association between ASD and AD or atopic diseases, four were case-control or cross-sectional studies.

Three studies were conducted by an Egyptian research group which aimed to correlate atopic diseases in ASD with other clinical conditions and biological dysfunctions [35–47].

In the first study [35], ASD and TD subjects were enrolled and analyzed for allergic symptoms (bronchial asthma, AD and allergic rhinitis), GI manifestations, neurological conditions, EEG abnormalities (ASD only) and IgE levels.

The authors found an increased prevalence of allergic diseases in ASD compared with TD (52 vs. 10 %; $p < 0.001$). In particular, AD alone was present in 16 % of ASD and in none of TD subjects, AD in conjunction with allergic rhinitis was found in 6 % of ASD and in 2 % of TD subjects, while AD in conjunction with asthma was reported in 4 % of both ASD and TD subjects. Moreover, a significant correlation between allergic symptoms and ASD severity, as well as GI and neurological manifestations and EEG abnormalities evaluated in ASD subjects was found.

The second study [36] aimed to link allergic manifestations in children with ASD with serum serotonin levels, which modulate immune responses [48]. In this study, children with ASD and TD were assessed for allergic

diseases, IgE levels, EEG abnormalities (ASD subjects only) and serum serotonin levels. The prevalence of allergic diseases was increased in the ASD group compared with the TD group (45 vs. 10 %; $p < 0.01$) and was associated with ASD severity. In particular, 7.5 % of children with ASD, but none of the TD children, had AD only, 2.5 % of both ASD and TD children had AD and asthma, 7.5 % of children with ASD and 2.5 % of TD children had AD and allergic rhinitis, and 2.5 % of children with ASD had all three atopic diseases, while none of the TD children showed all three atopic diseases. Furthermore in the ASD group, there was a significantly higher frequency of hyperserotonemia in subjects with allergic manifestations than in those ASD subjects without such manifestations, suggesting that hyperserotonemia was a condition related to allergic mechanisms in ASD.

More recently, the same group [37] investigated the link between allergic manifestations and brain-specific autoantibodies, specifically anti-myelin basic protein (anti-MBP) and anti-myelin-associated glycoprotein (anti-MAG), in a group of ASD and a group of TD subjects. Assessment for allergic conditions was only performed in the ASD group. The prevalence of allergic diseases in children with ASD was 47.6 %, with approximately 7 % having AD alone, approximately 3 % with both AD with allergic rhinitis and AD with asthma, and approximately 9.5 % having AD with allergic rhinitis and asthma. A positive correlation between allergic symptoms and ASD severity was found. Moreover, higher serum levels of autoantibodies in allergic ASD children compared with nonallergic ASD children was shown.

Another study by Magalhães et al. [38] focused on Asperger syndrome (AS). In this study, AS, atopic TD and nonatopic TD subjects were evaluated for atopic disorders, atopic history and IgE levels. Subjects with AS reported a significant increase of allergic problems compared with nonatopic TD children (80 vs. 20 %; $p < 0.05$), together with increased IgE levels. In particular, within the AS cohort, two children (13.3 %) had AD together with allergic rhinitis, while none of the control children in both the atopic and nonatopic groups had AD either alone or in conjunction with other atopic disorders. The prevalence of atopic history was also increased in children with ASD, and taking into account both the clinical findings and the atopic history, the final prevalence of atopy in the ASD group was 86.6 % versus less than 7 % in nonatopic TD children.

Recently, another case-control study [39] investigated the prevalence of immune-mediated conditions and autoimmune diseases in a large sample of subjects. The prevalence before and after the first diagnosis of ASD was also determined. All immune-mediated conditions (except asthma) and autoimmune diseases were found to be increased in the ASD compared with TD groups. However, the increase of AD in the ASD population was not significant (7.3 vs 6.9 %; OR 1.07, 95 % CI 0.95–1.20). The same pattern of results was found for immune-mediated conditions diagnosed before the age at first ASD diagnosis. During the period prior to the first ASD diagnosis, asthma was diagnosed less often, and allergy and autoimmune disorders were diagnosed more often among children with ASD compared with TD children. Furthermore, prevalence estimates were reported for the whole pool of allergy in the ASD group versus the TD group, and resulted in 18.7 versus 18.1 % (OR 1.06, 95 % CI 0.94–1.20) prior to the ASD diagnosis, and 5.3 versus 4.8 % (OR 1.15, 95 % CI 0.93–1.43) after an ASD diagnosis had been made.

Another three studies assessed the association between AD and ASD on the basis of nationwide or population-based survey study design.

In one study [40], the authors used data collected from the 2007 to 2008 NSCH and found a strong association between allergic diseases, mental health comorbidities and injuries. In particular, they found that the prevalence of AD in ASD was 27.3 and 15.8 % in TD subjects, and that AD was a significant risk factor for ASD (aOR 7.17, 95 % CI 2.56–20.04).

Another US survey study [41] used data from the 2006 through 2010 National Health Interview Surveys (NHIS), extracting information related to developmental conditions, allergic diseases and other medical conditions (i.e. FA, seizures or stomach/intestinal illness). Children with developmental disabilities had increased prevalence estimates for all the medical conditions examined. In particular, AD rates were increased in children with ASD compared with TD children (15.6 vs. 10.2 %; aOR 1.7, 95 % CI 1.2–2.5).

The third study was a population-based Japanese study [42] investigating the association between ASD, allergy and other medical conditions (FA, GI problems, ear infections, seizures and headaches). In particular, the authors explored the relationship between the abovementioned conditions and the items of the Japanese version of the Autism Screening Questionnaire (ASQ). With regard to AD, an elevated prevalence of this condition was found in the ASD population, with a rate of 64.2 %; however, the OR relating AD to ASD scores was quite low (OR 1.00, 95 % CI 0.71–1.41; $p = 0.986$). AD was not associated with any environmental factors, but was significantly associated with some of the ASQ items related to social reciprocal interaction, repetitive behavior and stereotyped patterns and communication.

Another three recent nationwide studies [43–45] have been run by the same research group using data from the National Health Insurance program implemented in Taiwan in 1995. In the first study [43], 1,000,000 persons were investigated for an ASD diagnosis, as well as the presence of allergic and autoimmune diseases. The survey found that

the prevalence of allergic comorbidities, but not autoimmune diseases, was significantly increased in the ASD population compared with TD subjects. In particular, with regard to AD, the prevalence rate was 17.8 % in the ASD group and 13.0 % in the TD group ($p < 0.001$). Furthermore, ASD subjects were significantly more prone to develop AD compared with TD subjects (OR 1.52, 95 % CI 1.30–1.78).

In another study by this group [44], the authors investigated the association between atopy in early childhood (before the age of 3 years) and the risk of ASD or ADHD in later life. A cohort of subjects with atopic diseases (atopic cohort) and a cohort of subjects without atopy (nonatopic cohort) were followed for approximately 10 years, identifying those subjects with ASD or ADHD. In the ASD group, the results showed that an early occurrence of any atopic disease in early childhood increased the risk of developing ASD in later life (HR 3.40, 95 % CI 1.95–5.93; $p < 0.001$) At follow-up, it was found that the prevalence of ASD was increased in the atopic cohort compared with the nonatopic cohort (0.8 vs. 0.2 %; $p < 0.001$). The prevalence of AD was 56.1 % in the whole atopic cohort, although the incidence in the ASD group was not specified.

The third study [45] investigated the effect of the comorbidity between ASD and ADHD on allergic diseases. The authors found that subjects with ASD alone, ADHD alone and ASD/ADHD had increased prevalence of allergic diseases compared with TD controls ($p < 0.001$), and the ASD/ADHD group had the highest incidence. In particular, regarding AD, the prevalence rate was 17.3 % in the ASD group, 17.9 % in the ASD/ADHD group and 11.3 % in the TD group. The ORs were evaluated for the whole pool of allergic diseases and demonstrated an increased risk of allergic comorbidities in the ASD group and ASD/ADHD group compared with TD group (OR 1.24, 95 % CI 1.04–1.48, and OR 2.26, 95 % CI 1.83–2.79, respectively).

### 3.4 Association between AD in the Family and ASD in Children

It is becoming widely accepted that the development of abnormal brain connectivity in ASD is influenced by prenatal and/or early postnatal environmental factors, presumably interacting with a genetic predisposition. Several studies tried to elucidate the link between familial diseases and ASD development. In particular, two studies assessed the association between allergic diseases, including AD, in a family of children with ASD, and ASD diagnosis. In the study by Croen and colleagues [46], the association between a history of maternal autoimmune diseases, allergies, and asthma during pregnancy and the subsequent diagnoses of ASD in the offspring was investigated. Among allergies, AD was also evaluated in pregnant mothers. Data contained in the clinical database of the Kaiser Permanente Medical Care Program were explored and all children with ASD were selected. For both ASD subjects and TD controls, maternal autoimmune diseases, asthma, and allergies were identified in the period 2 years preceding delivery through 2 years following delivery. With regard to AD, a significant increase in the condition was present in mothers of children with ASD (3.7 %) compared with mothers of TD controls (2.2 %; $p = 0.04$). However, after adjusting for other confounding factors, results were no longer significantly different. In addition, the overall incidence of maternal allergies (AD, allergic rhinitis, anaphylaxis and conjunctivitis) increased with the number of ASD-affected children in the sibship.

In the second study [47], the association between ASD diagnosis in children aged 6–8 years and prenatal and early infancy (from birth to 3 years) exposure to environmental factors and allergy was investigated. Among all the allergic symptoms, AD was also evaluated both in the family (mother and/or father and/or siblings) of children with ASD and in children themselves at baseline. The rate of association between the presence of AD in mothers at baseline and diagnosis of ASD at follow-up was significantly higher compared with the rate of associations between the absence of AD in mothers at baseline and diagnosis of ASD at follow-up (2.5 vs. 1.4 %; $p = 0.023$), suggesting that mothers with AD were more likely to have a child with a diagnosis of ASD in later life. The same association did not emerge with paternal symptoms of AD. When evaluating AD in children, no significant association was found between AD at baseline and ASD 5 years later (aOR 1.60, 95 % CI 0.96–2.67; $p = 0.08$).

## 4 Discussion

In this review, 18 studies investigating the association between AD and ASD were identified and systematically reviewed. Overall, these studies suggest a positive association between the two conditions, leading to the hypothesis that children with AD are more likely to be diagnosed as having ASD than children without this chronic disease. Some clinical and epidemiological evidence, combined with potential shared pathophysiologic mechanisms, such as shared genetic background, common immunological pathways and autoimmune processes, may account for this association (Fig. 2).

### 4.1 Clinical and Epidemiological Aspects

The results of this review, as already outlined, suggest an overall positive association between AD and ASD [30, 35–

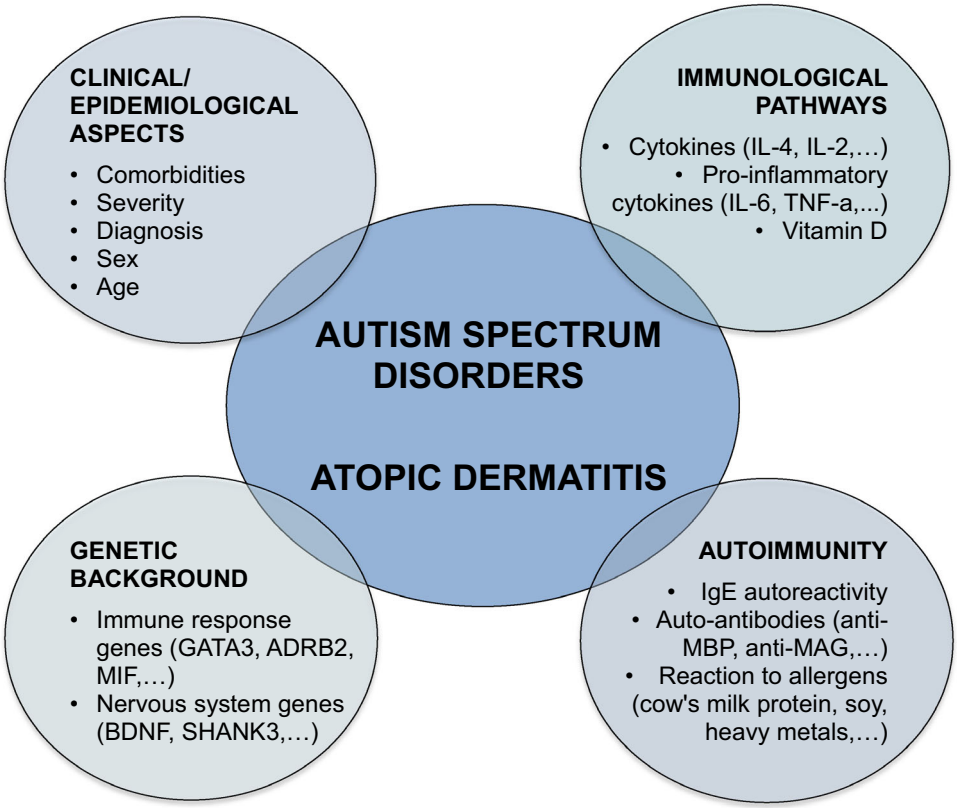


**Fig. 2** Factors of associations between autism spectrum disorders and atopic dermatitis. *IG* immunoglobulin, *IL* interleukin, *MAG* myelin-associated glycoprotein, *MBP* myelin basic protein, *TNF* tumor necrosis factor

38, 40–47]. Although this is the general result of the review, some studies are going in the opposite direction [31–34, 39]. Moreover, the entity of the association is somewhat inconsistent among the different studies.

In most of the studies, the association between AD and ASD was assessed using a univariate or multivariate analysis to estimate the prevalence of AD in ASD compared with a control group. The frequencies of AD in ASD, among the studies that found a positive association, were very different in the various studies and ranged from 7 % [37] to 64.2 % [42].

Using ORs or HRs, only a few studies estimated the risk of developing ASD associated with the presence of AD in the child or the mother, but again the ratios of this association ranged broadly among the studies. Indeed, three studies found a weak association with OR below 2 and a nonsignificant *p* value [39, 42, 47], and four studies [30, 40, 41, 43] found a moderate or strong association with OR ranging from 1.52 [43] to 7.17 [40] and a significant *p* value. In two studies [44, 45], OR or HR were not only provided for AD but also for the full set of atopic disorders. In both cases, the association between atopic disorders and ASD was strong, with a *p* value $<0.001$ and HR of 3.4 in Chen et al. [44], and OR of 1.24 in Lin et al. [45]. This finding may suggest that the presence of multiple atopic conditions in the subject increases the risk of ASD.

In one study [30], separate ORs were calculated according to AD severity, and a stronger association was found with increasing AD severity. This result may partially explain the inconsistent results of the previous studies. It is possible that calculating the OR without taking into account the severity of AD in children may underestimate the calculated risk of developing ASD. On the other hand, it should be considered that ASD severity and ASD symptoms also seem to be correlated with the prevalence of AD, as suggested in the studies by Mostafa et al. [35–37], who found a positive correlation between ASD severity and prevalence of AD, and in the study by Shibata et al. [42], who showed a positive association between AD and some of the core behavioral symptoms of ASD. Furthermore, some evidence shows that comorbidity with ADHD has an additive effect on the risk of atopic diseases in children with ASD [45].

Taking all these aspects into account, it becomes particularly relevant for study replication to use consistent criteria for sample selection and clinical assessment of the two conditions examined, i.e. ASD and AD. In the studies reviewed, the methods used to define ASD and AD are quite heterogeneous. ASD is evaluated in most of the studies using parent-, self-, and/or teacher-rated questionnaires on mental health problems not always specific for ASD, without confirming the diagnosis with validating

criteria. Only a few studies used standardized diagnostic criteria such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) [32–35, 38] or the Childhood Autism Rating Scale (CARS) [35–37]. These different approaches may have over-, under- or misestimated the diagnosis of ASD, concurring with biased results. In most cases, AD has been evaluated using parental reporting [30, 32, 40–42, 47], in some studies it has been estimated by a dermatological assessment but using nonspecific criteria [33, 38, 43–45], and in some studies the method of evaluation has not been specified [31, 39, 46]. AD has been assessed using standardized criteria in only four studies [34–37]. According to two past studies [49, 50], parental reports of doctor-diagnosed 'eczema' have acceptable sensitivity and specificity for the estimation of AD prevalence. Despite this evidence, it is difficult to exclude a priori that the heterogeneous criteria used for AD assessment may have a sporadic influence on the results.

Other factors may have influenced the estimated prevalence or ORs of the reviewed studies. First, the study populations are quite different, mainly in terms of sample size and age range. Age range is particularly important for AD prevalence estimation as AD typically starts early in the first few years of life and attenuates gradually. In affected children, 45 % develop the condition during the first 6 months of life, 60 % manifest symptoms during the first year of life, and up to 85 % present AD before 5 years of age. Approximately half of the children display a complete resolution of AD symptoms by the age of 7 years, and 60 % of cases resolve the condition by adulthood [17]. Consistent with this observation, the studies that enrolled children within an age range of 0–7 years found a higher prevalence of AD in the ASD group [40, 42].

Sex is another factor that can influence the prevalence of AD, as shown by Zerbo et al. [39]. In their study, the authors made a stratified analysis by sex and found that the associations between the different immune conditions and the risk of ASD is influenced by sex. In particular, a strong female bias in AD was found. Mostafa et al. [35] confirmed this finding, showing that the frequency of allergic conditions (AD, asthma and AR) was higher in girls with ASD than in boys with ASD. The sex differences observed in these studies seem to contrast with the fact that ASD effects vastly more males than females [51] and need to be verified with larger studies.

Geographical distribution can also influence the prevalence of both AD and ASD. Urban and metropolitan living may be associated with AD [21], in turn linked by some authors to the 'hygiene hypothesis' [52]. Geographical distribution of ASD is less clear, although there is some evidence towards an urban versus rural distribution [53, 54].

Finally, some studies hypothesize a possible association between handedness, neurodevelopmental disorders such as ASD, and immune conditions such as AD [55, 56]. They follow the hypothesis [57–59] that higher levels of testosterone during fetal development may act independently on both the thymus and the brain—the left hemisphere specifically—since it matures later than the right hemisphere and is more likely to be affected by an adverse environment for a longer period of time. However, these studies are still very preliminary and to date have provided inconsistent and contradictory results.

### 4.2 Genetic Background

Both AD and ASD are complex multifactorial conditions with a substantial genetic component [60–62]. The possibility of sharing vulnerability genes in individuals with AD and ASD may contribute to explaining the observed co-occurrence of the two conditions.

AD is known to be a multifactorial heterogeneous genetic disease occurring as a result of genetic–environmental factor interactions. A number of twin studies suggested a wide range of concordance rates, varying between 0.23 and 0.86 for monozygotic twins and between 0.15 and 0.5 for dizygotic twins [63–67]. Furthermore, total serum IgE levels showed a heritability of approximately 50 % [64, 65]. This evidence indicates the importance of genetic components in AD.

Indeed, early genome-wide linkage studies, association studies, and high-throughput expression profiling studies have revealed a complex network of genes associated with AD, which are related to skin barrier dysfunction in conjunction with innate and adaptive immune response [60, 68].

Genetics underpinning ASD are even more complex and heterogeneous. The phenotypic expression of these genetic components is also highly variable, ranging from fully penetrant point mutations to polygenic forms with multiple gene–gene and gene–environment interactions [69]. Some of the genes associated with AD have also been identified as candidate genes in ASD.

For example, GATA-3 is a gene associated with AD within the immune response pathway specifically involved in the differentiation of several cell types, including Th2 cells and serotonergic and sympathetic neurons, as in the synthesis of neurotransmitters and hormones [70–72]. Interestingly, the same pathways are likely to be involved in the etiology of ASD in humans or autism-like behaviors in animal models [73, 74]. Another candidate gene is ADRB2, coding for the β2-adrenergic receptor, a G-protein-coupled receptor that is expressed ubiquitously and influences many pathological states. The Glu27 allele of ADRB2 (β2-adrenergic receptor) has been associated with ASD [75, 76], and polymorphism in ADBR2 has also been linked to AD [77].

Macrophage migration inhibitory factor (MIF), which has a role in coding a cytokine involved in immunoregulation and inflammation at various levels [78, 79], has also been associated with both ASD and AD. MIF shows polymorphisms at its promoter level, associated with ASD [80], while elevated levels of MIF have been found in the SC of AD lesions [81].

A more relevant common gene to AD and ASD is the brain-derived neurotrophic factor (BDNF) gene, which plays an important role in neurogenesis, cortical lamination, synaptic plasticity, and neuron survival [82, 83]. Several studies, directly or indirectly, suggest an involvement of BDNF in ASD, usually showing that BDNF levels in the blood, serum and brain are increased in children with ASD compared with TD children [84].

Another possible example of the genetic association between ASD and AD is provided by the results of the case-report by Chen et al. [85]. These authors identified a deletion of chromosome 22q13.2 → qter in a boy with ASD, AD and elevated IgE levels. This region contains the SHANK3 gene, which has been associated with T-cell immune response [86], as well as with ASD [69, 87]. SHANK3 is predominantly expressed in the cerebral cortex and cerebellum, and functions as a master organizer of the postsynaptic density. ASD subjects with mutations of this gene are characterized by severe language impairment, often accompanied by intellectual disability and neurodevelopmental delay [69]. This study provides evidence that the 22q13 chromosome deletion syndrome may be associated with immune system dysfunction in addition to ASD.

Furthermore, findings from mothers with AD may also support the hypothesis of a genetic vulnerability triggered by environmental factors. Indeed, in the study by Larsson et al. [47] a significant association between maternal AD and the risk of developing ASD was observed. In the study by Croen et al. [46], no significant difference in AD prevalence in relation to ASD in the offspring was found after adjusting for confounding variables. Nevertheless, the authors observed that AD during pregnancy was more strongly associated with ASD in multiplex families with more than one ASD child affected, suggesting that genes underlying atopy may also be etiologically related to autism.

### 4.3 Immunological Pathway

The association between AD and ASD can also be partially explained in terms of immunological dysregulation, which seems to characterize the pathogenesis of both the disorders.

AD is a systemic chronic immunologic disorder with increased propensity toward inflammatory response [18]. Initiation of the atopic response in AD involves the uptake and processing of allergens by LCs after penetration through the compromised epithelial barrier. The activated LCs then migrate to skin and IL-4 promotes Th2 differentiation. Keratinocytes produce chemokines which recruit Th2 cells and eosinophils to the skin. In turn, the enhanced inflammatory response may complicate AD with bacterial infections. Staphylococcal exotoxins activate LCs to produce inflammatory mediators, including IL-1β and tumor necrosis factor (TNF)-α [88]. In some cases AD is characterized by an increase in IgE levels, which is responsible for antigen presentation [18].

Some evidence has shown that proinflammatory cytokines and cytokines that are produced during atopic response play an important role in the pathophysiology of ASD, and suggests that dysregulation of the inflammatory pathway may affect the central nervous system (CNS) and be involved in the pathophysiological mechanisms of this neurodevelopmental condition [89–92].

Indeed, it seems that proinflammatory cytokines would penetrate the blood–brain barrier [93] and activate neuroimmunological mechanisms involving some specific neural circuits (i.e. anterior cingulate gyrus and insula) related to behavioral and emotional modulation [92, 94]. Mast cells activated by allergic, environmental, immune, neurohormonal, stress, and toxic triggers seem to be responsible for the release of mediators that could disrupt the blood–brain barrier, thus contributing to the pathogenesis of ASD [95, 96].

Croonenberghs et al. found a significant trend toward an increased production of IL-6 and TNFα in children with ASD [89]. Wei et al. suggested that IL-6 was significantly increased in the cerebellum of ASD subjects, and altered the neural cell adhesion, migration and synaptic formation [90]. Singh et al. found a significant elevated concentration of serum IL-2 in children with ASD compared with healthy control children or children with mental retardation [91].

A few functional magnetic resonance imaging (fMRI) studies have shown how proinflammatory cytokines activated during atopic disease pathogenesis can influence brain activation. Ishiuji et al. found that subjects with AD showed a bilateral activation of the anterior cingulate cortex, posterior cingulate cortex, and dorso lateral prefrontal cortex, as well as contralateral activation of the caudate nucleus and putamen [92]. These authors also found a significant correlation between percentage changes in brain activation and severity of AD [92]. These results suggest the role of inflammation in modulating brain activity and may explain the possible link between AD and other atopic disorders, and the brain dysfunction of ASD.

In the study by Molloy et al. [32], a higher level of cytokines was found in ASD subjects compared with TD subjects. However, AD, as well as other atopic disorders,

was not significantly increased in the ASD group compared with the TD group. Nonetheless, the sample size was quite small and the diagnosis of atopic disorders was made on the basis of parental reports, therefore it might be misestimated.

Immunological dysregulation can lead to GI problems and FA, two conditions that are potentially associated with both AD and ASD [18, 97]. In particular, GI symptoms in ASD have been associated with abnormal immune function or elevated intestinal permeability [97]. Recently, a mouse model of ASD has been developed in which, for the first time, evidence of specific gut-related problems has been shown [98]. In addition, gut problems in ASD are also related to deviation in the establishment and maintenance of the gut microbiome [97]. An imbalance of the microbiome community can also determine pathological conditions of the skin, such as AD [99]. In particular, studies have shown that *Staphylococcus aureus* (*S. aureus*), a bacterium associated with certain GI diseases, is present on the skin of 90 % of patients who suffer from AD, while it is very rare on the skin of individuals who are not affected by the disease [100, 101]. In addition to *S. aureus*, *S. epidermidis* is also involved in the skin microbiome. The latter can produce molecules that selectively inhibit *S. aureus*, suggesting an antagonistic relationship; the two bacteria may also mutualistically interact to strengthen their intestinal colonization [100, 102].

In three of the reviewed studies [33–35], GI problems were also evaluated, together with AD in ASD subjects, with inconsistent results. In the studies by Jyonouchi et al. [33, 34], no correlation between AD and ASD was found but GI symptoms were found to be increased in the ASD group compared with the control group [34]. In the study by Mostafa and colleagues [35], where allergic manifestations were increased in children with ASD compared with TD children, GI symptoms were present in half of the children with ASD and were positively associated with allergic manifestations.

An increased prevalence of type I hypersensitivity reactions to foods in subjects with AD is also well-established [25]. In addition, some evidence suggests that certain foods, particularly foods containing gluten and casein, may worsen GI symptoms and behavioral symptoms in ASD subjects [103]. In four of the reviewed studies, FA was evaluated in ASD subjects [33, 34, 40, 41].

In two studies, despite a nonsignificant increase of AD in the ASD group, FA was shown to be associated with ASD [33, 34], while in the other two studies, AD was found to be significantly associated with ASD; the incidence of FA was also found to be higher in the ASD group compared with the control group of healthy individuals [40, 41].

Vitamin $D_3$ ($VD_3$), the most common form of vitamin D (VD) in humans, has an important role in immune function regulation. In the macrophages, $VD_3$ acts locally as a cytokine, stimulating the innate immune system and showing potent immunomodulatory properties at both cellular and molecular levels [104]. VD is able to enhance regulatory T (Treg) cell subsets, which in turn have shown therapeutic potential effects for treating a range of immune-mediated conditions in humans [104].

Recently, maternal/neonatal VD, in particular $VD_3$, deficiency has been proposed as a possible environmental risk factor for ASD [105, 106] due to its involvement in early brain development [107], immune system modulation [108], and gene regulation [109].

Moreover, a growing body of literature has linked VD deficiency with allergic diseases, particularly AD [110–112]. The metabolism of VD begins with absorption into the skin as $VD_3$. According to Liu et al. [113], a deficiency in VD production may increase the susceptibility to microbial infections. Similarities in $VD_3$ deficiency in AD and ASD, as well as the link with the innate immunity system, may support the hypothesis of an association between the two diseases. VD was measured in only one of the reviewed studies [31], and VD levels were found to be significantly decreased in the majority of subjects presenting a higher prevalence of AD. However, in this study, the rate of ASD was quite low in the population, and no inferences on $VD_3$ deficiency and ASD could be made. Further studies evaluating both AD and $VD_3$ in ASD should be conducted to elucidate the association among the different factors.

### 4.4 Autoimmunity

Autoimmunity is another mechanism that has an important role in the pathophysiology of both ASD and AD.

A connection between AD and autoimmunity has been hypothesized [18]. An increased incidence of autoimmune disorders was observed in atopic children, especially those with GI symptoms after milk ingestion [114]. More recently, atopy was disclosed as a risk factor for thyroid autoimmunity in children. It has been shown that AD patients exhibit IgE autoreactivity to human proteins in a variety of cell and tissue types [115]. The level of IgE autoantibodies is associated with the severity of disease [18]. These findings suggest autoimmunity as a mechanism in the pathogenesis of AD.

Furthermore, autoimmunity to CNS may have a pathogenic role in ASD [116, 117], which may be indicated by the presence of circulating brain-specific autoantibodies in some autistic children [118–124]. Immune response to some allergens may play a pathogenic role in a subgroup of ASD subjects through the induction of an autoimmune reaction to the CNS [117]. Allergy-induced ASD is an area of research wherein immune responses to some proteins

may play a causal role in ASD [125]. A significant improvement in the behavioral symptoms of autistic patients after an 8-week period of milk- and wheat-free diet, with a subsequent worsening of behavioral symptoms after food reintroduction, has been reported in literature [103]. In addition, some evidence suggests that immune response to *Hevea brasiliensis* (Hev-b) proteins, present in natural rubber latex (NRL), may induce cross-reactivity mechanisms and elicit IgE-secreting lymphocytes to form antibodies targeted to some endogenous (e.g. brain) and exogenous (e.g. food) proteins through cross-reaction mechanism [125].

The mechanism by which allergy may have a role in autism is possibly through the induction of the production of brain-specific autoantibodies secondary to exposure to allergens. Allergic responses in children with ASD have been associated with an increased number of Th2 cells [117], which in turn stimulates B lymphocytes to produce antibodies to allergens [126] that may cross-react with sequence homologies with brain, resulting in neuronal damage with subsequent release of neuronal antigens. The neuronal antigens release may finally result—in a cascade process—in an autoimmune reaction through the activation of inflammatory cells in genetically susceptible individuals [117, 127]. Environmental allergens include food allergies to certain peptides such as gliadin, cow's milk protein and soy [128], infectious agents [117], heavy metals exposure [129], and *Heavea brasiliensis* proteins in NRL [125].

Three of the studies included in this review have analyzed the association between atopic disease and autoimmunity in ASD. In one study [35], an increased prevalence of autoantibodies was found in subjects with ASD compared with TD subjects, with a strong correlation between ASD severity and the presence of AD and other atopic disorders. In the study by Chen et al. [43], an increased vulnerability to autoimmune diseases, together with an increased incidence of AD and other atopic conditions, was found in the ASD group compared with the TD group. Finally, in the study by Croen et al. [46], several autoimmune conditions were evaluated in the mothers of both ASD and TD children, and psoriasis prevalence, together with AD and other atopic diseases, was found to be elevated in mothers of children with ASD compared with mothers of TD children.

Overall, these considerations suggest that the hypothesis of an autoimmune component of both ASD and AD warrants further investigation. Such autoimmunity may be triggered in both conditions by environmental allergen exposure. Therefore, skin testing for common environmental allergen extracts should be considered for allergic ASD subjects for possible identification of the allergens. Immunoprophylaxis or immunotherapy could be investigated as potential target interventions in allergic ASD subjects.

### 4.5 Implications for Future Research

Taken together, these results support the hypothesis of a co-occurrence of AD and ASD. Nevertheless, more rigorous study designs and longitudinal studies are needed to clarify the causal relationship between these two conditions. Thus far, the study designs of the reviewed studies were quite heterogeneous and most of the studies discussed were surveys or case-control studies.

The longitudinal study design is the more appropriate to observe the impact of AD in early life on the development of ASD later in life. At present there is only one longitudinal study [44] whose results seem to confirm the hypothesis that atopic diseases in childhood increase the risk of developing ASD in later life. However, these results contrast with the study by Zerbo et al. [39] who did not find any relationship between the timing of allergy diagnosis and ASD. These differences may be due, among other factors, to the specific temporal window considered in the follow-up, and to the time of ASD diagnosis.

In both studies, all atopic diseases were evaluated before and after the ASD diagnosis, but the temporal sequence of the occurrence of the different atopic disorders was not investigated. In addition, atopic diagnoses before the age of 3 years were excluded. Since AD is the first of the atopic diseases to develop [16, 17], with a peak of incidence between the first and fifth year of life, it would be interesting to direct future research to the first years of life in order to investigate whether the occurrence of AD might be an early marker of the association between atopic conditions and ASD.

## 5 Conclusions

Overall, the results of this systematic review seem to reveal an association between ASD and AD, suggesting that subjects with ASD have an increased risk of presenting with AD compared with TD controls, and vice versa. The association between the two conditions is supported by clinical/epidemiological aspects, shared genetic background, and common immunological and autoimmune processes. Nevertheless, the variability in study population and design, and the presence of other risk factors acting as confounding factors, likely contribute to the inconsistent results. Further studies are needed to clarify the underlying pathophysiologic mechanism explaining the association between ASD and AD, and to explore the causal association between the two conditions, i.e. if AD in early life could increase the risk of developing ASD in childhood.

Ideally, these studies should be longitudinal, interdisciplinary, rigorous for study design and both ASD and AD diagnostic criteria, include genetic, clinical and biological measures.

Given that the prevalences of AD and ASD are consistently and progressively increasing in childhood over time, with a great impact on public health, a better understanding of the association between the two conditions might be potentially useful to investigate whether early targeted interventions directed to the shared genetic and biological factors—which seems to increase the susceptibility to AD and ASD in early infancy—would be effective in reducing the symptoms of ASD in later life.

**Compliance with Ethical Standards**

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