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Review

Family history of autoimmune diseases is associated with an increased risk of autism in children: A systematic review and meta-analysis

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ABSTRACT

Background: We conducted a systematic review and meta-analysis to summarize the current evidence on the relationship between family history of autoimmune diseases (ADs) and risk of autism in children, as current evidence suggests inconsistent results.
Methods: We identified relevant studies by searching PubMed, EmBase, and Web of Science databases up to Dec 2014. Risk estimates from individual studies were pooled using random-effects models. Subgroups analyses were conducted by some study-level factors. Publication bias was assessed by funnel plots, Egger's regression test and Begg–Mazumdar test.
Results: A total of 11 articles were included in the meta-analysis, including 3 cohort studies, 6 case-control studies, and 2 cross-sectional studies. The meta-analysis showed that family history of all ADs combined was associated with a 28% (95% CI: 12–48%) higher risk of autism in children. For some specific ADs, evidence synthesis for risk of autism in children showed a statistically significant association with family history of hypothyroidism (OR = 1.64, 95% CI: 1.07–2.50), type 1 diabetes (OR = 1.49, 95% CI: 1.23–1.81), rheumatoid arthritis (OR = 1.51, 95% CI: 1.19–1.91), and psoriasis (OR = 1.59, 95% CI: 1.28–1.97). The results varied in some subgroups.
Conclusion: An overall increased risk of autism in children with family history of ADs was identified. More mechanistic studies are needed to further explain the association between family history of ADs and increased risk of autism in children.

Contents

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1. Introduction

Autism is a neurologic disorder characterized by impairments in social interaction and communication along with restricted, repetitive, and stereotyped patterns of behaviors, interests, and activities (Lord et al., 2000). The prevalence of autism is about 1–2 per 1000 children worldwide and it occurs about four times more often in boys than girls (Danasekaran et al., 2014), which has greatly increased the burden for both the family and society. While many aspects of autism remain poorly understood, major advances have been made in terms of highlighting the role of genetic and environmental factors in its etiology.

Altered autoimmune responses have been reported among children with autism (Ashwood et al., 2006), as well as among their parents (Croen et al., 2005) and other family members (Sweeten et al., 2003). Immunogenetic research shows that genes long implicated in autoimmune diseases (ADs) such as rheumatoid arthritis (RA) and systemic lupus erythematosus are associated with autism (Fielder et al., 1983; Stastny, 1978; Warren et al., 1992). However, evidence from observational and epidemiological studies suggests an inconsistent relationship between family history of ADs and risk of autism in children. Some human studies suggest that family history of ADs such as hypothyroidism, type 1 diabetes and RA was associated with higher risk of autism (Comi et al., 1999; Keil et al., 2010), while other studies failed to find this association (Chonchaiya et al., 2010; Mouridsen et al., 2007).

Prevention will entail detecting infants at risk before the full syndrome is present and implementing treatments designed to alter the course of early behavioral and brain development (Dawson, 2008). Therefore, for the prevention of childhood autism, it is crucial to investigate how the disease is impacted by family history of ADs. If family history of ADs is indeed associated with childhood autism, prevention should be made by early intervention to such children. To our knowledge, no quantitative review has been undertaken previously to summarize the relationship between family history of ADs and childhood autism. We therefore conducted a systematic review and meta-analysis of the evidence for the relation between family history of ADs and risk of autism in children.

2. Methods

2.1. Search strategy and eligibility criteria

We followed the guidelines published by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group to complete the meta-analysis (Table S1) (Stroup et al., 2000). A systematic literature search of PubMed, EmBase, and Web of Science for identification of articles published between 1965 to Dec 2014 was performed by two investigators (SW and YD). We selected synonymous terms and used these to develop the search strategy (Panel S1). No language restriction was imposed. In addition, we also manually reviewed the references of all retrieved articles and recent reviews to identify relevant studies.

The eligible studies should meet the following inclusion criteria: (1) the study population consisted of children with infantile autism or autism spectrum disorder (ASD); (2) examination of family history of ADs as the variable of interest; (3) the association between family history of ADs and autism/ASD was assessed; and (4) presented risk estimates with confidence intervals (CIs) or sufficient information to calculate these. Cross-sectional, cohort, and case-control studies were all included in the analysis. Animal experiments, review researches and mechanistic studies were excluded from the analysis.

2.2. Data extraction and study quality evaluation

Study characteristics were extracted independently by two researchers (FW and JH). We extracted risk estimates (95% CI) for different family members separately when possible. If a study reported more than one measure of ADs, each AD was extracted separately. The most adjusted estimate was included when a study reported more than one risk estimate. The quality of each study was assessed by two researchers (FW and PM), using the Newcastle–Ottawa Scale recommended by Wells and colleagues (Wells et al., 2011).

2.3. Statistical analysis

The random effects model was used in this meta-analysis to take into account heterogeneity among studies, because the study design and measuring time were different across studies. The *I*-squared (I^2) statistic and *Q*-statistic were used to explore the heterogeneity among studies. Large I^2 (>50%) or $P < 0.10$ for *Q*-statistic suggests substantial heterogeneity among studies. We used funnel plots to visually assess the publication bias. Egger's regression test (Egger et al., 1997) and Begg–Mazumdar test (Begg and Mazumdar, 1994) were used to further assess publication bias. Subgroup analyses were performed according to the source of family history, outcome, design and adjustment, to test the possible impact factors. Statistical analyses were conducted using Stata Version 12.0 software (Stata Corp, College Station, TX).

3. Results

3.1. Search results

The article selection procedure is shown in Fig. 1. Briefly, 149 articles were screened after excluding the duplicate articles. We excluded 112 articles by screening title and abstract and assessed 37 full-text articles for eligibility. Finally, a total of 11 articles met the inclusion criteria and were included in the meta-analysis, including 3 cohort studies (Andersen et al., 2014; Atladottir et al., 2009; Roman et al., 2013), 6 case-control studies (Comi et al., 1999; Croen et al., 2005; George et al., 2014; Keil et al., 2010; Mostafa and Shehab, 2010; Mouridsen et al., 2007), and 2 cross-sectional studies (Chonchaiya et al., 2010; Valicenti-McDermott et al., 2006). All relevant studies identified were published in the English language. Characteristics of these 11 studies are provided in Table 1, and Tables S2–S4 present the quality assessment of the included studies in detail. The pooled relative risks of autism were calculated for family history of all ADs combined and some specific ADs (hypothyroidism, type 1 diabetes, RA, and psoriasis). Relative risks for other specific ADs were not calculated due to insufficient data.

Table 1
Study included in the systematic review and meta-analysis.

Study	Study site	Study period	Study design	Source of the study population	*n*	case-control ratio	Exposure	Outcome	Measure of effect	OR (95% CI)	Factors adjusted for
Andersen et al. (2014)	Denmark	1991–2004	Cohort	Danish nationwide registers	857,014	–	Father with hypothyroidism	ASD	HR	0.90 (0.57–1.44)	Birth weight, gestational age, Apgar score, and maternal psychiatric disease, pre-eclampsia/eclampsia, and diabetes
							Mother with hypothyroidism	ASD	HR	1.30 (1.11–1.53)	Gender, year of birth, and maternal variables including age, origin, residence, cohabitation, income, and parity
Atladottir et al. (2009)	Denmark	1993–2004	Cohort	Danish civil registration system	689,196	–	Family members with all ADs combined	ASD	IRR	1.04 (0.91–1.19)	Age, gender, calendar year, place of birth, and ages of the mother and father at the time of the child's birth.
							Father with all ADs combined	ASD	IRR	1.04 (0.83–1.29)	
							Mother with all ADs combined	ASD	IRR	1.02 (0.85–1.22)	
							Family members with type 1 diabetes	ASD	IRR	1.04 (0.77–1.38)	
							Father with type 1 diabetes	ASD	IRR	1.32 (0.90–1.85)	
							Mother with type 1 diabetes	ASD	IRR	0.93 (0.52–1.51)	
							Family members with RA	ASD	IRR	1.32 (0.88–1.90)	
							Mother with RA	ASD	IRR	1.70 (1.07–2.54)	
							Family members with psoriasis	ASD	IRR	1.41 (0.96–1.98)	
							Father with psoriasis	ASD	IRR	1.43 (0.78–2.35)	
							Mother with psoriasis	ASD	IRR	1.55 (0.91–2.45)	
							Family members with all ADs combined	Infantile autism	IRR	1.20 (0.95–1.50)	
							Father with all ADs combined	Infantile autism	IRR	1.42 (0.99–1.97)	
							Mother with all ADs combined	Infantile autism	IRR	1.07 (0.76–1.46)	
							Family members with type 1 diabetes	Infantile autism	IRR	1.78 (1.16–2.61)	
							Father with type 1 diabetes	Infantile autism	IRR	1.85 (1.02–3.06)	
							Mother with type 1 diabetes	Infantile autism	IRR	2.14 (1.07–3.77)	
							Family members with RA	Infantile autism	IRR	1.04 (0.41–2.11)	
							Family members with psoriasis	Infantile autism	IRR	1.23 (0.56–2.29)	
							Father with psoriasis	Infantile autism	IRR	2.15 (0.85–4.37)	

Chonchaiya et al. (2010)	United States	2003–2009	Cross-sectional	University of California Davis Health System	158	–	Mother with ADs	ASD	OR	1.27(0.62–2.61)	Mother's age, child's age, gender, number of offspring, whether a mother had a child before or after age 35, CGG repeat numbers, and mRNA levels.
Comi et al. (1999)	United States	Not reported	Case-control	Patients with autism associated with the East Tennessee Chapter of the Autism Society of America	102	1.2:1	Family members with ADs	Infantile autism	OR	1.91 (0.87–4.17)	None
							Parents with all ADs combined	Infantile autism	OR	5.96 (1.27–27.90)	
							Mother with ADs	Infantile autism	OR	8.82 (1.09–71.65)	
							Family members with hypothyroidism	Infantile autism	OR	1.66 (0.61–4.52)	
							Family members with type 1 diabetes	Infantile autism	OR	1.81 (0.63–5.18)	
							Family members with adult RA	Infantile autism	OR	2.06 (0.88–4.83)	
							Family members with juvenile RA	Infantile autism	OR	2.85 (0.56–14.43)	
							Family members with adult and juvenile RA	Infantile autism	OR	2.40 (1.05–5.51)	
Croen et al. (2005)	United States	1995–1999	Case-control	Kaiser Permanente outpatient clinical databases	2520	1:5	Mother with ADs	ASD	OR	1.20 (0.80–1.70)	Maternal age, maternal education, maternal race/ethnicity, and plurality
							Mother with psoriasis	ASD	OR	2.70 (1.30–5.80)	
							Mother with type 1 diabetes	ASD	OR	2.60 (0.80–7.90)	
George et al. (2014)	India	Not reported	Case-control	Recruited from the autism clinic of Child Development Centre in Thiruvananthapuram	343	0.7:1	Mother with hypothyroidism	Infantile autism	OR	4.25 (1.38–13.07)	Some confounding factors.
Keil et al. (2010)	Sweden	1977–2003	Case-control	Swedish Hospital Discharge Registry	31,920	0.04:1	Father with any ADs	ASD	OR	1.40 (1.00–2.00)	Child's age, hospital of birth, sex, and parents' ages at delivery, country of birth
							Mother with any ADs	ASD	OR	1.60 (1.10 -2.20)	
							Father with type 1 diabetes	ASD	OR	1.40 (0.80–2.20)	
							Mother with type 1 diabetes	ASD	OR	1.80 (1.00–2.90)	
							Father with psoriasis	ASD	OR	2.30 (0.70–7.60)	
							Mother with psoriasis	ASD	OR	2.20 (0.70–7.10)	

Table 1 (*Continued*)

Study	Study site	Study period	Study design	Source of the study population	*n*	case-control ratio	Exposure	Outcome	Measure of effect	OR (95% CI)	Factors adjusted for
Mostafa and Shehab (2010)	Egypt	Not reported	Case-control	Recruited from the Pediatric Neuropsychiatric Clinic, Children's Hospital, Faculty of Medicine of Ain Shams University	160	1:1	Family history of ADs	Infantile autism	OR	6.00 (2.50–14.10)	None
Mouridsen et al. (2007)	Denmark	1960–1984	Case-control	Patients attending the departments of child psychiatry in the university hospital of Copenhagen and Aarhus.	441	1:3	Father with any ADs	Infantile autism	OR	1.97 (0.84–4.64)	None
							Mother with any ADs	Infantile autism	OR	1.21 (0.6–2.46)	
							Mother with hypothyroidism	Infantile autism	OR	2.99 (0.19–48.22)	
							Father with type 1 diabetes	Infantile autism	OR	4.94 (1.37–17.85)	
							Mother with type 1 diabetes	Infantile autism	OR	1.50 (0.37–6.10)	
							Mother with RA	Infantile autism	OR	0.49 (0.06–4.12)	
Roman et al. (2013)	United states	2002–2006	Cohort	A population-based birth cohort	4039	–	Mother with hypothyroidism	Infantile autism	OR	3.89 (1.83–8.20)	Child's sex, ethnicity, gestational age at birth, birth weight, parental age, education, smoking history, prenatal psychopathology, thyroid medication during pregnancy, parity, marital status, time of thyroid sampling, and early pregnancy folate and CRP.
Valicenti-McDermott et al. (2006)	United states	Not reported	Cross-sectional	Recruited from Albert Einstein College of Medicine	146	–	Family history of ADs	ASD	OR	1.19 (0.58–2.44)	Age, sex, and ethic group
							Family history of hypothyroidism	ASD	OR	1.06 (0.34–3.30)	
							Family history of hyperthyroidism	ASD	OR	0.97 (0.34–2.73)	
							Family history of type 1 diabetes	ASD	OR	2.18 (0.42–11.24)	
							Family history of RA	ASD	OR	1.16 (0.43–3.12)	

OR = odds ratio. CI = confidence interval. ASD = autism spectrum disorder. HR = hazard ratio. IRR = incidence rate ratio. AD = autoimmune disease. RA = rheumatoid arthritis.

Table 2
Subgroup analysis for studies included in the analysis.

Subgroup analysis	Pooled OR (95% CI), I^2 statistics (%), *P*-value for the heterogeneity *Q* test, number of estimates in included studies (*n*)	
	n	Risk estimates of autism
All ADs combined		
Source of family history		
Family members	6	1.59 (1.10–2.32); I^2 = 77.5, *P* < 0.001
Father	4	1.27 (1.02–1.58); I^2 = 34.4, *P* = 0.206
Mother	7	1.20 (0.99–1.45); I^2 = 34.3, *P* = 0.166
Outcome		
ASD	8	1.12 (1.01–1.24); I^2 = 16.1, *P* = 0.304
Infantile autism	9	1.68 (1.22–2.32); I^2 = 64.8, *P* = 0.004
Design		
Cohort	6	1.08 (0.99–1.17); I^2 = 0.0, *P* = 0.542
Case-control	9	1.82 (1.32–2.50); I^2 = 55.9, *P* = 0.020
Cross-sectional	2	1.23 (0.74–2.04); I^2 = 0.0, *P* = 0.900
Adjustment for other factors		
Yes	11	1.13 (1.04–1.23); I^2 = 7.6, *P* = 0.371
No	6	2.71 (1.47–4.97); I^2 = 55.6, *P* = 0.046
Hypothyroidism		
Source of family history		
Family members	2	1.36 (0.64–2.89); I^2 = 0.0, *P* = 0.562
Father	1	0.90 (0.57–1.43)
Mother	4	2.53 (1.10–5.84); I^2 = 75.0, *P* = 0.007
Outcome		
ASD	3	1.21 (0.99–1.48); I^2 = 10.7, *P* = 0.326
Infantile autism	4	3.12 (1.86–5.25); I^2 = 0.0, *P* = 0.542
Design		
Cohort	3	1.51 (0.85–2.67); I^2 = 81.2, *P* = 0.005
Case-control	3	2.55 (1.24–5.24); I^2 = 0.0, *P* = 0.470
Cross-sectional	1	1.06 (0.34–3.30)
Adjustment for other factors		
Yes	5	1.64 (1.00–2.71); I^2 = 73.2, *P* = 0.005
No	2	1.78 (0.69–4.56); I^2 = 0.0, *P* = 0.695
Type 1 diabetes		
Source of family history		
Family members	4	1.40 (0.95–2.06); I^2 = 43.4, *P* = 0.151
Father	4	1.59 (1.14–2.21); I^2 = 32.1, *P* = 0.219
Mother	5	1.58 (1.08–2.31); I^2 = 28.9, *P* = 0.229
Outcome		
ASD	7	1.26 (1.03–1.53); I^2 = 11.7, *P* = 0.340
Infantile autism	6	1.93 (1.48–2.53); I^2 = 0.0, *P* = 0.780
Design		
Cohort	6	1.39 (1.08–1.78); I^2 = 50.1, *P* = 0.075
Case-control	6	1.77 (1.29–2.42); I^2 = 0.0, *P* = 0.582
Cross-sectional	1	2.18 (0.42–11.28)
Adjustment for other factors		
Yes	10	1.44 (1.19–1.75); I^2 = 29.0, *P* = 0.178
No	3	2.34 (1.16–4.72); I^2 = 0.0, *P* = 0.383
RA		
Source of family history		
Family members	6	1.46 (1.10–1.94); I^2 = 0.0, *P* = 0.580
Father	0	–
Mother	2	1.43 (0.61–3.33); I^2 = 21.6, *P* = 0.259
Outcome		
ASD	4	1.40 (1.08–1.82); I^2 = 0.0, *P* = 0.680
Infantile autism	4	2.08 (1.21–3.56); I^2 = 0.0, *P* = 0.561
Design		
Cohort	3	1.42 (1.08–1.86); I^2 = 0.0, *P* = 0.507
Case-control	4	2.08 (1.21–3.56); I^2 = 0.0, *P* = 0.561
Cross-sectional	1	1.16 (0.43–3.13)
Adjustment for other factors		
Yes	4	1.40 (1.08–1.82); I^2 = 0.0, *P* = 0.680
No	4	2.08 (1.21–3.56); I^2 = 0.0, *P* = 0.561
Psoriasis		
Source of family history		
Family members	2	1.37 (0.99–1.89); I^2 = 0.0, *P* = 0.735
Father	3	1.70 (1.11–2.60); I^2 = 0.0, *P* = 0.625
Mother	3	1.87 (1.27–2.76); I^2 = 0.0, *P* = 0.460
Outcome		
ASD	8	1.59 (1.28–1.97); I^2 = 0.0, *P* = 0.756
Infantile autism	0	–
Design		
Cohort	5	1.47 (1.17–1.86); I^2 = 0.0, *P* = 0.882
Case-control	3	2.49 (1.43–4.34); I^2 = 0.0, *P* = 0.948
Cross-sectional	0	
Adjustment for other factors		
Yes	8	1.59 (1.28–1.97); I^2 = 0.0, *P* = 0.756
No	0	–

OR = odds ratio; CI = confidence interval; ASD = autism spectrum disorder; AD = autoimmune disease; RA = rheumatoid arthritis.

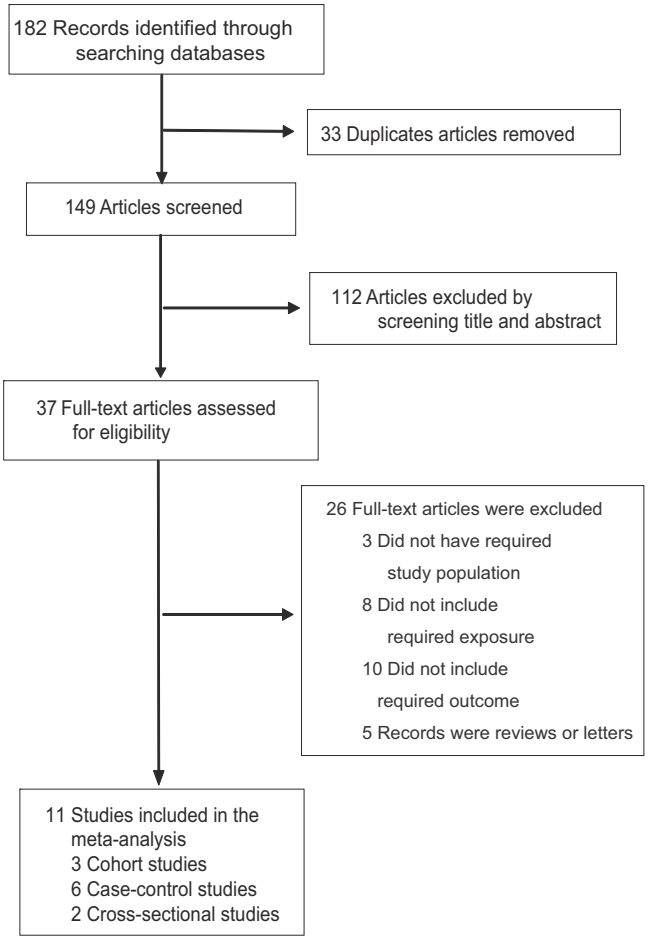

Fig. 1. Flowchart for the selection of eligible studies.

3.2. Meta-analysis: Family history of all ADs combined and risk of autism in children

In the pooled analysis, family history of all ADs combined was associated with a 28% (95% CI: 12–48%) higher risk of autism in children (Fig. 2), and there was potential heterogeneity among studies (I^2 = 56.1%, P = 0.003). Visual assessment of funnel plots (Fig. S1A) showed that the studies were distributed asymmetrically. Egger's regression test (P < 0.001) and Begg–Mazumdar test (P = 0.001) also showed that there was potential publication bias in the meta-analysis. After using the trim and fill approach, eight studies were filled and the pooled result did not reverse (OR = 1.09, 95% CI: 1.00–1.27) (Fig. S1B). In subgroup analysis, maternal ADs were not associated with childhood autism (OR = 1.20, 95% CI: 0.99–1.45) and significant relative risks were only found in case-control studies (Table 2). We found stronger effect of family history of ADs on infantile autism than on ASD in children (OR = 1.68, 95% CI: 1.22–1.45, and OR = 1.12, 95% CI: 1.01–1.24, respectively) (Table 2).

3.3. Meta-analysis: Family history of hypothyroidism and risk of autism in children

Evidence synthesis for childhood autism risk showed a statistically significant association with family history of hypothyroidism (OR = 1.64, 95% CI: 1.07–2.50) (Fig. 3), and there was potential heterogeneity among studies (I^2 = 61.1%, P = 0.017). We found no evidence of publication bias by visual assessment of funnel plots (Fig. S1C) and using Egger's regression test (P = 0.305) and Begg–Mazumdar test (P = 0.453). The associations between family history of hypothyroidism and risk of autism changed in some subgroups (Table 2). Significantly higher relative risks were only found in children with maternal hypothyroidism (OR = 2.53, 95% CI: 1.10–5.84) and in case-control studies (OR = 2.55, 95% CI: 1.24–5.24) (Table 2). The risk of infantile autism, but not ASD, was impacted by family history of hypothyroidism (OR = 3.12, 95% CI: 1.86–5.25, and OR = 1.21, 95% CI: 0.99–1.48, respectively) (Table 2).

3.4. Meta-analysis: Family history of type 1 diabetes and risk of autism in children

The pooled results showed that family history of type 1 diabetes was associated with a 49% (95% CI: 23–81%) higher risk of autism in children (Fig. 4), with no evidence of significant heterogeneity among individual studies (I^2 = 27.7%, P = 0.165). Visual assessment of funnel plots (Fig. S1D) showed that the studies were distributed a little asymmetrically. Begg–Mazumdar test showed that there was no potential publication bias (P = 0.113), but the result of Egger's regression test showed that there was potential publication bias (P = 0.024). After using the trim and fill approach, five studies were filled and the pooled result did not reverse (OR = 1.33, 95% CI: 1.09–1.62) (Fig. S1E). Subgroup analyses showed type 1 diabetes history from father and mother, but not other family members, was associated with increased risk of childhood autism (OR = 1.59, 95% CI: 1.14–2.21, and OR = 1.58, 95% CI:1.08–2.31, respectively) (Table 2). We found stronger effect of family history of type 1 diabetes on infantile autism than on ASD in children (OR = 1.93, 95% CI: 1.48–2.53, and OR = 1.26, 95% CI: 1.03–1.53, respectively) (Table 2).

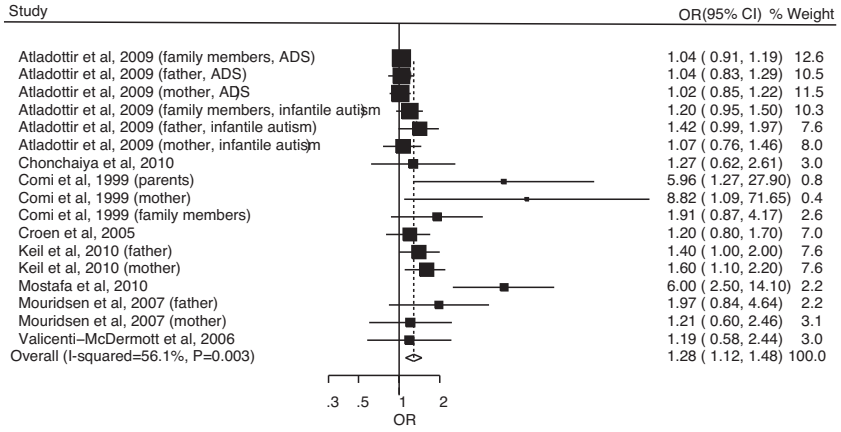

Fig. 2. Relative risk of autism in children with family history of all autoimmune diseases combined.

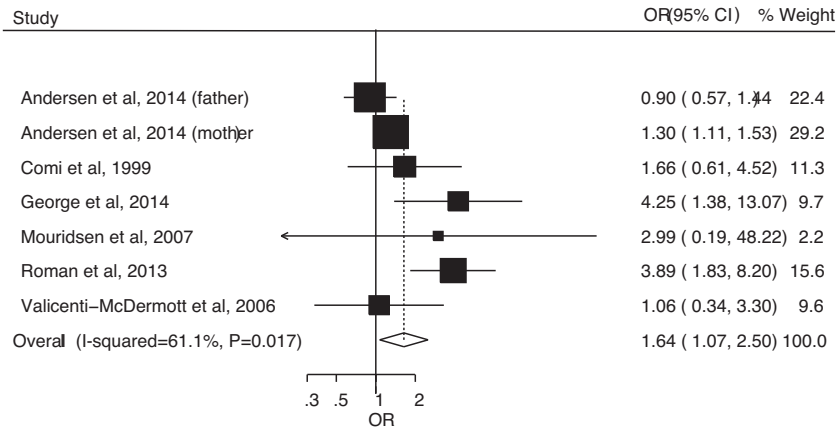

Fig. 3. Relative risk of autism in children with family history of hypothyroidism.

3.5. Meta-analysis: Family history of RA and risk of autism in children

The meta-analysis showed that family history of RA was associated with a 51% (95% CI: 19–91%) higher risk of autism in children (Fig. 5), and there was no statistically significant evidence for heterogeneity among studies (I^2 = 0.0%, P = 0.634). We found no evidence of publication bias by visual assessment of funnel plots (Fig. S1F) and using Egger's regression test (P = 0.987) and Begg–Mazumdar test (P = 1.000). In the subgroup analyses, significant relative risk was only found in family members (OR = 1.46, 95% CI: 1.10–1.94) (Table 2). Similarly, we found stronger effect of family history of RA on infantile autism than on ASD in children (OR = 2.08, 95% CI: 1.21–3.56, and OR = 1.40, 95% CI: 1.08–1.82, respectively) (Table 2).

3.6. Meta-analysis: Family history of psoriasis and risk of autism in children

The pooled results showed that family history of psoriasis was associated with a 59% (95% CI: 28–97%) higher risk of autism in children (Fig. 6), and there was no statistically significant evidence for heterogeneity among studies (I^2 = 0.0%, P = 0.756). There was no evidence of publication bias (Fig. S1G). Subgroup analyses showed psoriasis history from father and mother, but not other family members, was associated with increased risk of childhood autism (OR = 1.70, 95% CI: 1.11–2.60, and OR = 1.87, 95% CI:1.27–2.76, respectively) (Table 2).

4. Discussion

Our findings suggest an overall increased risk of autism in children with family history of ADs, whether measured by all ADs combined (28%), hypothyroidism (64%), type 1 diabetes (49%), RA (51%) or psoriasis (59%). The increased risk of infantile autism is higher than that of ASD. These findings are important since the trigger and mechanism for the underlying pathology in autism is still unknown (Gesundheit et al., 2013; Hertz-Picciotto et al., 2006; Molloy et al., 2006), and the identified risk factors may help to prevent this disease in children.

The results of the present study support the hypothesis that genetic and environmental factors contribute to autism (Deth et al., 2008; Hallmayer et al., 2011; Hertz-Picciotto et al., 2006). A previous meta-analysis found several prenatal factors were associated with autism risk, including advanced parental age at birth, maternal prenatal medication use, bleeding, gestational diabetes, being first born vs. third or later and having a mother born abroad (Gardener et al., 2009). Money et al. (1971) first proposed the association between family history of ADs and childhood autism by observing an unusually high number of ADs in a family with an autistic child. Comi et al. (1999) also reported that 66% of children with autism had at least one relative with an AD, compared to 50% of normally developing controls. However, in the majority of studies included in our meta-analysis, the relative risks of autism in children with family history of ADs were over 1 but didn't reach statistical significances. This may be due to the fact that these studies have relatively small sample size. Thus, the strengths of this meta-analysis are that

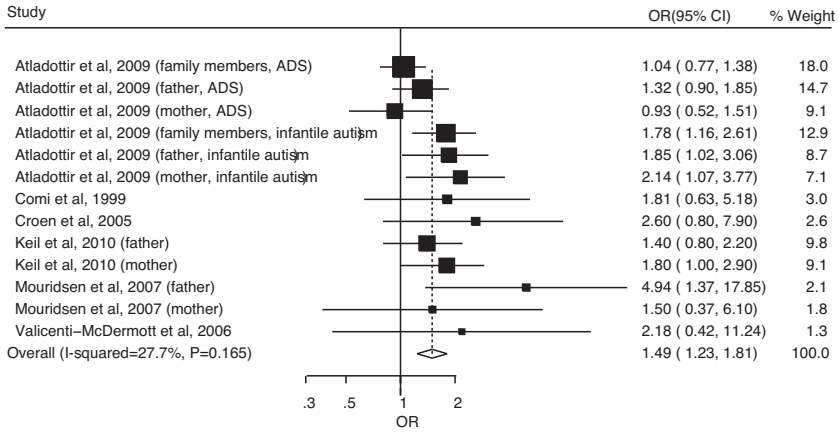

Fig. 4. Relative risk of autism in children with family history of type 1 diabetes.

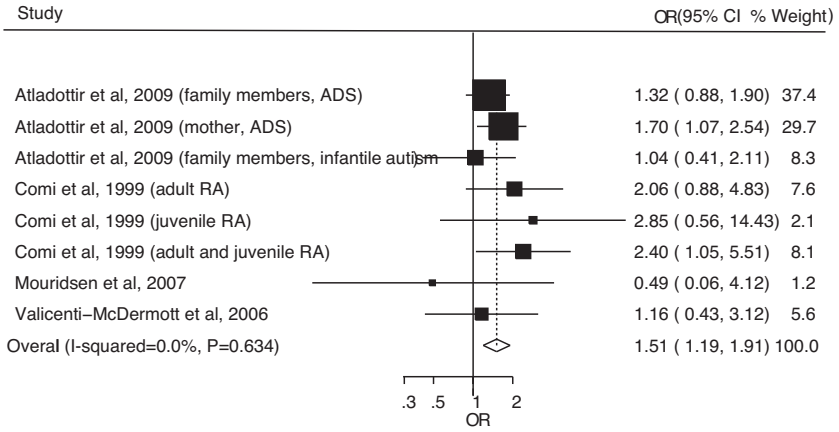

Fig. 5. Relative risk of autism in children with family history of rheumatoid arthritis.

we reviewed and included all current studies assessing the association between family history of ADs and risk of autism in children, and the pooled results were more precise with more narrow confidence intervals due to the much larger sample size, compared with each individual study. The pooled results showed that family history of ADs, no matter measured by all ADs combined or some specific ADs, was positively correlated with the risk of autism in children with statistical significances, although the most individual studies didn't reach statistical significances. Previous studies showed that family history of some other specific ADs, such as idiopathic thrombocytopenic purpura, systemic lupus erythematosus, myasthenia gravis, ulcerative colitis, rheumatic fever, and hyperthyroidism (Atladottir et al., 2009; Keil et al., 2010; Mouridsen et al., 2007; Sweeten et al., 2003), also increased the risk of autism in children, however, these diseases were not included in our study due to the insufficient data. In addition, Molloy et al. (2006) found that family history of ADs and autoimmune thyroid disease were risk factors for regression in children with ASD.

We found the strength of the increased autism risk was weaker in children when the family history of ADs was measured by all ADs combined than by a specific AD. This was not a surprising result, because different pathogenesis and etiologies apply for different ADs. Similar results were obtained by Atladottir et al. (2009) who found no general association between all ADs combined and ASD or infantile autism, but a positive association between some specific ADs and ASD or infantile autism. In the subgroup analyses, maternal ADs were not associated with childhood autism. However, history of hypothyroidism from mother, but not father or other family members, was associated with increased risk of autism. A previous study from Denmark also found maternal but not paternal hypothyroidism was associated with a higher risk of autism (Andersen et al., 2014). This may be due to the different etiologies and genetics for mother and other family members, and it may also be due to the lack of adequate studies in the subgroups of father and other family members in our meta-analysis. Thus, more studies are needed to assess the risk of autism in children with family history of hypothyroidism from father and other family members.

There are several plausible pathways by which family history of ADs might affect autism in children. Studies have implicated a role for MHC genes. It has been suggested that the MHC third hypervariable region sequences 1 and 2 are associated with both autism and RA (Comi et al., 1999; Warren et al., 1996; Weyand et al., 1995). Mostafa and Shehab (2010) indicated that C4B null allele may play an important role on autoimmunity in autism. They found C4B null allele had a significant risk for association with autism and with a family history of ADs. In addition, the MET proto-oncogene tyrosine kinase pathway which is involved in immune regulation has been shown to be associated with ASD (Campbell et al., 2010). Other studies have shown the serine and threonine kinase C gene PRKCB1 is linked to ASD (Gesundheit et al., 2013; Lintas et al., 2009). Other susceptibility genes which can alter immune function, such as macrophage inhibitory factor, NK cells, PTEN tumor suppressor gene, Reelin and mitochondrial respiratory chain diseases, have been associated with ASD (Gesundheit et al., 2013). More mechanistic studies are needed to further explain the association between family history of ADs and increased risk of autism in children.

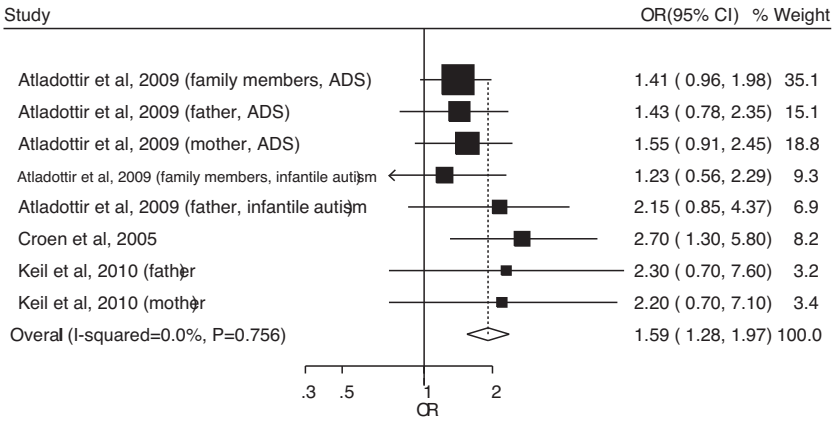

Fig. 6. Relative risk of autism in children with family history of psoriasis.

On the basis of our findings, we advocate that development programs should be an essential component of autism regression in children. It has been reported that pregnant women are more likely to suffer from RA (Silman, 1986). Another research has also indicated that pregnant women with type 1 diabetes have significantly higher prevalence of hypothyroidism and other ADs (Velkoska Nakova et al., 2010). Therefore, appropriate early intervention should be developed towards the children in high risk of autism, as the literature indicates that superior outcomes are associated with entry into intervention at the earliest possible age (Granpeesheh et al., 2009; Wallace and Rogers, 2010).

The possible publication bias is always a concern in a meta-analysis. In the present study, there was potential publication bias when assessing relative risk of autism in children with family history of all ADs combined and in children with family history of type 1 diabetes. We further applied trim and fill method to adjust for publication bias. However, results showed that the meta-analysis with or without the trim and fill did not draw different effect estimates. More importantly, the positive associations between family history of ADs and risk of autism in children appeared to be consistent across most studies. Thus, the likelihood that these findings are a result of selective publication seems to be minimal. Overall, the results of our meta-analysis are sound and reliable.

There are some limitations in our meta-analysis. First, our inference is based on observational studies, some included studies didn't make adjustment for other factors or only make adjustment for a few important factors, thus, we cannot exclude chance, residual or unmeasured confounding as alternative explanation for our findings. Second, there were potential heterogeneities in some of the analyses, and although we did random-effects and sub-group analyses, these are unlikely to have fully accounted for heterogeneity. Third, some of included studies were based on small sample size, and relied on self-response questionnaires in order to elicit the family history. This may lead to a potential recall bias. Other studies derived their information from national registries with extremely large sample size. Nevertheless, these studies have their own known limitations based on data selection, inconsistent diagnostic criteria, quality, and lack of validation. Finally, we only assessed a few specific ADs on the effect of autism in our meta-analysis, other specific ADs were not assessed due to the limited data. Therefore, further studies are needed to assess family history of other specific ADs and risk of autism in children.

In conclusion, this first systematic review and meta-analysis suggests a positive association between family history of ADs and risk of autism in children, no matter measured by all ADs combined, hypothyroidism, type 1 diabetes, RA or psoriasis. More detailed studies on the possible common genetic background of ADs and autism are suggested.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neubiorev.2015.05.004

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