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Evaluation of the Association Between Autism Spectrum Disorder and Attention-deficit/hyperactivity Disorder in the Offspring and Autoimmune and Autoinflammatory Disorders in Parents: A Systematic Review and Meta-analysis.

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ABSTRACT

Background and aim: Neurodevelopmental disorders (NDs) are types of mental disorders that affect the way the brain functions and alter neural development, causing problems in social, cognitive, and emotional functioning. Autoimmune and autoinflammatory disorders-causing factors may be involved in NDs. The present study evaluated the association between autism spectrum disorder and attention-deficit/hyperactivity disorder in the offspring and autoimmune and autoinflammatory disorders in parents.

Material and methods: All international databases (PubMed, Scopus, Science Direct, ISI, Web of Knowledge, and Embase) were searched from 2010 to May 2023 with keywords based on the objectives of the study. Data analysis using STATA/MP. v17 software was done in 95% confidence intervals.

Results: Five cohort studies and five cross-sectional studies were selected. The odds ratio of autism spectrum disorder and attention-deficit/hyperactivity disorder in the offspring between the experimental group (autoimmune and autoinflammatory disorders in the parent) and control group (healthy parents) was (OR, 0.16 95% CI 0.10, 0.22; p<0.05) and (OR, 1.28 95% CI 0.91, 1.65; p<0.05), respectively. The odds ratio of attention-deficit/hyperactivity disorder in children whose mothers had type 1 diabetes was 1.28 (OR, 1.28 95% CI 0.91, 1.65; p<0.05). The odds ratio of autism spectrum disorder in children whose fathers had type 1 diabetes was 1.09 (OR, 1.09 95% CI 0.48, 1.70; p<0.05).

Conclusions: Based on the findings of the present study, there is a positive and direct relationship between autoimmune and autoinflammatory disorders in mothers and fathers with increased risk of autism spectrum disorder and attention-deficit/hyperactivity disorder in children.

1. Introduction

Neurodevelopmental disorders (NDs) affect how the brain functions and alter neural development, causing problems in social, cognitive, and emotional functioning.[1] NDs usually start early in the developmental period, before the beginning of school age.[2] The most common NDs are autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD).[3] ASD is associated with a disability in social interactions and communication, limited and repetitive behavioral patterns, and unusual sensory sensitivities.[4] The global prevalence of autism in different regions is reported to be 100 per 10,000 children.[5] ADHD is characterized by excessive inattention, hyperactivity, and impulsivity that are pervasive, disruptive, and otherwise age-inappropriate.[6] Evidence suggests that genes and environment can determine NDs.[7] Studies have reported that environmental factors play a key role in the physiopathology of NDs.[8-10] Some studies have shown that immune-mediated events can increase the risk of developing NDs; For example, a high fever in a pregnant mother can increase the risk of NDs in children.[11, 12] Animal studies have reported that the innate immune system can be directly related to impaired brain development.[13] Autoimmune and autoinflammatory disorders (AID) can occur in 3 to 5% of the general population.[14] AID leads to tissue damage by releasing cytokines.

On the other hand, AIDS leads to the synthesis of organ-specific or systemic antibodies.14. Studies show that AIDS-causing factors may be involved in NDs.[15, 16] However, more studies are needed to confirm the evidence. Therefore, the present study aimed to determine the relationship between autism spectrum disorder and attention-deficit/hyperactivity disorder in the offspring and inflammatory disorders in parents.

2. Material and methods

Search strategy

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Systematic Review and Meta-ana is an evidence-based approach that provides an accurate and reliable report of previous research findings using the PRISMA 2020 checklist[17] as a standard tool and a systematic review of all empirical evidence with appropriate criteria to answer the question. In the current study, the use of the PECO strategy to construct the research question is specified in Table 1. The four elements of the PECO model include patient/population, exposure, comparison, and outcome. The PECO process begins with a case scenario from which a question related to the case is constructed and phrased to facilitate finding an answer.

Table 1. PECO strategy.

PECO Strategy	Description
P	Population: ASD and ADHD in the offspring
E	Exposure: AID in the parents
C	Comparison: healthy parents
O	Outcome: Positive association or negative association

All international databases PubMed, Scopus, Science Direct, ISI, Web of Knowledge, and Embase were searched from 2010 to May 2023, with keywords ("Neurodevelopmental Disorders"[Mesh]) OR ("Neurodevelopmental Disorders/etiology"[Mesh] OR "Neurodevelopmental Disorders/genetics"[Mesh] OR "Neurodevelopmental Disorders/history"[Mesh] OR "Neurodevelopmental Disorders/immunology"[Mesh])) OR "Attention Deficit and Disruptive Behavior Disorders"[Mesh]) OR ("Attention Deficit and Disruptive Behavior Disorders/etiology"[Mesh] OR "Attention Deficit and Disruptive Behavior Disorders/genetics"[Mesh] OR "Attention Deficit and Disruptive Behavior Disorders/history"[Mesh] OR "Attention Deficit and Disruptive Behavior Disorders/immunology"[Mesh])) OR "Autism Spectrum Disorder"[Mesh]) OR ("Autism Spectrum Disorder/etiology"[Mesh] OR "Autism Spectrum Disorder/genetics"[Mesh] OR "Autism Spectrum Disorder/history"[Mesh])) OR "Mental Disorders"[Mesh]) AND ("Child"[Mesh] OR "Adult Children"[Mesh] OR "Only Child"[Mesh])) AND ("Autoimmune Diseases"[Mesh] AND "Family"[Mesh]) OR "Parents"[Mesh]) OR "Fathers"[Mesh]) OR "Mothers"[Mesh].

Study selection criteria

Inclusion criteria included all studies that evaluate the association between NDs (DSM-5 definition) in the offspring and AID in the parents compared to the control group, access to the full text of the study, and the language of publication was English. The exclusion criteria included studies that assess only symptoms, incomplete results, case studies, case report studies, and review articles.

Data collection

A checklist was prepared by two independent and blind authors related to the data of the studies as a data collection tool. Then, a third independent and blind author checked both checklists and removed duplicate items. Each of the three income authors approved the final checklist. Two authors did Data extraction independently, and the information was recorded in the checklist. In case there is no agreement on a specific issue, the third referee's opinion was considered a criterion. The checklist included the author's name, year of publication, study design, Type of NDs, Type of AID, Number of NDs, Number of NDs with parents that have AID, and the number of control groups.

Risk assessment

Newcastle-Ottawa Scale (NOS)[18] was used to assess the quality of the cohort and cross-sectional, case-control, and case series studies. This scale measures three dimensions (selection, comparability of cohorts, and outcome) with nine items. In the analysis, any studies with NOS scores of 1-3, 4-6, and 7-9 were defined as low, medium, and high quality, respectively.

Data analysis

Data analysis using STATA/MP. V17 software was done in 95% confidence intervals. The odds ratio was calculated using the fixed effect model with the Mantel–Haenszel method. In addition, to check the heterogeneity between the studies, the chi-square test was used, and the I^2 coefficient value is less than 50% as low heterogeneity; Between 50 and 75% was considered moderate heterogeneity, and above 75% was high heterogeneity.

3. Results

Study selection

First, a search was conducted using keywords in international databases, and 1132 articles were found, all entered into End.Note.X8 software: Duplicate articles and records marked as ineligible by automation tools and for other reasons were removed. The abstracts of 793 articles were reviewed, and according to the inclusion and exclusion criteria, 739 studies were excluded, and the full text of 54 studies was reviewed. Finally, ten studies were selected according to the objectives of the present study and included in the meta-analysis (Fig. 1).

Study characteristics

The summary of demographic data is summarized in Table 2; according to this table, five cohort studies and five cross-sectional studies were selected. Seven studies investigated the relationship between ASD and AIDS, and five investigated the relationship between ADHD and AIDS.

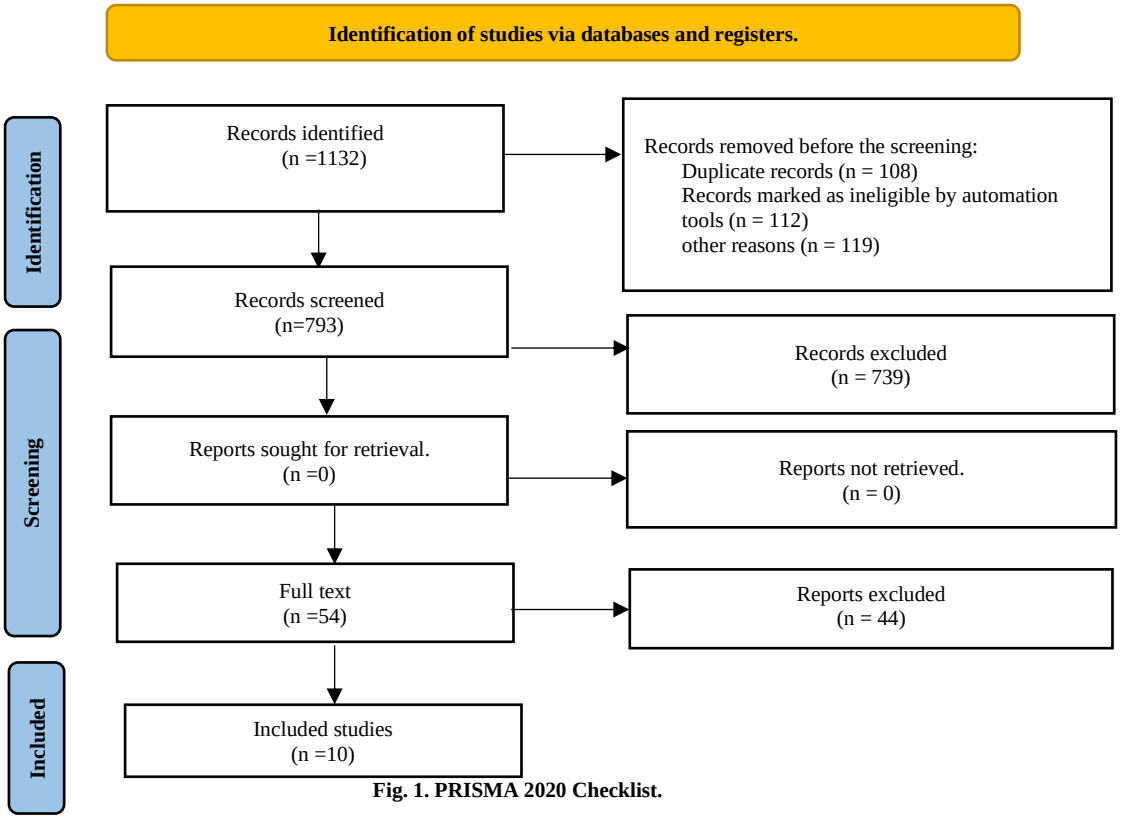

Fig. 1. PRISMA 2020 Checklist.

Table 2. Demographics and autoimmune diseases and child NDs.

Study. Years	Study Design	Type of Neurodevelop Mental Disease	Type of Autoimmune Disease	Prevalence of NDs	Prevalence of AID		Number of the Control Group	Number of Individuals with Both NDs and AID
					Mother	Father		
Hsu et al., 2023[19]	Cohort	ADHD	T1D	202	24,555		98220	Not reported
Lee et al., 2023[20]	Cohort	ADHD and ASD	Sj, SLE, RA, Ssc, Iim, T1D, MS, Mg, P, IBD, Vasculitis, AS, Behçet	ADHD: 28209 ASD:4506	1990	1327	705200	Not reported
Li et al., 2022[21]	Cohort	ADHD and ASD	RA, Sj, P, Sle, As	ADHD: 71219 ASD: 13885	35930	25247	1301156	Not reported
Hegvik et al., 2022[22]	Cross-sectional	ADHD	Celiac, Crohn, GD, MS, P, H, RA, S, Sj, T1D, Uc, Sle	118927	3069739	3053263	Not reported	5577
Spann et al., 2019[23]	Cross-sectional	ASD	Ah, celiac, DH, P, Ha, MS, On, RA, SLE, Sj, T, T1D, UC	4600	1479		5017	1479
Croen et al., 2018[24]	Cross-sectional	ASD	Ah, Celiac, Crohn, DH, P, Ha, RA, SLE, Sj, T, T1D, UC	984	322		915	380
Rom et al., 2018[25]	Cohort	ASD	RA	18200	15,615		1380829	84
Nielsen et al., 2016[26]	Cross-sectional	ADHD	SLE, UC, Crohn, P, RA, JA, AS, Addison, Celiac, PA, ITP, MS, IP, Iridocylitis, Ah, Alopecia Areata, Vitiligo, Polymyalgia Rheumatica, Mg, Sclerodermia, Sj	23645	30843		960035	1010
Andersen et al., 2014[27]	Cohort	ASD	IBD	16112	6330		1911393	62
Keil et al., 2010[28]	Cross-sectional	ASD	T1D, IBD, P, ITP, SLE, Mg, Rheumatic fever	1237	986		30925	67

ADHD: attention deficit/hyperactivity disorders; ASD: autism spectrum disorders; GD: Grave's disease; MS: multiple sclerosis; P: Psoriasis; h: Hashimoto; RA: rheumatoid arthritis; S: Sarcoidosis; Sj: Sjorgren; T1D: type 1 Diabetes; Uc: ulcerative colitis; Sle: systemic lupus erythematosus; Ah: Autoimmune hepatitis; DH: Dermatitis Herpetiformis; Ha: Hemolytic anemia; On: Optic neuritis; T: Thrombocytopenia; Sj: Sjogren; Ssc: Systemic sclerosis; Iim: Idiopathic inflammatory myositis; Mg: Myasthenia gravis; As: Ankylosing spondylitis; PA: Pernicious Anemia; IP: Idiopathic Polyneuritis; IBD: inflammatory bowel disease.

Quality of studies

According to the NOS tool, four studies had a total score of 6/9 (moderate quality), and six studies had a total score of 7/9 (high quality) (Table 3).

Association between AIDs and ASD

The odds ratio of ASD in the offspring between the experimental and control groups was 0.16 (OR, 0.16 95% CI 0.10, 0.22; $p<0.05$). Since a statistically significant difference was observed between the two groups, there is a direct relationship between AIDS and ASD. Based on I^2=44.30% ($p=0.08$), heterogeneity between studies was considered low (Fig. 2).

The odds ratio of ASD in the offspring between mothers in the experimental group and control group was 0.17 (OR, 0.17 95% CI 0.09, 0.26; $p<0.05$), and the odds ratio of ASD in the offspring between father in the experimental group and control group was 0.14 (OR, 0.14 95% CI 0.05, 0.23; $p<0.05$) (Fig. 2). Based on these findings, it was observed that there was a direct relationship between AID in fathers and mothers with ASD in children (Fig. 2). According to the test of group differences, there was no statistically significant difference between mothers and fathers ($p=0.62$).

Table 3. Risk of bias assessment (NOS tool).

Study. Years	Selection (5 scores)				Comparability (2 scores)	Outcome (2 scores)		Total Score
	Representative Sample	Sample Size	Non-respondents	Ascertainment of the Exposure	Based on Design and Analysis	Assessment of Outcome	Statistical Test	
Hsu et al., 2023[19]	1	1	1	0	2	1	1	7
Lee et al., 2023[20]	1	1	1	0	2	0	1	6
Li et al., 2022[21]	1	1	1	0	2	1	1	7
Hegvik et al., 2022[22]	1	1	1	0	1	1	1	6
Spann et al., 2019[23]	1	1	1	1	1	1	0	6
Croen et al., 2018[24]	1	1	1	0	2	1	1	7
Rom et al., 2018[25]	1	1	1	0	2	1	1	7
Nielsen et al., 2016[26]	1	1	1	0	2	1	1	7
Andersen et al., 2014[27]	1	1	1	0	2	1	1	7
Keil et al., 2010[28]	1	1	1	0	1	1	1	6

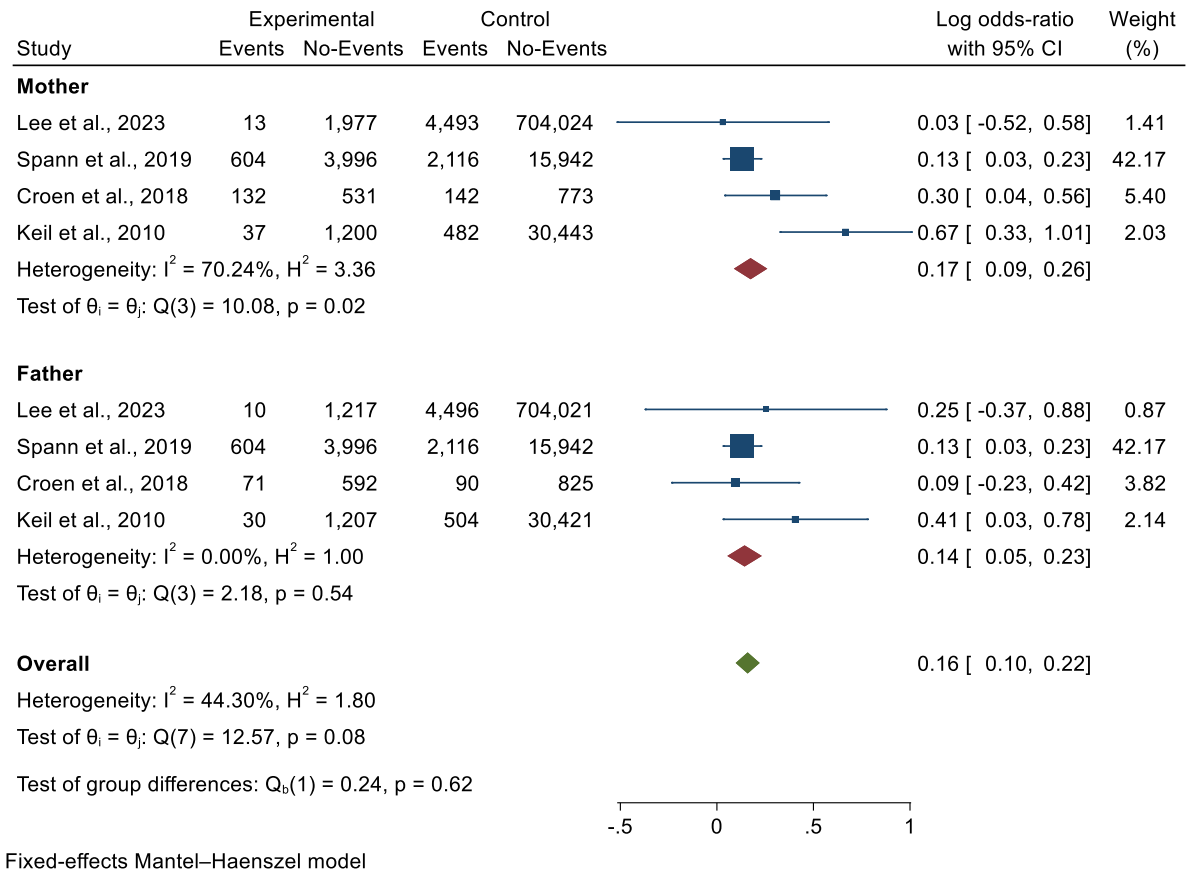

Fig. 2. Forest plots showed an association between AIDS and ASD.

Association between any AID in mothers and ASD in the offspring

The odds ratio of ASD in children whose mothers had type 1 diabetes was 1.65 (OR, 1.65 95% CI 1.04, 2.26; p<0.05); a direct association was observed between having type 1 diabetes in mothers and ASD in children. It should be mentioned that the odds ratio is very high, so it is important to pay attention to this variable (I^2=0% (p=0.70)) (Fig. 3).

The odds ratio of ASD in children whose mothers had psoriasis was 1.95 (OR, 1.95 95% CI 1.61, 2.29; p<0.05); a direct association was observed between having psoriasis in mothers and ASD in children (I^2=70.31% (p=0.03)) (Fig. 3).

The odds ratio of ASD in children whose mothers had rheumatoid arthritis was 1.32(OR, 1.32 95% CI 0.97, 1.67; p<0.05); a direct association was observed between having rheumatoid arthritis in mothers and ASD in children (I^2=70.31% (p=0.03)) (Fig. 3).

The odds ratio of ASD in children whose mothers had inflammatory bowel disease was 1.45 (OR, 1.45 95% CI 1.08, 1.82; p>0.05); special association was not observed between having inflammatory bowel disease in mothers and ASD in children (I^2=66.65% (p=0.05)) (Fig. 3).

Association between any AID in fathers and ASD in the offspring

The odds ratio of ASD in children whose fathers had type 1 diabetes was 1.09 (OR, 1.09 95% CI 0.48, 1.70; p<0.05); a direct association was observed between having type 1 diabetes in fathers and ASD in children (I2=0% (p=0.43)) (Fig. 4).

The odds ratio of ASD in children whose fathers had psoriasis was 1.82 (OR, 1.82 95% CI 1.50, 2.13; p>0.05); there was no association between having psoriasis in fathers and ASD in children (I^2=81.30% (p=0.00)) (Fig. 4).

The odds ratio of ASD in children whose fathers had inflammatory bowel disease was 1.87 (OR, 1.87 95% CI 1.50, 2.24; p>0.05); there was no association between having inflammatory bowel disease in fathers and ASD in children (I^2=92.63% (p=0.00)) (Fig. 4).

Association between AID and ADHD

The odds ratio of ADHD in the offspring between the experimental and control groups was 1.18 (OR, 0.18 95% CI 0.94, 1.42; p<0.05). Since a statistically significant difference was observed between the two groups, there is a direct relationship between AIDS and ADHD. Based on I2=0% (p=0.98), heterogeneity between studies was considered low (Fig. 5).

The odds ratio of ADHD in the offspring between mothers in the experimental group and control group was 1.19 (OR, 1.19 95% CI 0.85, 1.52; p<0.05), and the odds ratio of ADHD in the offspring between father in the experimental group and control group was 1.18 (OR, 0.1895% CI 0.83, 1,53; p<0.05) (Fig. 5). Based on these findings, it was observed that there was a direct relationship between AID in fathers and mothers with ADHD in children (Fig. 5). According to the test of group differences, there was no statistically significant difference between mothers and fathers (p=0.98).

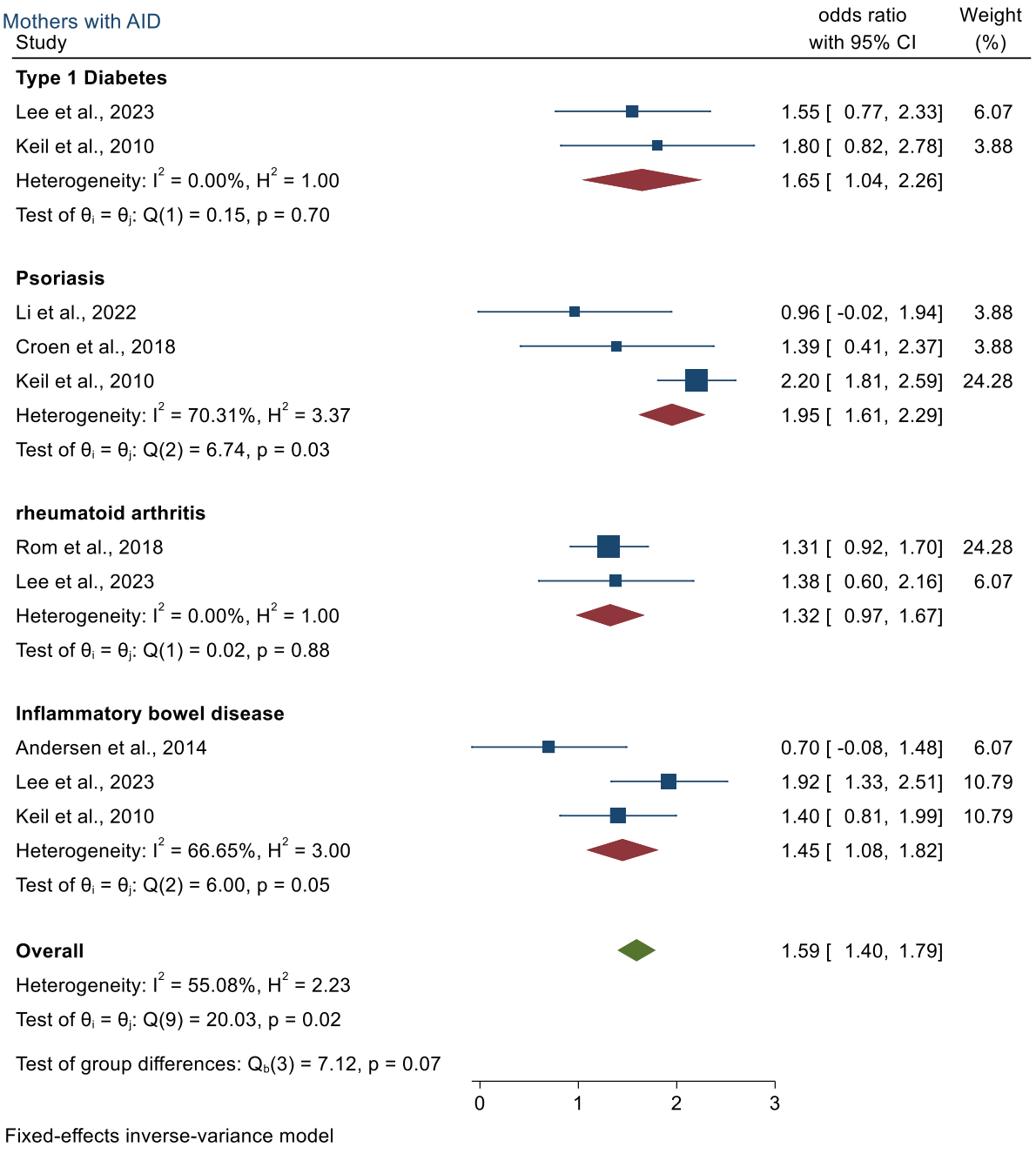

Fig. 3. Forest plots showed an association between any AID in mothers and ASD in the offspring.

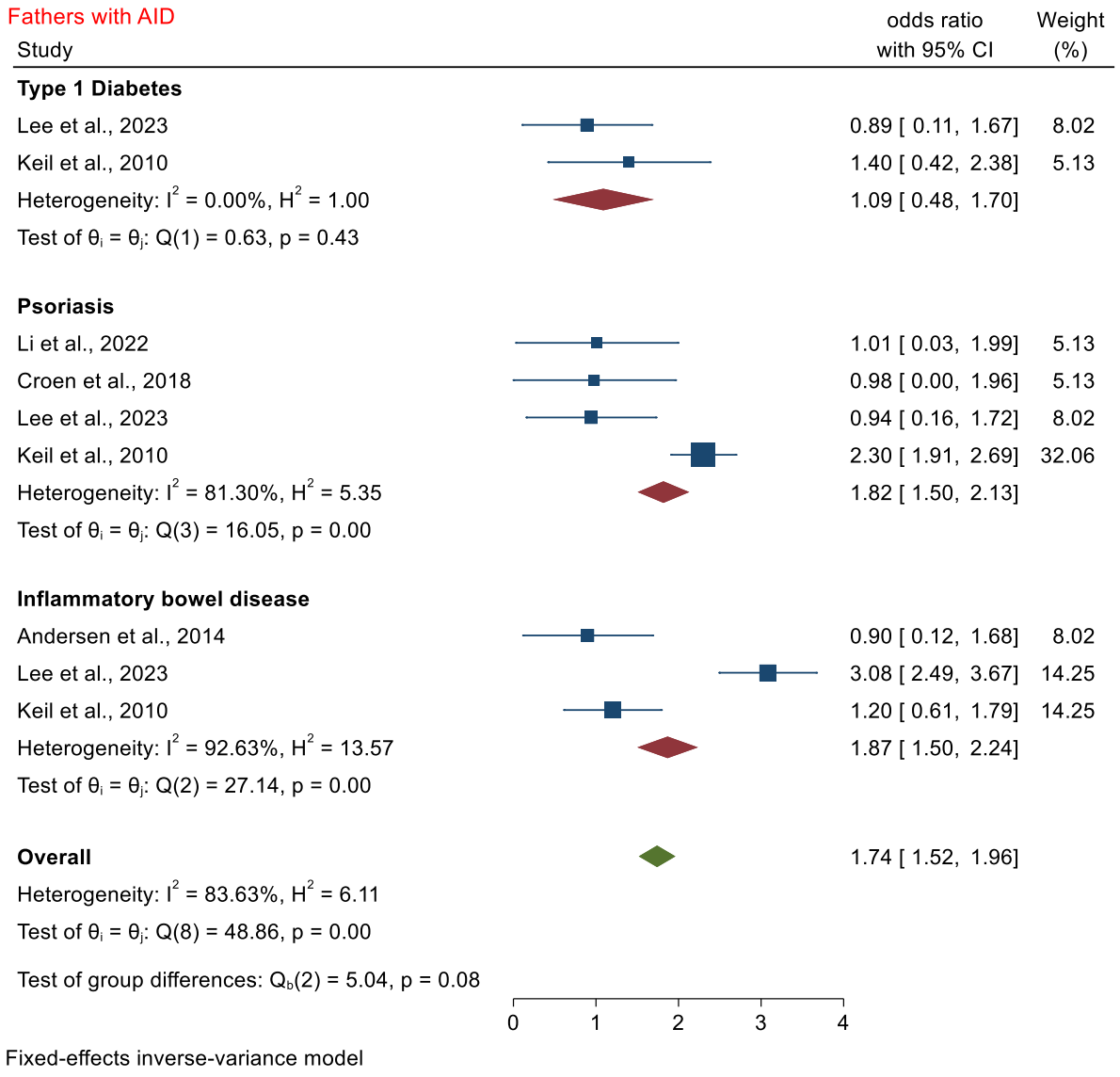

Fig. 4. Forest plots showed an association between any AID in fathers and ASD in the offspring.

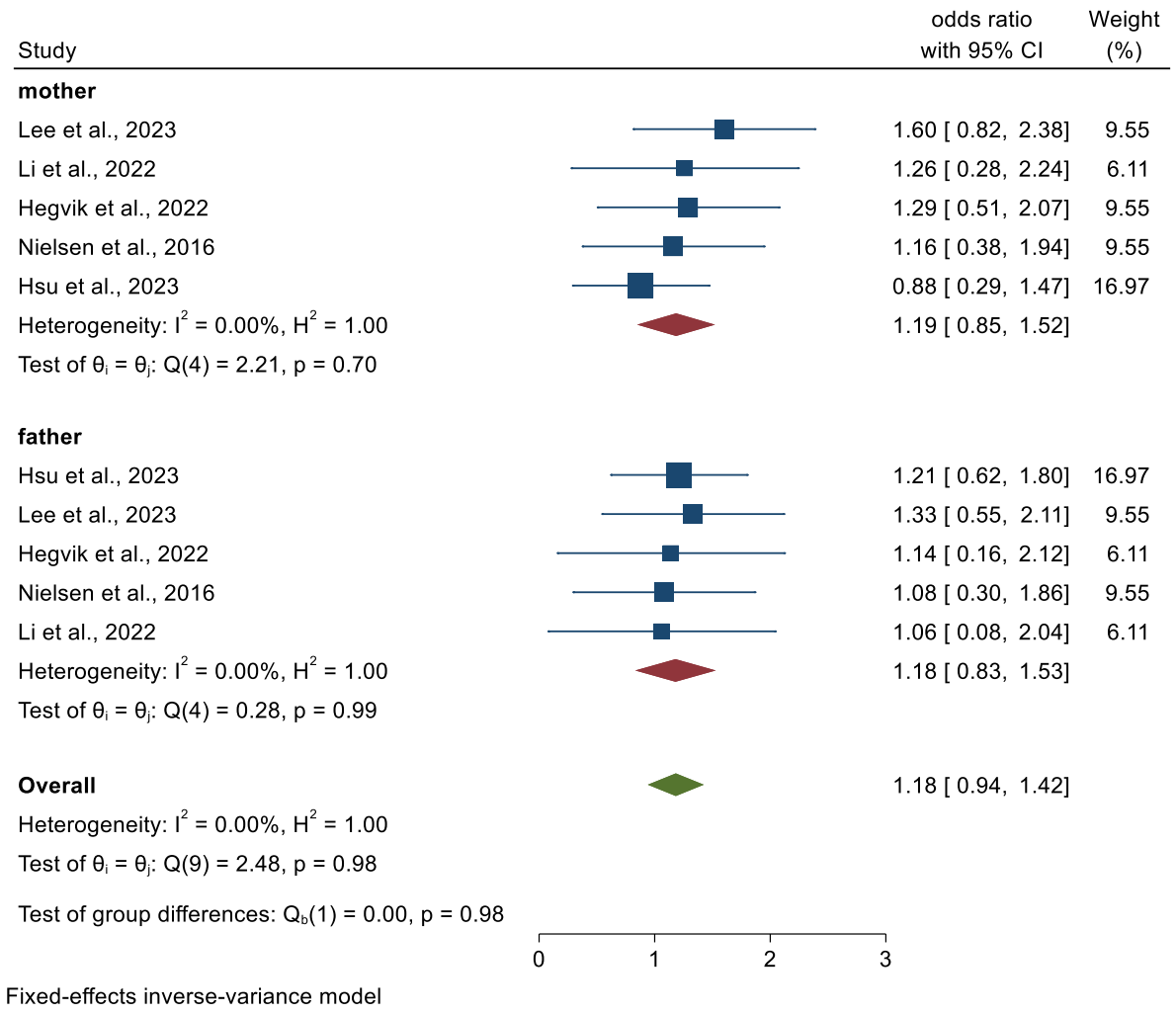

Fig. 5. forest plot showed an association between AIDS and ADHD.

Association between any AID in mothers and ADHD in the offspring

The odds ratio of ADHD in children whose mothers had type 1 diabetes was 1.28 (OR, 1.28 95% CI 0.91, 1.65; p<0.05); a direct association was observed between having type 1 diabetes in mothers and ADHD in children; (I^2=0% (p=0.57)) (Fig. 6).

The odds ratio of ADHD in children whose mothers had psoriasis was 1.46 (OR, 1.46 95% CI 1.09, 1.83; p<0.05); a direct association was observed between having psoriasis in mothers and ADHD in children (I^2=0% (p=0.73)) (Fig. 6).

The odds ratio of ADHD in children whose mothers had rheumatoid arthritis was 1.33(OR, 1.33 95% CI 0.94, 1.72; p<0.05); a direct association was observed between having rheumatoid arthritis in mothers and ADHD in children (I^2=0% (p=0.97)) (Fig. 6).

The odds ratio of ADHD in children whose mothers had inflammatory bowel disease was 1.30 (OR, 1.30 95% CI 0.99, 1.61; p>0.05); the special association was not observed between having inflammatory bowel disease in mothers and ADHD in children (I^2=62.56% (p=0.07)) (Fig. 6).

Association between any AID in fathers and ADHD in the offspring

The odds ratio of ADHD in children whose fathers had type 1 diabetes was 1.02 (OR, 1.02 95% CI 0.66 1.39; p<0.05); a direct association was observed between having type 1 diabetes in fathers and ADHD in children; (I^2=0% (p=0.64)) (Fig. 7).

The odds ratio of ADHD in children whose fathers had psoriasis was 1.25 (OR, 1.25 95% CI 0.86, 1.64; p<0.05); there was an association between having psoriasis in fathers and ADHD in children (I^2=0% (p=0.50)) (Fig. 7).

The odds ratio of ADHD in children whose mothers had rheumatoid arthritis was 1.18(OR, 1.18 95% CI 0.87, 1.49; p>0.05); there was no association between having rheumatoid arthritis in mothers and ADHD in children (I^2=28.76% (p=0.25)) (Fig. 7).

The odds ratio of ADHD in children whose fathers had inflammatory bowel disease was 1.00 (OR, 1.00 95% CI 0.52, 1.49; p>0.05); there was no association between having inflammatory bowel disease in fathers and ADHD in children (I^2=0% (p=0.91)) (Fig. 7). The funnel plot shows the relation between a study's effect size and precision (Figs. 8 and 9).

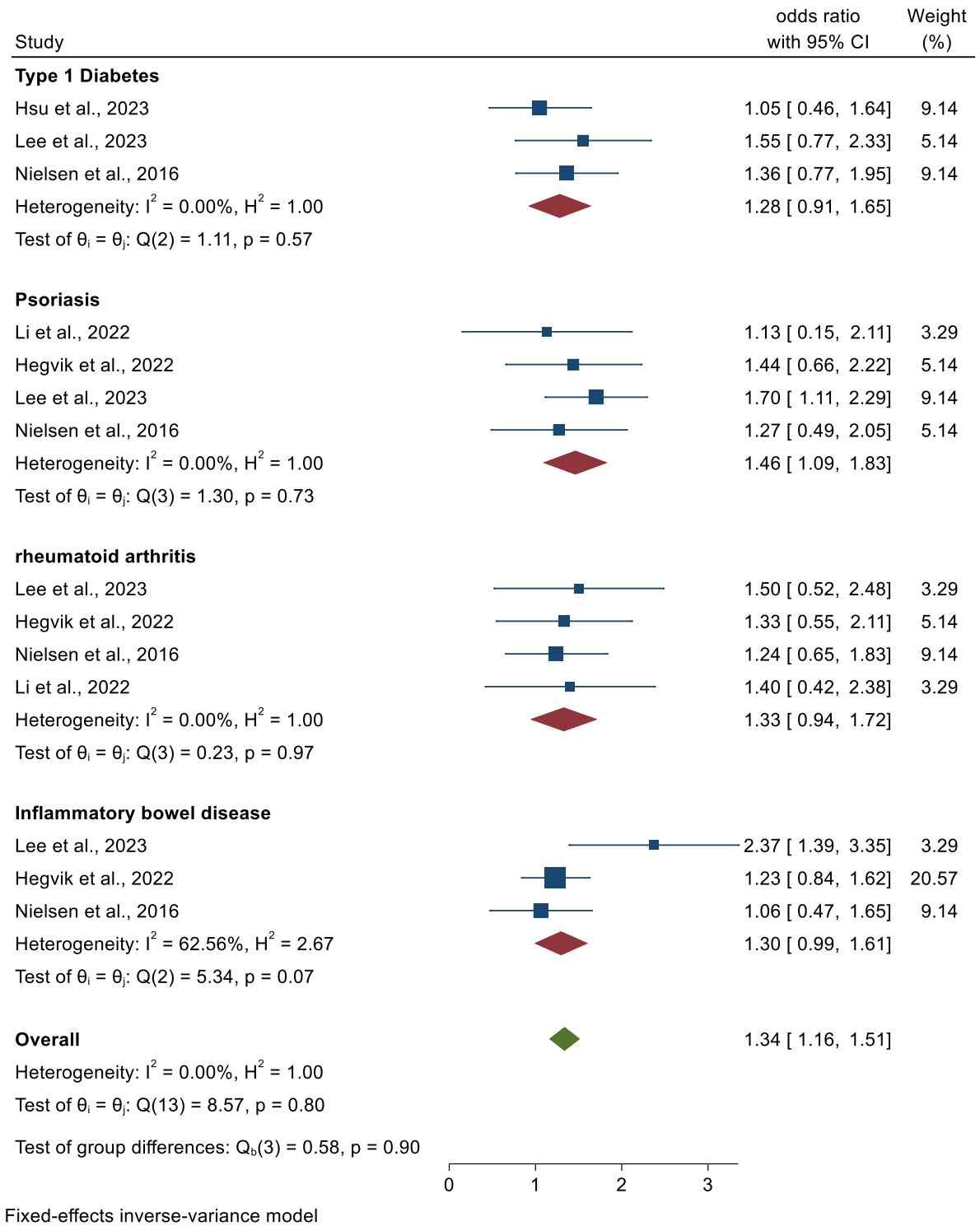

Fig. 6. Forest plots showed an association between AIDS in mothers and ADHD in the offspring.

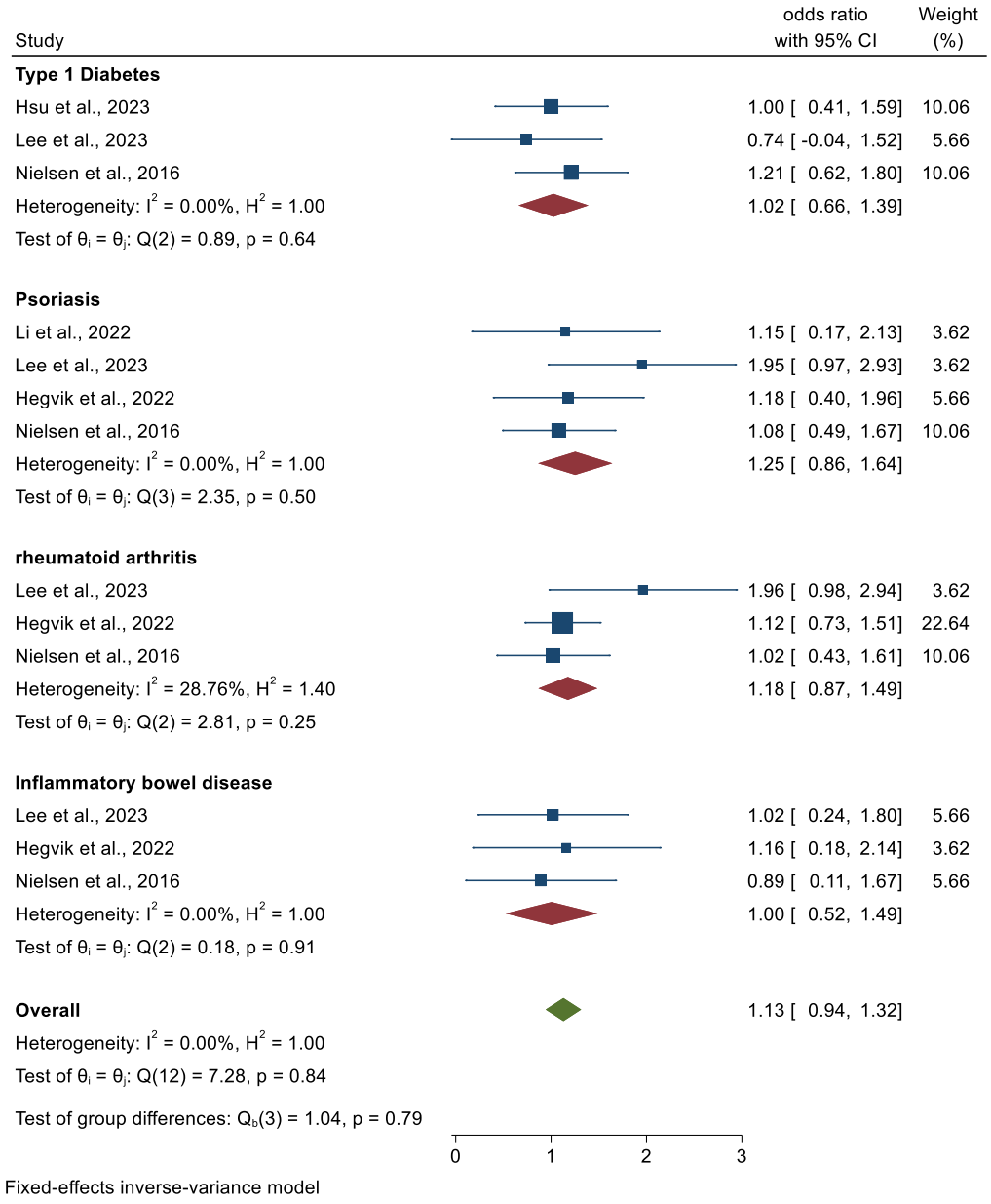

Fig. 7. Forest plots showed an association between AIDS in fathers and ADHD in the offspring.

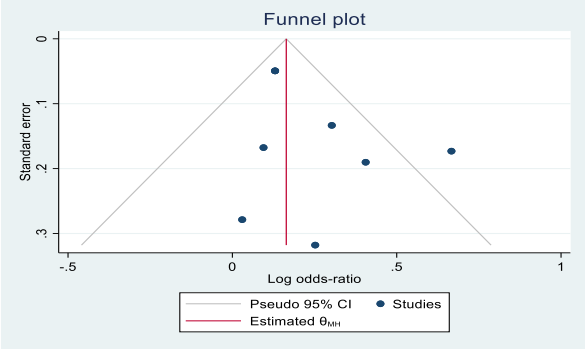

Fig. 8. funnel plot showed studies publication bias (ASD and AID).

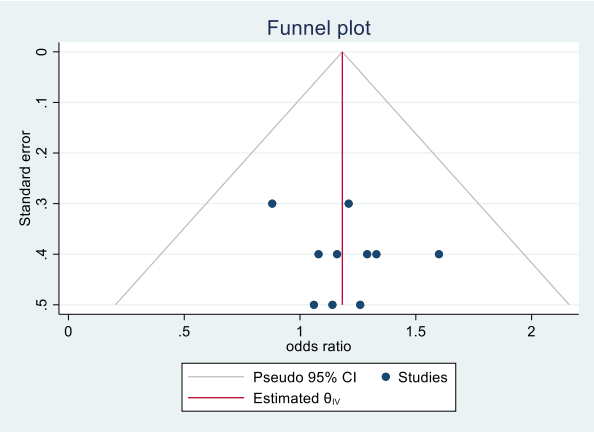

Fig. 9. funnel plot showed studies publication bias (ADHD and AID).

4. Discussion

In the studies investigating the relationship between AIDS and NDs, the risk ratio in children by parents and its relationship with AIDS in parents were investigated. Therefore, the present study attempted to investigate the relationship between types of AIDS and NDs (ASD and ADHD) by performing a subgroup meta-analysis. The present meta-analysis showed that the risk ratio of ASD and ADHD in the offspring is high in mothers and fathers with AID, and there is a direct relationship between AID and ASD and ADHD in the offspring.

On the other hand, a subgroup meta-analysis that examined the relationship between types of AID showed that in mothers and fathers with type 1 diabetes, there is a direct relationship between ASD and ADHD in the offspring. A study has shown that preexisting maternal type 1 diabetes is directly related to a 39% increase in the risk of ADHD in the infant, and in fathers with type 1 diabetes, this risk is associated with a 20% increase.[29] Another study has also shown that exposure to diabetes during pregnancy can cause neurodevelopmental disorders in the baby.[30] The study has shown that the risk of ADHD is directly related to the degree of glucose control of the mother's diabetes.[31] Studies report that maternal diabetes increases the risk of ASD in their children.[32] A genetic study showed that 16 loci showed both type 1 diabetes and ASD.[33]

The risk of ASD and ADHD in the offspring was significant in mothers with psoriasis and rheumatoid arthritis. A statistically significant relationship between inflammatory bowel disease in mothers with the risk of ASD and ADHD in the offspring was not observed. In the other case of AIDS, according to the findings of the studies, no significant correlation was observed, so they were not included in the subgroup meta-analysis. In fathers with psoriasis and inflammatory bowel disease, there was no correlation with the risk of ASD in the offspring. However, a significant relationship was observed between ADHD in the offspring and fathers with psoriasis. Also, the risk of ADHD in the offspring was not significant in fathers with rheumatoid arthritis and inflammatory bowel disease. Therefore, it can be stated that AIDS in mothers and fathers is a significant risk factor in increasing the risk of ASD and ADHD in children. Studies have shown that environmental factors are effective in AIDS.[34] Also, studies have shown that the environment directly correlates with the increased risk of NDs.[35] Studies have reported that smoking by parents is directly related to NDs in children.[36] Evidence also shows that the father's smoking can be transmitted through genetics and directly affect the fetus's brain.[37] Therefore, studies of smoking by parents with AID and the association of AID in those parents with NDs should be well studied. Studies have shown findings consistent with the results of the present study. A study has reported that the increased risk of ADHD is directly related to maternal ankylosing spondylitis, systemic lupus erythematosus, psoriasis, rheumatic arthritis, and also in fathers, paternal multiple sclerosis, and psoriasis increase the risk of children developing ADHD.[38, 39]

Studies that examine the role of the type 1 diabetes gene and the risk of developing NDs are needed because the risk of ASD and ADHD in the offspring was high and significant in fathers and mothers with type 1 diabetes to confirm the present findings.[39] Studies have shown a positive relationship between AIDS in second and third-degree relatives with neurodegenerative disorders; Therefore, the role of the environment should be further investigated.[22, 40] Therefore, the findings of the present study can be based on genetic pathways. It is observed that AIDS in mothers increases the risk of ASD and ADHD in the offspring, Comparing mothers with fathers. One of the main limitations of the present study is that the selected studies did not report whether AIDS was present during pregnancy or not. Also, the use of treatment during pregnancy by mothers was not reported. Because evidence shows that drug treatment for AIDS by mothers can increase the risk of ASD and ADHD in the offspring.[41] On the other hand, studies have reported that in the follow-up of children born to mothers who used immunosuppressive drugs during pregnancy, there was no relationship between ASD and ADHD.[42] More studies regarding the presence of AIDS before pregnancy, during pregnancy, the investigation of the drugs used during pregnancy, and the investigation of the role of genetics and environment are needed to confirm the current evidence.

5. Conclusion

Based on the findings of the present study, there is a positive and direct relationship between AIDS in mothers and fathers with an increased risk of ASD and ADHD in children. One of the most important factors that increase the risk of ASD and ADHD in children is the parents' type 1 diabetes, so the role of genetics can be considered effective. It is suggested that future studies examine children whose mothers had AIDS before and during pregnancy and received medication for treatment.

Conflict of Interest

The authors declared that there is no conflict of interest.

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