Review Paper

Associations Between Neonatal Jaundice and Autism Spectrum Disorder: A Systematic Review and Meta-analysis of Observational Studies

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ABSTRACT

Background: Autism spectrum disorder (ASD) is a neurodevelopmental disorder that affects social function. Multiple factors are involved in ASD development.

Objectives: This study aimed to review and meta-analyze observational studies examining the association between neonatal jaundice (NNJ) and ASD.

Methods: This is a systematic review and meta-analysis based on the PECO framework. Articles published up to 8 December 2024 were searched in national databases, including Danesh Gostar Barakat, Scientific Information Database (SID), MagIran, IranDoc, and international databases, including PubMed, Scopus, WOS, Cochrane, and Embase, as well as the Google Scholar search engine. Only observational studies were included. The quality of studies was assessed using the Newcastle-Ottawa scale (NOS). Data were analyzed using odds ratio (OR), relative risk (RR), and hazard ratio (HR) indices. The heterogeneity between the studies was evaluated using the I^2 indicator. Publication bias was examined using Begg's funnel plot. Data were analyzed in STATA software, version 14.

Results: Of 418 records, 26 observational studies were finally included (12 case-control studies, 10 cohort studies, and 4 cross-sectional studies). Overall, NNJ was associated with the risk of ASD with an OR of 1.65 (95% CI, 1.44%, 1.89%). Also, the OR of the NNJ association with increased risk of ASD in newborns undergoing phototherapy was 1.19 (95% CI, 1.11%, 1.27%). The OR was 1.25 in cohort studies (95% CI, 1.15%, 1.36%); 3.21 in case-control studies (95% CI, 1.89%, 5.45%); and 1.78 in cross-sectional studies (95% CI, 1.1%, 2.89%). The risk of ASD due to NNJ was higher in boys (OR: 1.95, 95% CI, 1.18%, 3.23%) than in girls (OR: 1.26, 95% CI, 1.07%, 1.49%). Furthermore, the OR of association between NNJ and ASD was significantly higher in Taiwan, the USA, India, Brazil, Canada, Vietnam, Nepal, Qatar, Egypt, and China. NNJ and ASD were not significantly correlated in Sweden, Turkey, and Denmark. The presence of publication bias was significant ($P<0.05$). In other words, studies that did not report a significant association between NNJ and the risk of ASD were less likely to be published.

Conclusions: NNJ is associated with an elevated risk of ASD. Boys with jaundice are more exposed to the risk of ASD than girls. Thus, NNJ is an important issue, particularly in boys, which can lead to numerous long-term complications.

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Introduction

Neonatal jaundice (NNJ) is a common condition during the neonatal period [1], and the bilirubin level is high in approximately 8-11% of newborns [2-4]. NNJ occurs in about 60% of term infants and 80% of preterm infants [1]. Neonatal hyperbilirubinemia (NNHB) is classified into physiological and pathological jaundice [4]. Although NNHB is generally benign, the elevated levels of bilirubin may lead to neurological dysfunction and kernicterus, whereas lower levels are associated with fewer complications [5, 6]. Additionally, unconjugated NNHB is associated with long-term adverse outcomes, including cerebral palsy, intellectual disability, brain dysfunction, attention deficit hyperactivity disorder, and autism spectrum disorder (ASD) [7, 8]. Therefore, a possible association between NNJ and ASD has been suggested [9].

The incidence of ASD is on the rise worldwide [10, 11]; its prevalence among infants increased by 52% from 2017 to 2020 [12]. In some Arabic countries, the incidence of ASD is reported to be 1.4-29 per 10,000 children [13-15]. Moreover, ASD is 4 times more prevalent in boys than in girls [16]. ASD is not considered a single-dimensional disorder; rather, it is influenced by multiple factors, including genetics, preterm factors, prenatal factors, postpartum factors, and environmental factors [17, 18]. In the prenatal period, the risk factors of ASD in children include maternal fever during pregnancy [19], maternal exposure to toxins (e.g. smoking and contaminants) during pregnancy [20, 21], premature birth, maternal age, and bleeding during pregnancy [22]. NNJ, congenital heart defects, and low birth weight are other risk factors for ASD [4, 23-25].

ASD is a disease with long-term consequences for children and families [26], and conflicting results have been reported on the association between NNJ and ASD risk in different studies [27, 28]. A previous meta-analysis conducted in 2021 included articles related to this association published up to February 2019 [4], which may have resulted in overlap and potential bias. Moreover, sources published in the Web of Science (WOS) database were not searched in this meta-analysis. Thus, this systematic review and meta-analysis aimed to consolidate the results of previous studies regarding the association between NNJ and ASD risk.

Materials and Methods

This systematic review and meta-analysis study was designed based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) [29]. Its protocol was registered in the PROSPERO (international prospective register of systematic reviews) and the Research Registry website. The articles published up to 8 December 2024 were searched in national databases, including Danesh Gostar Barakat, Scientific Information Database (SID), MagIran, IranDoc, and international databases including PubMed, Scopus, WOS, Cochrane, and Embase, as well as the Google Scholar search engine, without time or place limitations. Medical subject headings (MeSH) terms and their equivalents were used in the search strategy combined with Boolean operators (AND, OR). The search strategy used in the PubMed database was as follows: (autism spectrum disorder OR autistic spectrum disorder) AND ("jaundice, neonatal" OR severe jaundice in newborn OR physiological neonatal jaundice)

Based on the PECO framework, the study "population" consisted of articles that investigated the association between NNJ and ASD risk; the "exposure" was NNJ; the "comparison" group included healthy people; and the main "outcome" was the relationship between NNJ and the risk of ASD. Therefore, the observational studies that examined the association between NNJ and ASD risk were included. Duplicate studies, review studies, meta-analyses, studies with poor quality, studies with incomplete abstracts and without accessible full texts, studies lacking the required data for analysis, non-observational studies, and conference posters were excluded from this review.

Two authors assessed the quality of studies with the Newcastle-Ottawa scale (NOS), in which each question is assigned a maximum of one star (except for the comparison question which could be assigned two stars). The score of this scale ranges from 0 (the poorest quality) to 10 (the highest quality). Studies that acquired a score >6 were included in the current meta-analysis [30].

To collect data, a data extraction form in an Excel file was designed. The data including the author's name, study place, study year, study type, sample size, and the link between NNJ and ASD risk at 95% confidence interval (CI) were extracted by two authors. A third author examined the data to ensure accuracy and resolve contradictions.

Data were analyzed using the odds ratio (OR), relative risk (RR), and hazard ratio (HR), and the eligible studies were subsequently pooled. The heterogeneity between the studies was evaluated using the I^2 indicator, which classifies the heterogeneity level into three groups: low (<25%), moderate (25-75%), and severe (>75%) heterogeneity. A random-effects model was also used in this study. Statistical analyses were performed in STATA software, version 14, considering a significance level set at 0.05 for all statistical tests.

Results

The search in databases yielded 418 articles, among which 193 were excluded due to being duplicate records. After reviewing the abstracts of 225 articles, 9 studies with incomplete abstracts or unavailable full texts were removed. Of 216 articles with full texts, 59 articles were excluded due to lacking the required data for analysis. Subsequently, 157 articles were included in the next stage, 131 of which were removed based on the other exclusion criteria, and 26 observational studies remained for the review (Figure 1). They included 12 case-control studies, 10 cohort studies, and 4 cross-sectional studies, with a total of 766,422 participants (Table 1).

As shown in Figure 2, the risk of ASD increased due to NNJ with an overall OR of 1.65 (95% CI, 1.44%, 1.89%). According to Figure 3, the OR was 1.25 in cohort studies (95% CI, 1.15%, 1.36%); 3.21 in case-control studies (95% CI, 1.89%, 5.45%); and 1.78 in cross-sectional studies (95% CI, 1.1%, 2.89%).

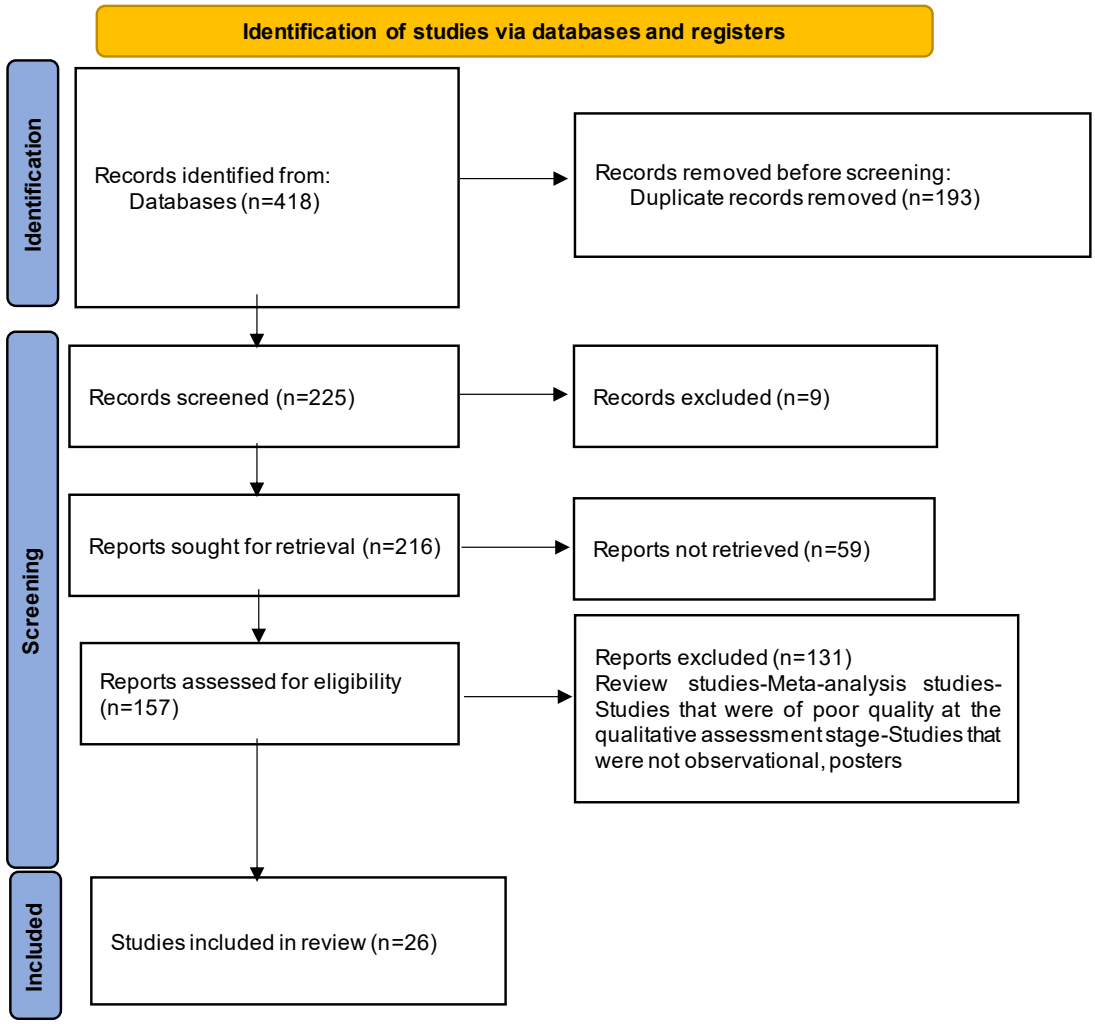

Figure 1. PRISMA flow chart of the study selection process

Table 1. Information of studies included in the systematic review and meta-analysis

Author(s), Year	Place	Type of Study	Duration of Study	Sample Size	Used Index	Risk of ASD	Lower Bound	Upper Bound	Quality Score
Sameea et al. 2024 [28]	Qatar	Cross-sectional	Between December 1, 2017, and August 31, 2018	600	OR	4.88	1.46	16.3	8
Chou et al. 2023 [31]	Taiwan	Cohort	2004-2010	7260	HR	1.3	1.01	1.69	7
				82990	HR	1.22	1.13	1.33	
				27927	HR	1.32	1.16	1.51	
Vui et al. 2023 [32]	Vietnam	Cross-sectional	2017-2018	42551	OR	1.7	1.1	2.9	7
Lee et al. 2022 [33]	Taiwan	Cohort	2000–2010	517	OR	1.32	1	1.74	7
Hung et al. 2021 [34]	Taiwan	Cohort	2000–2012	22339	HR	1.28	1.05	1.57	9
Tunc et al. 2021 [27]	Turkey	Cross-sectional	NR	119	OR	1.21	0.34	4.33	9
Hegazy et al. 2021 [35]	Egypt	Case-control	From April 2017 to January 2019	40	OR	11.15	2.95	42.2	8
Maia et al. 2019 [36]	Brazil	Case-control	NR	253	OR	1.43	1.01	2.02	8
Hisle-Gorman et al. 2018 [37]	USA	Cohort	2000-2013	8760	OR	1.13	1.07	1.18	8
Bhattarai et al. 2018 [38]	Nepal	Case-control	NR	58	OR	2.38	0.85	6.8	7
Malla et al. 2017 [39]	Nepal	Case-control	NR	52	OR	3.2	0.9	10.8	9
Wu et al. 2016 [17]	USA	Cohort	1995–2011	525409	HR	1.09	0.89	1.35	8
Ravi et al. 2016 [40]	India	Cross-sectional	June to August 2014	33	OR	1.19	0.39	3.63	7
Lozada et al. 2015 [41]	USA	Case-control	Between October 2002 and September 2009	2917	OR	1.18	1.06	1.31	7
Froehlich-Santino et al. 2014 [42]	USA	Cohort	NR	194	OR	1.88	1.13	3.11	9
Chen et al. 2014 [43]	Taiwan	Cohort	1999–2000	2016	HR	1.75	1.05	2.9	8
Duan et al. 2014 [44]	China	Case-control	2011-2013	286	OR	21.81	12.22	35.53	8
George et al. 2014 [45]	India	Case-control	NR	143	OR	1.47	0.78	2.77	7
Hwang et al. 2013 [46]	Taiwan	Cohort	1998-2009	411	OR	1	0.8	1.2	8
Mamidala et al. 2013 [47]	India	Cohort	NR	471	OR	2.89	1.58	5.28	8
El-Baz et al. 2011 [48]	Egypt	Case-control	From June 2008 to May 2010	100	OR	14.61	2.32	13.67	8
Zhang et al. 2010 [49]	China	Case-control	Between January and December, 2007	95	OR	12.31	1.56	97.36	7
Maimburg et al. 2010 [7]	Denmark	Cohort	1994-2004	35766	HR	1.56	1.05	2.3	9
Buchmayer et al. 2009 [50]	Sweden	Case-control	1987-2002	1216	OR	1.18	0.86	1.63	8
Jangaard et al. 2008 [51]	Canada	Case-control	1994-2000	3431	RR	1.6	1	2.5	7
Maimburg et al. 2008 [52]	Denmark	Case-control	1990-1999	473	OR	3.7	1.3	10.5	7

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Abbreviations: NR: Not reported; ASD: Autism spectrum disorder; OR: Odds ratio; HR: Hazard ratio; RR: Relative risk.

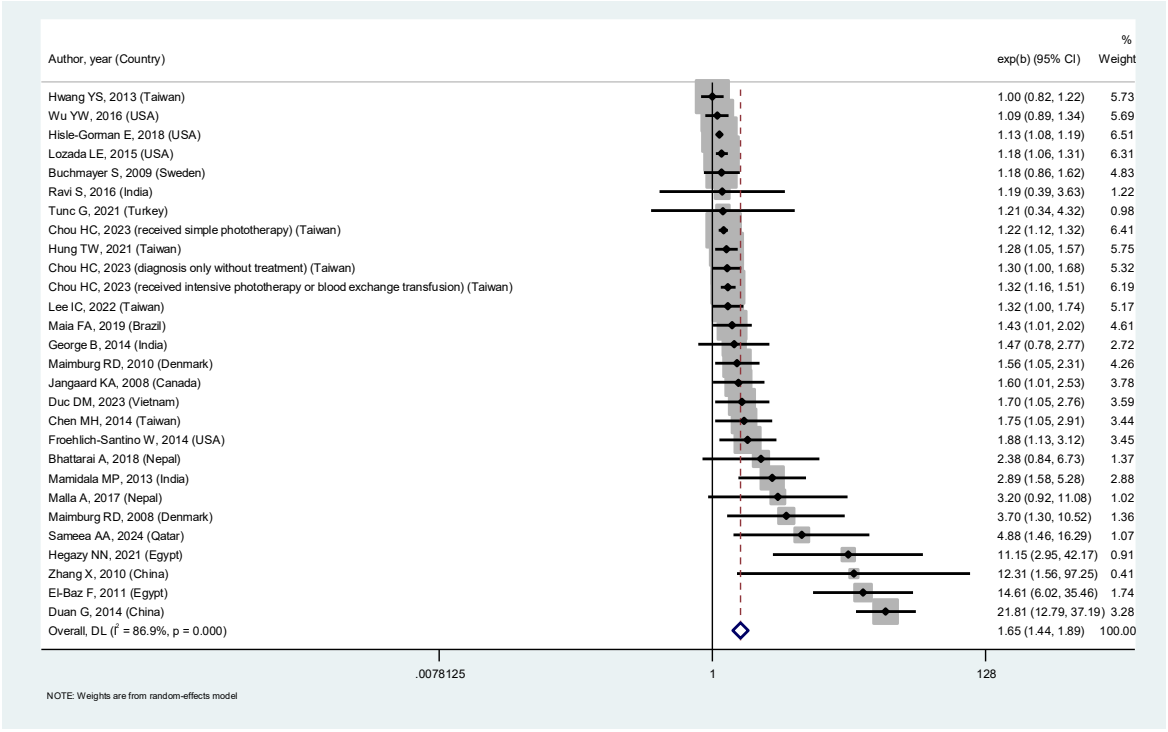

Figure 2. Forest plot showing the relationship between NNJ and ASD

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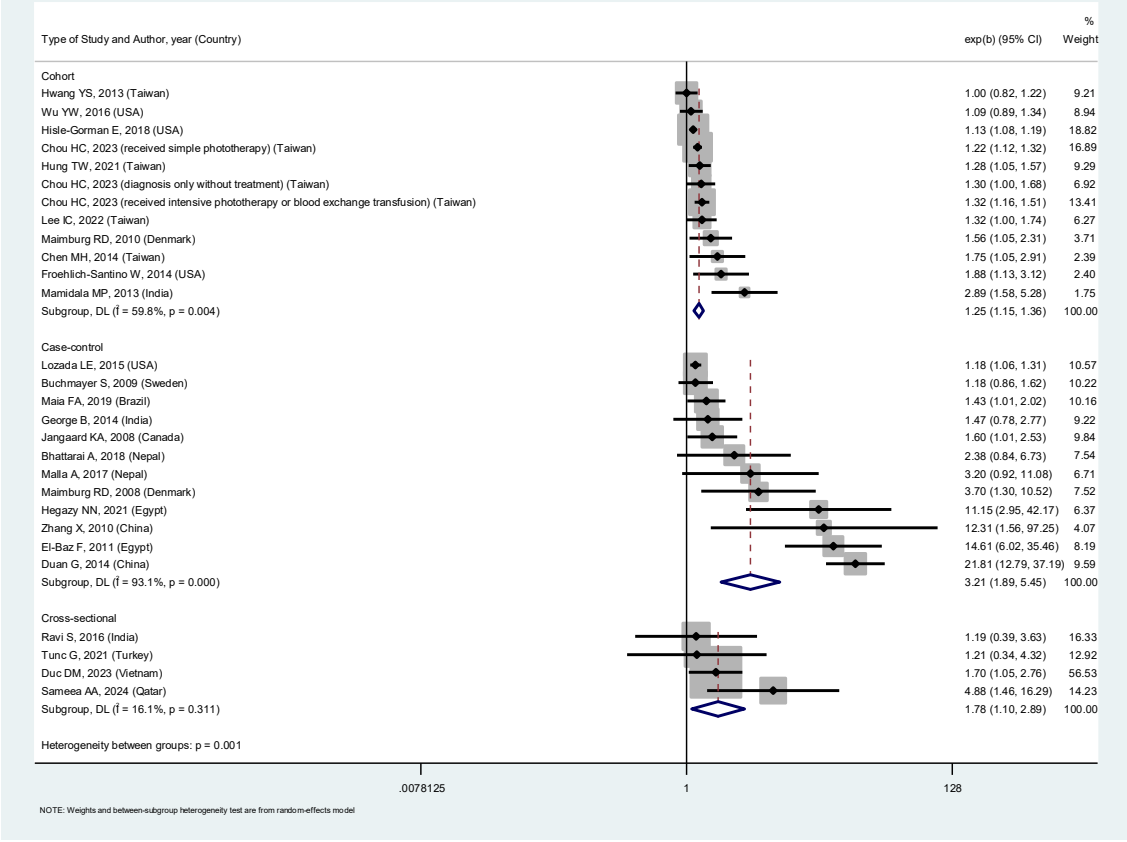

Figure 3. Forest plot showing the relationship between NNJ and ASD categorized by type of study

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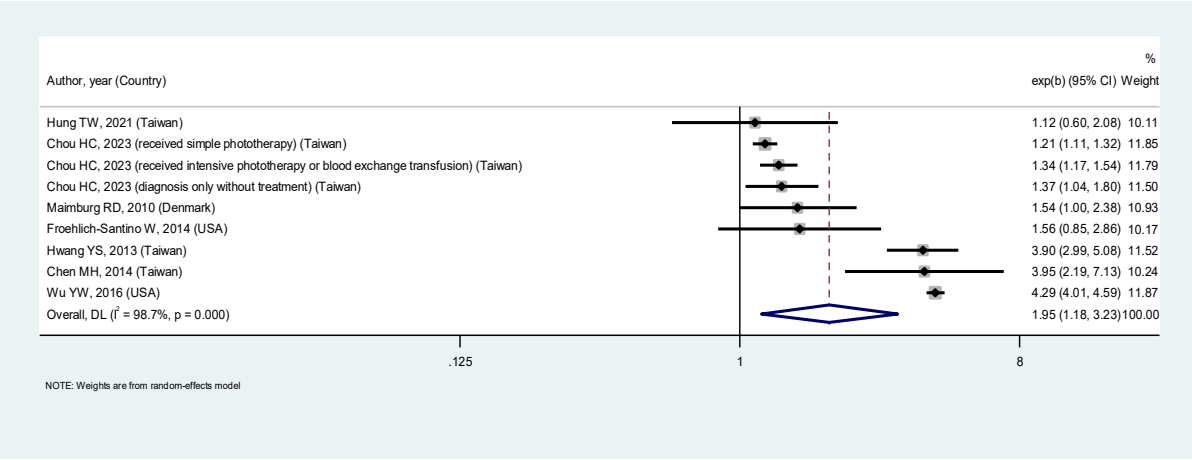

Figure 4. Forest plot showing the relationship between NNJ and ASD in boys

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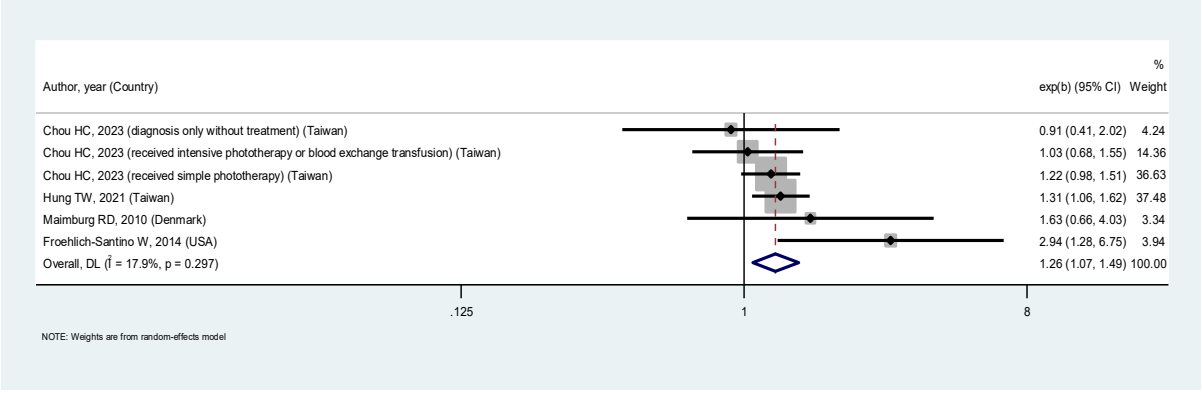

Figure 5. Forest plot showing the relationship between NNJ and ASD in girls

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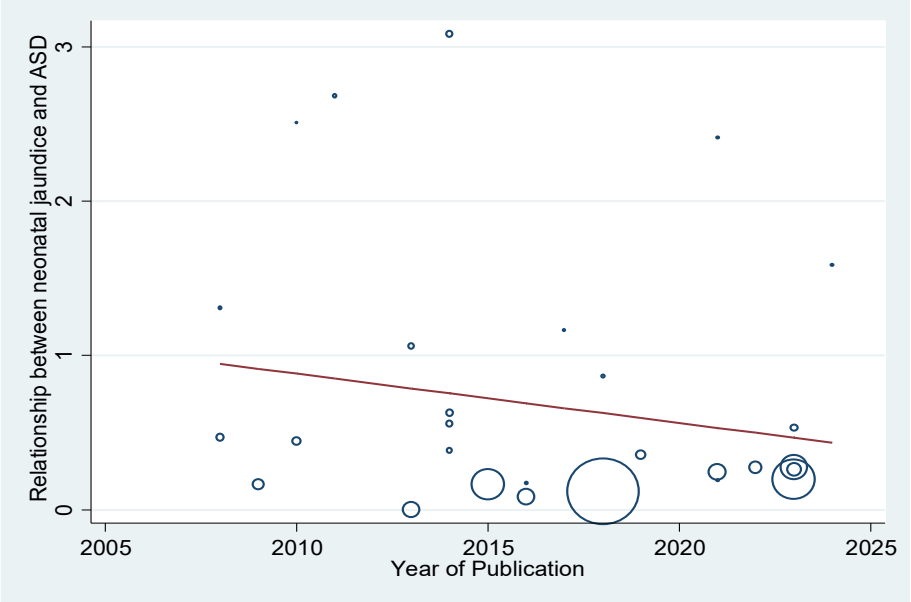

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Figure 6. The meta-regression analysis showing the relationship between NNJ and ASD by year of publication

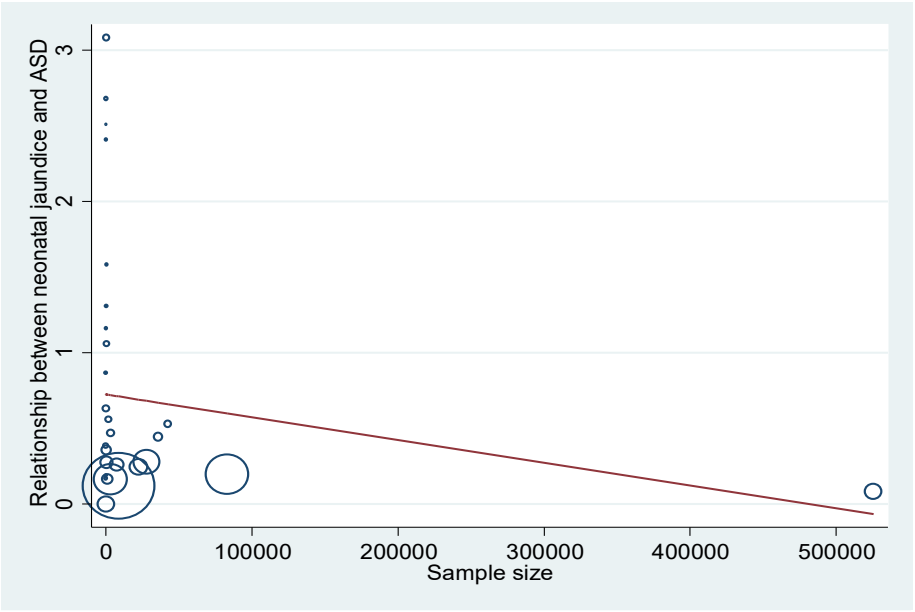

Figure 7. The meta-regression analysis showing the relationship between NNJ and ASD by sample size *Journal of Pediatrics Review*

The risk of ADHD also increased due to NNJ (OR: 1.17, 95% CI, 1.1%, 1.24%). NNJ multiplied the risk of ASD in infants undergoing phototherapy (OR: 1.19, 95% CI, 1.11%, 1.27%). The OR of association between ASD and NNJ was higher in boys (OR: 1.95, 95% CI, 1.18%, 3.23%) than in girls (OR: 1.26, 95% CI, 1.07%, 1.49%), according to Figures 4 and 5.

As shown in Table 2, the association of NNJ with increased risk of ASD in children was significant in Taiwan, the USA, India, Brazil, Canada, Vietnam, Nepal, Qatar, Egypt, and China, while it was not significant in Sweden, Turkey, and Denmark.

The meta-regression curves in Figures 6 and 7 indicated no statistically significant relationships between the NJJ and the ASD risk based on publication years (P=0.313) and sample size (P=0.309). According to Figure 8, the presence of publication bias was significant (P<0.05). In other words, studies that did not report a significant association between NNJ and the risk of ASD were less likely to be published.

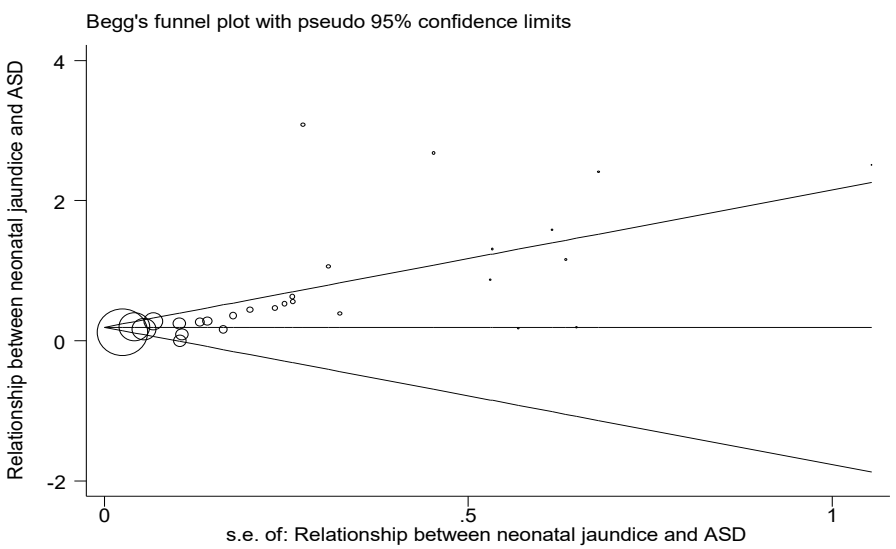

Figure 8. Begg's funnel plot of publication bias *Journal of Pediatrics Review*

Table 2. Relationship between NNJ and ASD categorized by countries

Place	OR	Upper Bound	Lower Bound	P	I^2 (%)	Significant?
Taiwan	1.24	1.15	1.34	0.275	20.3	Yes
USA	1.15	1.07	1.24	0.216	32.8	Yes
Sweden	1.18	0.86	1.62	-	-	No
India	1.88	1.1	3.2	0.207	36.5	Yes
Turkey	1.21	0.34	4.32	-	-	No
Brazil	1.43	1.01	2.02	-	-	Yes
Denmark	2.09	0.94	4.64	0.129	56.6	No
Canada	1.6	1.01	2.53	-	0	Yes
Vietnam	1.7	1.05	2.76	-	0	Yes
Nepal	2.69	1.21	5.97	0.72	0	Yes
Qatar	4.88	1.46	16.29	-	0	Yes
Egypt	13.44	6.43	28.12	0.74	0	Yes
China	21.04	12.55	35.28	0.599	0	Yes

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Discussion

In total, 26 observational studies (12 case-control, 10 cohort, and four cross-sectional studies) were reviewed in this study. The OR obtained from case-control studies (OR=3.21) was more than twice that in cohort studies (OR=1.25). The difference in the number of studies by study type may be one reason for this difference. The NNJ increased the risk of ASD and ADHD by 65% and 17%, respectively, and boys were more exposed to the risk of ASD than girls. Additionally, the risk of ASD due to NNJ was significantly higher in Taiwan, the USA, India, Brazil, Canada, Vietnam, Nepal, Qatar, Egypt, and China. No significant associations were found between NNJ and ASD in Sweden, Turkey, and Denmark. This result suggests that ethnicity and race may be involved in the association between NNJ and ASD development.

In a meta-analysis by Jenabi et al. [53], a significant association was identified between NNJ and ASD in children [(OR: 1.35; 95% CI, 1.02%, 1.68%) or (RR: 1.39; 95% CI, 1.05%, 1.74%)]. Another meta-analysis by Amin et al. [9] revealed that NNJ was associated with an elevated risk of ASD (OR=1.43, 95% CI, 1.22%, 1.67%). Gardener et al. [54] reported an association between NNJ and the risk of ASD development in a meta-analysis (summary effect estimate: 1.87, 95% CI, 1.01%, 3.47%). In an umbrella review by Salehi et al. [55], NNJ was also a risk factor for ASD (OR: 1.74; 95% CI, 1.42%, 2.12%). Our results are consistent with the results of these studies. In a meta-analysis by Kujabi et al. [4], NNJ and ASD were not significantly associated with each other in the cohort (RR: 1.09, 95% CI, 0.99%, 1.2%) and case-control (RR: 1.29, 95% CI, 0.95%, 1.76%) studies. A meta-analysis on newborn infants by Lai et al. [56] indicated that total serum bilirubin was related to the kernicterus spectrum disorder in high-risk newborns (OR: 1.1, 95% CI, 1.07%, 1.13%). However, total serum bilirubin (OR: 1.1, 95% CI, 0.98%, 1.23%) and hyperbilirubinemia (OR: 1, 95% CI, 0.51%, 1.95%) were not associated with kernicterus or neural detection in the general neonate population. These results are not in agreement with our findings. This discrepancy seems natural due to the different ages and bilirubin levels of participants.

In a cross-sectional study by Sameea et al. on children aged 18-48 months, ASD was linked to the history of NNHB (OR: 4.88; 95% CI, 1.5%, 16.3%) [28]. In our meta-analysis of cross-sectional studies, it was also indicated that the risk of ASD was intensified by NNJ. In a case-control study, Maia et al. [36] presented evidence that NNJ was a risk factor for ASD (OR: 1.43; 95% CI, 1.01%, 2.02%). Similarly, the meta-analysis of case-control studies in our study showed the occurrence of ASD in childhood due to NNJ. The results of a cohort study by Chou et al. [31] demonstrated that NNJ groups, includ-

ing diagnosed only (HR: 1.3, 95% CI, 1.01%, 1.69%), simple phototherapy (HR: 1.22, 95% CI, 1.13%, 1.33%), and intensive phototherapy or blood exchange transfusion (HR: 1.32, 95% CI, 1.16, 1.16%) were significantly linked to ASD; besides, NNJ was correlated with ADHD. Based on a cohort study by Hung et al. [34], infants with hyperbilirubinemia were exposed to an increased risk of ASD (HR: 1.28, 95% CI, 1.05%, 1.57%), and boys were almost 6 times more exposed to ASD risk than girls (HR: 5.89, 95% CI, 4.41%, 7.86%). In our meta-analysis, the meta-analysis of cohort studies also showed that NNJ is a risk factor for ASD development. Additionally, the risk of ASD was greater in boys with jaundice than in girls; hence, the male gender is a risk factor for ASD development in NNJ populations.

There were some limitations in this study. Since ASD is a long-term complication of NNJ and may occur in childhood or adolescence, it was not possible to categorize studies by age, because the age groups reported in the reviewed studies were diverse and scattered. As a result, subgroup analysis for the age variable was not performed, and the role of age in the association between NNJ and the risk of ASD was not examined. Very few studies had examined the association between NNJ and ASD risk by gender, and there was a lack of studies in this field. Therefore, the results presented by gender may not be generalizable to the entire study population. The reviewed studies did not examine the association between NNJ and the risk of ASD by severity of jaundice (low, moderate, high). The severity of jaundice plays an important role in the occurrence of complications, including ASD. Therefore, the lack of studies to examine this important factor causes heterogeneity. Very few studies reported the treatment method of NNJ (phototherapy, blood exchange transfusion, or drug therapy). Therefore, it was not possible to compare the risk of ASD in infants of these three treatment groups, which also causes heterogeneity between studies.

Conclusion

The present findings indicate that NNJ is associated with an increased risk of both ASD and ADHD, with a more pronounced vulnerability observed in boys than in girls. These results support the hypothesis that early neonatal factors may contribute to neurodevelopmental outcomes. While the observed associations do not establish causality, they underscore the importance of careful monitoring and timely management of NNJ, as well as heightened developmental surveillance for affected infants.

Ethical Considerations

Compliance with ethical guidelines

This protocol was registered on the PROSPERO website (Code: CRD42025521493).

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Authors contributions

Conceptualization, study design, data analysis, and data interpretation: Moloud Fakhri; Writing and final approval: All authors.

Conflicts of interest

The authors declared no conflict of interest.

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