Pediatric RESEARCH

SYSTEMATIC REVIEW

Neonatal jaundice and autism spectrum disorder: a systematic review and meta-analysis

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BACKGROUND: Two meta-analyses concluded that jaundice was associated with an increased risk of autism. We hypothesize that these findings were due to methodological limitations of the studies included. Neonatal jaundice affects many infants and risks of later morbidity may prompt physicians towards more aggressive treatment.
METHODS: To conduct a systematic literature review and a meta-analysis of the association between neonatal jaundice and autism with particular attention given to *low risk of bias studies*. Pubmed, Scopus, Embase, Cochrane, and Google Scholar were searched for publications until February 2019. Data was extracted by use of pre-piloted structured sheets. *Low risk of bias studies* were identified through predefined criteria.
RESULTS: A total of 32 studies met the inclusion criteria. The meta-analysis of six *low risk of bias studies* showed no association between neonatal jaundice and autism; cohort studies risk ratio 1.09, 95% CI, 0.99–1.20, case-control studies odds ratio 1.29 95% CI 0.95, 1.76. Funnel plot of all studies suggested a high risk of publication bias.
CONCLUSIONS: We found a high risk of publication bias, selection bias, and potential confounding in all studies. Based on the *low risk of bias studies* there was no convincing evidence to support an association between neonatal jaundice and autism.

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IMPACT:

- Meta-analysis of data from six *low risk of bias studies* indicated no association between neonatal jaundice and autism spectrum disorder.
- Previous studies show inconsistent results, which may be explained by unadjusted confounding and selection bias.
- Funnel plot suggested high risk of publication bias when including all studies.
- There is no evidence to suggest jaundice should be treated more aggressively to prevent autism.

INTRODUCTION

Autism spectrum disorder (ASD) is a disease defined by symptoms in the following three domains; social interaction, communicative disorders, and stereotyped, repetitive or restricted behavior.[1] This review focuses on ASD, including all subtypes. The prevalence of ASD is 1−2%, and has increased since the 1940s.[2–4] ASD is more than four times as prevalent in boys than in girls.[2] The etiology of ASD is unknown, but studies indicate involvement of both genetic[5–7] and non-inheritable factors.[8,9] ASD is a disease with long-term consequences for both the child and the family.[10] Accordingly, there is a need to identify preventable causes of ASD. Neonatal jaundice occurs in some 80% of neonates.[11] Unconjugated bilirubin crosses the blood−brain barrier in the newborn and high levels may cause acute bilirubin-induced encephalopathy and permanent brain damage.[12] The most common neuropathological findings in children with ASD are a decreased number of purkinje cells in the cerebellum, decreased neuronal cell size, and increased cell packing density in the cerebral cortex.[13,14] These areas may also be damaged by bilirubin deposition in brain tissue.[12,15,16] Accordingly, an association between hyperbilirubinemia and ASD seems plausible.[17] Reviews by Amin et al.[16] and Jenabi et al.[18] concluded that neonatal jaundice was associated with an increased risk of ASD. In the review by Amin et al. no structured quality assessment was performed and the conclusion was based on a meta-analysis of all studies regardless of their quality. Jenabi et al. rated 19 out of 21 studies as *high quality* despite methodological limitations of some studies including no adjustment for confounders. The purpose of this systematic review was to compile and critically review the existing evidence of the association between jaundice and ASD and to base the conclusion only on studies with *low risk of bias*.

METHODS

Search strategy

This study is conducted in accordance with the PRISMA guideline (see PRISMA checklist). A systematic literature search was carried out according to the review protocol published in PROSPERO, protocol number: CRD42016025927. Pubmed, Scopus, Embase, Cochrane, and Google Scholar were searched for publications until February 2019. The search terms included autism, autistic disorder,

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pervasive developmental disorder (PDD), ASD, Asperger, hyperbilirubinemia, jaundice, icterus, bilirubin, newborn/perinatal/neonatal risk factor (s), phototherapy. MESH terms were used whenever available. The full search strategy can be found in Supplementary Text S1 (online). References of included studies and other relevant reviews were screened to identify additional studies.

Inclusion/exclusion criteria

All case−control and cohort studies examining the association between jaundice, hyperbilirubinemia, or phototherapy and ASD, that provided absolute numbers were eligible.

Exposure measures had to be either neonatal hyperbilirubinemia or jaundice based on clinical assessment, parental report, laboratory confirmation by estimating serum bilirubin during the neonatal period (within 28 days after birth), or phototherapy treatment.

The outcome measure was ASD, which include childhood/infantile autism, autistic disorder, pervasive developmental disorder—not otherwise specified, and Asperger's. In the literature the terms autism, ASD, and PDD are often used interchangeably; thus, all were included.

To be able to tease out the details of each study, only studies in English peer-reviewed journals were included. Conference abstracts and studies without a reference group such as case series or case reports were excluded.

Studies that adjusted for confounding factors, but did not include the adjusted results, were excluded from the meta-analysis. Studies that investigated preterm infants only were included in a sub-analysis of preterm infants.

Study selection and data extraction

Titles and abstracts of all identified records were screened for eligibility according to the inclusion and exclusion criteria. If immediate exclusion based on title and abstract was not possible, the full text was assessed for eligibility. Structured sheets piloted prior to the search were used for data extraction from each study (see Table 1).

Low risk of bias studies

Studies passed the threshold for strong methodological quality, if they met the following criteria: ASD diagnosis based on International Classification of Diseases/Diagnostic and Statistical Manual of Mental Disorder (ICD/DSM), jaundice was based on TSB measurement or jaundice diagnosis from medical records, and adjustment for at least sex[2] and either gestational age (e.g. term vs. preterm or gestational week at birth) or birth weight.[19] These quality criteria were defined after the development of the PROSPERO protocol, but prior to data extraction. Studies that met the quality criteria were defined as *low risk of bias studies*. Only *low risk of bias studies* were subjected to further quality assessment.

Quality assessment

The quality-assessment was guided by the Cochrane Handbook for systematic reviews of interventions,[20] the STROBE checklist[21] (STrengthening the Reporting of OBservational studies in Epidemiology), and the Newcastle-Ottawa Scale.[22] We defined *essential confounders* as: sex,[2] gestational age[19] or birth weight,[19] birth year,[4] and Apgar score.[19] According to current evidence, these may likely influence the association and should be adjusted for.[23] Other potential confounding factors such as pregnancy complications, parental age, education, and socioeconomic status were also considered, but not deemed essential due to the paucity of studies between these variables and ASD. To further evaluate the quality of the *low risk of bias studies*, the risk of bias in predefined areas (ASD selection, representativeness of ASD cases, selection of controls, ascertainment of hyperbilirubinemia, jaundice selection, assessment of ASD, age at ASD assessment, confounding) were rated as low, high or unclear risk of bias (Fig. 1). This assessment aimed to show the quality of the studies without suggesting how that might influence the effect estimates. The quality-assessment was based on a risk of bias table (Supplementary Table S2 (online)) and assessment of confounders (Supplementary Table S3 (online)) made a priori by the authors.

Literature search, inclusion, data extraction, selection of *low risk of bias studies*, and quality assessment of *low risk of bias studies* were conducted independently by two authors (M.L.K. and M.V.P.). In case of discrepancy between the two authors, a third author (T. B.H.) was conferred.

Data analysis

Data were analyzed using the Cochrane Collaboration Review Manager Software (RevMan version 5.3).[24] Adjusted effect measures were used when available. The unadjusted risk ratio (RR) or odds ratio (OR) was calculated from absolute numbers with 95% confidence intervals (CIs) if adjusted estimates were unavailable. Effect measures were entered into RevMan using the "generic inverse variance" outcome. OR and RR were analyzed separately in the meta-analysis because case−control and cohort studies are heterogenic and may have different challenges related to methodology. A random-effects model was used to analyze the included studies as a random sample of a hypothetical population of studies. Between-study heterogeneity was assessed using I^2, which describes the percentage of variation across studies that is due to heterogeneity rather than chance.[25,26] A forest plot and meta-analyses using a logarithmic scale were made for all studies, the *low risk of bias studies*, and for preterm infants. A funnel plot was used to assess selective reporting.

RESULTS

Literature search

Literature search was conducted in February 2019 (PRISMA flow chart in Fig. 2) identifying a total of 32 studies to be included in this review. Two studies by Maimburg et al.[27,28] were both included, despite overlapping by 5 years. However, they also represent 10 years without overlap.

Study characteristics

Table 1 shows the main characteristics and effect estimates from all 32 included studies. The earliest study dates back to 1979. The total number of children with ASD across all studies was 29,299. Differences in the definition of jaundice (parental assessment by self-administered questionnaires, clinical diagnosis, diagnosis by TSB levels, the need for treatment by phototherapy) and the definition of ASD (diagnosis by ICD-8, 9 or 10 or DSM-III, IV or V) compromised overall comparability.

Nine studies met the *low risk of bias* criteria. The *low risk of bias studies* included 24,440 children with ASD. The studies that were not included in the *low risk of bias studies* failed to adjust for any potential confounding factors or they based the information on jaundice on parental recall. Fig. 1 shows the quality assessment of each of these nine studies and Supplementary Table S3 (online) shows the potential confounders adjusted for. As seen in Fig. 1 even the studies we considered *low risk of bias studies* had several limitations. Of the nine studies two reported an increased risk of ASD with jaundice,[28,29] the seven remaining studies showed no association between jaundice and ASD.[27,30–35] These nine studies were thoroughly reviewed and their main characteristics are summarized in the following narrative syntheses ordered according to their weight in the meta-analyses, with cohort studies first.

Narrative description of *low risk of bias studies*

Wu et al.[31] based their cohort study on 457,855 children born 1995–2011 at 15 Kaiser Permanente Northern California hospitals (KPNC) covering 40% of the insured population. They found no

Table 1. Characteristics and main results of included studies.

Year, author	Inclusion period	Country of study population	Study population Inclusion/exclusion criteria.	Jaundice definition	ASD definition	No. unexposed (ASD) No. exposed (ASD)	Effect estimate (RR, 95% CI) In studies with several effect estimates the effect estimate included in the meta-analysis are highlighted as bold.
Cohort studies							
2016, Wu[31a]	1995–2011	United States	Children born at 15 Kaiser Permanente Northern California (KNPC) hospitals. Age: >3.5 years GA > 35 weeks Exclusion: Downs syndrome, other chromosomal abnormalities, congenital abnormalities (except nasolacrimal passage abnormality).	Highest TSB from medical records up to 30 days of age. 51% had TSB measured. Jaundice frequency: 30% >10 mg/dL	ASD/Asperger/PDD. ICD-9: 299.0/8/9 62% identified through KNPC Autism Centers 38% by a clinical specialist or pediatrician, ASD frequency: 1.3%.	393,839 (4985) 64,016 (994)	TSB: 10–14.9 mg/dL: 1.06 (0.98–1.14) **TSB: 15–19.9 mg/dL: 1.07 (0.98–1.17)** TSB > 20 mg/dL: 1.09 (0.89–1.35) Phototherapy: 1.10 (0.98–1.24) Adjusted for confounders.
2014, Chen[75]	1999–2000	Taiwan	National Health Insurance Research Database (NHIRD) (covers 99% of Taiwan). Follow-up until December 31, 2011.	ICD-9-CM: 774 (all types of neonatal jaundice).	PDD ICD-9-CM: 299 Psychiatrist. ASD frequency: 0.8%	2016 (26) 8064 (59)	**HR: 1.75 (1.05–2.90)** Phototherapy: 1.82 (0.79–4.20) Term: 1.69 (1.00–2.86) Preterm: 1.73 (0.68–4.41) Adjusted for confounders.
2010, Maimburg[28,36a]	1994–2004	Denmark	Children in the Danish Medical Birth Register.	ICD-10; P57.0–P59.9 from (99.9% were jaundice, unspecified) Danish Medical Birth Register. Jaundice frequency: 4.9%.	PDD ICD-10: F84–84.9. Danish Psychiatric Central Register. In- and outpatient. Child psychiatrist. Autism frequency: 0.84%.	698,060 35,766 (ASD total: 6171[c])	**1.07 (0.94–1.21)[c]** > 37 weeks: 1.06 (0.90–1.25)[c] < 37 weeks: 1.05 (0.83–1.32)[c] Adjusted for confounders.
2008, Jangaard[32a]	1994–2000	Canada	Children in Nova Scotia Atlee Perinatal database. (covers 94% of the province. Health care is free) GA: > 35 weeks Age: >2 year Exclusion: Documented Rh factor isoimmunization, significant congenital anomalies, severe peripartum asphyxia, or documented hypoxic-ischemic encephalopathy.	TSB > 13.5 mg/dL within 28 days after birth. Nova Scotia Atlee Perinatal Database. Jaundice frequency: 6.7%.	ASD ICD-9. Medical Service Insurance (physician billings) and the hospital Discharge Abstract Database. Physician. ASD frequency: 0.33%.	52,240 (168) 3779 (19)	1.6 (1.0–2.56) Adjusted for confounders.

Author	Inclusion period	Country of study population	Study population Inclusion/exclusion criteria. How cases and controls are matched.	Jaundice definition	ASD definition	No. cases (exposed) No. controls (exposed)	Effect estimate (OR, 95% CI) In studies with several effect estimates the effect estimate included in the meta-analysis are highlighted as bold.
Case–control studies							
2019, Chien[71]	No information	Taiwan	Cases: From Department of Psychiatry of two medical centers in Northern Taiwan. Controls: Sibling or typically developing control recruited from the community through advertisement or from regular classes. Absence of mental problems ensured by questionnaire screening. Exclusion: Fragile X syndrome and Rett's disorder.	Phototherapy. Reported in parents' interview. If a prenatal/perinatal event was reported, medical records were checked when available (around 15%) for validation. Maternal reports were generally consistent with medical records.	Asperger and autistic disorder. DSM-IV. Confirmed by ADI-R. Child psychiatrist.	323 (138) Sibling: 257(82) Typically developing control: 1504 (353)	**Sibling: 1.42 (0.79–2.56)** Typically developing control: 10.36 (7.09–15.14) Adjusted for confounders.
2018, Hisle-Gorman[35a]	2000–2013	United States	Military Health System database for uniformed services' members and their family members. Cases: ICD diagnosis at two separate encounters. Controls: For each case three controls matched on age, sex, and enrolment time frame. Age: 2–18 years. Exclusion: childhood disintegrative disorder, controls with diagnosis of ASD.	Neonatal jaundice and phototherapy procedure codes. ICD-9. Inpatient and outpatient medical records for the first 90 days.	ASD. ICD-9.	8760 (3401) 26,280 (9483)	1.13 (1.07–1.18) Unadjusted Non-significant after adjustment, but effect estimate not presented.
2018, Geetha[58]	2017–2018	India	Cases: from three autism rehabilitation centers Controls: For each case one control matched by age and sex. From various pediatric outpatient well-children clinics. Without history of learning and psychiatric abnormalities. Age: 3–12 years. Exclusion: Tuberous sclerosis, neurofibromatosis, fragile X syndrome and Down syndrome.	Neonatal hyperbilirubinemia. Parents interview or medical records and phone-calls to parents.	DSM-5. Pediatrician and a psychologist. Using CARS.	55 (22) 55 (16)	1.63 (0.74–3.59) Not adjusted for confounders[b].
2018, Bhattarai[67]	No information	Nepal	National Children's Hospital, a tertiary Government Hospital. Cases: ASD diagnosis. Controls: patients with similar age and sex who visited the general OPD clinic. Age: 4–14 years	Jaundice. Parents questionnaire.	No information.	58 (7) 58 (0)	17.04 (0.95–305.68) Not adjusted for confounders[b].

Table 1. continued

Author	Inclusion period	Country of study population	Study population Inclusion/exclusion criteria. How cases and controls are matched.	Jaundice definition	ASD definition	No. cases (exposed) No. controls (exposed)	Effect estimate (OR, 95% CI) In studies with several effect estimates the effect estimate included in the meta-analysis are highlighted as bold.
2016, Ravi[57]	2014 (June to August)	India	Pediatric outpatient department of JIPMER, tertiary hospital. Cases: ASD diagnosis Controls: no ASD diagnosis Age: 16–30 months Exclusion: Visual or hearing impairments, acute medical illness.	Severe neonatal jaundice. Maternal interviews. When possible, information was collected from medical records.	M-CHAT-R high risk category, followed by psychiatric evaluation.	33 (4) 317 (33)	1.19 (0.39–3.59) Not adjusted for confounders.
2015, Lozada[29a]	2000–2009	United States	TRICARE management Activity's Military Health System (MHS) database. Cases: ASD diagnosis. Controls: For each case three children matched on sex and age without any outpatient ASD diagnosis. Age: >3 years.	Jaundice during hospitalization or phototherapy/transfusion within the first month of life. ICD-9-CM MHS database. Jaundice frequency: 19%. Treatment with phototherapy: 2.9%.	ASD ICD-9-CM: 299.0/8/9. MHS database. Minimum 1 outpatient visit to a pediatric specialist. Autism frequency: 2917 of 783047 files = 0.37%.	2917 (640) 8751 (1614)	**1.18 (1.06–1.31)** < 37 weeks: 1.06 (0.77–1.47) Phototherapy: 1.33 (1.04–1.69) Adjusted for confounders.
2014, Duan[74]	2011–2013	China	Cases: From Third Affiliated Hospital Children's Psychological Clinic, Zhengzhou, China. Control: for each case one control matched on age, sex, socioeconomic background from 3 local kindergartens. Age: 3–6 years. Exclusion: undefined diagnosis, other organic diseases of the nervous system, serious heart, liver, kidney, endocrine, or blood diseases, simple mental retardation, fragile X syndrome, and other pervasive developmental disabilities.	Severe jaundice. No further information.	Childhood Autism DSM-IV. CARS > 30. Pediatric Specialist.	286 (49) 286 (6)	21.81 (12.21–35.54) Adjusted for confounders.
2014, Froehlich-Santiano[62]	1987–2004	United States (California)	Cases: From the Department of Development Services in California by invitation to parents. Controls: Twin siblings. Age: 4–18 years. Exclusion: Neurogenetic conditions associated with autism and mental age less than 18 months.	Jaundice. Parents' questionnaire.	ASD: broad phenotype. DSM-IV. Expert (ADI-R and ADOS).	245 (113) 134 (45)	1.69 (1.09–2.62) Adjusted for confounders.
2014, George[63]	No information	India	Thiruvananthapuram, India. Cases: From autism clinic of Child Development Centre. Controls: recruited from immunization clinic. Age: 2–6 years.	Jaundice. Pre-piloted questionnaires. Interviewed by Senior Social Scientist.	Childhood Autism. CARS > 30.	143 (22) 200 (22)	1.47 (0.78–2.77) Not adjusted for confounders.

Table 1. continued

Author	Inclusion period	Country of study population	Study population Inclusion/exclusion criteria. How cases and controls are matched.	Jaundice definition	ASD definition	No. cases (exposed) No. controls (exposed)	Effect estimate (OR, 95% CI) In studies with several effect estimates the effect estimate included in the meta-analysis are highlighted as bold.
2014, Elsedfy[70]	2010–2012	Saudi Arabia	Cases: from psychiatric and pediatric clinics in Al-Ahsa City Hospital. Controls: For each case one control matched on age. Without psychiatric or medical disorders or developmental delay who came for vaccination. Age: 3–8 years.	Hyperbilirubinemia, Parents interview. Birth records studied for unfavorable neonatal events.	Autism DSM IV-TR. Confirmed by using ADOS.	43 (14) 43 (15)	0.90 (0.37–2.20) Not adjusted for confounders[b].
2013, Hwang[34a]	1998–2001	Taiwan	Children born preterm registered in Taiwan National Health Insurance Research Database NHIRD (covers 99% of Taiwan). Cases: ASD diagnosis Controls: No ASD diagnosis GA: <37 weeks Age: 8–11 years.	Neonatal jaundice associated with preterm delivery. ICD-9: 774.2, Inpatient and outpatient. Jaundice frequency in preterms: 32.8%.	Infantile Autism ICD-9-CM. 299.0 Inpatient and outpatient data. Physician. ASD frequency: 0.6%	411 (134) 29,614 (9710)	<37 weeks: 1.0 (0.8–1.2) Adjusted for confounders.
2013, Mamidala[68]	2000–2012	India	8 Indian cities. Cases: From 65 centers dealing with autism. Controls: For each case one control matched on sex and age, from schools and random houses, with no history of learning or psychiatric disabilities. Age: 2–10 years. Exclusion: No formal ASD diagnosis, cerebral palsy, Downs syndrome.	Jaundice. Questionnaire filled by direct interaction from authors or trained staff.	ASD ICD/DSM/CARS. Parents report confirmed through diagnostic report made by psychiatrist mostly.	471 (64) 471 (17)	2.89 (1.58–5.28) Adjusted for confounders.
2013, Mrozek-Budzyn[53]	1992–2005	Poland	Cases: From a single psychiatric outpatient clinic in Voivodship. Controls: For each case two controls matched on age and sex from the same general practice. Age: 2–15 years. Exclusion: Autistic children with genetic syndromes.	Jaundice. Physicians' records.	Childhood autism and atypical autism ICD-10: F84.0–1. Outpatient. Pediatric psychiatrist.	96 (28) 192 (69)	0.73 (0.43–1.25) Not adjusted for confounders[b].
2012, Nath[54]	No information	India	Seth Sukhlal Karnani Memorial Hospital at Kolkata, India. Cases: From the Neurodevelopment and Early Intervention Clinic following children after ante/perinatal complications. Controls: Matched on age, from a general pediatric outpatient clinic of the same hospital. Age: >3 years. Exclusion: Hearing or visual impairment.	Pathological jaundice. No further information.	ASD. DSM-IV-TR. Screening by parents' interview.	31 (2) 100 (8)	0.79 (0.16–3.90) Not adjusted for confounders[b].

Table 1. continued

Author	Inclusion period	Country of study population	Study population Inclusion/exclusion criteria. How cases and controls are matched.	Jaundice definition	ASD definition	No. cases (exposed) No. controls (exposed)	Effect estimate (OR, 95% CI) In studies with several effect estimates the effect estimate included in the meta-analysis are highlighted as bold.
2011, El baz[60]	1995–2008	Egypt	Cases: From the Psychiatric clinic, pediatric hospital, Ain Shams University, Egypt. Controls: For each case two controls matched on age, sex, environment and habitat, recruited from different outpatient clinics, referred to psychiatric clinic to rule out ASD. Age: 2–13 years.	Neonatal jaundice. No further information.	ASD. DSM-IV-TR. CARS > 21.	100 (24) 200 (10)	14.6 (2.33–13.68) Revman: 14.6 (2.33–91.49) Not adjusted for confounders.
2011, Elhameed[61]	No information	Egypt	Minia city. Cases: Supposed autistic children in JBAD (Organisation for mentally ill children), Egypt. Controls: Siblings. Age: 4–18 years.	Jaundice. Parents' questionnaire.	Autism CARS.	14 (2) 28 (1)	4.5 (0.37–54.73) Not adjusted for confounders[b].
2010, Zhang[55]	1986–2004	China	Tianjin region. Cases: From one of six public special education schools or one of two preschools. Control: For each case one control matched on sex and age attending a public school with same socioeconomic level. Age: 3–21 years.	Neonatal jaundice. Self-administered questionnaires by parents, assisted by trained staff.	Autism ICD-10. CARS > 30. Pediatric specialist.	95 (11) 95 (1)	12.31 (1.56–97.36) Not adjusted for confounders.
2010, Ahmed[72]	No information	Saudi Arabia	Cases: from the rehabilitation center at Riyadh city. Controls: Outpatient department of Security Forces Hospital at Riyadh city.	Serum bilirubin test results in medical records, highest level within 30 days. Phototherapy derived from inpatient databases.	No information.	50 (50) 50 (21)	138.59 (8.09–2372.93) Not adjusted for confounders[b].
2009, Buchmayer[33a]	1987–2002	Sweden	Swedish Medical Birth Register. Cases: From the Hospital Discharge Register. Controls: For each case five randomly selected controls matched on sex, birth year, birth hospital. Without autistic diagnosis. Age: 0–10 years.	Neonatal jaundice. ICD-9: 773 + 4 ICD-10: P55–59. Inpatient Hospital Discharge Register. Frequency of jaundice in controls: 38.1% preterm 2.4% term.	ASD ICD-9: 299ABWX, ICD-10: F84.0–5 + 48–9. Inpatient Hospital Discharge Register. Screening at 4 years and referred to child psychiatric specialist unit.	1216 (74) 6080 (285)	**1.18 (0.86–1.63)** >37 weeks: 1.3 (0.9–1.9) <37 weeks: 0.7 (0.5–1.2) Adjusted for confounders and interaction with being preterm.

Table 1. continued

Author	Inclusion period	Country of study population	Study population Inclusion/exclusion criteria. How cases and controls are matched.	Jaundice definition	ASD definition	No. cases (exposed) No. controls (exposed)	Effect estimate (OR, 95% CI) In studies with several effect estimates the effect estimate included in the meta-analysis are highlighted as bold.
2009, Sugie[73]	1980–1999	Japan	Cases: Diagnosed at Hamamatsu City Medical Centre for developmental medicine. Controls: Children with normal cognitive development in routine examination. Exclusion: pervasive developmental disorder, underlying diseases, delay in motor developments, evident chromosomal aberrations.	Hyperbilirubinemia. Maternity records.	Autistic disorder. DSM-IV. Pediatric Neurologist and clinical psychologist.	225 (31) 1580 (109)	**2.16 (1.41–3.30)** Phototherapy: 2.45 (1.50–4) Not adjusted for confounders[b].
2008, Maimburg[28a]	1990–1999	Denmark	Cases: Danish Psychiatric Central Register. Controls: For each case one control matched on sex, birth year, county of birth. Randomly selected from Danish Civil Registration System. 4.6 years of age without diagnosis of infantile autism. Age: <10 years. Exclusion: Foreign-born children.	Hyperbilirubinemia: µmol/L exceeded the numeric value of 10% of weight in g. or <1000 g: 5.8 mg/dL. >3000 g: 20 mg/dL. Danish Medical Birth Registry. Jaundice frequency: 3.6%. 18% of cases and 13% of controls had TSB tested.	Infantile Autism ICD-8/10: 299.0/F84.0. Danish psychiatric central register Inpatient and from 1995 outpatient data. Pediatric Psychiatrist.	461 (28) 461 (5)	Based on individual infants' weight: **3.7 (1.3–10.5)** Based on birth weight for all infants: 3.8 (1.2–12.1) >37 weeks: 9 (1.14–71.04) <37 weeks: 1 (0.06–15.99) Phototherapy: 3.3 (1.0–10.1) Adjusted for confounders.
2005, Croen[30a]	1995–1998	United States	Northern California Kaiser Permanent facility. Children with GA > 35 weeks. (30% of the insured population >3.2 mill. residents). Cases: ASD, Asperger's syndrome or pervasive developmental disorder. Controls: for each case 5 controls matched on sex, birth year, hospital of birth. GA: >35 weeks Age: 4–7 years.	Serum bilirubin > 15 mg/dL. Highest level within 30 days. Inpatient record for phototherapy. Laboratory database. Jaundice frequency >10 mg/dL: 21% >16 mg/dL: 10% 28% were tested.	ASD. ICD-9-CM: 299.0/8/9. Outpatient database. General physician. 35 cases were reviewed: All had ASD either according to DSM-5 or review of data by ASD pediatric specialist.	>15 mg/dL: 338 (34) 1817 (220)	**>15 mg/dL: 0.67 (0.43–1.05)** >20 mg/dL: 0.69 (0.28–1.69) >25 mg /dL: 1.22 (0.12–12.68) Adjusted for confounders.
1999, Matsuishi[66]	1983–1987	Japan	St Marys Hospital, Kurume City, Japan. Cases: From NICU admissions. Controls: Children with normal outcome randomly selected from the same NICU. Age: 5–8 years.	Hyperbilirubinemia. No further information.	Autistic disorder. DSM-III-R. Pediatric Neurologist.	18 (10) 214 (81)	2.05 (0.78–5.39) Not adjusted for confounders[b].

Table 1. continued

Author	Inclusion period	Country of study population	Study population Inclusion/exclusion criteria. How cases and controls are matched.	Jaundice definition	ASD definition	No. cases (exposed) No. controls (exposed)	Effect estimate (OR, 95% CI) In studies with several effect estimates the effect estimate included in the meta-analysis are highlighted as bold.
1993, Piven[56]	No information	United States	Cases: From a voluntary organization, one private school for autistic children and three public schools in Baltimore. Control: siblings. Age: 5–25 years. Exclusion: only for cases: evidence of blindness, deafness, known disorders associated with autism.	Hyperbilirubinemia. Questionnaires (31%) and records (69%).	Autism ICD-10.ADI, ADOS. Physician.	39 (6) 39 (1)	6.91 (0.79–60.44) Not adjusted for confounders[b].
1990, Mason-Brothers[69]	1965–1984	United States	Cases: From the Epidemiological survey of Utah. Extensive 4-year media campaign, practitioners, agencies, patient groups, hospitals, school and relations. Control: Siblings.	Jaundice. Medical records.	Autism DSM-III. At least two trained clinicians.	223 (99) 57 (23)	1.18 (0.65–2.14) Not adjusted for confounders[b].
1983, Gillberg[41]	1962–1976	Sweden	Cases: Reported as autistic by pediatricians and child psychiatrist when approached by the authors. Controls: for each case one control matched on sex and birth year from the same obstetric ward. Age: >2.5 years. Exclusion: Foreign born.	Hyperbilirubinemia. >15 mg/dL with birth weight < 2500 g. >20 mg/dL with birth weight > 2500 g. Medical records.	Infantile autism. Pediatricians or child psychiatrist.	25 (1) 25 (0)	3.12 (0.12–80.39) Not adjusted for confounders[b].
1980, Deykin[59]	1975–1977	United States	Cases: Referred to authors by 19 autism care clinics, centers, and schools by invitation to parents in Massachusetts. Control: siblings. Age: <6 years. Exclusion: Cases without siblings, siblingships with more than one autistic child.	Jaundice. Family interviews.	Autistic symptoms described in record, confirmed by parents' interview, included if symptoms in one out of three areas.	145 (10) 330 (21)	1.1 (0.7–1.7) Adjusted for confounders.
1979, Finegan[42]	No information	Canada	No description of population Cases: autistic diagnosis. Controls: Siblings.	Serum bilirubin >16 mg/dL Medical records.	Infantile autism. Child psychiatrist.	15 (3) 15 (0)	8.68 (0.41–184.28) Not adjusted for confounders[b].

ASD autism spectrum disorder, *AD* autistic disorder, *ICD* International Classification of Diseases, *WHO, DSM* Diagnostic and Statistical Manual of Mental Disorders, American Psychiatric Association, *TSB* total serum bilirubin, *ADI (R)* Autism Diagnostic Interview (revised), *ADOS* Autism Diagnostic Observation Schedule, *CARS* Childhood Autism Rating Scale.
1 mg/dL = 17,1 µmol/L
[a]Low risk of bias studies, defined as: ASD diagnosis based on ICD/DSM, jaundice based on TSB measurement or jaundice diagnosis from medical records, and adjustment for at least sex and either gestational age (e.g. term vs. preterm or gestational week at birth) or birth weight.
[b]Effect estimates and 95% CI are calculated based on information provided in the publication.
[c]Data from revised analysis by Maimburg et al., including patients from Danish Psychiatric Central Register instead of Danish Medical Birth Register.

Reference	ASD selection[c]	Representativeness of ASD cases	Selection of controls	Ascertainment of hyperbilirubinemia	Jaundice selection[c], %	Assessment of ASD	Age at ASD diagnosis	Confounding
2018, Hisle-Gorman (4)					**36.1**			
2016, Wu (5)	**1.3**		**N/A**		**30**			
2015, Lozada (6)	**0.37**				**19**			
2013, Hwang (7)	**0.6**				**32.8 (PT)**			
2010, Maimburg (8)	**0.8**		**N/A**		**4.9**			
2009, Buchmayer (9)	**1216**[a]				**38.1 (PT)** **2.4 (T)**			
2008, Jangaard (10)	**0.3**		**N/A**		**6.7**			
2008, Maimburg (11)	**461**[b]				**3.6**			
2005, Croen (12)	**0.54**				**21**			

Red: high risk of bias; Yellow: unclear risk of bias; Green: low risk of bias; White: not applicable

PT: preterm; T: term; ASD: Autism Spectrum Disorders

[a] Total amount from the Swedish (1987-2002) national birth register

[b] Total amount from Danish (1990-1999) national birth register

[c] Numbers in the boxes indicate the frequency in % reported by the study author

Low risk of bias studies, defined as: ASD diagnosis based on ICD/DSM, jaundice based on TSB measurement or jaundice diagnosis from medical records, had more than 150 ASD cases included, and adjustment for at least sex and either gestational age (e.g. term vs. preterm or gestational week at birth) or birth weight.

Fig. 1 Qualitative assessment of *low risk of bias* studies based on predefined criteria (Supplementary Table S2).

association between jaundice and ASD (RR 1.07, 95% CI, 0.98–1.17). Neonatal jaundice was found in 30% and ASD in 1.3% of the included population. Jaundice was defined as TSB > 10 mg/dL, and 51% of all newborns in the study had TSB measured. ASD was defined according to ICD-9 and retrieved from the KPNC registry. Children were either diagnosed at autism evaluation centres, by a clinical specialist outside the ASD center, or by a general pediatrician. The study adjusted for all our predefined essential confounders. They estimated the effect of phototherapy, and found that use of phototherapy did not change the association between jaundice and ASD.

Maimburg et al.[27] (revised ASD selection[36]) based their cohort study on all Danish children born 1994–2004. They found no association between jaundice and ASD (RR 1.07, 95% CI, 0.94–1.21). They included 733,826 children, 5% were jaundiced and 0.8% had ASD. Jaundice was defined according to ICD-10 retrieved from the National Patient Registry. Several neurodevelopmental disorders (F80−F84.9 and F88−F88.9), including autism/pervasive developmental disorders, were studied. ASD was defined by ICD-10 from the Danish Psychiatric Central Register (in- and outpatients). Results were adjusted for all the predefined essential confounders except birth year. In children born preterm no association was found (RR 1.05, 95% CI, 0.83–1.33).

Jangaard et al.[32] based their cohort study on the Canadian Nova Scotia Atlee Perinatal Database including 94% of all newborns 1994–2000 in the province. They found an association between jaundice and ASD (RR 1.60, 95% CI, 1.00–2.56). A total of 56,019 children were included, 7% were jaundiced and 0.33% had ASD. The study assessed the association between serum bilirubin levels and four outcomes including autism. Jaundice was defined as TSB level above 13.5 mg/dL. The Medical Service Insurance (physician billings) and the hospital Discharge Abstract Database provided ASD diagnosis by ICD-9. The study adjusted for all predefined essential confounders except birth year and Apgar score.

Lozada et al.[29] found that neonatal jaundice was associated with an increased risk of ASD (OR 1.18, 95% CI, 1.06–1.31). This case−control study was based on data from the United States (US) Military Health System database. It included 2917 cases born 2000–2009 and 8751 controls matched by sex and age. Jaundice and ASD was defined according to ICD-9-CM; only inpatient diagnoses were used for jaundice. Eighteen percent of infants in the control group were jaundiced. ASD was ascertained from a minimum of one outpatient visit to a pediatric specialist, with no description of how children were referred. ASD was found in 0.37% of 783,047 births recorded. Our defined essential confounders apart from Apgar score and birth year were assessed. When studying preterm children only, the association disappeared (OR 1.06, 95% CI, 0.77–1.46).

Buchmayer et al.[33] based their case−control study on the Swedish Medical Birth Register and included 1216 ASD cases born 1987–2002 and 6080 controls matched by sex, birth year and birth hospital. They found no association between jaundice and ASD

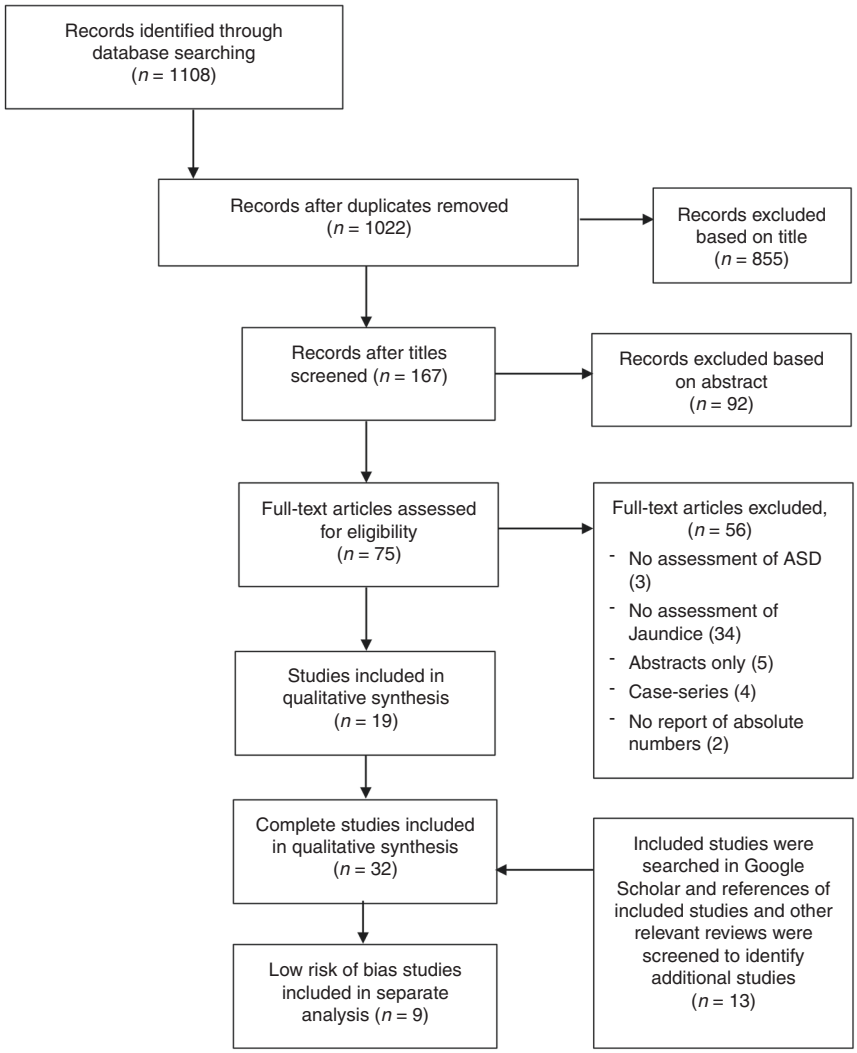

Fig. 2 PRISMA flow chart. PRISMA flow chart for the systematic review detailing the number of abstracts and full-text screened and number of studies excluded.

(OR 1.18, 95% CI, 0.83–1.68). Jaundice was one of many perinatal factors studied. Jaundice and ASD was defined by ICD-9 and ICD-10 from inpatient medical records, 5% of infants in the control group were jaundiced. ASD was verified by a child psychiatrist. The study adjusted for all the predefined essential confounders and 16 other risk factors. When preterm infants were assessed no association was seen (OR 0.70, 95% CI, 0.50–0.98).

Croen et al.[30] based their case−control study on children born at one of the KPNC hospitals in Northern California covering 30% of the insured population. They found no association between jaundice and ASD (OR 0.67, 95% CI, 0.43−1.04). It included 338 ASD cases born 1995–1998 and 1718 controls matched by sex, birth year, and hospital of birth. Jaundice was defined as TSB > 15 mg/dL, 28% of cases and controls had TSB measured and 12% of infants in the control group were jaundiced. ASD was defined by ICD-9-CM and obtained from the outpatient databases. The study adjusted for all our predefined essential confounders except Apgar score.

Maimburg et al.[28] found that TSB > 17.5 mg/dL (300 µmol/L) was associated with increased odds of ASD (OR 3.70, 95% CI, 1.30–10.53). Maimburg et al. based their case−control study on all children born in Denmark 1990–1999. The study included 461 cases and 461 controls from the national civil registration system matched by sex, birth year and county of birth. The study assessed the association between seven neonatal risk factors and ASD. TSB values were retrieved from medical records; 18% of cases and 13% of controls had a TSB measured, jaundice frequency was 3.6%. ASD was defined by psychiatrists' ICD-8 and ICD-10 codes. ASD cases were ascertained from the Danish Psychiatric Central Register including all inpatients in Denmark 1990–1995 and in- and outpatients 1995–1999. Apgar score was the only essential confounder not adjusted for. When preterm infants were considered the association disappeared (OR 1.00, 95% CI, 0.06–16.67).

Hilse-Gorman et al.[35] based their case−control study on the US Military Health System. They included 8760 ASD cases born 2000–2013. They claimed to find no association in the adjusted analyses. However, the adjusted results were not presented. Each case was matched by three controls by age, sex, and enrollment time frame. Jaundice was one of 28 different risk factors studied. Information on jaundice and ASD was based on ICD-9 from inpatient and outpatient data. Thirty-six percent of infants in the control group were jaundiced (highest rate in any study in this review). All essential confounders were adjusted for. Adjusted results were not shown, and therefore not included in our meta-analysis.

Hwang et al.[34] based their case−control study on Taiwan National Health Insurance Research Database covering 99% of Taiwanese population. They found no association between jaundice in preterm neonates and ASD (OR 0.99, 95% CI, 0.81–1.21). The aim was to

identify neonatal risk factors for autism in preterm children. The study included 411 ASD cases and 29,614 controls born 1998–2001. Jaundice was defined by ICD-9-CM from in- and outpatient databases, ASD was only from outpatient databases, 33% of infants in the control group were jaundiced. All predefined essential confounders except for Apgar score were adjusted for.

Meta-analysis and funnel plot

When restricting the analysis to the *low risk of bias studies*, there was no significant association between neonatal jaundice and ASD. Three case−control studies were excluded from the meta-analysis, one only studied preterm infants[34] and one did not show the adjusted OR.[35] The third study had an overlapping population with that of Wu et al.[31] Croen et al.[30] included one KNPC hospital while Wu et al.[31] included 15 KNPC hospitals of Northern California. The meta-analysis of the three *low risk of bias* cohort studies revealed an RR of 1.09 (95% CI, 0.99–1.20), and of the three *low risk of bias* case−control studies an OR of 1.29 (95% CI, 0.95–1.76) (Fig. 3). If the study by Croen et al.[30] was included in the meta-analysis of the case−control studies, the OR was 1.14 (95% CI, 0.80–1.61). In addition, we found no statistically significant association from the meta-analysis of all four cohort studies (RR 1.14, 95% CI, 0.99–1.30), while the meta-analysis of all 29 case−control studies showed an association OR 1.74 (95% CI, 1.42–2.12) (Fig. 4). The meta-analysis based on preterm infants only showed no significant association (OR 0.93, 95% CI, 0.77–1.12) (Fig. 5). The meta-analysis of all studies found a high degree of heterogeneity (I^2 of 51% (cohort studies) and 83% (case−control studies)). Furthermore, funnel plots (Fig. 6) indicated selective reporting of studies that found an association.

DISCUSSION

We identified 32 studies that qualified for this review of the association between neonatal jaundice and ASD. In the meta-analysis of all studies we found an association between neonatal jaundice and ASD. A funnel plot demonstrated a high risk of publication bias. Due to the large variation in the quality of the studies, a meta-analysis of all studies should be interpreted with caution. The *low risk of bias studies* were based on ICD/DSM and not on parental recall, and most of them had a predefined primary aim to study jaundice and ASD, making publication bias and type 1 errors less likely. Although not significant, our meta-analysis restricted to the three *low risk of bias* cohort studies showed an increased risk of ASD of 9% (RR 1.09, 95% CI, 0.99–1.20). If not due to random variation, this could be explained by methodological limitations such as residual confounding and selection bias even in the *low risk of bias studies* (Fig. 1).

A challenge in all studies was a reliable jaundice diagnosis. No studies defined the criteria for diagnosing jaundice or measuring TSB level, e.g., referral criteria. In most settings bilirubin testing is not used as a screening procedure for all newborns, and since jaundice often develops some days after birth, discharged newborns may be less likely to be diagnosed. Accordingly, the neonate who has been discharged may rarely have a diagnosis of hyperbilirubinemia from the hospital system[37–39]; at nine KPNC hospitals the number of infants with TSB 15–19.9 mg/dL increased by 56% after implementation of universal bilirubin screening.[40] This suggests that the jaundice diagnosis is an indicator of being hospitalized rather than having a bilirubin level different from non-hospitalized newborns, in particular when jaundice is defined by the lower cut-off levels of bilirubin. In our *low risk of bias studies* we included jaundice based on medical records and even among studies using serum values[28,30–32,41,42] highly variable definitions of jaundice were seen resulting in frequencies differing between 1 and 36%. In conclusion, availability and criteria of TSB testing and TSB cut-off values may influence the frequency of jaundice, the risk of selection bias, and the interpretation of the exposure in the studies. All studies qualified as low quality on jaundice selection, because they did not explain which infants had TSB measured or controlled for hospitalization or in other ways reflected on the frequency of TSB measurement/hyperbilirubinemia.

If hospitalized children are more likely to be categorized as exposed, interpretation of results may be difficult. Compared to the background population, hospitalized newborns may differ in several ways: they are more likely to be the first child, to have had a complicated delivery, to be of low birth weight, or to be preterm. These are all factors associated with ASD. Comparing children hospitalized in the newborn period who may much more often be diagnosed with jaundice to non-hospitalized children with a much lower risk of being diagnosed with jaundice might lead to bias towards an association between jaundice and ASD. We have illustrated this by a directed acyclic graph (DAG)[43]; if hospitalization is a cause of jaundice diagnosis it opens numerous potential biasing pathways (Supplementary Fig. 5). According to the DAG, studies of a causal relationship should either adjust for all covariates causing both neonatal hospitalization and ASD, should be based on exposures obtained from universal bilirubin screening, or should adjust for hospitalization for reasons other than suspected hyperbilirubinemia. Using a conservative cut-off level may decrease but not eliminate this bias.

Accordingly, studies in preterm newborns that are all hospitalized after birth may illustrate the points made on jaundice and hospitalization; in six of the included studies, preterm neonates were analyzed independently. Five of these studies were *low risk*

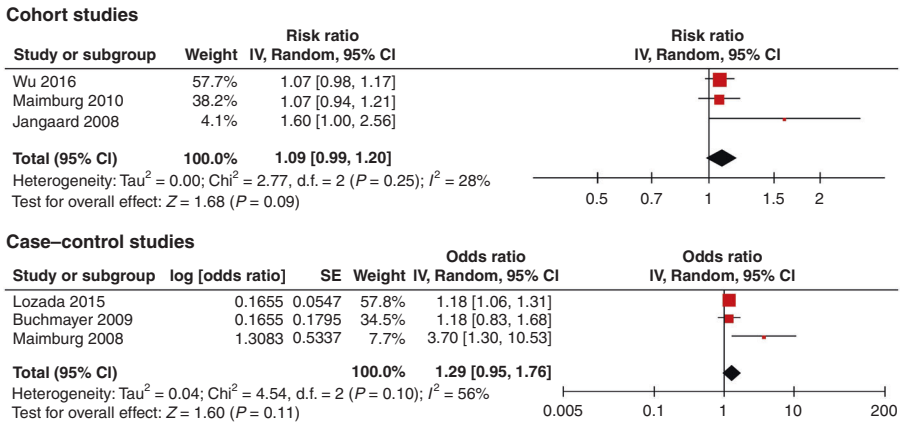

Fig. 3 Forest plot of the association between neonatal jaundice and ASD, low risk of bias studies. The squares show the average effect size of each study. The diamonds show the combined average effect size.

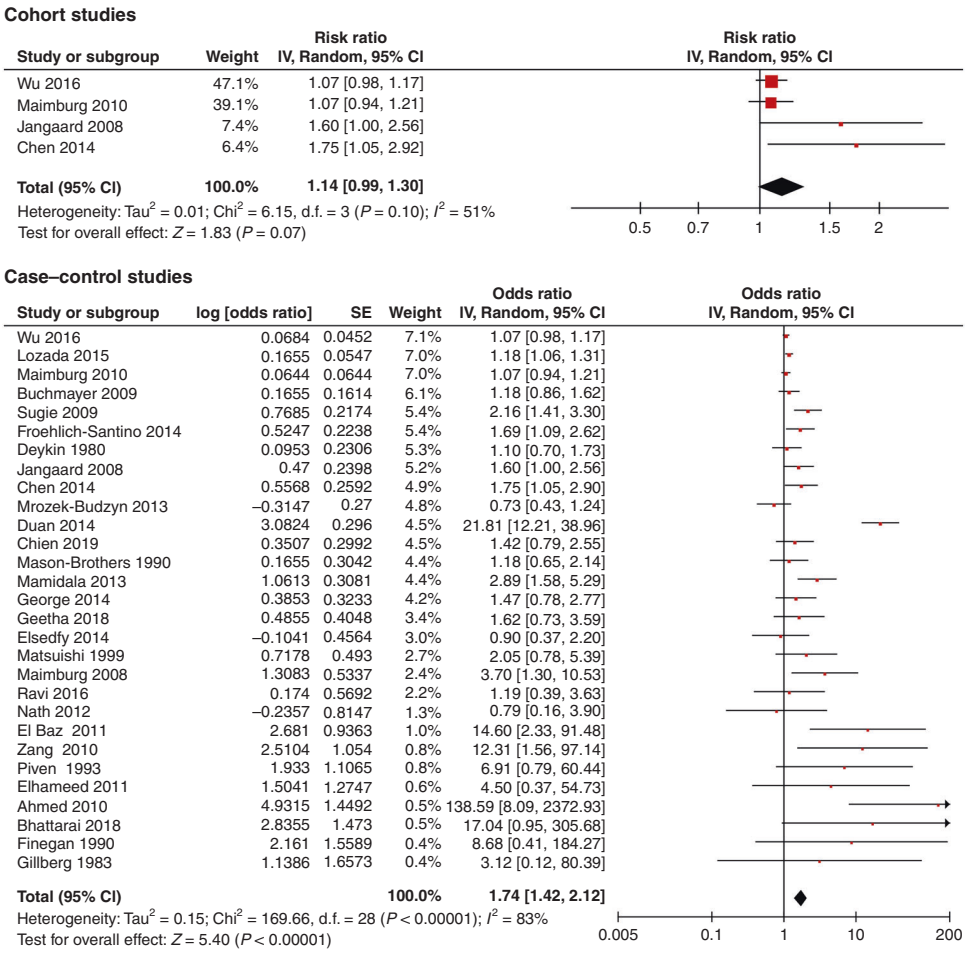

Fig. 4 Forest plot of the association between neonatal jaundice and ASD, all studies. The squares show the average effect size of each study. The diamonds show the combined average effect size.

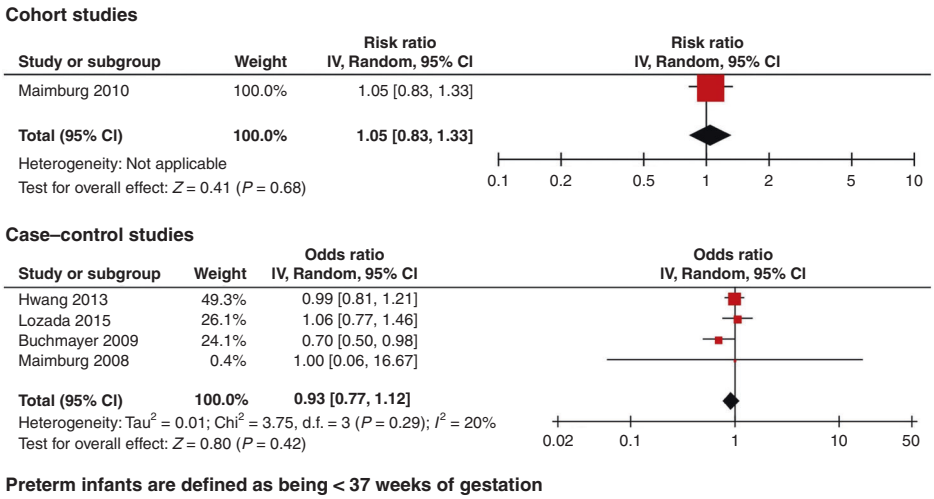

Fig. 5 Forest plot of the association between neonatal jaundice and ASD, preterm infants. The squares show the average effect size of each study. The diamonds show the combined average effect size.

of bias and all showed no association between jaundice and ASD in preterm newborns (Fig. 5).

Confounding factors may influence the relationship between bilirubin levels and ASD. Potential confounders could be newborn infections, asphyxia, parental age, and complicated delivery; however, other factors such as genetic and socioeconomic factors may also be involved. Whether it is possible to fully adjust for all potential confounders is questionable.

Several studies used parental recall of neonatal jaundice as the exposure, which may result in recall bias. None of these studies were considered *low risk of bias studies* in this review.

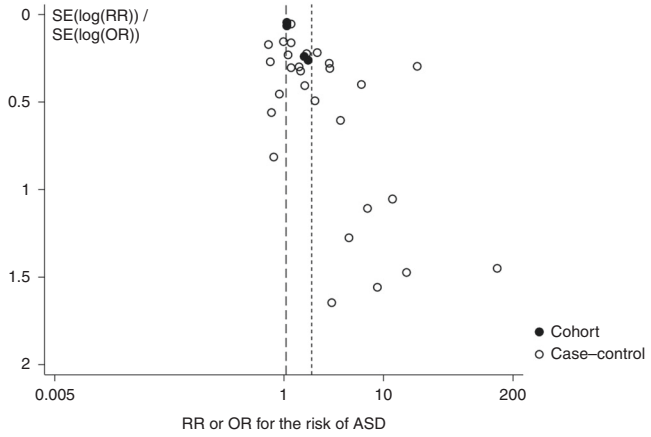

Fig. 6 Funnel plot of studies investigating the association between neonatal jaundice and ASD.

The Autism and Development Disabilities Monitoring Network suggested an increase in estimated prevalence of ASD by roughly 123% since 2002, which is supported by several other sources.[4,44–46] This is thought to be explained by other factors than a true increase, i.e., diagnostic criteria, service availability, increased funding, and population awareness.[3,46–49] Furthermore, new guidelines on the diagnosis of hyperbilirubinemia (one particularly from 1994[37]) have emerged, and contributed to an increase in admissions for neonatal jaundice.[32,50,51] The majority of studies collected data over time periods of some 15 years. Therefore, if time is not adjusted for, changes in diagnostic practices, could bias results related to the association between jaundice and ASD.

The majority of included studies offered no description on how infants with ASD were referred for diagnostic evaluation. Reported frequencies of ASD were as low as 0.3%[29,32] and as high as 1.3%[31] (the latter being close to the expected prevalence[2].) The low number of ASD cases seen in some studies could be due to the use of hospital-based databases.[28,30,33–35,52] In somatic hospital databases only children with somatic diseases will be admitted to the hospital and an additional ASD diagnosis may depend on availability of patient history from other contacts e.g., general practice or history taken from parents. While studies with small numbers of children with autism argue that they have more severe cases, the cases might also differ in other aspects. Thus, studies with a low frequency that did not provide valid arguments for the occurrence were rated as low quality on ASD selection.

Maimburg et al. published two studies based on information from Danish health registries with overlapping study periods. They differed substantially in the number of identified cases; a case−control study including 461 cases born 1990−1999[28] and a cohort study including 6171 cases born between 1994 and 2004.[27] The case−control study showed a threefold increased risk of ASD with jaundice, while the cohort study found no association. Thus, selection bias might contribute significantly to the associations seen.

The study by Wu et al.[31] investigated the effect of phototherapy and found no indication of a protective effect. So, even if there would be an association between jaundice and ASD, it does not seem to be affected by the use of phototherapy.

STRENGTHS AND LIMITATIONS

Our inclusion criteria were broad to allow for a high number of studies. Consequently, we made no restrictions to studies with particular methodological strengths. Many studies examined a variety of newborn complications with no a priori hypotheses related to jaundice.[41,42,53–66] A number of studies had other methodological weaknesses such as the use of parents' information to diagnose neonatal jaundice[55–59,61–63,67–71] and no adjustment for confounding factors.[41,42,53–58,60,61,63,66,67,69,70,72,73] However, we were able to restrict our main analysis to include only *low risk of bias studies*. The *low risk of bias studies* were identified based on a priori defined quality criteria. Thus, providing a reliable final conclusion based on *low risk of bias studies*. Our criteria could have been stricter, since the *low risk of bias studies* also had limitations.

CONCLUSION

We identified a high risk of publication bias in all studies on jaundice and ASD. We also pointed out selection and information bias and lack of adjustment for potential confounding factors in a number of studies, which may explain previous findings. When restricting the meta-analysis to *low risk of bias studies*, we found no convincing evidence of an association between neonatal jaundice and ASD. Furthermore, one study investigated the effect of phototherapy and found no indication of a protective effect. However, further high-quality studies are warranted to provide more firm conclusions. A more aggressive use of phototherapy to lower any potential risk of ASD in jaundiced infants should not be encouraged based on current evidence.

AUTHOR CONTRIBUTIONS

Each author has met the *Pediatric Research* authorship requirements listed below: Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; Drafting the article or revising it critically for important intellectual content; and final approval of the version to be published. M.L.K., J.P.P., and T.B.H. contributed substantially to conception and design, M.L.K. and M.V.P. contributed substantially to the acquisition of data. All authors contributed substantially to the analysis and interpretation of data; M.L.K. drafted the article; the remaining authors contributed in revising it critically for important intellectual content. All authors have approved the final version to be published.

ADDITIONAL INFORMATION

The online version of this article (https://doi.org/10.1038/s41390-020-01272-x) contains supplementary material, which is available to authorized users.

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