Neurodevelopmental Outcomes After Neonatal Surgery for Major Noncardiac Anomalies

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abstract

CONTEXT: Increasing concerns have been raised about the incidence of neurodevelopmental delay in children with noncardiac congenital anomalies (NCCA) requiring neonatal surgery.

OBJECTIVE: This study aimed to determine the incidence and potential risk factors for developmental delay after neonatal surgery for major NCCA.

DATA SOURCES: A systematic search in PubMed, Embase and the Cochrane Library was performed through March 2015.

STUDY SELECTION: Original research articles on standardized cognitive or motor skills tests.

DATA EXTRACTION: Data on neurodevelopmental outcome, the Bayley Scales of Infant Development, and risk factors for delay were extracted.

RESULTS: In total, 23 eligible studies were included, reporting on 895 children. Meta-analysis was performed with data of 511 children, assessed by the Bayley Scales of Infant Development at 12 and 24 months of age. Delay in cognitive development was reported in a median of 23% (3%–56%). Meta-analysis showed a cognitive score of 0.5 SD below the population average (Mental Development Index 92 ± 13, mean ± SD; $P < .001$). Motor development was delayed in 25% (0%–77%). Meta-analysis showed a motor score of 0.6 SD below average (Psychomotor Development Index 91 ± 14; $P < .001$). Several of these studies report risk factors for psychomotor delay, including low birth weight, a higher number of congenital anomalies, duration of hospital admission, and repeated surgery.

LIMITATIONS: All data were retrieved from studies with small sample sizes and various congenital anomalies using different neurodevelopmental assessment tools.

CONCLUSIONS: Cognitive and motor developmental delay was found in 23% of patients with NCCA. Meta-analysis showed that the mean neurodevelopmental outcome scores were 0.5 SD below the normative score of the healthy population.

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Dr Stolwijk conceptualized and designed the study, carried out the initial analyses, and drafted the initial manuscript; Dr Lemmers supervised the data collection and analyses, and contributed to the writing, revision, and reviewing of the manuscript; Ms Harmsen carried out the data collection and analyses and contributed to the paper writing; Dr Groenendaal contributed to the data analyses and statistics and revised and reviewed the manuscript; Dr de Vries reviewed the study design and critically reviewed the manuscript; Drs van der Zee and Benders supervised the progress of the study and reviewed and revised the manuscript; Dr van

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Approximately 2% to 3% of all neonates are born with major congenital anomalies[1–4] requiring surgical intervention in the neonatal period. With the reduction in mortality to <5%,[5] attention has shifted to morbidity, which has increasingly become the major concern.

Many studies provide evidence of neurodevelopmental delay and behavioral problems after cardiac surgery in infants. However, for noncardiac congenital anomalies (NCCA), there are limited data regarding the impact on neurodevelopmental outcomes, and results from existing studies are contradictory. Laing et al[6] reported a concerning rate of up to 50% mild to significant neurodevelopmental delay in these children; conversely Gischler et al[7] found no delay in cognitive outcome in this group. The latter did find a significant delay in motor development, however. In a high percentage of the cardiac patients, both preoperative and de novo postoperative brain damage were visible on MRI.[8,9] These lesions could contribute to the risk of adverse neurodevelopmental outcome. The mechanism and factors increasing the risk of neurodevelopmental delay in NCCA remain unknown. In vitro and in vivo experimental studies have demonstrated the neurotoxic effect of general anesthetics on the young, animal brain.[10–13] Large retrospective cohort studies in humans show a significantly higher rate of behavioral problems in children who have undergone multiple surgical procedures at a young age,[14,15] although the causes for this are unclear.[16] In short, data for both incidence and risk factors regarding neurodevelopmental delay are scarce and inconsistent.

The aim of this systematic review and meta-analysis is to provide an overview of the current evidence for the incidence of neurodevelopmental delay in children with major NCCA requiring neonatal surgery, and to identify possible associated risk factors.

METHODS

Search Strategy

This literature search for human studies provides an update on the current evidence regarding the neurodevelopmental outcome and the incidence of delay after neonatal surgery for major NCCA. The systematic review is conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement.[17] A structured literature search was performed using predefined search terms in PubMed (1960–2015), Embase (1980–2015), and the Cochrane Library (issue 3 of 12, March 2015) until March 2, 2015. For PubMed, the following search terms were used: (neonat*[Title/Abstract] OR infant*[Title/Abstract] OR newborn*[Title/Abstract]) AND (congenital anomal*[Title/Abstract] OR birth defect[Title/Abstract] OR gastroschisis[Title/Abstract] OR omphalocele[Title/Abstract] OR atresia[Title/Abstract] OR agenes*[Title/Abstract] OR malformation[Title/Abstract] OR diaphragmatic hernia[Title/Abstract] OR hirschsprung[Title/Abstract] OR choan*[Title/Abstract] OR abdominal wall defect[Title/Abstract]) AND (surg*[Title/Abstract] OR repair[Title/Abstract] OR correction[Title/Abstract] OR closure[Title/Abstract]) AND (neurodevelopment*[Title/Abstract] OR outcome[Title/Abstract] OR psychomotor[Title/Abstract] OR behavior*[Title/Abstract] OR behavior*[Title/Abstract] OR deficit*[Title/Abstract] OR impairment[Title/Abstract] OR cognitive[Title/Abstract] OR learning[Title/Abstract] OR iq[Title/Abstract]. We used the same search strategy in Embase, replacing "[Title/Abstract]" by; "ab,ti" and in The Cochrane Library by replacing "[Title/Abstract]" by "ti,ab,kw". Additionally, reference lists of included studies were examined to identify additional studies for inclusion. Search limits were not used in the databases, and language restrictions were not applied.

Assessment of Study Eligibility

Each article was independently assessed for eligibility using the following predefined criteria:

Domain: the study population was neonates ≤44 weeks postmenstrual age.

Determinant: the intervention consisted of neonatal surgery for a major NCCA.

Study outcome: neurodevelopment as measured by the Bayley Scales of Infant Development (BSID)-II and -III,[18] the Griffiths Mental Development Scales,[19] the Wechsler Intelligence Scale for Children,[20] Wechsler Preschool and Primary Scale of Intelligence, and the Movement Assessment Battery for Children (M-ABC).[21]

Study design: originally published articles.

Studies were excluded from analysis if the articles did not contain original patient data or did not match the inclusion criteria.

Outcomes of Interest

Studies that were eligible for inclusion reported on NCCA requiring neonatal surgery and described neurodevelopmental outcome in children by a standardized cognitive or motor skills test. Primary outcomes of interest for meta-analysis were cognitive and motor outcomes at 12 and 24 months of age using the BSID. All studies defined neurodevelopmental outcome as mildly delayed if scores on developmental testing deviated between 1 and 2 SD from the normative mean of 100 (70–85) and

significantly delayed if scores were <2 SDs below the mean (≤69).

Articles were also examined for evidence of risk factors and their association with poor neurocognitive outcomes. These risk factors consisted of birth weight, gestational age, prematurity, comorbidity, growth delay, occipitofrontal circumference, number of congenital anomalies, number of surgical interventions in first 24 months, age at first surgery, number of days of assisted ventilation and supplemental inspired oxygen, neurologic complications, injury visible with neuroimaging, length of hospital stay, number of hospital admissions, surgical technique, educational level of parents, and sociodemographic characteristics.

Data Extraction

Titles and abstracts as well as full text articles were independently screened by 2 authors (LJS and MH) according to the PRISMA statement.[17] The following data were extracted from all included articles: study population characteristics, study design, assessment tool, duration of follow-up, number of participating subjects, and number followed up. A third author (MvH-L) was consulted in case of discrepancies, and agreement was reached by consensus. Authors of included studies were contacted and provided additional data if necessary.

Risk of Bias Assessment

The risk of bias of each article included in the meta-analysis was assessed on the basis of the Cochrane Collaboration's tool and the Newcastle Ottawa Scale.[22]

Statistical Analysis

For the primary outcomes of interest, studies were pooled in a meta-analysis. Data were separated into subgroups: studies reporting on congenital diaphragmatic hernia, abdominal wall defects, and esophageal atresia. Because all included articles were observational cohort studies, there was no control group to perform an Inverse Variance Random Effect weighted meta-analysis. Because the original data of the studies that were used in the analysis were not available, random numbers with the same mean and SD of these studies were generated using SPSS. This procedure was repeated 10 times. Subsequently, these combined numbers were compared using a 1-sample *t* test versus a reference population consisting of a normative healthy population mean (Mental Development Index [MDI] or Psychomotor Development Index [PDI]) of 100 and SD of 15. The results are displayed in forest plots. Since multiple studies have shown that the BSID-III overestimates development in comparison with the BSID-II, we decided to subtract 8 points from results obtained with BSID-III to combine these with BSID-II data.[18,23,24] The value of I^2 was used[25] (Higgins et al.) to describe the percentage of total variation across studies, to give a value to the inconsistency of the studies'

TABLE 1 Clinical Trials Reporting Neurodevelopmental Outcome in Surgical Patients With NCCA

Study	Year	Period of Inclusion	Single Anomaly	*n*	Assessment Tool	Age at Assessment (mo) or Mean ± SD (Range)
Meta-analysis						
d'Agostino et al	1995	1990–1992	CDH	13	BSID-II	12
Ahmad,et al	1999	1985–1994	CDH	11	BSID-II	24
Cortes et al	2005	NR	CDH	16	BSID-II	24
Chen et al	2007	2000–2003	CDH	13	BSID-II	19 (8–40)
South et al	2008	2003–2005	Gastroschisis	17	BSID-II	20 (16–24)
Faugli et al	2009	1999–2002	EA	36	BSID-II	12
Gischler et al	2009	1999–2003	—	69	BSID-II	24
Danzer et al	2010	2004–2007	CDH	27	BSID-III	24, 36, 60
Laing et al	2011	2002–2004	—	45	BSID-III	24.2 ± 4.29 (18–35)
Aite et al	2013	2008–2012	Low-risk EA	30	BSID-III	12
Walker et al	2013	2006–2008	EA	31	BSID-III	12
Wynn et al	2013	2007–2010	CDH	48	BSID-III	24.6 ± 1.3
Bevilacqua et al	2015	2008–2012	—	155	BSID-III	12
Systematic review						
Davenport et al	1992	1983–1989	CDH	23	GMDS	56 (18–94)
Stolar et al	1995	1983–1993	CDH	51	GMDS	31 (2–86)
Somaschini et al	1999	1994–1998	CDH	12	GMDS	12
Buesing et al	2007	2001–2005	CDH	30	BSID-II	3, 6, 12, 24
Cammen-van Zijp et al	2010	1999–2003	—	102	M-ABC	6, 12, 24, 60
Payne et al	2010	1999–2007	Gastroschisis	57	BSID-III	39.1 ± 26.2
Rocha et al	2012	1997–2010	CDH	39	GMDS	3, 6, 9, 12, 18, 24
Gorra et al	2012	2001–2008	Gastroschisis	46	TIPS	24
Benjamin et al	2013	2001–2005	CDH	16	WPPSI-III	59
Van Eijck et al	2013	2004–2007	Omphalocele	8	M-ABC-II	71 (42–141)

EA, esophageal atresia; GMDS, Griffiths' Mental Development Scales; TIPS, Developmental Tracking Infant Progress Statewide; WPPSI, Wechsler Preschool and Primary Scale of Intelligence

results, and to quantify the effect of heterogeneity. A regression analysis on the meta-analysis on specific risk factors was not performed due to both the heterogeneity of the studies and the study designs being observational. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement was followed where appropriate.

RESULTS

The literature search identified 2310 potentially relevant publications. After screening of title/abstract followed by full text, 23 papers[6,7,25–44] reporting on 895 children met our inclusion and exclusion criteria and were selected for systematic review (Table 1). There was a wide range in follow-up duration and time of assessment from 12 months up to 60 months of age. Details of selection and exclusion of studies are specified in Fig 1. Almost all studies (n = 14) used a prospective cohort design (Tables 2 and 3). Thirteen[6,7,25,26,28,29,31,36–41] of 23 studies were eligible for conducting a meta-analysis. These studies were published between 1995 and 2015 and reported data using BSID from a total of 511 children at 12 or 24 months of age, after excluding syndromal and genetic disorders(Table 3).

Cognitive Development

Systematic Review

By reviewing all articles, a delay in cognitive development in all children with NCCA was found to be reported in a median of 23% (range 3%–56%).

Meta-Analysis

Meta-analysis in 498 infants showed a cognitive development score of 0.5 SD below the population reference mean, expressed as MDI score of 92 ± 13 (mean ± SD)[6,7,25,26,28,29,31,36–38,40,41] (Fig 2A), with data from BSID-II and

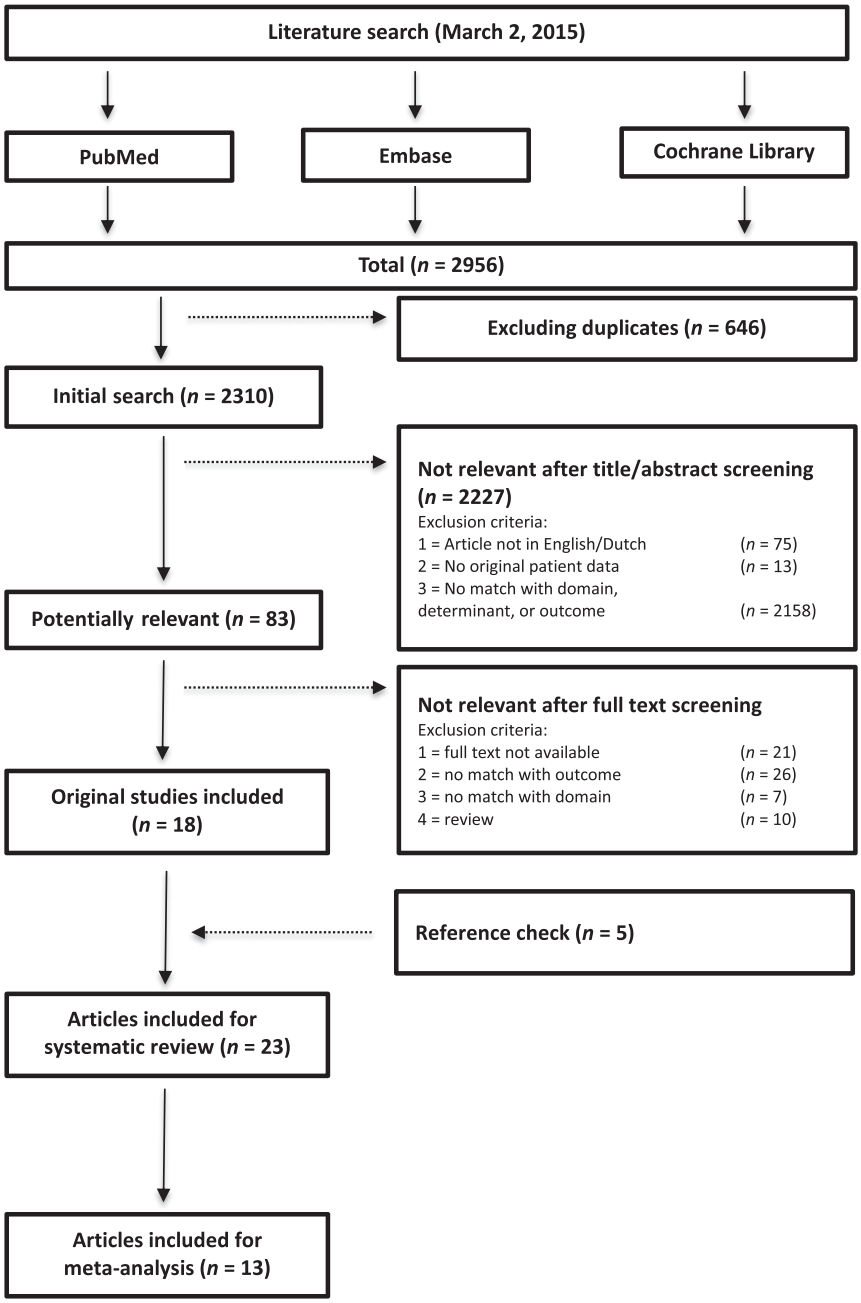

FIGURE 1
Flow chart illustrating details of the search strategy and the study selection process.

-III at 12 and 24 months of age. One-sample t tests demonstrated that the mean MDI was significantly lower than the healthy population mean of 100 (P < .001; 95%, confidence interval [CI] 91.7–94.2).

Selecting only data assessed at age 24 months, a similar result was found (n = 185, MDI 92 ± 15, P < .001; Fig 2B). Including only studies from the past 10 years, the same result was found (MDI 92 ± 13; P < .001; 95% CI 91.6–94.1). The heterogeneity of the study results was found to be high. Factors including gestational age, birth weight, prematurity, diagnosis, exclusion of chromosomal and genetic syndromes and correction of the neurodevelopmental score for gestational age could not be identified as possible explanations

TABLE 2 Risk of Bias Summary Included Studies Meta-analysis

	d'Agostino et al (1995)	Ahmad et al (1999)	Cortes et al (2005)	Chen et al (2007)	South et al (2008)	Faugli et al (2009)	Gischler et al (2009)	Danzer et al (2010)	Laing et al (2011)	Aite et al (2013)	Walker et al (2013)	Wynn et al (2013)	Bevilacqua et al (2015)
Prospective design	+	–	+	–	+	+	+	+	+	+	+	+	+
Complete report on loss to follow-up	+	+	+	+	+	+	+	+	+	+	+	+	–
Exclusion of genetic/ syndromal	NR	–	+	+	–	+	+	+	+	+	+	–	+
Potential other sources of bias[a]	(a)	(a, b, c)	(e)	(c)	(c, d)	–	–	–	–	(f)	(b, c)	–	–

NR, Not reported.

[a] Potential other biases: a, included only children who required ECMO; b, no report on complications; c, no report on multiple surgeries; d, no report on multiple hospitalizations; e, included only severe left CDH; f, included only low-risk esophageal atresia.

for this heterogeneity. More patients were lost to follow-up in the older studies (18%–48%) compared with more recent studies (9%–28%).

Motor Development

Systematic Review

Examining all studies, median delay in motor development in all children with NCCA was 25%, ranging from 0% to 77%. In 1 study, the motor development of 102 children with NCCA was investigated with the M-ABC at a mean age of 5.7 years.[30] A delay in motor development (<1 SD) was found in 29% of those with NCCA. Most of these patients had CDH or esophageal atresia, and a significant correlation with repeat surgery was found. The motor score correlated negatively with the total number of congenital anomalies.

Meta-Analysis

Thirteen studies contributed data to the quantitative motor outcome analysis.[6,7,25,26,28,29,31,36–41] This meta-analysis in 511 children resulted in a motor development score of 0.6 SD below the population average, indicated by the PDI score of 91 ± 14 (Fig 3A). One-sample *t* tests demonstrated that the mean PDI was significantly lower than the healthy population mean of 100 (P < .001; 95% CI 89.8–92.1). Using only data assessed at 24 months of age, a similar result was found (n = 185; PDI 90 ± 14; P < .001; Fig 3B). Including only studies from the past 10 years, the same result was found (PDI 91 ± 13; P < .001; 95% CI 90.1–92.4).

Subgroups

Data were reported separately in 3 NCCAs: congenital diaphragmatic hernia (CDH), abdominal wall defects, and esophageal atresia.

CDH

When systematically reviewing all articles reporting on congenital diaphragmatic hernia, the need for extracorporeal membrane oxygenation (ECMO) was reported as a predictor for worse outcome.[31,38] Neuroimaging with cerebral computed tomography (CT) scanning in patients who had undergone ECMO for CDH revealed abnormalities in 75% of patients with neurodevelopmental delay in 42%.[45]

To evaluate the data on CDH patients quantitatively with a meta-analysis, we divided patients with NCCA into 2 subgroups: studies solely reporting on CDH[26,31,39–41] (n = 128, "CDH only") and studies reporting on all other NCCA[6,7,27–29,36–38] (n = 383, "Other group"), with a limited percentage of CDH (25% at most). Table 4 shows that the MDI and PDI scores of the subgroup with CDH patients are 1 SD below the population mean, indicating a mild to moderate delay, with low heterogeneity among these studies.

Abdominal Wall Defects

By reviewing all studies reporting on abdominal wall defects, neurodevelopmental delay was reported in 0% to 24% of 128 patients with abdominal wall defects.[28,32,33,46] In 1 study (n = 46), neurodevelopment was assessed as part of a state-sponsored follow-up program for all infants discharged from intensive care in the state of Nebraska, United States (the Developmental Tracking Infant Progress Statewide program). No differences were found in delay between patients with simple gastroschisis and matched control subjects.[32] Motor outcome in 8 patients with giant omphalocele, tested with the M-ABC at 6 years of age, was found to be normal.[46]

Esophageal Atresia

Three articles[25,29,36] reported solely on infants with esophageal atresia and their short-term neurodevelopmental outcome at 1 year of age. By systematically reviewing these articles, a delay was reported in 11% to 38%. Meta-analysis (n = 100) showed an MDI score and motor score of 0.5 SD below the reference population (MDI 94 ± 13 and PDI 92 ± 14; P = .009).

Risk Factors

When reviewing all studies for risk factors, only 5 studies[6,7,28,30,37]

TABLE 3 Patient Characteristics Meta-analysis

Study	*n*	Patient Characteristics		Boys, *n* (%)	Apgar Score 1 Minute	Apgar Score 5 Minute	Age at First Surgery (d)	Surgery specifications		LOS (d)	Follow-Up Neuro-developmental Delay (%)
		Gestational Age (wk)	Birth Weight (g)					Surgical Interventions First 24 Months	Assisted Ventilation (d)		
D'Agostino et al (1995)	13	38.0 ± 2	3180 ± 460	9 (56%)	4 ± 3	6 ± 3	1–8	NR	29 (4–605)	86.5 (15–605)	46
Ahmad et al (1999)	11	38.5 ± 2.4	3170 ± 620	53%	5 (1-8)	7 (2–9)	NR	NR	NR	NR	NS
Cortes et al (2004)	16	37.4 ± 1	3150 ± 490	13 (81%)	NR	NR	6.4 ± 2.1	3.75	29.6 ± 10	62.1 ± 28.7	57
Chen et al (2007)	13	37.6 ± 1.6	3000 ± 500	8 (61.5%)	NR	7 (1–9)	39.1 ± 2.0[a]	NR	14 (5–55)	53 (26–295)	77
South et al (2008)	17	35.5 ± 1.9	2360 ± 731	6 (35%)	NR	NR	NR	NR	6.5 ± 5.3	33 (21–50)	24
Faugli et al (2009)	36	NR	2830 (595–4570)	27 (69%)	NR	NR	2	1 (1–5)	NR	21 (13–270)	11
Gischler et al (2009)	88	38.3 (36.8–40.0)	3000 (2500–3300)	47 (53.4%)	8 (7–9)	9 (8–9)	NR	3 (1–4)	NR	30 (21–64)	25
Danzer et al (2010)	41	37.2 ± 2.7	2971 ± 508.8	20 (49%)	6 (1–9)	8 (4–9)	6.8 ± 5.8	NR	25.8 ± 32.2	NR	54
Laing et al (2011)	45	38.2 ± 1.84	3174 (1852–4215)	32 (71%)	9 (1–9)	9 (3–0)	2 ± 4	1.5 ± 0.94	2.42 ± 4.54	23.3 ± 17.13	43
Aite et al (2013)	30	38 (33–42)	2650 (1595–3575)	NR	NR	NR	NR	3 (1–7)	5 (1–30)	22.5 (14–138)	NS
Wynn et al (2013)	48	38 ± 1.6	0.60–1.07[b]	NR	6 ± 2	8 ± 2	NR	NR	NR	39 (11–211)	48
Walker et al (2013)	31	37.6	2718 ± 717	11 (36%)	NR	NR	1–2	NR	NR	19 (8–134)	23
Bevilacqua et al (2015)	156	38 (36–39)	2870 (2437–3258)	99 (63.9%)	NR	NR	NR	1 (1–2)	4 (0–8)	27 (18.5–49.8)	19

LOS, length of hospital stay; NR, not reported; NS, not specified.

[a] Postmenstrual age.

[b] Birth weight *z* score.

were found to report on perinatal risk factors associated with an increased risk of an adverse neurodevelopmental outcome. Two studies found that low birth weight[6] and prematurity[28] were associated with lower PDI scores. A higher number of congenital anomalies also significantly increased the risk of neurodevelopmental delay.[7,30,37]

Neuroimaging with either cerebral ultrasonography, CT, or MRI scanning was reported in 11 studies,[7,26,27,31,34,35,40–42,45,47] and 10 of these articles reported solely on CDH. In 7 studies,[7,34,40–42,45,47] the correlation between brain damage and neurodevelopmental outcome was not explored, and in 4 studies,[26,27,31,35] no significant correlation was found.

Duration of hospital admission was positively correlated with a delay in neurodevelopment.[7,26,28,37,40] A higher number of surgical interventions was found to be correlated with a lower cognitive and motor outcome.[6,7,29,30,37] Duration of mechanical ventilation[29,31,35,37,40,42] and the need for supplemental oxygen at discharge[26] were both reported as risk factors for neurodevelopmental delay.

A delay in growth after neonatal surgery for NCCA during follow-up was reported in 5 studies with an incidence of 13% to 35%[25,26,28,31,40] (Supplemental Table 5). Only 1 study showed neurodevelopmental scores to be significantly lower in children with a delay in growth at 1 year of age.[25] None of the studies reported on nutritional information.

Socioeconomic parameters, such as educational level of the parents, were reported in 7 studies including 383 patients.[6,7,25,29,37,38,43] One study showed a positive correlation of educational level with neurodevelopmental outcome[43] (Supplemental Table 6).

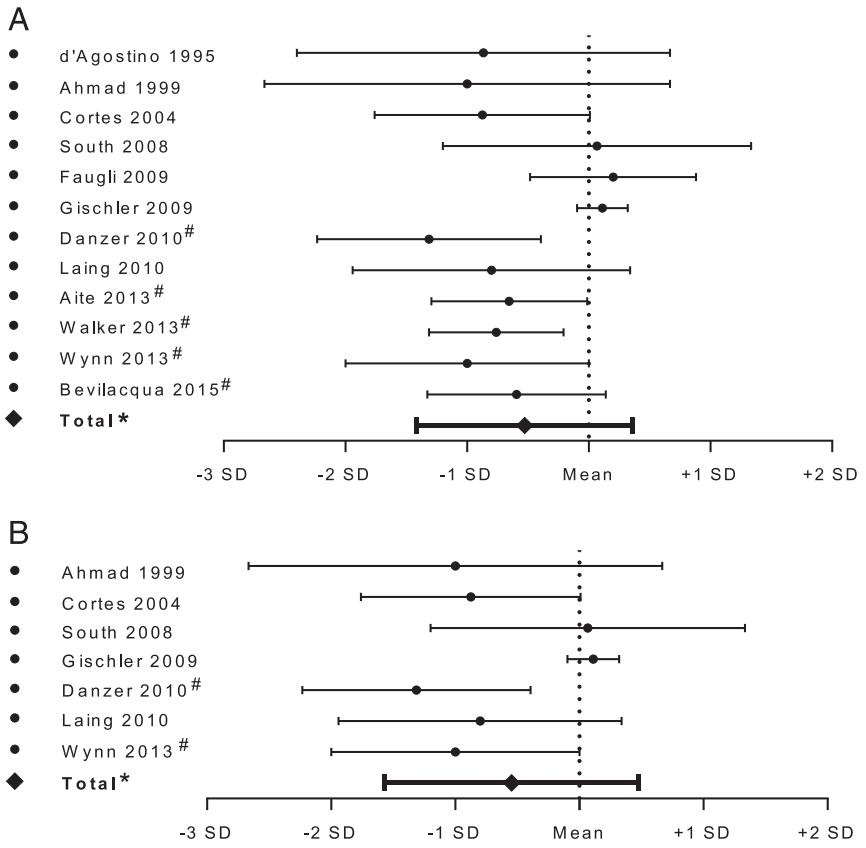

FIGURE 2

Forest plot of meta-analysis of the cognitive developmental outcome in all patients with NCCA, expressed by the MDI score of the BSID-II and -III at (A) 12 and 24 months of age and (B) at 24 months of age only. The scores are displayed compared with the reference scores of the healthy population. * One-sample t tests demonstrated that the mean MDI was significantly lower than the population mean of 100 (P < .001). **# BSID-III, for which 8 points are subtracted from the mean.**

TABLE 4 Meta-analysis CDH

	All NCCA (n = 511)	CDH only (n = 128)	Other NCCA[a] (n = 383)
MDI score (mean ± SD)[b]	92.1 ± 13	84.5 ± 15	94.0 ± 12
PDI score (mean ± SD)[b]	90.6 ± 14	85.2 ± 15	91.8 ± 13

[a] Studies reporting on all other NCCA, with a limited percentage of CDH (25% at most).

[b] One-sample t tests demonstrated that the mean was significantly lower than the population mean of 100 ($P < .001$).

DISCUSSION

Our systematic review and meta-analysis identified >2000 publications by searching the available databases for neurodevelopmental outcomes in children with major NCCA requiring neonatal surgery. Only 23 prospective and retrospective cohort studies that reported neurodevelopmental outcome after neonatal surgery for NCCA could be identified, representing 895 patients. Of these, data from only 13 articles could be pooled in a meta-analysis. The majority of studies on neurodevelopment and NCCA are heterogeneous and lack standardization in follow-up assessment.

In this systematic review, the median reported neurodevelopmental delay was 23% but varied widely (0%–77%) for several reasons. First, in most studies, patient groups were heterogeneous, consisting of various congenital anomalies. As a result of small patient numbers, authors chose to pool different congenital malformations that shared a requirement for neonatal surgery.[6,7,30,37] Second, parameters that may influence neurodevelopmental outcome, such as gestational age,[28] duration of hospital admission,[7,26,28,40] and repeat surgery,[6,7,29,30] varied within and among patient cohorts.

The meta-analysis showed a mean cognitive and motor score (determined by the BSID) of 0.5 to 0.6 SD below the normative score of the healthy population. Interestingly, short outcome scores at 12 months of age did not differ from outcome scores at age 24 months (Figs 2 and 3). Children with NCCA are systematically excluded from longitudinal studies because of their higher risk of chromosomal disorders and syndromes, influencing neurodevelopment.[7,48] The evidence gathered in this study shows that even after exclusion of syndromal and chromosomal disorders, these children have a 23% risk of an adverse neurodevelopmental outcome. Surprisingly, excluding data from studies of >10 years ago did not influence the neurodevelopmental outcome scores: even though survival has increased, neurodevelopmental outcome remains unchanged. This pattern is similar to that reported in extremely preterm infants. The EPICure studies have shown increased survival of infants born between 22 and 25 weeks' gestation, while their morbidity was not affected.[49] These results stress even further the importance of monitoring neurodevelopmental outcomes in patients with NCCA.

The subgroup with CDH demonstrated a mean cognitive score below –1 SD. These patients generally represent the most severe group of

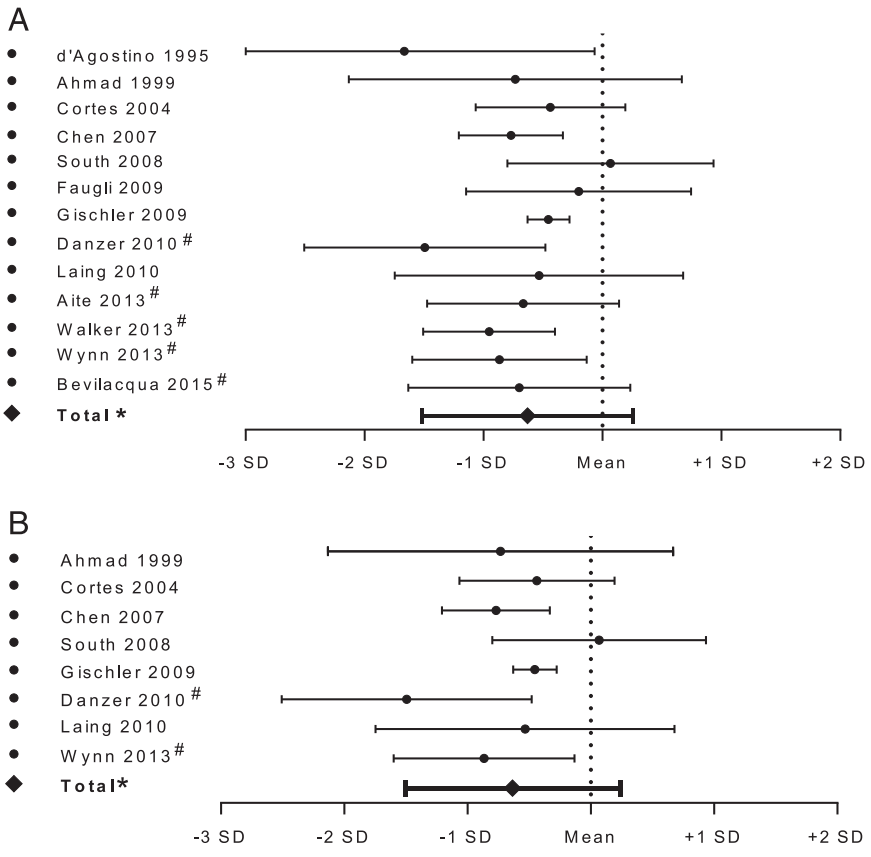

FIGURE 3

Forest plot of meta-analysis of motor outcome in all patients with NCCA, expressed by the PDI score of the BSID-II and -III at (A) 12 and 24 months of age and (B) at 24 months of age only. The scores are displayed compared with the reference scores of the healthy population. * One-sample t tests demonstrated that the mean PDI was significantly lower than the population mean of 100 ($P < .001$). **# BSID-III, for which 8 points are subtracted from the mean.**

NCCA because they can develop more complications, including prolonged periods of hypoxia and the need for ECMO, due to lung hypoplasia and pulmonary hypertension. The incidence of neurodevelopmental delay in the subgroup of abdominal wall defects is remarkably low. This may be explained by the small sample sizes of these studies[28,32,33,46] ($n = 8$ and $n = 17$). Payne et al reported "a generally encouraging outcome of patients with gastroschisis." However, considering the severity of the anomaly, the authors advised close follow-up throughout childhood.

Risk factors that negatively influence neurodevelopment include low birth weight,[6] higher number of congenital anomalies,[7] a longer hospital stay,[7,26,28,40] duration of mechanical ventilation,[29,31,35,40,42] and need for supplemental oxygen at discharge.[26] However, data to evaluate longer-term neurocognitive outcomes associated with these risk factors were limited in the studies that were included in this review.

Neuroimaging after surgery in children with congenital heart disease has revealed brain injury occurring in the perioperative period, possibly contributing to the risk of adverse neurodevelopment.[8] Also, impairment in brain growth and maturation has been described,[50,51] with an increased vulnerability to white matter injury. To date, the prevalence of brain lesions in surgical patients with NCCA is unknown.[12] Several studies in this review have reported on neuroimaging, but none showed a correlation with development. Ultrasound or CT were most frequently used, whereas MRI was not performed routinely in any study, despite it being the most sensitive diagnostic tool for detection of brain injury. Theoretically, comparable to the cardiac group, patients with NCCA are also at risk for developing perioperative brain damage.[14,52] Inflammation is among the known risk factors for developing brain injury.[53,54] Patients with NCCA can be more susceptible to neuronal damage, and preoperative inflammation in patients with gastroschisis can be considerable.[55] The discussion on the neurotoxic effect of inhalational anesthetics on the immature brain is also ongoing.[10] To date, there is no clinical evidence of the adverse effect in the human brain.

A number of limitations need to be considered. First, a limitation of this systematic review is the heterogeneity of the included studies. All data were obtained from studies with small sample sizes and various congenital anomalies using different neurodevelopmental assessment tools. Moreover, the studies described are all observational. Because longitudinal follow-up data are scarce, it is unclear whether these children have delayed longer-term neurodevelopment or grow into their deficits after age 2. Second, different versions of the BSID are used, the BSID-II and the BSID-III. After considering multiple reports about the higher scores of the BSID-III, we decided to subtract 8 points from the mean of the BSID-III, on the basis of several recent studies,

to be able to compare these scores to the BSID-II. Because even larger differences have been reported, we believe this method is reasonable, although consensus in the literature has not yet been reached.[18,23,24]

CONCLUSIONS

Our systematic review and meta-analysis show that patients with NCCA requiring surgery have a higher risk of neurodevelopmental delay. Although it is crucial to identify which parameters increase the risk for delay, data about risk factors are scarce. Future studies are required to perform structured follow-up with specific neurodevelopmental assessment tests and neuroimaging in children with NCCA to elucidate early brain injury as a probable cause of developmental delay.

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ABBREVIATIONS

BSID: Bayley Scales of Infant Development
CDH: congenital diaphragmatic hernia
CI: confidence interval
CT: computed tomography
ECMO: extracorporeal membrane oxygenation
M-ABC: Movement Assessment Battery for Children
MDI: Mental Development Index
NCCA: noncardiac congenital anomalies
PDI: Psychomotor Development Index

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