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Systematic Review and Meta-analysis

Long-term neurodevelopment in children born with esophageal atresia: a systematic review

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SUMMARY. ***Background:*** **Although the survival rate of esophageal atresia (EA) has increased to over 90%, the risk of functional long-term neurodevelopmental deficits is uncertain. Studies on long-term outcomes of children with EA show conflicting results. Therefore, we provide an overview of the current knowledge on the long-term neurodevelopmental outcome of children with EA.** ***Methods:*** **We performed a structured literature search in Embase, Medline Ovid, Web of Science, Cochrane CENTRAL, and Google scholar on November 8, 2020 with the keywords 'esophageal atresia', 'long-term outcome', 'motor development', 'cognitive development', and 'neurodevelopment'.** ***Results:*** **The initial search identified 945 studies, of which 15 were included. Five of these published outcomes of multiple tests or tested at multiple ages. Regarding infants, one of six studies found impaired neurodevelopment at 1 year of age. Regarding preschoolers, two of five studies found impaired neurodevelopment; the one study assessing cognitive development found normal cognitive outcome. Both studies on motor function reported impairment. Regarding school-agers, the one study on neurodevelopmental outcome reported impairment. Cognitive impairment was found in two out of four studies, and motor function was impaired in both studies studying motor function.** ***Conclusions:*** **Long-term neurodevelopment of children born with EA has been assessed with various instruments, with contrasting results. Impairments were mostly found in motor function, but also in cognitive performance. Generally, the long-term outcome of these children is reason for concern. Structured, multidisciplinary long-term follow-up programs for children born with EA would allow to timely detect neurodevelopmental impairments and to intervene, if necessary.**

KEY WORDS: **children, esophageal atresia, neurology.**

INTRODUCTION

Esophageal atresia (EA) is a congenital deformity in which the upper esophagus does not connect to the lower esophagus and the stomach, which occurs in 2.43 per 10,000 live births.[1] After correction of the defect, >90% of the children born with EA survive nowadays.[2] Therefore, long-term outcome requires growing attention. The evaluation of long-term outcome in children born with EA focuses on several aspects, such as gastroesophageal reflux, dysphagia, respiratory problems, weight, growth, quality of life (QOL), psychological status, social behavior, and neurodevelopment.[2–4]

Most research on long-term outcome of EA has focused on physical impairments or QOL, both in children and young adults.[5,6] A recent elaborate review on health related QOL (HrQOL) of patients born with EA concluded that clinical subgroups of children with EA present with impaired HrQOL, and that digestive symptomology negatively influences the HrQOL.[6] Neurodevelopment has been less well studied, and available studies reported conflicting results. Furthermore, the variety of used test instruments and

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cohorts make it difficult for clinicians to interpret these results, and a comparative study is lacking.

More research on neurodevelopmental outcome has been performed in neonates with other conditions. After extracorporeal membrane oxygenation (ECMO) treatment, 10–50% of children showed cognitive impairment of >2 standard deviation (SD), and motor impairment was found in 12%.[7] In children born with diaphragmatic hernia, significantly more problems with motor function, concentration, and behavioral attention were found, compared with reference groups. Intelligence quotient (IQ) levels were lower for those who had received ECMO treatment.[8,9]

The risk factors children born with EA are exposed to are similar to the risk factors patients with congenital diaphragmatic hernia and/or ECMO face. This includes, amongst others, neonatal surgery, metabolic derangements during surgery, admission to the intensive care unit, and endotracheal intubation.[9,10] Therefore, it cannot be ruled out that patients born with EA suffer comparable neurodevelopmental impairments as these patient populations do.

Neurodevelopment is the brain's ability to develop neurological pathways facilitating performance in daily life. These pathways support the functioning of the brain, including motor function (e.g. agility and balance) and cognitive performance (e.g. think, learn, and remember). Motor function and cognitive performance are strongly interrelated and interdependent, displaying marked parallels, and multiple points of connection in the brain.[11] Therefore, these factors cannot be seen as separate factors and are always impacted by the other and integrated in a test.

Better insight in long-term neurodevelopmental outcome is important for healthcare professionals as well as for children with EA and their parents, and will be helpful to guide future counselling, follow-up, and treatment. In this systematic review we therefore aim to inventory the current knowledge on long-term neurodevelopmental outcome—including cognitive and motor functioning—in children who underwent primary surgery for EA.

METHODS

A broad systematic literature search was performed to identify clinical research on long-term neurodevelopment in children born with EA, following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.[12] A structured electronic search was performed on November 8th, 2020 in the EMBASE, MEDLINE, Web of Science, COCHRANE, and Google scholar databases.[13] The search terms were the following: "esophageal atresia', 'long-term outcome', 'motor development', 'cognitive development', and 'neurodevelopment' (complete search strategy is provided in Supplementary Material). Limits were set to English language and human studies. This systematic review was registered in the PROSPERO database (registration number CRD42020203189).

After deduplication of the retrieved citations in Endnote,[14] the titles and abstracts of the remaining studies were screened by two investigators (CvH and CtK), independently and in a systematic fashion. The inclusion criteria were: studies in children born with EA between 6 months and 18 years of age, with long-term neurodevelopment (either motor function and/or cognitive functioning) as primary outcome. Studies including children younger than 6 months old were excluded, since these were considered to describe the short-term effects of surgery and anesthesia. Neurodevelopment had to be assessed by means of neuropsychological evaluation or a validated questionnaire to assess neurodevelopment. Studies that focused only on QOL, psychological development, respiratory complications, or physical comorbidities were excluded. These types of studies were excluded because clinical presentation of patients EA is very heterogenic, which makes it hard to compare outcome variables. Last, studies not originally published in a peer-reviewed journal were excluded.

The remaining studies were selected for full-text analysis. Both investigators (CvH and CtK) independently read the full-texts of these citations. Discrepancies were solved through discussion, or by mediation from a third investigator (JdG), which resulted in the final selection.

The following data were extracted: number of patients, age, outcome measure (motor or cognitive functioning), test method, and test results. As various age-dependent tests are available to assess neurodevelopment in children, we report the search results for three age groups: infants <2 years old, preschoolers aged 2–5 years old, and school-aged children of 6–18 years old. This division is based on the age groups used for assessing neurodevelopment in children, based on developmental stages.[15]

Risk of bias was analyzed using the methodological index for non-randomized studies (MINORS).[16] Due to small amount of included studies and the heterogeneity of the data provided by the included studies, we were not able to perform a meta-analysis of the data.

RESULTS

The search strategy yielded 1774 citations, of which 945 studies remained after deduplication. Based on the predetermined exclusion criteria, 908 studies were excluded after initial screening of title and abstract. Of the remaining 37 studies selected for full-text analysis, 22 studies were excluded (Fig. 1). We found 9 studies in which questionnaires were used to assess

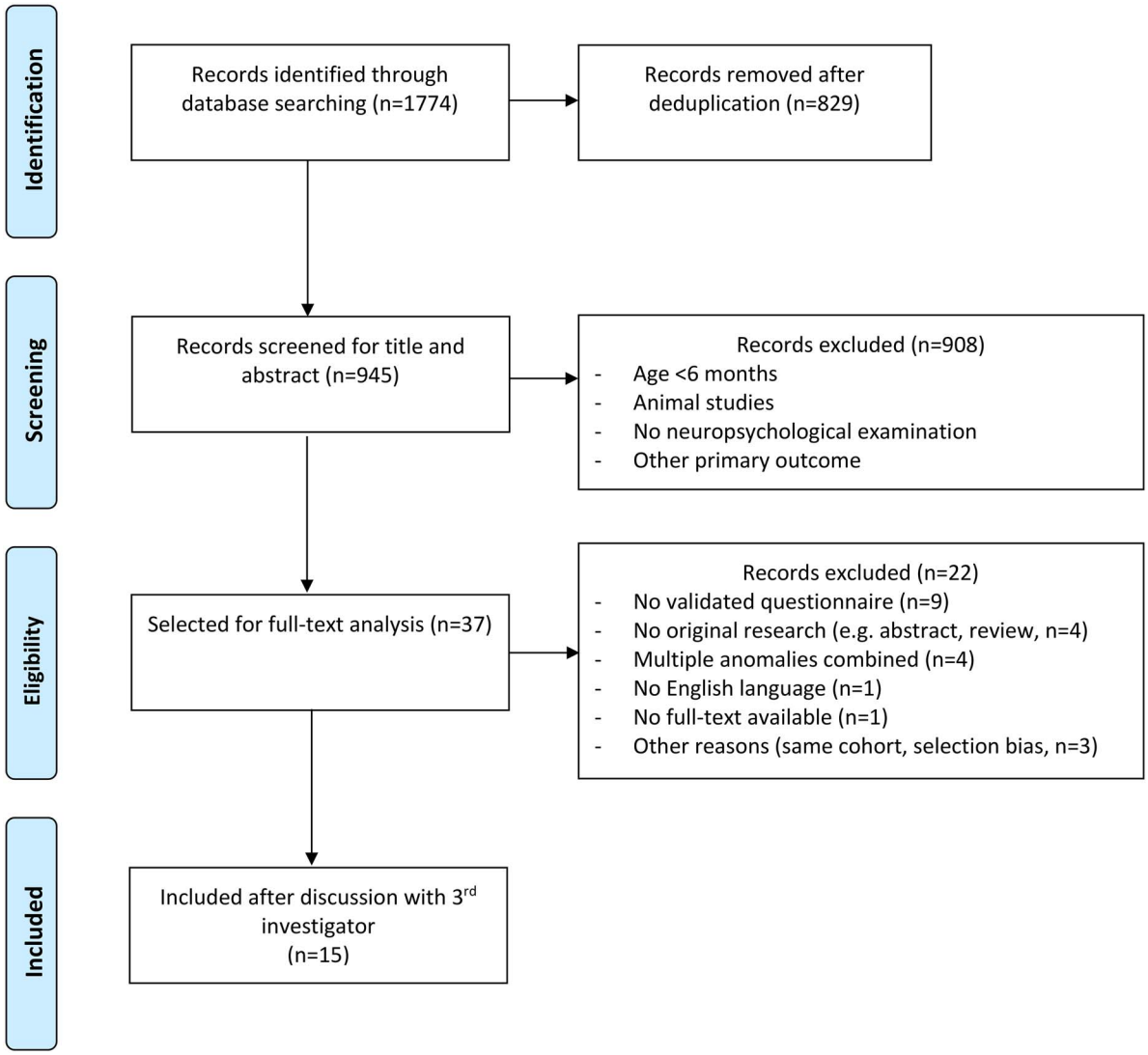

Fig. 1 Inclusion flowchart.

neurodevelopment of the patients. These studies did not use validated questionnaires and were therefore not included in this systematic review. Only one study used the ages and stages questionnaire (ASQ) to screen patients for patients to be tested with Bayley-3 (see further).[17] Four studies were published as conference abstract or as a review only, and two reported on a subgroup of another study.[18,19] Four other studies combined multiple congenital anomalies without specifying the test results for the patients with EA. One article was not written in English, and another article was excluded as we had no access to the full-text. One article was excluded due to an inclusion bias; development was only evaluated when a developmental disorder was already suspected.

Ultimately, 15 studies were included in this systematic literature review, with a large variation of tests and age groups. Some studies investigated neurodevelopment of the study group at various ages (Table 1 and Fig. 2).

Neurodevelopmental outcome was described for infants (<2 years old) in six studies, for preschoolers (2–5 years old) in eight studies,[17,20–26] and for school-aged children (>6 years old) in six studies[20,23,24,27–29] (Tables 2–4). The sample size ranged from 6 to 182 children; the children's ages ranged from 6 months to 17 years old. A total of 769 tests were conducted, in which the Bayley Scales of Infant and Toddler Development (BSID-I, BSID-II, and Bayley-3), the Movement assessment battery for children (M-ABC) and the Wechsler Intelligence Scale for Children (WISC) were most frequently used. BSID has been internationally validated for children up to 42 months old; the most recent version measures five domains of development, including motor skills and cognition.[30] To measure motor skills of children aged 4 up to and including 16 years old, the M-ABC has been developed and validated internationally.[31,32] For cognitive performance, the WISC is available for children from 6 to 16 years old.[33]

Table 1 Baseline characteristics of included studies ($n = 15$)

Author, year	Type of study	Operated/born/tested	Age tests	Tests	Reference population	No. of patients included*	Mortality (*n*)	No. at follow-up	Type of EA	Gestational age (weeks) birth weight	Comorbidities
Bouman[27] Netherlands, 1999	Prospective cohort study	NR	8–12 years	WISC-RN	Dutch references	36	NR	36	Isolated EA $n = 5$ EA with TEF $n = 31$	NR NR	NR
Faugli[36] Norway, 2009	Prospective cohort study	Born 1999–2002	1 year	BSID-II	US references	44	2	39 (36)	10% delayed repair	23% born < 37 weeks 2830 (595–4570)[A]	20% ≥1 associated anomaly (tetralogy of Fallot, biliary atresia, anorectal malformation, tracheomalacia)
Gischler[36] Netherlands, 2009	Prospective longitudinal cohort study	Tested 1999–2003	6, 12, 18, and 24 months	BSID-I/II**	Dutch references	17	NR	13	NR	38.6 (36.9–40.1)[B] 3000 (2600–3200)[B]	Syndromal/chromosomal $n = 1$, severe neurologic impairment $n = 2$, major congenital anomalies $n = 1$[#]
Van der Cammen-van Zijp[25] Netherlands, 2010	Prospective cohort study	Born 1999–2003	5 years	MABC	Dutch references	29	NR	29	NR	38.4 (28.6–42.0)[A] 2900 (800–4500)	31% ≥1 associated anomaly
Kubota[29] Japan, 2011	Prospective cohort study	NR	6–17 years	WISC-3 KSPD	Japanese references	23	NR	23	NR	NR NR	NR
Walker[35] Australia, 2013	Prospective case–control study	Operated Aug 2006–Dec 2008	1 year	Bayley-3	Study control group	34	1	31	NR	37.6[C] 2718 ± 717[D]	44% ≥1 associated anomaly
Francesca[34] Italy, 2020	Observational prospective cohort study	Born 2009–2017	6 and 12 months	Bayley-3	Age-normed	90	NR	82 59	Type C and D	38 (37–39)[B] 2700 (2450–3030)	NR
Bakal[20] Turkey, 2016	Cross-sectional study	Operated Jan 1996–Dec 2011	6–16 years	ADSI WISC-R	Turkish references	57	18	24 ADSI 15 WISC-R	Type A $n = 6$ Type C $n = 50$ Type E $n = 1$	40% born < 37 weeks 2255.26 ± 600.27[D]	35% ≥1 associated anomaly
Giúdici[23] Argentina, 2016	Prospective cohort study	Born Jan 2003–Dec 2014	1, 3, and 6 years	CAT/ CLAMS PRUNAPE	Argentinian references	23	4	21 at 1 year 14 at 3 years 10 at 6 years	Type A $n = 3$ Type C $n = 20$	38.3 ± 1.6[D] 2917 ± 440[D]	Trisomy 21 $n = 1$, Edwards syndrome $n = 1$
Walker[26] Australia, 2016	Prospective case–control study	Operated Aug 2006–Dec 2008	3 years	Bayley-3	Study control group	31	0	24	NR	38[C] 2765[C]	NR
Harmsen[24] Netherlands, 2017	Prospective cohort study	Born Jan 1999–May 2006	5 and 8 years	MABC I/II WISC-3-NL RAKIT	Dutch references	78	7	54 motor 49 cognitive	91% type C	39 (29–42)[A] 2830 (750–4505)[A]	12% cardiac anomaly, 5% VACTERL association
König[28] Germany, 2018	Cross-sectional study	NR	3–12 years	Deutscher Motorik Test	German references	17	NR	12	NR	54% born < 37 weeks 23% <1500 grams	46% congenital heart disease, 38% developmental delay, 28% skeletal deformity, 15% anorectal malformation
Mawlana[17] Canada, 2018	Retrospective chart review	Operated Jan 2000–Dec 2015	2–3 years	Bayley-3	US references	253	21	182	Type A $n = 13$ Type B $n = 2$ Type C $n = 149$ Type D $n = 4$ Type E $n = 14$	36.8 ± 3.2[D] 2589 ± 800[D]	NR
Costerus[21] Netherlands, 2019	Prospective cohort study	Operated Aug 2011–Aug 2013	1 and 2 years	BSID-II	Dutch references	6	NR	5	NR	39.0 (34.0–40.0)[A] 2850 (1941–3338)[A]	Tetralogy of Fallot $n = 1$, kidney dysplasia $n = 1$, Feingold syndrome $n = 1$, intestinal malrotation $n = 1$
Batta[37] Australia, 2020	Retrospective study	Born 2005–2014	1 year	GMDS-II	General population references	44	1	27	NR	37.6 (36.4–39.1)[B] 3000 (2590–3405)[B]	NR

EA, esophageal atresia; NR, not reported; TEF, tracheoesophageal fistula. Type of EA according to gross classification.[54] VACTERL, vertebral, anorectal, tracheoesophageal, renal, or limb defects[55]

[A] Median (range).

[B] Median (IQR).

[C] Mean.

[D] Mean ± SD.

These four patients were excluded from neurodevelopmental assessment.

*Included in neurodevelopmental assessment.

**Dutch version of the BISD I/II: BOS 2-30.

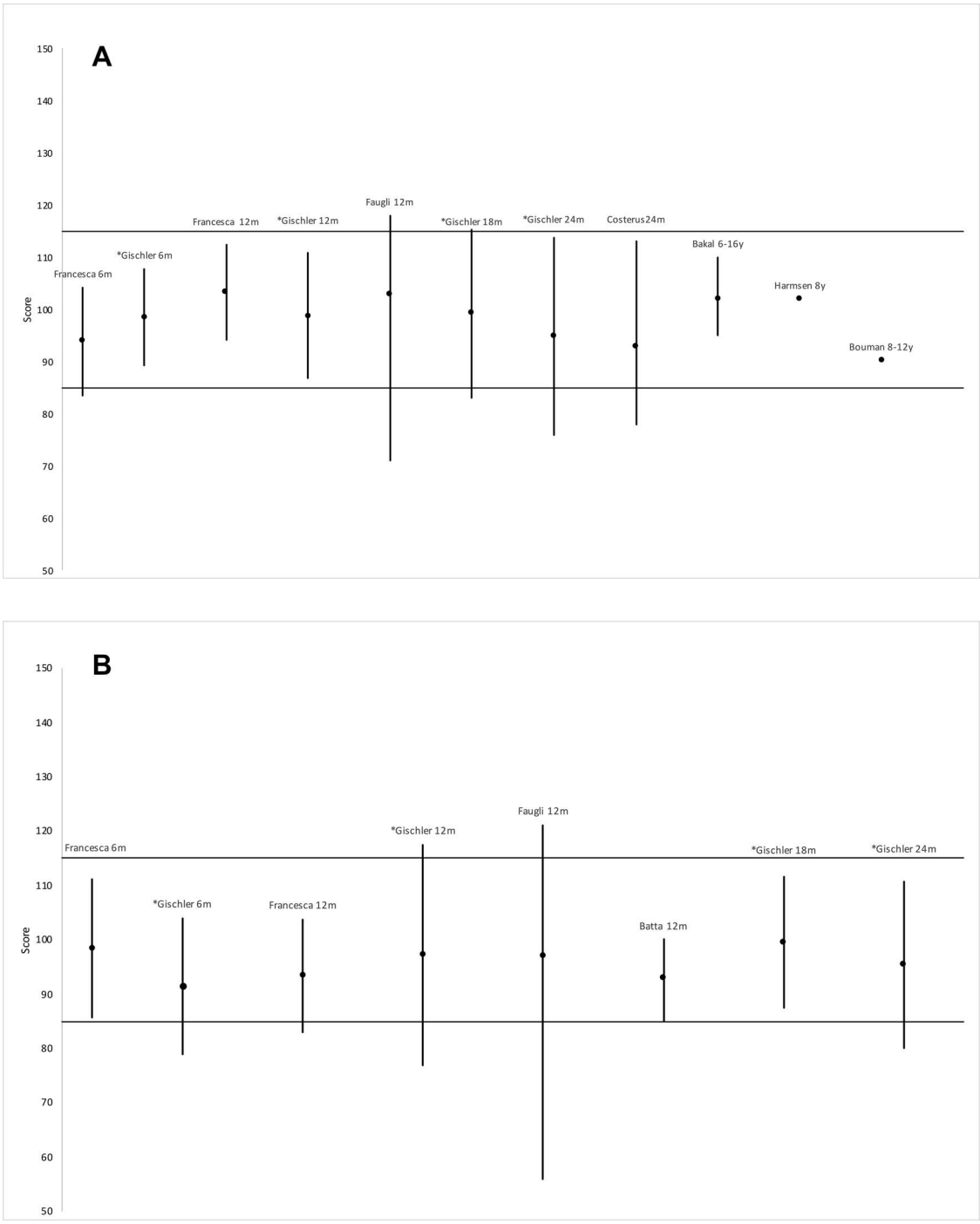

Fig. 2 (A). Outcome scores cognitive performance. Each line represents cognitive performance (mean [SD]) per study at the specified age in month (m). The dot represents the mean test result, the line represents the SD. Studies from which no crude test scores could be obtained are not included in this graph. ∗95% CI reported instead of mean (SD). The normal score ranges from 85 to 115, displayed by the lines at 85 and 115. (B) Outcome scores motor function. Each line represents motor outcome (mean [SD]) per study. The dot represents the mean test result, the line represents the SD at the specified age group in months (m). *95% CI reported instead of mean (SD). The normal score ranges from 85 to 115, displayed by the lines at 85 and 115. Outcome data from van der Cammen-van Zijp and Harmsen could not be included in this graph due to their reported outcome measures lacking mean (SD) data.

Characteristics of the included studies are summarized in Table 1. Risk of bias was present in all studies (Table 5). None of the studies had performed a sample size calculation. One study was retrospective, whereas all others were prospective studies that included patients in consecutive order.

Infants (<2 years old)

Six studies evaluated neurodevelopmental outcome in children under 2 years old (Table 2 and Fig. 2). One study used BSID-I, one study used BSID-II, and two studies used the Bayley-3. The BSID-I and the BSID-II contain two domains (motor and cognitive

Table 2 Neurodevelopmental outcome in infants (<2 years old) born with esophageal atresia

Age (months)	Author, year	No. of patients (*n*)	Test method	Outcome measure	Test result	Conclusion
6	Gischler*[22] Netherlands, 2009	13	BSID-I	Motor Cognition	98.5 (89.3–107.7)[A] 91.5 (79.0–104.0)	Normal
	Francesca[34] Italy, 2020	82	Bayley-3	Motor Cognition	98.4 ± 12.8[B] 93.9 ± 10.4	Normal
12	Gischler[22] Netherlands, 2009	13	BSID-I	Motor Cognition	98.8 (86.8–110.8)[A] 97.2 (77.0–117.5)	Normal
	Faugli[36] Norway, 2009	36	BSID-II	Motor Cognition	97 (56–121)[C] 103 (71–118)	Normal
	Walker[35] Australia, 2013	31	Bayley-3	Fine motor Gross motor Cognition Receptive language Expressive language	9.16[D] 8.37 11.00 10.23 9.03	Expressive language impaired ($P < 0.05$), other scales normal
	Francesca[34] Italy, 2020	59	Bayley-3	Motor Cognition	93.4 ± 10.3[B] 103.3 ± 9.1	Normal
	Giúdici[23] Argentina, 2016	21	CAT/CLAMS	Visomotor & receptive and expressive language skills	Normal in $n = 16$ (76%) Abnormal $n = 5$ (24%)	Significantly lower than normal
	Batta[37] Australia, 2020	27	GMDS-II	Neurodevelopment	93 (85–100)[E]	Normal
18	Gischler[22] Netherlands, 2009	13	BSID-I	Motor Cognition Cognition	99.2 (83.0–115.4)[A] 99.6 (87.5–111.6) 93 (78–113)	Normal

BOS, Bayley Ontwikkelings Schalen (Dutch version of BSID-I); BSID, Bayley Scales of Infant and Toddler Development; CAT/CLAMS, Capute Scale Clinical Adaptive Test/Clinical Auditory Milestone Scale; GMDS, Griffiths Mental Development Scales; US, United States.
[A]Mean (95% confidence interval).
[B]Mean ± standard deviation.
[C]Mean (range).
[D]Mean.
[E]Median (IQR).

Table 3 Neurodevelopmental outcome in preschoolers (2–5 years old) born with esophageal atresia

Age (months)	(Year)	Author, year	No. of patients (*n*)	Test method	Outcome measure	Test result	Conclusion
	2	Gischler[22] Netherlands, 2009	13	BSID-I	Motor Cognition	94.8 (75.9–113.7)[A] 95.4 (80.0–110.8)	Normal
	2	Costerus[21] Netherlands, 2019	5	BSID-II-NL	Motor Cognition	87 (83–96)[B] 93 (78–113)	Normal
24 ± 9[C]		Mawlana[17] Canada, 2018	182	Bayley-3	Motor Cognition Language	Delay >1 SD $n = 32$ (18%) Delay >1 SD $n = 44$ (24%) Delay >1 SD $n = 40$ (22%)	Significantly lower than normal
	3	Walker[26] Australia, 2016	24	Bayley-3	Fine motor Gross motor Cognition Receptive language Expressive language	10.96[D] 9.25 9.71 11.42 10.67	Receptive language improved ($P < 0.001$), other scales normal
	3	Giúdici[23] Argentina, 2016	14	CAT/CLAMS	Visomotor & receptive and expressive language skills	Normal in $n = 7$ (50%)	Significantly lower than normal
	5	Harmsen[24] Netherlands, 2017	54	M-ABC & M-ABC-II	Motor	z-score − 0.75 ± 0.83[E]	Impaired ($P < 0.001$)
	5.9 ± 0.5[A]	Van der Cammen-van Zijp[25] Netherlands, 2010	29	M-ABC	Total impairment score Manual Dexterity Ball skills Balance skills	Impaired $P \leq 15$ $n = 10$ (34%) Impaired $P < \leq 5$ $n = 2$ (7%) Impaired $P \leq 15$ $n = 14$ (48%) Impaired $P \leq 15$ $n = 12$ (41%)	Total impairment score ($P < 0.05$), ball skills ($P < 0.01$) and balance skills (<0.01) impaired, manual dexterity normal
	0–6[C]	Bakal[20] Turkey, 2016	24	ADSI	Cognition	Normal in all (100%)	Normal

ADSI, Ankara Developmental Screening Inventory; BSID, Bayley Scales of Infant and Toddler Development; CAT/CLAMS, Capute Scale Clinical Adaptive Test/Clinical Auditory Milestone Scale; M-ABC, Movement-Assessment Battery for Children; US, United States.
[A]Mean (95% confidence interval).
[B]Median (range).
[C]Mean ± SD.
[D]Mean.
[E]Range.

Table 4 Neurodevelopmental outcome in school-aged children (≥6 years old) born with esophageal atresia

Age (year)	Author, year	No. of patients (*n*)	Test method	Outcome measure	Test result	Conclusion
6	Giúdici[23] Argentina, 2016	10	PRUNAPE	Fine and gross motor function, language skills and social area	Normal in $n = 3$ (30%)	Significantly lower than normal
7 (3–12)[A]	König[28] Germany, 2018	12	KTT/DMT	Motor	2.19[B]	Impaired compared with controls ($P = 0.04$) and norm values ($P = 0.00$)
8	Harmsen[24] Netherlands, 2017	49	M-ABC & M-ABC-II	Motor	*z*-score -0.53 ± 0.91[C]	Impaired ($P < 0.001$)
		46	WISC-III-NL & RAKIT	Full-scale IQ Total verbal IQ Total performance IQ	102 ± 14[C] 103 ± 14[C] 98 ± 14[C]	Normal
6–17[D]	Kubota[29] Japan, 2011	20	WISC-III & KSPD	Cognition	IQ < 70 in $n = 5$ (25%)	Higher incidence of mental retardation compared with the reference population (2–3%).
6–16[D]	Bakal[20] Turkey, 2016	15	WISC-R	Cognition	IQ 95–110[E]	Normal
10.2 (8–12)[E]	Bouman[27] Netherlands, 1999	36	WISC-RN	Cognition	IQ 90.2 ± 16[C]	Impaired ($P < 0.01$)

KTT/DMT, Kinderturntest Plus/Deutscher Motorik Test; KSPD, Kyoto Scale of Psychological Development; M-ABC, Movement-Assessment Battery for Children; PRUNAPE, Prueba Nacional de Pesquisa (Argentine Screening Test); RAKIT, Revised Amsterdam Intelligence Test; US, United States; WISC, Wechsler Intelligence Scale for Children.
[A]Median (range).
[B]Mean.
[C]Mean ± SD.
[D]Range.
[E]Mean (range).

Table 5 Risk of bias analysis MINORS

Study	A clearly stated aim	Inclusion of consecutive patients	Prospective collection of data	Endpoint appropriate to the aim of the study	Unbiased assessment of the study endpoint	Follow-up period appropriate to the aim of the study	Loss to follow-up less than 5%	Prospective calculation of the study size	An adequate control group	Contemporary groups	Baseline equivalence of groups	Adequate statistical analysis	Total
Bouman[27]	2	2	2	2	2	2	NR	0	NR	NR	NR	NR	**12/24**
Francesca[34]	2	2	2	2	2	2	0	0	0	NR	NR	2	**14/24**
Gischler[22]	2	2	2	2	2	2	2	0	NR	NR	NR	NR	**14/24**
Walker 2013[35]	2	2	2	2	2	2	NR	0	2	2	2	2	**20/24**
Faugli[36]	2	2	2	2	2	2	NR	0	NR	NR	NR	2	**14/24**
Costerus[21]	2	2	2	2	2	2	2	0	NR	NR	NR	NR	**14/24**
Giudici[23]	1	2	2	2	2	2	0	0	NR	NR	NR	NR	**11/24**
Walker 2016[26]	2	2	2	2	2	2	1	0	2	2	2	2	**21/24**
Mawlana[17]	2	2	2	2	2	2	NR	0	NR	NR	NR	NR	**12/24**
Konig[28]	2	2	2	2	2	2	1	0	2	NR	2	2	**19/24**
van der Cammen[25]	2	2	2	2	2	2	NR	0	NR	NR	NR	NR	**12/24**
Harmsen[24]	2	2	2	2	2	2	1	0	NR	NR	NR	NR	**13/24**
Bakal[20]	2	2	2	2	2	2	NR	0	NR	NR	NR	NR	**12/24**
Kubota[29]	2	2	2	2	2	2	NR	0	NR	NR	NR	NR	**12/24**
Batta[37]	2	2	0	2	2	2	0	0	2	NR	NR	2	**14/24**

NR, not reported.

functioning), whereas the Bayley-3 also contains a domain on language skills. The other studies used the CAT/CLAMS (Capute Scale Clinical Adaptive Test/Clinical Auditory Milestone Scale) and the GMDS-II (Griffiths Mental Development Scales-II).

At 6 months of age, normal neurodevelopment was found in two longitudinal cohort studies: Gischler *et al.* (BSID-I, ages 6, 12, 18, and 24 months, $n = 13$)[22] and Francesca *et al.* (Bayley-3, ages 6 and 12 months, $n = 82$).[34] At 12 months of age, both these studies again found normal motor and cognitive functioning.[22,34] Francesca *et al.* found a delay with time. They found a significantly lower median motor score at 12 months, compared with the score at 6 months old ($P = 0.033$), but higher cognitive function at 12 months compared with the score at 6 months ($P = 0.000$). Gischler *et al.* found no differences at 12 months compared with the scores of the same cohort at age 6 months, and results at age 18 months also showed normal motor and cognitive functioning.[22]

One other study that administered the Bayley-3 at 12 months of age found normal motor, cognitive and receptive language functions but a significantly impaired expressive language functioning ($n = 31$, $P < 0.05$).[35] A study using the BSID-II reported a normal neurodevelopment ($n = 36$).[36] A retrospective study using the GMDS-II at age 12 months ($n = 27$) found normal neurodevelopment.[37]

A longitudinal study from Argentina (CAT/-CLAMS, ages 1, 2, and 6 years, $n = 23$) found an abnormally low neurologic-psychomotor developmental index (NPDI) in five (24%) children at 1 year of age.[23]

In summary, most studies in infants show normal neurodevelopment compared with healthy controls, whereas only one study found impaired expressive language functioning at 12 months of age.[35]

Preschoolers (2–5 years old)

Eight studies assessed children's neurodevelopment at preschool age (Table 3 and Fig. 2). Full-range neurodevelopment was assessed in five studies; two used the BSID-I or -II[17,21]; two used the Bayley-3[22,26]; and one the CAT/CLAMS.[23] One study measured cognitive functioning with the Ankara developmental screening inventory (ADSI), a validated Turkish instrument, to measure cognitive functioning.[20] Motor functioning was assessed with the M-ABC in two studies.[24,25]

Within the framework of a structured longitudinal follow-up program, Gischler *et al.* (BSID-I, ages 6, 12, 18, and 24 months, $n = 13$) showed normal motor and cognitive functioning at age 24 months.[22] Costerus *et al.* (BSID-II, age 2 years, $n = 5$) found normal outcome scores, although one child, diagnosed with Feingold syndrome, showed delayed cognitive functioning and one other child slightly delayed motor function.[21]

A retrospective study in Canadian children (Bayley-3, age 24 months, $n = 182$) found a significant delay of >1 SD for all domains of the Bayley-3.[17] During the first period of this study, children were only assessed if the result of the ASQ—a validated screening instrument for communication, gross motor, fine motor, problem solving, and personal–social skills—had raised concerns.[38] During the remaining study period, each child was standardly assessed with the Bayley-3. Another cross-sectional study from a Turkish group (ADSI, age 0–6 years, $n = 24$) found intellectual levels in accordance with the children's age.[20]

The children in the Australian study who had been tested at the age of 1 year,[35] showed at 3 years of age no significant differences in all subdomains of the Bayley-3, but significantly improved receptive language skills ($P = 0.001$, Bayley-3, age 3 years, $n = 24$).[26] The Argentinian group (CAT/CLAMS, ages 1, 2, and 6 years, $n = 14$) found abnormal NPDI in 7 out of 14 (50%) children.[23]

Two studies—with partly the same cohort—appraised the motor function of 5-year-old children with the use of the M-ABC, within the framework of a structured longitudinal follow-up program. Van der Cammen-van Zijp *et al.* (M-ABC, age 5.9 years, $n = 29$, cohort born 1999– 2003) found a significantly lower total impairment score ($P < 0.05$), ball skills, and balance skills ($P < 0.01$), whereas manual dexterity was within normal ranges, compared with Dutch reference values.[25] Harmsen *et al.* (M-ABC and M-ABC II, ages 5 and 8 years, $n = 54$, cohort born 1999–2006) showed a significantly ($P < 0.001$) reduced motor function at 5 years, characterized by impaired gross motor skills, although fine motor skills were not impaired.[24]

In summary, preschoolers show impaired neurodevelopment in 2/5 studies,[17,23] normal cognitive performance in 1/1 study,[20] and impaired motor function in 2/2 studies.[24,25]

School-aged children (≥6 years old)

Six studies assessed the neurodevelopment of children aged 6 years or older (Table 4 and Fig. 2). One study assessed the full-range neurodevelopment using the Prueba Nacional de Pesquisa (PRUNAPE, Argentine Screening Test).[23] Cognitive performance was assessed in four studies with the WISC,[20,24,27,29] and in one of these additionally with the Revised Amsterdam Intelligence Test (RAKIT).[24] The two other studies assessed motor functioning; one with the M-ABC[24] and the other with the Kinderturntest Plus/Deutscher Motorik Test (KTT/DMT).[28]

The Argentinian study group (CAT/CLAMS, ages 1, 2, and 6 years, $n = 10$) found borderline or impaired neurodevelopment in seven patients (70%). Four out of the seven patients with a normal NPDI at age 1 year

had abnormal rest results at age 6 years (McNemar's test, $P = 0.04$).[23]

Four studies evaluated cognitive performance with the WISC in school-aged children. Kubota *et al.* (WISC-III & KSPD, age 6–17 years, $n = 20$) showed that five of the children (25%) had IQ-scores < 70, defined as intellectual disability, which proportion was significantly higher than the 2–3% incidence in the general Japanese population.[29] Bakal *et al.* (WISC-R, age 6–16 years, $n = 15$) found IQ levels within normal range (range 95–110).[20] Bouman *et al.* (WISC-RN, age 10.2 years, $n = 36$) found a 10-points lower IQ (90.2 vs. 100, $P < 0.01$) than Dutch reference norms ($P < 0.01$).[27] The prospective study of Harmsen *et al.* (WISC-III-NL & RAKIT, age 8 years, $n = 46$) found normal IQ levels ($P = 0.26$).[24] This study also assessed motor function (M-ABC and M-ABC II, ages 5 and 8 years, $n = 49$); the mean M-ABC *z*-score was significantly lower than normative values ($P < 0.001$), and did not improve significantly from age 5 years to 8 years (linear mixed model, *z*-score + 0.24, $P = 0.074$).[24]

A German cross-sectional study (KTT/DMT, age 7 years, $n = 17$) assessed motor functioning. The children born with EA scored significantly lower than both age-matched healthy controls and the reference population.[28]

In summary, school-aged children show impaired neurodevelopment in 1/1 study,[23] impaired cognitive performance in 2/4 studies,[27,29] and impaired motor function in 2/2 studies compared with healthy controls.[24,28]

Associations with neurodevelopment

In total, five studies reported statistical data on the association between covariables and neurodevelopment. Gischler *et al.* used random regression modelling, which revealed that a higher number of congenital anomalies, higher severity of illness during admission, the higher number of surgical interventions in the first 24 months, and additional medical problems (e.g. O_2 or tracheostomy at home) were associated with an impaired motor and cognitive functioning (all $P < 0.05$). Length of stay in the first 6 months was negatively associated with motor functioning as well ($P < 0.05$).[22] With multivariate regression, Francesca *et al.* found birth weight to be positively associated with motor function at 6 months of age, whereas length of stay and weight at 12 months beneath the 5th percentile were both negatively associated with motor function at 12 months.[34]

The total number of major congenital anomalies correlated negatively with motor functioning (Spearman, $P = 0.007$) in the study of van der Cammen-van Zijp *et al*. They also found a significant negative correlation with duration of hospitalization ($P = 0.003$) and number of surgical interventions ($P = 0006$).[25] Furthermore, a longitudinal linear mixed model analysis of Harmsen *et al* revealed that duration of anesthetic exposure within the first 24 months was negatively associated with motor functioning ($P = 0.018$). Sports participation was positively associated with motor functioning at 8 years ($P = 0.002$).[24] The study of Batta *et al* found that birthweight and length of stay in the hospital were associated with neurodevelopment at 1 year of age.[37]

DISCUSSION

We conducted this systematic review to provide an overview on the current knowledge on the long-term neurodevelopmental outcome—including both motor function and cognitive performance—of children born with EA. Most studies found cognitive performance comparable with the reference population (Fig. 2A) and motor function below normal (Fig. 2B). Two of the six studies in infants found developmental problems; i.e. impaired expressive language and impaired overall neurodevelopment, respectively. Regarding preschoolers, five of eight studies found developmental problems. One of these found receptive language to be improved, two found overall neurodevelopment to be impaired, and two found motor function to be impaired. Regarding school-aged children, five of six studies found developmental problems, three in overall neurodevelopment and two in motor function.

Heterogeneity of included studies

The overview provided by this systematic review highlights the heterogeneity of the published data on the neurodevelopmental outcome of children with EA. Unfortunately, various studies only report a dichotomous outcome, without detailed results.[17,20,23,25,29,39] Moreover, both the data and the reference values differ between studies which complicates drawing conclusions on neurodevelopment over time. Therefore, given the wide variety in tests, ages, and sample sizes, a meta-analysis could not be performed.

Interpretation of the results

Infants (0–2 years): Up to 12 months of age, both cognitive and motor functioning were within normal limits in most studies, and only one study found an impairment for expressive language.[35] This would indicate that infants do not suffer neurodevelopmental impairments. More problems were revealed, however, at older ages.

Preschoolers (2–5 years): In preschoolers, two neurodevelopmental studies found cognitive impairments.[17,23] Both motor function studies found mild motor problems and two out of five studies that assessed neurodevelopment also found motor

function impairments.[17,23–25] This would indicate that preschoolers start showing neurodevelopmental impairments, more than found in studies performed in infants.

School-aged children (6–18 years): Two out of four cognitive studies found an impaired cognitive performance with lower IQ levels.[27,29] Both studies assessing motor function found an impaired motor functioning.[24,28] In addition, one neurodevelopment study found motor impairment.[23] This would indicate that the eldest studied patients suffer the most neurodevelopmental impairments of all assessed subgroups.

A study analyzing change over time, found unchanged impaired motor function at ages 5 and 8 years.[24] Sports participation was reported for 8-year-old children only, and correlated positively with motor function at that age.

Giúdici *et al* reported a significant decrease in the number of patients with a normal NPDI with increasing age.[23] However, the NPDI had been assessed with the CAT/CLAMS at ages 1 and 3 years, and with the PRUNAPE at age 6 years. The results should therefore be interpreted with caution. Since 11 out of the 21 children in that study were lost to follow-up and characteristics of those children were not reported, an inclusion bias cannot be ruled out. Lastly, although described in two separate papers, Walker *et al* evaluated the same study population at ages 1 and 3 years and found impaired expressive language at age 1 year and improved receptive language at age 3 years.[26,35]

Causes of neurodevelopmental impairments

Neurodevelopment has already been studied in critically ill children and children born with other anatomical malformations than EA. Neurodevelopmental impairments have been reported in children who received ECMO treatment and children who received ECMO treatment after surgery for congenital diaphragmatic hernia.[7,8] The systematic review on ECMO treatment also struggled with the heterogeneity of the included studies, but their results suggested a wide range of disabilities.[7]

There is an ongoing discussion on the cause of impaired neurodevelopment in children born with a congenital malformation. Previous research in anesthesia showed that this impairment might be associated with various intraoperative surgical and anesthesiologic events.[40] Ventilator time and repeated exposure to anesthesia have been associated with impaired long-term neurodevelopmental outcome.[41] Repeated exposure is of increased importance in patients undergoing complex surgeries and surgical complications.[24,42,43] Animal studies showed a clear relationship between anesthetic dose and duration of anesthesia and impaired development, but doses administered in animals are not comparable with doses administered in human populations.[44] However, the potential neurotoxic effect of anesthetics is less clear in clinical studies. A review found only little evidence for the risk of adverse developmental outcome after neonatal surgery.[45] Potentially, the harmfulness of anesthetic exposure is determined by the combination of the type of anesthesia, the duration of exposure, the child's age, and the effects of anesthetics on the perfusion of the brain, but future research is required to explore this hypothesis. Another hypothesis has it that impaired neurodevelopment is inherent to the congenital malformation.

Furthermore, it has been hypothesized that after neonatal critical illness the hippocampus is affected by a combination of factors including hypoxia, neuroinflammation, (surgical) stress, and exposure to anaesthetics.[46] Comparative studies on this issue can gain more insight in the potential causes of long-term developmental impairment in all patient groups, and in ways to stimulate cognitive development.[47]

The results from the present review show that children born with EA are at risk for impaired neurodevelopmental outcome as well as for impaired cognitive and motor development. A structured, longitudinal follow-up program focused on motoric and neurodevelopment run by a multidisciplinary team may help to solve uncertainties for the parents and to offer timely intervention, for instance physiotherapy, when necessary. If there is indeed a developmental problem in this population, longitudinal studies with standardized follow-up at various ages could be helpful to reveal potential causes and give insight in the effects of interventions.[48]

Strengths, limitations, and recommendations

To our knowledge, this is the first systematic review addressing neurodevelopmental outcome in children with EA. One of the strengths is the thorough search strategy. Also, the wide age spread gives an overview of the neurodevelopment during multiple stages of a child's life. However, several limitations need to be addressed. First, although the quality of each included study seems good (Table 5), a broad range of tests were used to assess neurodevelopment, including national instruments such as the PRUNAPE, ADSI, RAKIT, and KSPD. Nevertheless, these instruments have all been validated, and test results were compared with local reference norms.[49–52] In some cases, different versions of an instrument sometimes assessed slightly different developmental skills. For example, the cognitive scale of the BSID-II included more linguistic skills than the Bayley-3. This variety in tests complicates the comparison between studies.

Secondly, selection bias could have affected results. An example is the retrospective chart review of Mawlana *et al*, in which during an unspecified part of the study period the Bayley-3 was assessed only if the ASQ was abnormal.[17] Nevertheless, we have decided

to include this study because of its large sample size. Moreover, data on non-participants, which could have influenced the outcomes of the tested cohorts for better or for worse, were missing in all studies but one. Only Harmsen *et al* disclosed background information about the non-participants.[24] Furthermore, referral bias may have occurred in that parents of children without problems may have not to participate in follow-up programs. Overall, inclusion criteria varied among studies. Four studies clearly stated to have excluded patients with syndromal or chromosomal abnormalities, neurological impairment, or intellectual disability,[22,24,25,37] whereas others did not. For example, the cohort of Giúdici *et al* contained one patient with trisomy 21, one with Edwards syndrome and two with cerebral palsy.[23]

Our search did not identify studies that used validated questionnaires to assess the neurodevelopment of patients born with EA. This type of studies could be of additional value to the studies discussed in this systematic review, which all used validated physical assessment tools to assess the neurodevelopment.

The present study highlights the potential neurodevelopmental impairments of these children. International standardization of testing protocols is advocated.[53] Recommendations would include testing with the instruments and reporting more detailed data, for instance using standard deviation and/or *z*-scores. This would facilitate meta-analyses and drawing accurate conclusions.

CONCLUSION

In conclusion, this systematic review shows that impairments were mostly found in motor function, but also in cognitive performance. In general, the findings of this review raise concerns regarding the long-term outcome of children after congenital EA surgery. Participation in a structured long-term follow-up program for this patient population is recommended, because this allows timely detection and treatment of neurodevelopmental problems.

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