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Neurodevelopmental outcome of patients with congenital gastrointestinal malformations: a systematic review and meta-analysis

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ABSTRACT

Aim Children with congenital gastrointestinal malformations may be at risk of neurodevelopmental impairment due to challenges to the developing brain, including perioperative haemodynamic changes, exposure to anaesthetics and postoperative inflammatory influences. This study aggregates existing evidence on neurodevelopmental outcome in these patients using meta-analysis.

Method PubMed, Embase and Web of Science were searched for peer-reviewed articles published until October 2019. Out of the 5316 unique articles that were identified, 47 studies met the inclusion criteria and were included. Standardised mean differences (Cohen's *d*) between cognitive, motor and language outcome of patients with congenital gastrointestinal malformations and normative data (39 studies) or the studies' control group (8 studies) were aggregated across studies using random-effects meta-analysis. The value of (clinical) moderators was studied using meta-regression and diagnostic subgroups were compared.

Results The 47 included studies encompassed 62 cohorts, representing 2312 patients. Children with congenital gastrointestinal malformations had small-sized cognitive impairment ($d=-0.435$, $p<0.001$; 95% CI -0.567 to -0.302), medium-sized motor impairment ($d=-0.610$, $p<0.001$; 95% CI -0.769 to -0.451) and medium-sized language impairment ($d=-0.670$, $p<0.001$; 95% CI -0.914 to -0.425). Patients with short bowel syndrome had worse motor outcome. Neurodevelopmental outcome was related to the number of surgeries and length of total hospital stay, while no relations were observed with gestational age, birth weight, age and sex.

Interpretation This study shows that children with congenital gastrointestinal malformations exhibit impairments in neurodevelopmental outcome, highlighting the need for routine screening of neurodevelopment during follow-up.

INTRODUCTION

Congenital gastrointestinal malformations (ie, oesophageal atresia, gastroschisis, omphalocele, intestinal atresia, Hirschsprung's disease and anorectal malformations) are relatively uncommon conditions with a total prevalence of about 15 per 10 000 European births a year.¹ Although survival in these patients has improved over the past decades, morbidity remains high.²⁻⁸ Recent evidence suggests

What is already known on this topic?

- Patients with non-cardiac congenital malformations are at risk of motor and cognitive impairment up to the age of 2 years.
- Patients with gastrointestinal malformations are subject to several potential aetiological factors contributing to negative impact on the developing brain.

What this study adds?

- Patients with congenital gastrointestinal malformations have impaired neurodevelopmental outcome up to adolescence.
- Cognitive impairment was small-sized, whereas motor and language impairment was medium-sized.
- Impairment was related to length of hospital stay and number of surgeries.

that there may also be an impact on the central nervous system of these patients.⁹

The available literature provides evidence for several pathways implicated in congenital gastrointestinal malformations that may contribute to a negative impact on the developing central nervous system: (1) genetic abnormalities^{10 11}; (2) perinatal influences, such as maternal smoking,¹² use of medication,^{13 14} preterm birth¹⁵ and low birth weight¹⁵; (3) early, long and/or repeated exposure to anaesthetics necessary for surgical correction(s)¹⁶⁻¹⁸; (4) perioperative haemodynamics and respiratory functioning¹⁹⁻²¹; (5) postoperative inflammatory challenges^{22 23}; and (6) poor nutritional status that can lead to an altered microbiome, influencing the developing brain through the gut-brain axis.²⁴⁻²⁷ All these harmful challenges to the central nervous system may lead to neurodevelopmental impairment, which in turn may interfere with development in important domains of functioning, including academic achievement, behavioural functioning, and social and economic well-being.²⁸⁻³⁰

The primary aim of the current systematic review is to quantitatively aggregate all available empirical evidence on the effects of having a congenital gastrointestinal malformation on neurodevelopment using



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meta-analysis. This review focuses on congenital gastrointestinal malformations other than congenital diaphragmatic hernia (CDH), to not include the confounding effect of the pulmonary comorbidity in patients with CDH,^{31–33} which may require treatment with extracorporeal membrane oxygenation.^{34,35} The secondary aim is to study differences between specific types of congenital gastrointestinal malformations and the contribution of possible moderating factors for neurodevelopmental impairment, using meta-regression.

METHODS

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (see online supplemental material).³⁶

Search and selection

The search strategy combined three groups of search terms and their equivalents: (1) terms related to the congenital malformations of interest, (2) terms defining age groups, (3) terms defining (the validated measures of) the outcomes. The full search strategy can be found in the online supplemental material. PubMed, Embase and Web of Science were searched using both simple search terms and hierarchical family forms (eg, Medical Subject Headings, Thesaurus, Emtree). The reference lists of eligible articles were also screened for additional articles. The last search was conducted in October 2019.

A flow diagram of the study search and selection is provided in figure 1. A total of 6675 records were identified corresponding to 5316 unique articles. Two authors (DR and LES) independently assessed each article for eligibility using Covidence, an online tool for systematic reviews.³⁷ Conflicts in the selection process were solved by consensus, or a third party was consulted.

Inclusion criteria

Studies were included in this systematic review and meta-analysis if they: (1) included patients with a congenital gastrointestinal malformation (ie, oesophageal atresia, omphalocele, gastroschisis, intestinal atresia, Hirschsprung's disease, anorectal malformations and short bowel syndrome), excluding CDH, (2) included subjects within the age range from infancy to adolescence (0–18 years), (3) reported cognitive, motor or language outcome measured with any standardised and/or validated measure, compared with a selected control group or normative population, (4) used an observational or controlled design, (5) were published in a peer-reviewed journal, (6) were published after 1990, and (7) were written in the English language. Studies reporting on adults only, or studies reporting on both children and adults without detailing the results for only children, were excluded, as well as review papers and case reports. A cohort was defined as a subgroup of the total group of patients included in a study, mostly defined in terms of a particular congenital malformation, and in few studies defined in terms of age at follow-up. How selection was done in case multiple studies reported on (partly) overlapping cohorts is described in the online supplemental material. Authors of studies were contacted in case a study did not report all data required for the planned analyses. In total, 47 studies were included in the meta-analysis. A reference list is provided in the online supplemental material.

Data extraction

The following data were extracted by two authors (DR and LES): (1) mean raw or standardised scores, accompanying SDs and sample sizes for all outcome measures were extracted for all separate cohorts of cases and, if applicable, control groups. If this information was not available, the proportion of individuals with neurodevelopmental outcome in the standardised normal range was compared between patients and the normative or control sample, in which case sample sizes and relevant p values were extracted. (2) Study characteristics, including: sample sizes, type(s) of malformation(s) assessed, instrument(s) used to assess neurodevelopment, length of follow-up, attrition of the study sample at follow-up; and (3) potential (clinical) moderating factors of neurodevelopmental outcome (listed in online supplemental material tables 1 and 3).

Quality assessment

Quality of the included studies was independently assessed by two authors (DR and LES) using the Newcastle–Ottawa Scale (NOS), based on selection of subjects (4 points), comparability of patient and control groups (2 points) and outcome measurements (3 points).^{38,39} Adjustments to the tool according to the manual and scoring methods are described in the online supplemental material. Rating discrepancies were resolved by consensus.

Statistics

Analyses were performed using Comprehensive Meta-Analysis (CMA) software (V.3.0, Biostat). Using the extracted mean (SD) of raw or standardised scores on cognitive, motor and/or language outcome of cases, and of controls (8 studies) or normative data (39 studies), we calculated effect sizes as the standardised mean difference (Cohen's d) between groups. Outcome measures in the current meta-analyses were: overall neurodevelopmental outcome and three domains of neurodevelopmental outcome: cognitive outcome, motor outcome and language outcome. Overall

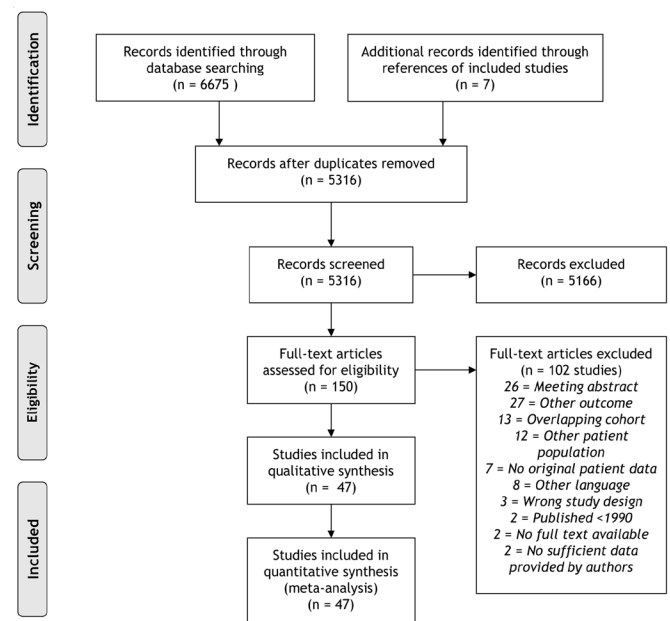


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart.

Table 2 Differences between types of malformations in overall neurodevelopmental outcome

Type of malformation	Number of studies	Cohen's d (95% CI, p value) on overall neurodevelopmental outcome	Type of malformation versus other types of malformation, Q-values, p values
Abdominal wall defects (ie, gastroschisis, omphalocele)	17	-0.375 (-0.567 to -0.182, p<0.001)	Q=1.14, p=0.286
Colorectal malformations (ie, Hirschsprung's disease, anorectal malformations)	10	-0.485 (-0.765 to -0.206, p=0.001)	Q=0.024, p=0.877
Oesophageal atresia	17	-0.521 (-0.713 to -0.328, p<0.001)	Q=0.433, p=0.506
Intestinal atresia	5	-0.251 (-0.585 to -0.082, p=0.140)	Q=1.657, p=0.190
Short bowel syndrome	6	-1.000 (-1.324 to -0.675, p<0.001)	Q=11.639, p=0.002

with the weighted average effect sizes of outcome data (Cohen's d) at study level. When studies reported the median with IQRs, means and SD were calculated.⁴⁰⁻⁴¹ Furthermore, subgroup comparisons were performed to test for possible differences between diagnostic subgroups (ie, different types of malformations) and domains of outcome. Effect sizes were interpreted as small ($d=0.2-0.5$) medium ($d=0.5-0.8$) or large ($d\geq 0.8$), according to Cohen.⁴² Heterogeneity was interpreted as small ($I^2\leq 0.25$), medium ($I^2=0.25-0.50$) or strong ($I^2\geq 0.50$), according to Higgins.⁴³ The possibility of publication bias was assessed by visual inspection of Funnel plots and by calculating Funnel plot asymmetry expressed as the Egger's regression intercept t .⁴⁴ To test for bias caused by studies with a fair or poor quality of design, sensitivity analyses were conducted on studies of good quality only.

RESULTS

Sample description

This systematic review and meta-analysis represents a total of 2312 patients described in 47 studies (online supplemental table 1). A detailed sample description in terms of distribution of types of malformation, sex, age groups, birth weight and gestational age can be found in the online supplemental material.

Overall neurodevelopmental outcome

The meta-analysis on overall neurodevelopmental outcome included all 47 studies ($n=2312$ patients; [figure 2](#)). Nineteen of the 47 studies showed significantly poorer overall neurodevelopmental outcome of patients with congenital gastrointestinal malformations compared with normative data or healthy controls. Meta-analytical aggregation of all findings showed a small-sized negative effect on overall neurodevelopmental outcome ($d=-0.494$, $p<0.001$; 95% CI -0.605 to -0.382 , $I^2=56.2\%$; [table 1](#)).

Cognitive outcome

The meta-analysis on cognitive outcome included 39 studies ($n=2055$ patients). In 12 of the 39 studies, cognitive outcome of patients with congenital gastrointestinal malformations was significantly worse compared with normative data or healthy controls. Meta-analytical aggregation showed a small-sized negative effect on cognitive outcome ($d=-0.435$, $p<0.001$; 95% CI -0.567 to -0.302 , $I^2=63.7\%$; [table 1](#)).

Motor outcome

The meta-analysis on motor outcome included 33 studies ($n=1821$ patients). In 14 of 33 studies, motor outcome of patients with congenital gastrointestinal malformation was

significantly worse compared with the normative population or healthy controls. Meta-analytical aggregation showed a medium-sized negative effect on motor outcome ($d=-0.610$, $p<0.001$; 95% CI -0.769 to -0.451 , $I^2=70.3\%$; [table 1](#)).

Language outcome

The meta-analysis on language outcome included 14 studies ($n=701$ patients). Ten out of 14 studies showed a significant negative difference between language development of patients with a congenital gastrointestinal malformation and the normative population or healthy controls. Meta-analytical aggregation showed a medium-sized negative effect ($d=-0.670$, $p<0.001$; 95% CI -0.914 to -0.425 , $I^2=68.4\%$; [table 1](#)).

Influence of possible presence of chromosomal abnormalities

Sensitivity analyses excluding three studies that may have included subjects with chromosomal abnormalities showed comparable (if not larger) impairments on overall neurodevelopmental outcome ($d=-0.519$, $p<0.001$), cognitive outcome ($d=-0.458$, $p<0.001$), motor outcome ($d=-0.658$, $p<0.001$) and language outcome ($d=-0.780$, $p<0.001$).

Meta-regression of possible moderators of neurodevelopmental outcome

Meta-regression showed that worse overall neurodevelopmental and worse motor outcome were related to longer mean total length of hospital stay, worse overall neurodevelopmental, worse cognitive and worse motor outcome were related to a higher mean number of surgeries, while no relations were observed with mean age, mean gestational age, mean birth weight and percentage of boys in a study, as shown in [table 1](#) and online supplemental table 2.

Differences between types of malformations

When comparing meta-analytical effect sizes of subgroups of different types of malformations, we found a significant difference in the magnitude of effect sizes for overall neurodevelopmental outcome ($Q=11.52$; $p=0.021$) ([table 2](#)), that was traced down in further analyses to significantly poorer overall neurodevelopmental outcome for patients with short bowel syndrome compared with all remaining patient groups ($d=-1.000$ and $d=-0.412$, respectively, $Q=11.639$; $p=0.001$). Further tests assessing differences between types of malformations are shown in the online supplemental material.

Quality of studies and risk of bias analysis

Results of the quality assessment are presented in [table 3](#). NOS scores ranged from 4 to 9. Most studies had good

Table 3 Quality of included studies as assessed with the Newcastle–Ottawa Scale (NOS)

Study	Selection of subjects	Comparability of cases and controls	Outcome measurements	Total score*	Quality†
Aite, 2014 ⁵⁷	3	1	2	6	Good
Beers, 2000 ²⁵	4	2	3	9	Good
Bevilacqua, 2014 ⁴⁶	3	1	3	7	Good
Bevilacqua, 2015 ⁵⁸	3	1	2	6	Good
Bouman, 1999 ⁶⁵	3	1	2	6	Good
Burnett, 2018 ⁶⁶	3	1	2	6	Good
Chesley, 2016 ²⁶	3	1	3	7	Good
Costerus, 2019 ⁶⁷	3	1	2	6	Good
Danzer, 2019 ⁶²	3	1	2	6	Good
Doberschuetz, 2016 ⁶⁸	4	2	3	9	Good
Elsinga, 2013 ⁴⁹	3	1	2	6	Good
Faugli, 2009 ⁶⁹	2	1	2	5	Fair
Gischler, 2009 ⁸	3	1	3	7	Good
Giudici, 2016 ⁷⁰	3	0	3	6	Poor
Giudici, 2016 ⁷¹	3	0	2	5	Poor
Gorra, 2012 ⁷²	3	2	2	7	Good
Harmsen, 2017 ⁵⁹	3	1	3	7	Good
Harris, 2016 ⁷³	3	1	2	6	Good
Hijkoop, 2017 ⁷⁴	3	1	3	7	Good
Huang, 2008 ²²	3	1	3	7	Good
Kato, 1993 ⁶⁰	2	1	3	6	Fair
Konig, 2018 ⁷⁵	2	1	3	6	Fair
Kubota, 2011 ⁴⁷	2	1	2	5	Fair
Kumari, 2019 ⁷⁶	3	0	1	4	Poor
Laing, 2011 ⁷⁷	1	1	3	5	Poor
Ludman, 1990 ⁶¹	3	2	3	8	Good
Ludman, 1993 ⁷⁸	3	2	3	8	Good
Maheshwari, 2013 ⁷⁹	3	1	3	7	Good
Mazer, 2010 ³	3	1	3	7	Good
Mawlana, 2018 ⁸⁰	3	1	3	7	Good
Minutillo, 2013 ⁸¹	3	1	3	7	Good
Moran, 2019 ⁸²	3	2	2	7	Good
More, 2014 ⁸³	3	1	2	6	Good
Newton, 2016 ⁸⁴	4	2	2	8	Good
Payne, 2010 ⁸⁵	4	2	3	9	Good
Plummer, 2019 ⁸⁶	2	1	2	5	Fair
Sirichaipornsak, 2011 ⁸⁷	3	1	2	6	Good
So, 2016 ⁸⁸	3	1	3	7	Good
So, 2019 ⁸⁹	2	1	2	5	Fair
So, 2019 ⁹⁰	2	1	3	6	Fair
South, 2008 ⁹¹	3	1	3	7	Good
Van den Hondel, 2013 ⁹²	3	1	3	7	Good
Van den Hondel, 2016 ⁹³	3	1	3	7	Good
Van der Cammen-van Zijp, 2010 ⁸	3	1	2	6	Good
Van Eijck, 2013 ⁵⁰	3	1	2	6	Good
Walker, 2013 ⁹⁴	3	2	3	8	Good
Walker, 2015 ⁹⁵	3	2	2	7	Good

*The NOS allows study quality of observational studies to be quantified on the basis of the methods used to select subjects (4 points), comparability of case and control groups (2 points) and outcome measurements (3 points).

†Scores were converted to the Agency for Healthcare Research and Quality standards, in order to judge quality as 'good', 'fair' or 'poor'.

quality (77%), with only a minority of studies qualifying as fair (15%) or poor (8%). Results of the sensitivity analysis on studies of good quality, risk of publication bias (see also [table 1](#)) and risk of other bias analyses are described in the online supplemental material.

DISCUSSION

This systematic review and meta-analysis of 47 studies representing 2012 patients revealed evidence for small-sized overall

neurodevelopmental impairment in children with congenital gastrointestinal malformations compared with normative data or healthy controls, reflecting small-sized cognitive impairment, medium-sized motor impairment and medium-sized language impairment. These findings translate into an average difference in 6.5 IQ points and implicate a 3.6% increase in the number of children with cognitive delay, a 5.9% increase in the number of children with motor delay and 6.9% increase in the number of children with language delay.

Excluding studies that may have included syndromal patients did not lead to altered conclusions. Our findings implicate that patients with congenital gastrointestinal malformations have increased risk of neurodevelopmental impairment. Our findings are in line with an earlier meta-analysis of cognitive and motor impairment in infants (up to 24 months of age) with non-cardiac congenital malformations,⁴⁵ although the slightly larger effects obtained in that meta-analysis may be explained by the inclusion of patients with CDH.⁴⁶

Robust evidence for neurodevelopmental impairment was found in all types of congenital gastrointestinal malformations. Contrary to what has been indicated in previous reports,^{46,47} no differences in meta-analytical effect sizes of overall neurodevelopmental outcome were found between patients with specific types of congenital gastrointestinal malformations, except for relatively poorer overall neurodevelopment and motor development in patients with short bowel syndrome.

Considering moderating factors, the results revealed that longer mean length of stay and a higher mean number of surgeries were related to greater overall neurodevelopmental impairment and motor development. This may suggest that the more complex the course of disease and/or treatment that is required, the more profound the impact is on neurodevelopmental outcome. The results of our meta-regression analyses showed no differences in the magnitude of effect between the different age groups. This cross-sectional finding suggests that the magnitude of neurodevelopmental impairment remains relatively stable over developmental stages, but remains to be investigated by longitudinal studies.

Although preterm birth and low birth weight are associated with neurodevelopmental impairment,^{26,48–54} meta-regression analyses found no evidence for the possibility that our findings reflect the effects of gestational age or birth weight. This suggests that other common aetiological factors for neurodevelopmental impairment may play a (more important) role in the neurodevelopmental impairments of patients with congenital gastrointestinal malformations, such as factors related to intrauterine development,^{55,56} surgical treatment,^{19,26,57–62} compromised bowel function and feeding support,^{50,57,62} and parental social economic status.⁶³ We consider this an important issue in future research and suggest prospective registration of potential aetiological factors and neurodevelopment outcomes.

The evidence found in this meta-analysis was primarily based on studies with good quality (74%). Excluding studies with fair or poor quality did not result in altered conclusions. Risk of publication bias analyses indicated a potential influence of publication bias on the meta-analytical estimations, indicating that these estimations should be interpreted with caution and emphasising importance for preregistration of study protocols.

Limitations

The findings of the current systematic review and meta-analysis are limited by the use of normative data in the majority of included studies (38 of 47), which does not control for differences in variables such as sex and socio-economic status. Second, there was heterogeneity in the measures used to assess neurodevelopmental outcome, while some evidence suggests that the Bayley Scales of Infant Development (BSID)-III may overestimate neurodevelopment as compared with the BSID-II.⁶⁴ Third, the tests of subgroup differences on type of malformations and type of outcome domain were limited by partially overlapping subjects across subgroups. However, since related observations tend to decrease variance, this would make the comparison more sensitive for group differences, which were not observed.

Fourth, the quantity of available literature allowed inclusion of only a limited number of potentially moderating aetiological factors in meta-regression and was subject to distinct heterogeneity in terms of construct definitions. Lastly, due to the limited number of studies, our findings for language outcome and the possible influence of moderating factors on all outcomes await replication before a firm conclusion may be drawn.

CONCLUSIONS AND CLINICAL IMPLICATIONS

In conclusion, this systematic review and meta-analysis presents robust evidence that patients with congenital gastrointestinal malformations are at risk of small-sized to medium-sized impairment in neurodevelopmental outcome, emphasising the need for routine neurodevelopmental screening of these patients.

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Supplementary Material

SEARCH STRATEGY PUBMED

("Congenital Abnormalities"[Mesh:NoExp] OR congenital abnormalit*[tiab] OR congenital deformit*[tiab] OR congenital defect*[tiab] OR birth defect*[tiab] OR congenital anomal*[tiab] OR "Esophageal Atresia"[Mesh] OR esophageal atresia*[tiab] OR oesophageal atresia*[tiab] OR "Gastroschisis"[Mesh] OR gastroschis*[tiab] OR Congenital Fissure of the Abdominal Cavity[tiab] OR ("Hernia, Umbilical"[Mesh] AND congenital*[tiab]) OR exomphalos[tiab] OR omphalocele*[tiab] OR "Hirschsprung Disease"[Mesh] OR hirschsprung disease[tiab] OR congenital megacolon[tiab] OR hirschsprung's disease[tiab] OR hirschsprungs disease[tiab] OR aganglionic megacolon[tiab] OR Rectosigmoid Colon Aganglionosis[tiab] OR Rectosigmoid Aganglionosis[tiab] OR Congenital Intestinal Aganglionosis[tiab] OR Colonic Aganglionosis[tiab] OR Total Colonic Aganglionosis[tiab] OR "Anorectal Malformations"[Mesh] OR Anorectal Malformation*[tiab] OR Anorectal Anomal*[tiab] OR Anorectal Atresia*[tiab] OR Anorectal Stenos*[tiab] OR "Anus, Imperforate"[Mesh] OR imperforate anus[tiab] OR anal atresi*[tiab] OR "Short Bowel Syndrome"[Mesh] OR Short Bowel Syndrome*[tiab] OR intestinal failure[tiab] OR pediatric intestinal failure[tiab] OR paediatric intestinal failure[tiab] OR "Intestinal Atresia"[Mesh] OR Congenital Intestinal Atresia*[tiab] OR Apple Peel Syndrome*[tiab] OR Apple-Peel Intestinal Atresia*[tiab] OR Jejunal Atresia[tiab] OR Apple Peel Small Bowel Syndrome[tiab] OR Familial Apple Peel Jejunal Atresia[tiab]) AND (Infan*[tiab] OR newborn*[tiab] OR new-born*[tiab] OR perinat*[tiab] OR neonat*[tiab] OR baby[tiab] OR baby*[tiab] OR babies[tiab] OR toddler*[tiab] OR minors[tiab] OR minors*[tiab] OR boy[tiab] OR boys[tiab] OR boyfriend[tiab] OR boyhood[tiab] OR girl*[tiab] OR kid[tiab] OR kids[tiab] OR child[tiab] OR child*[tiab] OR children*[tiab] OR schoolchild*[tiab] OR schoolchild[tiab] OR school child[tiab] OR school child*[tiab] OR adolescen*[tiab] OR juvenil*[tiab] OR youth*[tiab] OR teen*[tiab] OR under*age*[tiab] OR pubescen*[tiab] OR pediatrics[mesh] OR pediatric*[tiab] OR paediatric*[tiab] OR peadiatric*[tiab] OR school[tiab] OR school*[tiab] OR prematur* OR preterm*) AND ("Child Development"[Mesh] OR Child Development[tiab] OR Infant Development[tiab] OR neurocogniti*[tiab] OR neuropsych*[tiab] OR cogniti*[tiab] OR neurodevelopment*[tiab] OR developmental[tiab] OR motor*[tiab] OR movement[tiab] OR psychomotor[tiab] OR intell*[tiab] OR intellect*[tiab] OR intellectual[tiab] OR intelligence[tiab] OR psychomotor performanc*[tiab] OR neurocognitive performanc*[tiab] OR psychomotor skil*[tiab] OR neurocognitive skil*[tiab] OR neuropsychological funct*[tiab] OR psychomotor funct*[tiab] OR neuropsychological outcom*[tiab] OR psychomotor outcom*[tiab] OR neurocognitive outcom*[tiab] OR "Wechsler Scales"[Mesh] OR Wechsler Scale*[tiab] OR WPPSI[tiab] OR WISC[tiab] OR Wechsler Intelligence Scale for Children[tiab] OR Wechsler Preschool and Primary Scale of

Intelligence[tiab] OR BSID[tiab] OR Bayley[tiab] OR Bayley Scales of Infant Development[tiab] OR MABC[tiab] OR Movement Assessment Battery for Children[tiab] OR AIMS[tiab] OR Alberta Infant Motor Scale[tiab] OR Infant Motor Scale[tiab] OR BOTMP[tiab] OR Bruininks-Oseretsky[tiab] OR Bruininks*[tiab] OR Griffiths[tiab] OR Griffiths Mental Development Scale[tiab] OR GMSD[tiab] OR Griffith score*[tiab] OR Mullen[tiab] OR Mullen Scales of Early Learning[tiab] OR MSEL[tiab] OR Ages and stages questionnaire[tiab] OR ASQ[tiab] OR CBCL[tiab] OR Child Behavioural Checklist[tiab] OR Child Behavioral Checklist[tiab] OR NEPSY[tiab]) AND ("Case-Control Studies"[Mesh] OR "Cohort Studies"[Mesh] OR "Observational Study" [Publication Type] OR case-control[tiab] OR cohort[tiab] OR retrospective[tiab] OR prospective[tiab] OR observational stud*[tiab] OR descriptive study[tiab] OR "Cross-Sectional Studies"[Mesh] OR cross sectional[tiab])

SELECTION OF STUDIES DESCRIBING OVERLAPPING COHORTS

In case multiple articles reported on (partly) overlapping cohorts, we included the article that: (1) reported the longest follow-up period, (2) reported separately on subgroups of patients to allow differentiation for malformation type and/or (3) had the largest sample size to maximize generalizability of the sample and statistical power of meta-analysis (decisions were made in this order).

ADJUSTED USE OF THE NEWCASTLE OTTAWA SCALE FOR QUALITY ASSESSMENT OF INCLUDED STUDIES

In accordance with the manual, the NOS tool was adjusted to enable quality assessment of observational cohort studies. One aspect of the scale (“demonstration that outcome of interest was not present at start of the study”) was not applicable and was therefore omitted from quality assessment. An extra point for selection was given when studies had a design with a control group instead of using normative scores.

In accordance with the Agency for Healthcare Research and Quality (AHRQ) standards, quality of studies was considered:

- ‘good’, in case of a score of 3-4 points for selection of subjects AND a score of 1-2 points for comparability of cases and controls AND a score of 2-3 points for outcome measurements
- ‘fair’, in case of a score of 2 points for selection of subjects AND a score of 1-2 points for comparability of cases and controls AND a score of 2-3 points for outcome measurements
- ‘poor’, in case of a score of 0-1 points for selection of subjects OR 0 for comparability of cases and controls OR 0-1 for outcome measurements

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STUDY CHARACTERISTICS OF INCLUDED STUDIES

sTable 1 Study characteristics of included studies

Author	Period of inclusion ^a	Country	Sample size ^b	Assessed type of malformation ^b	Tool ^c	Normative sample	Included in meta-analysis of overall neurodevelopmental outcome	Included in meta-analysis of motor outcome	Included in meta-analysis of cognitive outcome	Included in meta-analysis of language outcome	Age at assessment (months) ^{a,d,e,f}	Mean (SD) GA (wk) ^{a,d,f}	Mean (SD) BW (gram) ^{a,d,f}	Mean (SD) number of surgeries ^{a,d,e,f}	Mean (SD) length of total hospital stay ^{a,d,e,f}
Aite, 2014	2008-2012	Italy	30	EA	BSID-III	Italian norm ¹	X	X	X		6 / 12	38 (2)	2635 (470)	1.1 (0.2)/ 1.2 (0.5)	NR
Beers, 2000	NR	USA	8	SB	WISC-III	North-American norm ²	X	X	X		117	34 (3)	19889 (826)	NR	NR
Bevilacqua, 2014	2008-2010	Italy	150 (37 EA, 43)	Mix	BSID-III	Italian norm ¹	X	X	X		6	38 (1)	2944 (636)	1.7 (1.5)	34.9 (23.2)

			CDH, 29 MM, 16 CAWD, 25 CR)												
			156 (38 EA, 40 CDH, 35 MM, 17 CAWD, 26 CR)	Mix	BSID-III	Italian norm ¹	X	X	X		12	38 (1)	2935 (643)	2 (1.5)	40.4 (30.7)
			84 (15 EA, 30 CDH, 19 MM, 12 CAWD, 8 CR)	Mix	BSID-III	Italian norm ¹	X	X	X		24	38 (2)	2853 (547)	2 (1.5)	40.9 (27.2)
Bevilacqua, 2015	2008-2012	Italy	41	EA	BSID-III	Italian norm ¹	X	X	X		6 / 12	38 (2)	2714 (553)	1.4 (0.8) / 1.4 (0.8)	36.8 (27.7) / 39.4

															(30.7)
			34	IA	BSID-III	Italian norm ¹	X	X	X		6 / 12	37 (2)	2763 (667)	2 (1.5) / 2 (1.5)	56.0 (49.0) / 55.2 (48.8)
			18	GS, OM	BSID-III	Italian norm ¹	X	X	X		6 / 12	37 (2)	2614 (607)	1.4 (0.8) / 1.4 (0.8)	30.4 (9.5) / 30.4 (9.5)
			20	HD, ARM	BSID-III	Italian norm ¹	X	X	X		6 / 12	39 (2)	3326 (618)	2.3 (1.6) / 2.4 (1.8)	33.3 (26.1) / 34.5 (28.9)
Bouman, 1999	NR	Netherlan ds	36	EA	WISC- RN	Dutch norm ³	X		X		122	NR	NR	3.4 (1.9)	NR
Burnett, 2018	2006- 2014	Australia	39	GS	BSID-III	North- American norm ⁴	X	X	X	X	2	36 (2)	2194 (400)	NR	39.6 (25.4)

			20	GS	WPPSI-III	North-American norm ⁵			X		72	35 (2)	2304 (614)	NR	47.9 (41.9)
			20	OM	BSID-III	North American norm ⁴	X	X	X	X	24	39 (2)	3351 (596)	NR	15.4 (14.3)
			10	OM	WPPSI-III	North American norm ⁵			X		72	39 (1)	3492 (532)	NR	11.5 (7.7)
Chesley, 2016	NR	USA	15	SB	BSID-II	North American norm ⁶	X	X	X		17	34 (4)	NR	11 (5.7)	145.9 (93.7)
Costerus, 2019	2011-2013	Netherlands	5	EA	BSID-II	Dutch norm ⁷	X	X	X		24	38 (2)	2742 (545)	NR	NR
Danzer, 2019	2004-2015	USA	47	OM	BSID-II; BSID-III, WPPSI-III,	NR	X	X	X	X	41	35 (3)	2525 (735)	NR	132.8 (86.3)

					WPPSI-IV										
Doberschuetz, 2016	2008-2011	Germany	40 (9 EA, 9 GS, 5 IA, 4 OM, 3 CDH, 2 ARM, 1 HD, 3 combination)	Mix	BSID-II	Control group – but normative data was included	X	X	X		25	37 (2)	2782 (674)	2.0 (NR)	43.9 (40.3)
Elsinga, 2013	1995-2002	Netherlands	27	IA	M-ABC, WISC-III, NEPSY-II	Dutch norm ^{8,9,10}	X	X	X		114	36 (3)	2972 (1091)	NR	NR
Faugli, 2009	1999-2002	Norway	39	EA	BSID-II	North American	X	X	X		13	NR	2780 (926)	1.4 (0.9)	NR

						norm ¹¹									
Gischler, 2009	1999- 2003	Netherlan ds	17	EA	BOS 2- 30	Dutch norm ¹²	X	X	X		6 / 12 / 18 / 24	39 (3)	2928 (485)	4.4 (4.0)	77.2 (78.8) / 79.8 (80.8) / NR / NR
			34	IA	BOS 2- 30	Dutch norm ¹²	X	X	X		6 / 12 / 18 / 24	37 (3)	2964 (697)	2 (1.5)	46.1 (44.3) / 49.0 (47.2) / NR / NR
			19	GS, OM	BOS 2- 30	Dutch norm ¹²	X	X	X		6 / 12 / 18 / 24	39 (3)	2744 (641)	2.3 (1.6)	48.2 (36.8) / 55.4 (52.9) / NR / NR
Giudici, 2016	2003- 2013	Argentini a	27/14/13	EA	CATCL AMS /	North American	X	X	X	X	12 / 36 / 72	38 (2)	2917 (440)	NR	NR

					PRUNA PE	norm (Catclams), ¹³ Argentinian norm (Prunape) ¹⁴									
Giudici, 2016	2003- 2014	Argentini a	52/34/20	GS	CATCL AMS / PRUNA PE	North American norm (Catclams) ¹³ Argentinian norm (Prunape) ¹⁴	X	X	X	X	12 / 36 / 72	37 (2)	2403 (427)	NR	NR
Gorra, 2012	2001- 2008	USA	46	GS	BSID-II	Control group – but normative data was included	X				24	36 (NR)	2542 (NR)	NR	54.0 (NR)
Harmsen, 2017	1999- 2006	Netherlan ds	54	EA	MABC, MABC- II,	Dutch norm ^{8,15,9}	X	X	X		60 / 96	38 (3)	2798 (816)	NR / NR	84.6 (99.6) / NR

					WISC-III										
Harris, 2016	1992-2005	Australia	39	GS	WPPSI-III, WISC-IV	Australian norm ^{5,16}	X		X		120	36 (2)	2496 (174)	NR	NR
Hijkoop, 2017	2000-2012	Netherlands	54	GS	BOS 2-30, BSID-II	Dutch norm ^{12,7}	X	X	X		12 / 24	36 (2)	2313 (NR)	NR	NR
Huang, 2008	2005-2006	China	8	SB	BSID-I, WPPSI-R, WISC-R, WAIS-R	North American norm ¹⁷⁻²⁰	X	X	X		80	38 (1)	3291 (377)	NR	NR
Kato, 1993	1978-1983	Japan	8	GS, OM	WISC-R	NR	X		X		107	NR	NR	NR	NR
			6	HD	WISC-R	NR	X		X		101	NR	NR	NR	NR

			13	ARM	WISC-R	NR	X		X		94	NR	NR	NR	NR
Konig, 2018	NR	Germany	12	EA	KTT; DMT	Control group	X	X			84	NR	NR	NR	NR
Kubota, 2011	NR	Japan	20	EA	WISC- III	North American norm ²¹	X		X		NR	NR	NR	NR	NR
			25	ARM	WISC- III	North American norm ²¹	X		X		NR	NR	NR	NR	NR
Kumari, 2019	2012- 2017	India	32	EA	DASII	Indian norm ²²	X		X		17	37 (3)	2360 (639)	NR	NR
Laing, 2011	2002- 2004	Australia	46	Mix	BSID-II	North American norm ⁶	X	X	X		24	38 (2)	3174 (578)	1.5 (0.9)	28.0 (20.8)
Ludman, 1990	1983- 1984	UK	30	Mix	GMDS	Control group	X	X	X	X	12	NR	NR	NR	52.5 (65.6)
Ludman, 1993	1983- 1985	UK	29	Mix	GMDS	Control group	X	X	X	X	6 / 36	NR	NR	NR / NR	NR / NR

Maheshwari, 2013	2006-2011	Australia	3	EA	BSID-III	NR	X	X	X	X	5-13	NR	NR	NR	NR
Mawlana, 2018	2000-2015	Canada	182	EA (TEF)	BSID-II	North American norm ⁴	X	X	X	X	24	37 (3)	2589 (800)	NR	NR
Mazer, 2010	1999-2002	Netherlands	15	EA	BOS 2-30, MABC	Dutch norm ^{12,8}	X	X	X		6 / 12/ 24 / 60	NR	NR	NR / NR / NR	NR / NR / NR
			18	IA,	BOS 2-30, MABC	Dutch norm ^{12,8}	X	X	X		6 / 12/ 24 / 60	NR	NR	NR / NR / NR	NR / NR / NR
			27	GS, OM	BOS 2-30, MABC	Dutch norm ^{12,8}	X	X	X		6 / 12/ 24 / 60	NR	NR	NR / NR / NR	NR / NR / NR
			6	HD	BOS 2-30, MABC	Dutch norm ^{12,8}	X	X	X		6 / 12/ 24 / 60	NR	NR	NR / NR / NR	NR / NR / NR
			15	ARM	MABC, BOS 2-	Dutch norm ^{12,8}	X	X	X		60	NR	NR	NR	NR

					30										
Minutillo, 2013	1997-2010	Australia	67	GS	GMDS	NR	X		X		12	NR	NR	NR	NR
Moran, 2019	2011-2013	Australia	27 (10 EA, 17 CAWD)	Mix	BSID-III	Control group	X	X	X	X	26	38 (32-40)	2940 (NR)	NR	NR
More, 2014	2001-2010	Australia	31	HD	GMDS	British norm ²³	X		X		12	NR	NR	NR	NR
Newton, 2016	2001-2014	USA	34	EA (TEF)	BSID-II, BSID-III	Control group	X				35	35 (NR)	2244 (NR)	NR	57.7 (NR)
Payne, 2010	1999-2007	USA	57	GS	BSID-III	Control group	X				39	36 (NR)	2365 (NR)	NR	54.2 (42.6)
Plummer, 2019	2016-2018	USA	34	CGIA	NIH Toolbox	British norm ²⁴	X		X	X	56	38 (2)	3220 (690)	NR	NR
Sirichaipornsak, 2011	2007-2008	Thailand	15	GS	BSID-III	NR	X	X	X	X	22	37 (2)	2289 (477)	NR	42.4 (29.3)

So, 2016	2011-2013	Canada	33	SB	AIMS, MAI	North American norm ^{25,26}	X	X			11	33 (5)	1877 (1031)	2.4 (0.8)	165.5 (99.6)
So, 2019	2011-2013	Canada	30	SB	MSEL	North American norm ²⁷	X	X	X	X	12-15 / 26-32	33 (5)	1949 (995)	NR / NR	NR / NR
So, 2019	2015-2016	Canada	30	SB	BOT2	North American norm ²⁸	X	X			84	35 (5)	2198 (848)	3.6 (2.3)	198.0 (128.4)
South, 2008	2003-2005	USA	17	GS	BSID-II	North American norm ⁶	X				20	36 (2)	2360 (731)	NR	NR
Van den Hondel, 2013	1999-2011	Netherlands	37	ARM	RAKIT, MABC	Dutch norm ^{29,8}	X	X			60	38 (NR)	3010 (NR)	3.9 (3.5)	NR
Van den Hondel, 2016	1999-2006	Netherlands	43	HD, ARM	WISC-III, RAKIT	Dutch norm ^{9,29}	X	X	X		96	NR	NR	NR	NR

Van der Cammen-van Zijp, 2010	1999-2003	Netherlands	29	EA	MABC	Dutch norm ⁸	X	X			71	37 (3)	2839 (913)	NR	76.9 (69.3)
			25	IA	MABC	Dutch norm ⁸	X	X			71	37 (3)	2747 (509)	NR	49.4 (51.2)
			24	GS, OM	MABC	Dutch norm ⁸	X	X			71	38 (2)	2702 (591)		59.8 (64.5)
Van Eijck, 2013	2004-2007	Netherlands	8	OM	MABC-II	Dutch norm ¹⁵	X	X			72	NR	NR	NR	NR
Walker, 2013	2006-2008	Australia	31	EA (TEF)	BSID-III	Control group	X	X	X	X	12	38 (NR)	2718 (717)	NR	31.1 (30.7)
Walker, 2015	2006-2008	Australia	124	Mix	BSID-III	Control group	X	X	X	X	36	NR	NR	NR	NR

^aNR = not reported

^bARM = anorectal malformations; BA = biliary atresia; CGIA = Congenital Gastrointestinal Anomalies; EA = esophageal atresia; GS = gastroschisis; HD = Hirschsprungs disease; IA = intestinal atresia / midgut malformations ; NCCA = non-cardiac congenital malformations; OM = omphalocele; SB = short bowel syndrome / intestinal failure

^cAIMS = Alberta Infant Motor Scales; BSID = Bayley Scales of Infant Development; CATCLAMS = cognitive adaptive test/clinical linguistic and auditory milestone scale; DASII = Developmental Assessment Scale of Indian Infants; DMT = Deutscher Motorik Test; GMDS = Griffiths Mental Development Scale; KTT = Kinderturtest; MABC = Movement Assessment Battery for Children; MELS = Mullen Early Learning Scales; PRUNAPE = prueba nacional de pesquisa, a national screening program in Argentina; RAKIT = Revisie Amsterdamse Kinder Intelligentie Test (Dutch intelligence test); WAIS = Wechsler Adult Scale of Intelligence; WPPSI = Wechsler Prechool and Primary Scale of Intelligence; WISC = Wechsler Infant Scale of Intelligence

^d Reported median (range) and median (IQR) were recalculated into Mean (SD) using <http://www.math.hkbu.edu.hk/~tongt/papers/median2mean.html>

^e Repeated measures are indicated by a “/” in this table.

^f For all moderator variables a weighted average was calculated and included in meta-regression.

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SAMPLE DESCRIPTION

Seventeen studies reported on a cohort of patients with one single malformation, whereas most studies reported on multiple subgroups of different malformations (30 studies), together resulting in a total of 62 cohorts: esophageal atresia (17 cohorts, n=603 patients), congenital abdominal wall defects (18 cohorts, n=585 patients), followed by colorectal malformations (10 cohorts, n=172 patients), intestinal atresia (5 cohorts, n=131 patients) and intestinal failure (4 cohorts, n=102 patients) and a combination of different congenital malformations (8 cohorts, n=486 patients). Neurodevelopmental outcomes in infants or toddlers (up to 36 months of age) were described in 29 studies (n=1,768 patients), whereas in 21 studies (n=794 patients) neurodevelopmental outcomes of children (up to a maximum age of 13 years) were described. Mean birthweight of patients ranged from 1,980 to 3,492 grams, with 13 studies reporting on cohorts with a mean birthweight < 2500 grams. Mean gestational age of patients ranged from 34 to 39 weeks, with 22 studies reporting on cohorts with a mean gestational age below 37 weeks. The mean proportion of males represented was 55% (ranging from 29% to 80%).

RESULTS OF META-REGRESSION ANALYSES

The following potential moderating factors were assessed in the current meta-analysis: mean age at neurodevelopmental testing, mean gestational age, mean birthweight, sex, comorbidity, growth impairment, neurological complications, age at primary surgery, number of surgeries, number of anesthetic exposures, length of total hospital stay, mean days of mechanical ventilation, mean days of parental nutrition, educational level of parents and socio-economic status of parents.

sTable 2 Moderating effects of studies' effect sizes of studies' mean age, mean gestational age, mean birthweight and proportion of males on overall neurodevelopmental outcomes, cognitive outcomes and motor outcomes

	Overall neurodevelopmental outcomes		Cognitive outcomes		Motor outcomes		Language outcomes ^b
	Number	Significance	Number	Statistical	Number	Statistical	

	<i>of patients</i>	<i>effect in meta-regression</i>	<i>of patients</i>	<i>effect in meta-regression</i>	<i>of patients</i>	<i>effect in meta-regression</i>	
Mean age at testing in months	<i>n</i> =1182	<i>p</i> =0.43	<i>n</i> =847	<i>p</i> =0.29	<i>n</i> =880	<i>p</i> =0.94	NA
Mean gestational age in weeks	<i>n</i> =1260	<i>p</i> =0.07	<i>n</i> =1155	<i>p</i> =0.12	<i>n</i> =1014	<i>p</i> =0.10	NA
Mean birthweight in grams	<i>n</i> =1255	<i>p</i> =0.08	<i>n</i> =1194	<i>p</i> =0.07	<i>n</i> =1009	<i>p</i> =0.45	NA
Sex ^a	<i>n</i> =790	<i>p</i> =0.24	<i>n</i> =608	<i>p</i> =0.20	<i>n</i> =545	<i>p</i> =0.45	NA
Mean total length of hospital stay in days	<i>n</i> =1098	<i>p</i> <0.001	<i>n</i> =931	<i>p</i> =0.24	<i>n</i> =817	<i>p</i> =0.008	NA
Mean number of surgeries	<i>n</i> =983	<i>P</i> =0.003	<i>n</i> =920	<i>p</i> =0.04	<i>n</i> =834	<i>p</i> =0.001	NA
a. Sex was expressed as the percentage of male subjects in each cohort b. NA= not assessed							

sTable 3 Potential moderating factors not assessed in meta-regression

Author	Comorbidity	Growth	Times exposure to anesthesia	Age at 1st surgery in days	Neurologic complications	Feeding	Ventilation	Parental education	Parental SES
Aite		<i>n (%) weight <5th percentile</i>					<i>Median (range) number of days ventilation</i>	<i>n (%) by categories (below high school, high school, degree) by type of parent</i>	<i>n (%) by categories (salaried, intermediate, working class, unemployed) by type of parent</i>
Beers		<i>n by categories of percentile weight scores (<5th, 5-10th, 10-25th, 25-50th, 75th)</i>							
Bevilacqua	<i>n (%) associated malformations (1, more than 1)</i>							<i>n (%) by categories (primary school, secondary school, high school, degree) by type of parent</i>	
Bevilacqua	<i>n (%) associated malformations (none, 1, more than 1)</i>		<i>Median (IQR) by follow-up duration</i>		<i>n intracranial hemorrhage</i>	<i>n (%) medical appliances for feeding</i>	<i>median (IQR) ventilatory time in hours n (%) medical appliances for respiratory</i>	<i>n by categories (primary school, secondary school, high school, degree) by type of parent</i>	<i>n by categories (class 1-4) by type of parent</i>
Bouman							<i>Proportion assisted ventilation</i>		<i>Categorical (mid, low, high) by type of parent</i>
Burnett	<i>n (%) chromosomal abnormality</i>	<i>n (%) small for gestational age at birth (<10th)</i>		<i>Median (IQR) in days by type malformation and age</i>		<i>n (%) discharged with tube feeding</i>		<i>n (%) low maternal education</i>	<i>n (%) receiving government assistance</i>

Author	Comorbidity	Growth	Times exposure to anesthesia	Age at 1st surgery in days	Neurologic complications	Feeding	Ventilation	Parental education	Parental SES
Chesley					<i>n with cerebral palsy</i>	<i>n with TPN; Median (range) number of days exposed to PN</i>			
Costerus	<i>n with comorbidity</i>			<i>Median (range) in days</i>			<i>Median (range) number of days ventilation</i>		
Danzer				<i>Median (range) in days</i>		<i>Mean (SD) age at initial feeding</i>	<i>Median (range) number of days ventilation</i>	<i>n (%) maternal education by categories (none, parttime, fulltime)</i>	<i>n (%) maternal education by categories (high school, partly college/college degree, graduate degree)</i>
Doberschuetz	<i>n (%) combined malformations</i>		<i>Mean (95%CI) duration in hours</i>	<i>Mean (95%CI) in hours</i>	<i>n with hearing impairment</i>	<i>Mean (SD) / median (range) number of days PN, Mean (SD) / Median (range) number of days tube feeding</i>	<i>Mean (SD) / median ((range) number of hours ventilation, Mean (SD) / Median (range) number of days oxygen</i>		<i>mean score (low, medium, high)</i>
Elsinga	<i>n (%) late onset sepsis or BPD</i>	<i>median weight</i>		<i>Median (range) in days</i>					
Faugli	<i>n with associated malformations</i>					<i>n (%) with feeding difficulties</i>	<i>n (%) assisted ventilation</i>	<i>median (range) number of years of maternal education</i>	

Author	Comorbidity	Growth	Times exposure to anesthesia	Age at 1st surgery in days	Neurologic complications	Feeding	Ventilation	Parental education	Parental SES
Gischler	<i>n (%) additional medical problems, n (%) septic complications, n (%) , median (IQR) number of congenital anomalies</i>				<i>n (%) neurologic complications</i>	<i>n (%) NG tube at home, n (%) enterostomy at home</i>	<i>n (%) tracheostomy, n (%) oxygen at home</i>		<i>n (%) by categories (low, middle, high)</i>
Giudici		<i>n (%) weight <10th percentile</i>			<i>n with cerebral palsy; n with hearing loss</i>	<i>Mean (SD) / Median (IQR) number of days PN</i>	<i>Mean (Sd) and median (IQR) number of days assisted ventilation</i>		
Giudici		<i>n (%) weight <10th percentile</i>			<i>n with cerebral palsy; n with hearing loss</i>	<i>Mean (SD) / Median (IQR) number of days PN</i>	<i>Mean (Sd) and median (IQR) number of days assisted ventilation</i>		
Gorra									
Harmsen	<i>n (%) sepsis; n (%) vacterl-association; n (%) cardiac anomaly</i>		<i>Median (range) in hours, median (range) number of anesthetic exposures</i>			<i>Median (range) number of days PN</i>	<i>Median (range) number of days ventilation</i>		<i>n (%) by categories (low, middle, high)</i>
Harris					<i>n with amblyopia; n with cerebral palsy; n with hearing loss</i>				

Author	Comorbidity	Growth	Times exposure to anesthesia	Age at 1st surgery in days	Neurologic complications	Feeding	Ventilation	Parental education	Parental SES
Hijkoop	<i>n (%) multiple congenital anomalies, n (%) complications</i>	<i>n (%) SGA at birth</i>	<i>Median (IQR) procedures under GA</i>			<i>n (%) with intestinal failure; Median (IQR) number of days to full enteral feeding</i>	<i>Median (IQR) number of days ventilation by type of malformation</i>		<i>median (IQR) maternal SES score, n (%) low maternal SES score</i>
Huang		<i>weight for age Z-score per subject</i>		<i>age in days per subject</i>		<i>Duration of PN in days per subject</i>			
Kato									
Konig		<i>n (%) weight for age Z-score < 2</i>							
Kubota									
Kumari	<i>n (%) associated congenital anomalies</i>	<i>n (%) -3SD weight for age</i>					<i>n (%) on mechanical ventilation</i>	<i>n (%) graduated mothers</i>	<i>n (%) homemakers and monthly family income</i>
Laing				<i>Median (IQR) in days</i>	<i>n (%) with microcephaly</i>		<i>Median (IQR) hours assisted ventilation</i>	<i>n (%) by categories (<12y schooling, >12y, tertiary or further, bachelor or higher degree) by type of parent</i>	<i>n (%) occupation father (skilled, unskilled, associate professional, professional)</i>
Ludman							<i>n (%) assisted ventilation >4 days</i>		<i>n (%) by categories (manual, non-manual, single mom)</i>
Ludman									
Maheswari									

Author	Comorbidity	Growth	Times exposure to anesthesia	Age at 1st surgery in days	Neurologic complications	Feeding	Ventilation	Parental education	Parental SES
Mawlana	<i>n (%) VACTERL, n (%) associated anomalies, n (%) chromosomal anomalies</i>	<i>n (%) weight <10th percentile</i>				<i>n (%) with gastrostomy</i>			
Mazer	<i>Median (IQR) number of congenital anomalies, n (%) syndromal / chromosomal abnormality</i>					<i>Median (IQR) medical appliances (O2 or tracheostomy) at discharge</i>	<i>Median (IQR) medical appliances (NG tube or enterostomy) at discharge</i>		
Minutillo									
Moran					<i>MRI abnormalities</i>			<i>n (%) maternal tertiary education</i>	<i>n (%) higher social risk</i>
More				<i>Median (IQR) age in days</i>					
Newton							<i>Mean days on ventilator</i>		
Payne		<i>% weight <10th percentile</i>				<i>n (%) all per oris feeding at discharge</i>	<i>Mean (SD) ventilator days</i>		<i>n (%) single mother</i>
Plummer		<i>weight for age z score</i>				<i>Median (IQR) number of days PN; Percentage PN < >7days; Percentage gastrostomy</i>	<i>Median (IQR) days of assisted ventilation; Percentage >2 days assisted ventilation</i>	<i>n (%) maternal education (college or higher)</i>	
Sirichaiponsak									

Author	Comorbidity	Growth	Times exposure to anesthesia	Age at 1st surgery in days	Neurologic complications	Feeding	Ventilation	Parental education	Parental SES
So					<i>n with cerebral palsy</i>	<i>Median (IQR) number of days PN first year; Percentage patients 100% full enteral feeding first year</i>			
So		<i>weight for age Z-score</i>			<i>n with microcephaly</i>	<i>Median (IQR) number of days PN; % PN dependance at follow-up; % enterostomy</i>			
So					<i>n with CNS comorbidity; n with cerebral palsy; n with hearing loss; n with visual comorbidity</i>	<i>Median (IQR) number of days PN first year/ first two years; n (% PN at follow-up of two years; n (%) 100% full enteral feeds at follow-up of two years</i>			
South		<i>% weight <10th percentile</i>			<i>n (%) abnormal neurological exam</i>	<i>Mean (SD) number of days to full enteral feedings; mean (sd) number of days PN</i>	<i>Mean (SD) number of days assisted ventilation</i>		

Author	Comorbidity	Growth	Times exposure to anesthesia	Age at 1st surgery in days	Neurologic complications	Feeding	Ventilation	Parental education	Parental SES
Van den Hondel 2013	<i>n (%) at least 1 major associated anomaly; n with suspected (not diagnosed) syndrome</i>	<i>n (%) Small for gestational age at birth</i>				<i>n (%) gastrostomy</i>			
Van den Hondel	<i>n (%) major comorbidity present</i>		<i>Median (IQR) by type of malformation; Median (IQR) by follow-up duration</i>						<i>n (%) by categories (low, middle, high) by type of malformation</i>
Van der Cammen-van Zijp	<i>n (%) associated malformations</i>	<i>n (%) Small for gestational age at birth</i>					<i>Median (range) days ventilation support, n (%) ECMO</i>		
Van Eijck	<i>n with congenital tethered spinal cord syndrome</i>								
Walker	<i>n (%) of associated malformations</i>								
Walker									
Reason for exclusion from univariate meta regression	Heterogeneity of definitions	Heterogeneity of definitions	Not enough studies	Not enough studies	Heterogeneity of definitions	Too biased by type of malformation	Too biased by type of malformation	Heterogeneity of definitions	Heterogeneity of definitions

RESULTS OF SUBGROUP ANALYSES ON TYPE OF MALFORMATION

Motor outcomes were significantly different across subgroups of malformations ($Q=11.704$, $p=0.020$). Cognitive ($Q=3.798$, $p=0.434$) and language outcomes ($Q=0.589$, $p=0.745$) did not significantly differ across different types of malformations.

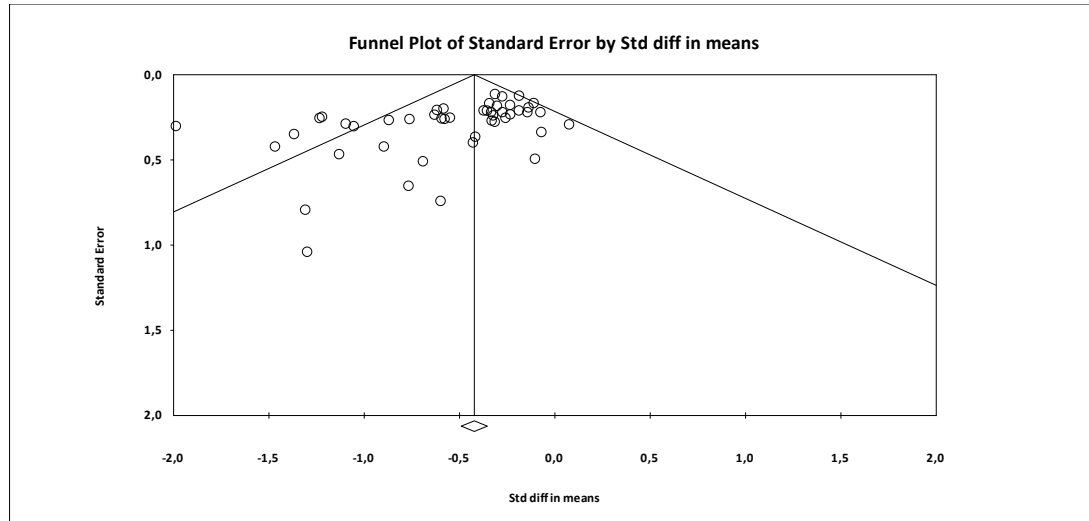
Further analyses showed that patients with short bowel syndrome had significantly worse motor outcomes compared to all remaining patient groups ($d=-1.062$ and $d=-0.474$, $Q=7.682$; $p=0.006$), but comparable cognitive outcomes ($d=-0.241$ and $d=-0.432$, $Q=2.875$; $p=0.09$) and language outcomes ($d=-0.692$ and $d=-0.598$, $Q=0.038$; $p=0.85$).

RESULTS OF SENSITIVITY ANALYSIS OF STUDIES OF GOOD QUALITY

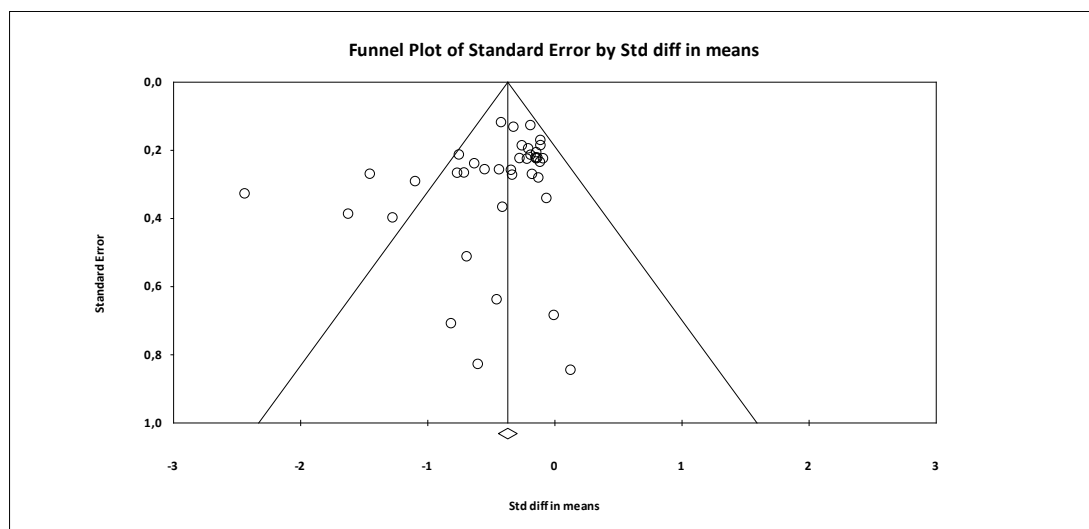
Effect sizes for overall neurocognitive outcomes and cognitive outcomes differed between studies of different quality ratings ($Q=21.46$, $p<0.001$ and $Q=45.53$, $p<0.001$, respectively). Sensitivity analysis on studies of good quality ($n=36$), showed that the reported meta-analytic findings (impairments) were replicated for overall neurodevelopmental outcomes ($d=-0.371$, 95%CI: $-0.462 - 0.280$, $p<0.001$), cognitive outcomes ($d=-0.281$, 95%CI: $-0.363 - -0.199$, $p<0.001$), motor outcomes ($d=-.0568$, 95%CI: $-0.738 - -0.398$, $p<0.001$) and language outcomes ($d=-0.570$, 95%CI: $-0.865 - -0.274$, $p<0.001$).

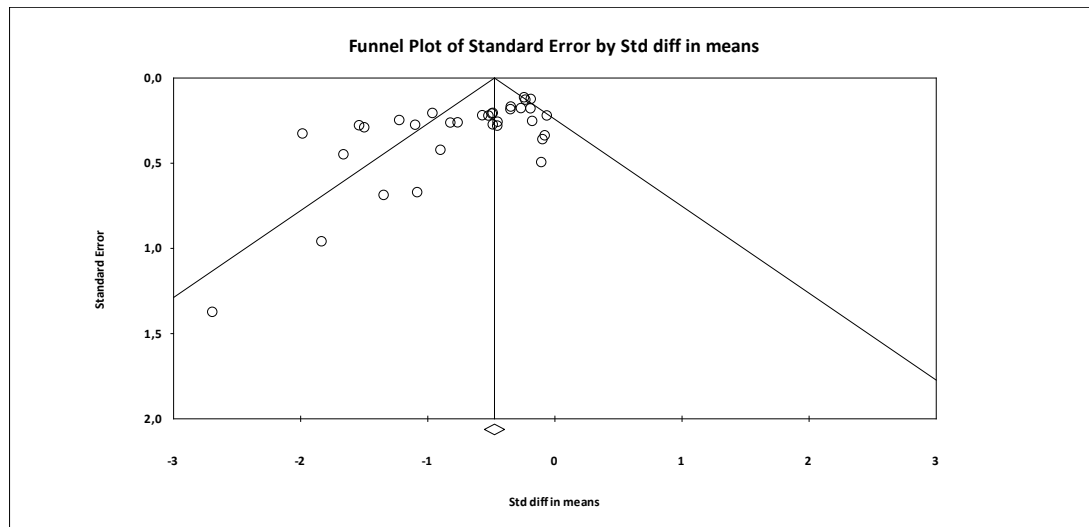
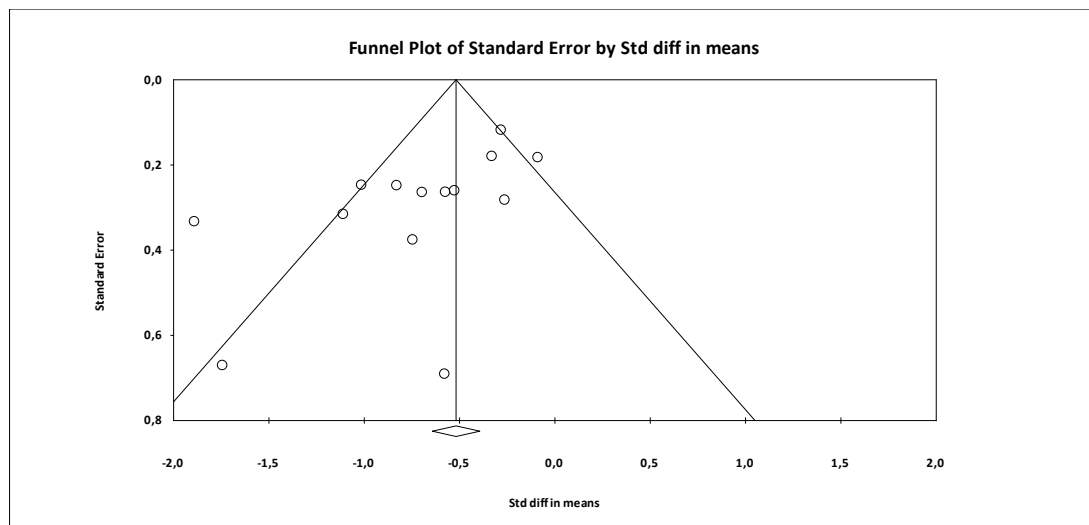
RISK OF BIAS ANALYSIS

sFigure1 Funnelplot of overall neurodevelopmental outcomes



sFigure2 Funnelplot of cognitive outcomes



sFigure 3 Funnelplot of motor outcomes*sFigure 4* Funnelplot of language outcomes

All funnel plots were symmetric on visual inspection and showed no asymmetry. However, Egger's regression showed significant risk of publication bias for all meta-analyses. Risk of potential assessment bias was found for (a) 39 of the 47 studies because these studies compared patient data with normative data standardized for age only, leaving other potentially confounding factors uncontrolled, and (b) 22 of the 47 studies because of loss to follow-up of more than 70% of the participants which may lead to a potential bias either due to loss of high-functioning patients or due to loss of severely impaired patients with co-morbidity and subsequent higher mortality.

PRISMA CHECKLIST

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A. The study protocol can be provided by authors.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6, see Search and Selection
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5, see Search and Selection
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary Material.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5, see Search and Selection
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7, see Data-extraction
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7, see Data-extraction
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how	7-8 - See Quality assessment

		this information is to be used in any data synthesis.	and Statistics
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7, See Statistics: Cohen's d
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7-8, see Statistics: - I^2 - Random-effects meta-analysis
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7-8, see Statistics: - Visual inspection funneplots - Eggers intercept
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7-8, see Statistics: Sensitivity analysis were done to compare outcomes at different domains of neurodevelopment, to compare different types of malformations and to compare evidence of different study quality.
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5-6, see Search and Selection; Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Supplementary Table, sTable 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 2 / Table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-11, described in results section, Table 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12-13
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11-15, Supplementary Table sTable 2
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16-17, summary of findings was given in the first part of the discussion

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	18, limitations were discussed under “limitations”
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18, see Conclusions
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A