Cognitive Outcomes in Children With Conditions Affecting the Small Intestine: A Systematic Review and Meta-analysis

**ABSTRACT**

**Objectives:** The aim of the study was to assess cognitive outcomes in children with intestinal failure (IF) and children at high risk of IF with conditions affecting the small intestine requiring parenteral nutrition. **Methods:** EMBASE, Cochrane, Web of Science, Google Scholar, MEDLINE, and PsychINFO were searched from inception to October 2020. Studies were included constituting original data on developmental quotient (DQ), intelligence quotient (IQ) and/or severe developmental delay/disability (SDD) rates assessed with standardized tests. We used appropriate standardized tools to extract data and assess study quality. We performed random effects meta-analyses to estimate pooled means of DQ/IQ and pooled SDD rates (general population mean for DQ/IQ: 100, for percentage with SDD: 1.8%) for 4 groups: IF, surgical necrotizing enterocolitis (NEC), abdominal wall defects (AWD), and midgut malformations (MM). Associations of patient characteristics with DQ/IQ were evaluated with meta-regressions. **Results:** Thirty studies met the inclusion criteria. The pooled mean DQ/IQ for IF, NEC, AWD, and MM were 86.8, 83.3, 96.6, and 99.5, respectively. The pooled SDD rates for IF, NEC, AWD, and MM were 28.6%, 32.8%, 8.5%, and 3.7%, respectively. Meta-regressions indicated that lower gestational age, longer hospital stay, and higher number of surgeries but not parenteral nutrition duration, were associated with lower DQ/IQ. **Conclusions:** Adverse developmental outcomes are common in children with IF and NEC, and to a much lesser extent in children with AWD and MM. It is important to monitor cognitive development in children with conditions affecting the small intestine and to explore avenues for prevention and remediation. **Key Words:** cognition, intestinal failure, necrotizing enterocolitis, neurodevelopment, short bowel syndrome

An infographic is available for this article at: http://links.lww.com/MPGC623.

Abstract in Japanese

What Is Known

- Children with intestinal failure are at risk of delayed psychomotor and cognitive development.
- Early causes of intestinal failure include surgical necrotizing enterocolitis, abdominal wall defects, and midgut malformations. It is unclear whether neurodevelopmental delay seen in intestinal failure results from underlying disease or parenteral nutrition.

What Is New

- Adverse cognitive outcomes are common in children with intestinal failure and necrotizing enterocolitis but less in children with abdominal wall defects and midgut malformations.
- Those with a low gestational age, long hospitalization, multiple surgical procedures, but not necessarily long duration of parenteral nutrition-dependency, are especially prone.

In infants with conditions affecting the small intestine, the gut insufficiently absorbs nutrients and fluids needed for growth. Therefore, these infants depend on parenteral nutrition (PN) (1). Some of them (23%–35% of infants with surgically treated necrotizing enterocolitis (NEC) (2), 10% to 34% of infants with abdominal wall defects (3,4), 12% of infants with intestinal atresia (5), around 80% of children with pediatric intestinal pseudo-obstruction syndrome (6) and almost all children with microvillus inclusion disease (7)) become long-term PN-dependent and therewith develop intestinal failure (IF). New challenges in children with...
IF have become apparent, including neurodevelopment. Hukinen et al reviewed available literature and concluded that children with IF are at significant risk of delayed psychomotor and cognitive development but this was based on few and small studies with varying methodology (8). It is unclear if the neurodevelopmental deficits are related to the prolonged administration of PN or to other disease-specific or more generic factors. Systematically evaluating available literature concerning cognitive development in children with neonatal underlying diseases of IF will enhance our knowledge on early protective and risk factors for less optimal outcomes in children with IF. This will help clinicians to better inform parents and to take measures that support vulnerable children to prevent or remediate deficits later in life.

The aims of this systematic review and meta-analysis were to assess cognitive outcomes both in children with IF receiving long-term PN and in children at high risk of developing IF, and to examine the influence of patient characteristics on reported outcomes.

**METHODS**

The protocol and objectives for this study were established a priori and registered in PROSPERO, an international database of prospectively registered systematic reviews in health and social care (protocol number 173400). The systematic review and meta-analysis were performed according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (9).

**Search Strategy**

A systematic literature search was conducted on October 26, 2020 in EMBASE, Cochrane, Web of Science, Google Scholar, MEDLINE, and PsycINFO by a biomedical information specialist of the Medical Library of the Erasmus University Medical Center. The inclusion criteria were studies reporting on cognitive outcomes in children with IF and at high risk of IF, with no limitation on age of study is not an important differentiating factor. The following search terms were used: neonate, infant, child, adolescent; neurodevelopment, cognition, learning disorder, intelligence quotient (IQ); IF, PN, and the different underlying diseases of IF as described in File S1 (Supplemental Digital Content 1, http://links.lww.com/MPG/C624). Only studies using standardized developmental/intelligence tests and/or a clear definition of severe developmental delay/disability (SDD) based on cognitive testing were included. These tests include the Bayley Scales of Infant Development (BSID) (without motor functioning scale), the Mullen Scales of Early Learning (MSEL) (without motor functioning scale), the Wechsler Preschool and Primary Scale of Intelligence (WPPSI), and the Wechsler Intelligence Scale for Children (WISC), which are all standardized validated tools. Studies were excluded if they were not written in English, not in human subjects, and if they were reviews, case reports or case series including less than 10 patients. Abstracts, posters, editorials, letters, and books were also excluded.

**Study Selection and Data Extraction**

Two investigators (L.E.V. and M.W.V.) independently screened all titles and abstracts in EndNote, blinded to each other’s decisions. A selection was made for full-text screening based on title and abstract, after which full-text assessment led to final inclusion. The reference lists of the included studies and reviews were examined for additional eligible studies. In case of discrepancy at any stage, the reviewers tried to reach consensus by discussion and if not reached, a third independent reviewer was consulted (J.S.L.). If studies were based on an identical cohort sample, only 1 study was included (the most recent study with the biggest sample size).

The following data were extracted into Comprehensive Meta-analysis software version 2.0 (Biostat Inc, NJ): study design and setting, patient characteristics (number of patients, sex, gestational age, birth weight, underlying disease, number of surgeries, duration of hospital admission, PN-dependency duration, age at cognitive assessment), study objective, intelligence test, mean developmental quotient (DQ) (assessed with BSID or MSEL) and IQ (assessed with WPPSI or WISC), and number of patients with SDD (defined as a DQ/IQ of >2 standard deviations [SDs] below the population mean; this was a DQ/IQ of <70 since in the general population the mean DQ/IQ is 100 and SD is 15). DQ was equivalent to mental development index for BSID-II, cognitive composite score for BSID-III and early learning composite for MSEL; IQ was equivalent to full scale IQ for WPPSI and total IQ for WISC (10). In case of missing data in a specific study, the corresponding authors were contacted by email and asked to provide us with missing information (eg, means and SDs for PN-dependency duration).

**Quality Assessment**

The quality of the individual studies was assessed using checklists from the National Heart, Lung, and Blood Institute (NIH Quality Assessment Tools for Observational Cohort and Cross-Sectional studies, and for Case-Control Studies) (11). Criteria assessing internal validity and risk of bias were checked for every study and the quality of each study was rated independently by 2 authors (L.E.V. and M.W.V.) as “Good,” “Fair,” or “Poor.” In case of disagreement between the authors, consensus was reached through discussion or by consulting a third author (J.S.L.). The items used for quality assessment are shown in Table S1 (Supplemental Digital Content 2, http://links.lww.com/MPG/C625).
Statistical Analysis

Descriptive statistics are reported as frequency (percentage) for categorical variables and mean (SD) for continuous variables. When medians and interquartile ranges or ranges were given, means and SDs were estimated using Wan’s and Hozo’s method in order to combine results for the meta-analysis (12,13). Because of expected between-study heterogeneity because of varying underlying diseases and age ranges, we performed random effects meta-analyses to calculate pooled means of DQ/IQ with 95% confidence intervals (CIs), and the pooled prevalence of SDD with 95% CIs. Inverse variance weighting was conducted according to the number of patients included. Data were analyzed separately for subgroups of patients: IF and short bowel syndrome, surgical NEC and intestinal perforation, abdominal wall defects (gastrochisis and omphalocele), and midgut malformations (intestinal atresia, intestinal stenosis, or intestinal malrotation). We also performed subgroup analyses for children aged <3 years (assessing DQ) and older children (assessing IQ). Pooled estimates were visualized in forest plots, in which DQ/IQ and percentages of patients with SDD were compared with the general population mean. For DQ/IQ, this was a general population mean of 100; for SDD, we used a mean percentage of 1.8%, known from a population-based meta-analysis (14). Heterogeneity was assessed using Cochran Q homogeneity and I²-statistic (percentage of unexplained variance) for the degree of inconsistency. Values of I² of ≥75% indicate substantial heterogeneity (15). Publication bias was examined in a funnel plot and with Egger tests (16). Meta-regressions were performed to examine the impact of the moderator variables’ duration of PN-dependency, age at time of cognitive assessment, gestational age, duration of hospital stay, and number of surgeries on DQ/IQ. Statistical analyses were performed using Comprehensive Meta-analysis software version 2.0 (Biostat Inc, Englewood, NJ) and the meta (17) and metafor (18) packages from R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org/).

RESULTS

Study Selection

The study selection process is displayed in Figure 1. Following title and abstract screening, 182 out of 5005 studies were eligible (98% reviewer consensus). Full-text screening led to inclusion of 33 studies (86% reviewer consensus). The corresponding authors of 4 studies were able to provide us with additional data (19–22). After taking into account sample overlap, 30 articles were selected for data extraction. Twenty-six studies were included in the meta-analysis assessing DQ/IQ and 21 studies in the meta-analysis assessing prevalence of SDD.

![Flow chart of study inclusion in the systematic review and meta-analysis](FIGURE 1. Flow chart of study inclusion in the systematic review and meta-analysis. DQ = developmental quotient; IQ = intelligence quotient; SDD = severe developmental delay/disability.)

Records identified through database searching (n = 7,938) Additional records identified through other sources (n = 0)

Records after duplicates removed (n = 5,005)

Records screened by title and abstract (n = 5,005) Records excluded (n = 4,823)

Added after reference check (n = 0) Full-text articles assessed for eligibility (n = 182)

Studies included in systematic review and meta-analyses (n = 30)

Studies reporting on DQ/IQ (n = 26) Studies reporting on SDD (n = 21)

Full-text articles excluded (n = 152)
  - No original study (n = 49)
  - No definition of cognitive development or no standardized tool used (n = 36)
  - No underlying disease of intestinal failure (n = 45)
  - <10 patients in study (n = 6)
  - No children (n = 2)
  - Not available in English (n = 8)
  - No full-text available (n = 5)
Study Characteristics

Eleven studies were of retrospective design (19,23–32), 19 of prospective design (20–22,33–48). Sample size across studies ranged from 10 to 449 patients. Children were assessed for cognitive development at an age ranging between 1 and 16 years old. In most studies (66%), the BSID was used, at around 2 years of age. Six studies involved children with chronic IF/short bowel syndrome, 12 with surgical NEC/intestinal perforation, 10 with abdominal wall defects, and 2 with midgut malformations. No studies were found involving children with enteropathsies or motility disorders (except the studies on chronic IF but not as separate underlying disease). In Table 1, the study characteristics of the included studies are shown.

Quality Assessment

Ten studies had an overall rating of “Good.” 20 studies were rated “Fair,” and none were rated “Poor.” In general, studies lacked sample size justification and adjustment for key potential confounding variables. The quality rating per study is shown in Table 1.

Meta-analyses

Developmental Quotient/Intelligence Quotient

The meta-analysis for pooled means of DQ/IQ included 788 patients from 26 nonoverlapping studies. The highest DQ/IQ were found in children with midgut malformations and abdominal wall defects (mean 99.5 (n = 2 studies, n = 61 patients; 95% CI 89.2–109.8) and 96.6 (n = 9 studies, n = 285 patients; 95% CI 91.6–101.6), respectively), followed by children with IF (mean 86.1 (n = 6 studies, n = 124 patients; 95% CI 79.7–92.5)), and the lowest scores were seen in children with surgical NEC/intestinal perforation with mean 83.3 (n = 9 studies, n = 318 patients; 95% CI 78.2–88.4). Estimates of DQ/IQ for each study are visualized in comparison with the general population mean in the forest plot from Figure 2A. When looking at children ages <3 years (assessed with BSID or MSEL) separately, pooled mean DQ in IF was 84.1 (n = 2 studies, n = 43 patients; 95% CI 70.8–97.4), 82.6 in surgical NEC/intestinal perforation (n = 7 studies, n = 256 patients; 95% CI 75.7–89.6), 96.3 in abdominal wall defects (n = 6 studies, n = 208 patients; 95% CI 88.8–103.7) and 101.4 in midgut malformations (n = 1 study, n = 34 patients; 95% CI 83.9–118.9). For older children (assessed with WPPSI or WISC), pooled mean IQ in IF was 89.4 (n = 3 studies, n = 66 patients; 95% CI 82–96.8), 85.7 in surgical NEC/intestinal perforation (n = 2 studies, n = 62 patients; 95% CI 77.4–94.1), 97 in abdominal wall defects (n = 3 studies, n = 77 patients; 95% CI 90.1–103.8), and 97.3 in midgut malformations (n = 1 study, n = 27 patients; 95% CI 85.2–109.4).

Severe Developmental Delay/Disability

The meta-analysis for pooled prevalences of SDD (DQ/IQ < 70) included 1231 patients from 21 nonoverlapping studies. The lowest percentages were found in studies including children with midgut malformations and abdominal wall defects (3.7% (n = 1 study, n = 27 patients) and 8.5% (n = 7 studies, n = 225 patients; 95% CI 3.7–18.5), respectively) and the highest rates in children with surgical NEC/intestinal perforation with 32.8% (n = 10 studies, n = 908 patients; 95% CI 22–45.9). In children with IF, overall SDD was found in 28.6% (n = 3 studies, n = 71 patients; 95% CI 12.5–52.9). The percentages of SDD and 95% CI for each study are shown in the forest plot from Figure 2B. The 95% CI for 3 out of 4 pooled SDD rates do not include the 1.8% SDD rate of the general population. When looking at children ages <3 years (assessed with BSID or MSEL) separately, pooled SDD rate in IF was 26.7% (n = 1 study, n = 30 patients; 95% CI 5.7–68.5), 32.2% in surgical NEC/intestinal perforation (n = 9 studies, n = 889 patients; 95% CI 20.7–46.5), and 13.2% in abdominal wall defects (n = 4 studies, n = 131 patients; 95% CI 4.8–31.2). For older children (assessed with WPPSI or WISC), pooled SDD rate in IF was 38.5% (n = 1 study, n = 26 patients; 95% CI 22.1–57.9), 36.8% in surgical NEC/intestinal perforation (n = 1 study, n = 19 patients; 95% CI 18.7–59.7), 3.6% in abdominal wall defects (n = 2 studies, n = 55 patients; 95% CI 0.7–16.2), and 3.7% in midgut malformations (n = 1 study, n = 27 patients; 95% CI 0.5–22.1).

Publication Bias

Funnel plots for DQ/IQ and SDD prevalence showed asymmetry (see Figures S1 and S2, Supplemental Digital Content 3, http://links.lww.com/MPG/C626 and 4, http://links.lww.com/MPG/C627), but Egger’s regression asymmetry tests did not confirm the presence of a significant publication bias for DQ/IQ (P = 0.386) or SDD (P = 0.115).

Heterogeneity

Substantial heterogeneity was found between studies within the same disease groups (IF/short bowel syndrome: I² = 84.8%, surgical NEC/intestinal perforation: I² = 93.3%, abdominal wall defects: I² = 71.2%), except for the midgut malformation group (I² = 25.3%). Causes of heterogeneity may be explained by differences in patient characteristics that were analyzed in the meta-regressions.

Meta-regressions

Meta-regression outcomes of the associations between the moderator variables and overall DQ/IQ are shown in Table 2. Duration of PN-dependency was not associated with DQ/IQ, neither was age at assessment. A lower gestational age, longer hospital stay, and more surgical procedures were all significantly related to a lower overall DQ/IQ (shown in the scatterplots of Figures S3–S5, Supplemental Digital Content 5, http://links.lww.com/MPG/C628, 6, http://links.lww.com/MPG/C629 and 7, http://links.lww.com/MPG/C630).

DISCUSSION

In this systematic review and meta-analysis, including 30 studies, we found that children with IF and surgically treated NEC have lower overall DQ/IQ and higher percentages of SDD compared with the general population. This was seen to a much lesser extent in children with abdominal wall defects and midgut malformations. Early, hospital admission-related factors but not duration of PN-dependency, were predictive of developmental outcome. There was a wide variation in mean DQ/IQ (72–102.3) and percentage of SDD (1%–51%) between studies; also within the same disease groups. Extent of disease may explain the variation. For example, in one of the studies, children with complex gastrochisis (accompanied by intestinal atresia, necrosis, perforation, and/or volvulus) had worse outcomes compared with simple gastrochisis patients; and complex gastrochisis patients are also the ones more likely to develop IF (19). Moreover, there may be underrepresentation of the actual clinical population, as in 10 studies, children with comorbidities, such as intraventricular haemorrhage, bronchopulmonary disease, and congenital syndromes.
### TABLE 1. Study characteristics

| Number | Study | Year | Inclusion period | Sample size, N | Boys, n (%) | Underlying disease | Duration of PN, weeks mean (SD) | Gestational age, weeks mean (SD) | Age at follow-up, years mean (SD) | Assessment tool | DQ/IQ mean (SD) | Severe developmental disability, n (%) | Quality assessment score |
|--------|-------|------|------------------|----------------|-------------|-------------------|-------------------------------|-------------------------------|-------------------------------|----------------|----------------|----------------------------------------|-------------------------|
| 1      | Chelsy et al 2016 | Unknown | 2016 | 15 | 12 (80) Surgical and functional | 12.00 (6.87) | 34.8 (4.2) | 2.4 (1.3) | BSID-II WPPSI-II | 79.5 (15.6) | 3 (20) | Fair |
| 2      | Gold et al 2020 | 2012 to 2016 | 28 | 15 (54) Surgical and functional | 51.6 (25.8) | 35.0 (5.5) | 6.0 (4.0) | WPPSI-IV WISC-IV/V | 80.0 (17.2) | NA | Fair |
| 3      | Guner et al 2020 | 2017 to 2018 | 30.26 | 24 (69) Surgical and functional | 56.5 (10.6) | 35.0 (7.8) | 7.5 (4.1) | WPPSI-III WISC-V | 70.3 (10.4) | 1 (35) | Good |
| 4      | O'Connor et al 1988 | 1977 to 1986 | 12 | 9 (75) Surgical and functional | 22.7 (6.4) | 34.8 (4.7) | 22.2 to 2.7 | WPPSI WISC-C | 101.5 (14.3) | NA | Fair |
| 5      | So et al 2019 | 2011 to 2013 | 31/30 | 17 (55) Surgical and functional | 31.3 (64.6) | 34.8 (4.7) | 2.2 to 2.7 | MSEL | 81.0 (19.4) | 8 (27) | Good |
| 6      | Soreff et al 2017 | 2012 to 2013 | 13 | 6 (46) Surgical and functional | 27.8 (20.6) | 27.9 (2.8) | 1.6 | BSID-II | 73.4 (59.9) | NA | Fair |
| 7      | Aesopat et al 2016 | 1996 to 1999 | 28/21 | 22 (79) Surgical NEC with intestinal perforation | 14.9 (6.1) | 26 (2.0) | 1.0 | BSID-II | 77.0 (17.0) | 7 (33) | Good |
| 8      | Allendorf et al 2018 | 2006 to 2013 | 24 | NA Surgical NEC | 7.1 (4.5) | 27.9 (4.4) | 2.0 | BSID-II | 85.0 (13.7) | 2 (8) | Fair |
| 9      | Burnett et al 2018 | 2009 to 2014 | 59 | 29 (49) Surgical NEC | 36.1 (3.8) | 37.1 (3.0) | 8.5 (1.9) | WISC-III | 98.3 (16.4) | 1 (4) | Good |
| 10     | Danzer et al 2010 | 2002 to 2007 | 15 | 9 (60) Giant omphalocele | 3.0 (1.7) | 35.5 (3.3) | 1.0 (0.6) | BSID-III | 79.5 (19.1) | 7 (47) | Fair |
| 11     | Harris et al 2016 | 1972 to 1981 | 22 | 8 (36) Giant omphalocele | 3.4 (3.3) | NA | 10.1 (2.9) | WISC-R | 100.1 (15.9) | NA | Fair |
| 12     | Hijkoop et al 2018 | 2000 to 2012 | 103/84 | 62 (51) Surgical NEC | 7.0 (5.4) | 35.5 (3.1) | 1.5 to 1.8 | BSID-II | 78.1 (19.1) | NA | Fair |
| 13     | Lap et al 2017 | 1999 to 2006 | 16 | 9 (56) Surgical NEC | 15.8 (16.2) | 37.1 (3.0) | 8.8 (2.3) | WISC-III | 92.3 (13.3) | 1 (6) | Good |
| 14     | Elsinga et al 2013 | 2007 to 2008 | 15 | 11 (73) Surgical NEC | 6.0 (4.2) | 36.6 (1.7) | 1.8 (0.3) | BSID-III | 90.5 (8.9) | 0 (0) | Fair |
| 15     | Van Manen et al 2013 | 2005 to 2008 | 61/39 | 38 (60) Surgical NEC | 6.1 (9.2) | 36.2 (2.2) | 2.1 (0.7) | BSID-II | 85.0 (17.0) | 8 (33) | Good |

Data are presented as n (%) or mean (SD). Severe developmental delay/disability was defined as deviation in DQ/IQ of >2 SD below the normal population mean (DQ/IQ < 70). BSID = Bayley Scales of Infant Development; DQ = developmental quotient; IQ = intelligence quotient; MSEL = Mullen Scales of Early Learning; NA = not assessed; PN = parenteral nutrition; SD = standard deviation; WISC = Wechsler Intelligence Scale for Children; WPPSI = Wechsler Preschool and Primary Scale of Intelligence. Cognitive development was evaluated in a selection of the study population. Surgical includes NEC, volvulus, meconium peritonitis, intestinal atresia, gastrochisis; functional includes dismotility, enteropathy. In the same article, 2 underlying disease groups were evaluated and therefore shown separately. In 2 articles, the same underlying disease group (abdominal wall defects separated in gastrochisis and omphalocele) from the same cohort and time period was evaluated and therefore shown combined.
A large part of the IF population is born preterm. Exponential brain growth occurs during fetal and infant maturation. A disruption of the organization of the brain of the neonate born prematurely can affect subsequent cognitive development (49). In several studies, preterm born children are found to have worse neurodevelopmental outcomes compared with term born children (50–52). In case-control studies included in the current meta-analysis, surgical NEC patients and gastrochisis patients had significantly lower DQ/IQ than gestational age-matched controls, suggesting that the impaired cognitive outcomes cannot be fully attributed to prematurity (25–27,29,30,38,41). Other factors, such as underlying inflammation, present in NEC and gastrochisis, may explain the differences in cognitive development (53–56).

Length of hospital stay was found to be a predictor of overall intelligence. This was also reported in large studies concerning infants after noncardiac surgery (57) and cardiac surgery (58). When infants are hospitalized for a long period of time, this may impede exploratory play, and thus delay cognitive development (49).

### TABLE 2. Meta-regressions of the associations of patient characteristics with developmental quotient/intelligence quotient

| Characteristic                  | Number of studies | Number of patients | Slope (SE) | 95% CI | τ² | P value |
|--------------------------------|-------------------|--------------------|------------|--------|----|---------|
| Duration of parenteral nutrition dependency in weeks | 17 | 402 | 0.1 (0.1) | −0.1 to 0.1 | 65.5 | 0.347 |
| Age at time of cognitive assessment in years | 25 | 749 | 0.5 (0.7) | −0.8 to 1.8 | 95.0 | 0.527 |
| Gestational age in weeks | 23 | 636 | 1.1 (0.4) | 0.4 to 1.8 | 43.9 | 0.041 |
| Duration of hospital stay in weeks | 21 | 668 | −0.9 (0.2) | −1.3 to −0.5 | 51.6 | 0.014 |
| Number of surgeries | 13 | 367 | −1.7 (0.7) | −3.1 to −0.3 | 30.7 | 0.033 |

Higher gestational age was associated with higher DQ/IQ, whereas longer hospital stay and higher number of surgeries were associated with lower DQ/IQ. When a patient is hospitalized for 10 weeks longer, the patient’s DQ/IQ is 9 points lower (with a slope of −0.9). CI = confidence interval; DQ = developmental quotient; IQ = intelligence quotient; SE = standard error; τ² = tau-squared (represents the absolute value of true between-study variance, reflects heterogeneity).
development. Possibly, length of hospital stay is a proxy for the severity of illness that could explain the cognitive impairment.

The finding that surgery impacted cognitive development is supported by studies showing lower DQ/IQ in other patient populations requiring major neonatal surgery (59,60). In our meta-analysis, the association between surgery and developmental outcome seemed to be explained by 1 outlier study (35) with a mean of 11 surgical procedures (Figure S5, Supplemental Digital Content 7, http://links.lww.com/MPG/C630), supporting that most likely multiple surgeries are associated with impaired outcome. It is unclear what aspect of surgery is linked to the developmental changes. The role of anesthetics is subject of debate. A randomized controlled trial comparing infants undergoing surgery receiving general anesthesia with those receiving awake-regional anesthesia found no difference in developmental outcome at 5 years old (61). In that study, however, a single short length of anesthesia for a minor surgical procedure was examined. In other retrospective studies, longer or repeated anesthesia exposures were found to be associated with learning disabilities or worse DQ (62,63). A combination of exposure to general anesthesia and other perioperative factors is thought to make children vulnerable for memory impairment and school problems (64). Cerebral perfusion, nutritional and metabolic changes, physiologic stress, pain, and inflammation may impact neurodevelopment (65). In addition, just as length of hospital stay, the number of surgeries may be a proxy for critical illness.

Our results showed that there was no association between age at assessment and developmental outcome. Most studies, however, included children up to 2 years old. Little is known about the cognitive abilities of older children in the different underlying disease groups. In general, when children become older, tasks get more complex and demanding and deficits may become more apparent as a result of growing into deficit.

We expected a longer duration of PN dependency to be associated with lower DQ/IQ as there is growing evidence that early nutrition (especially essential fatty acids, zinc, and iron) could have long-term influence on cognitive abilities (66). PN can differ in composition of macronutrients and micronutrients from enteral nutrition. Also, PN is given through a central venous line, which is often accompanied by recurrent infections and limited freedom of movement, affecting cognitive development (67–69). The expected association was not confirmed in the meta-regression, which is reassuring.

The risk factors from the univariable meta-regressions may interact with one another but because of the limited number of studies (<10) with data on all predictors together, we were not able to perform a multivariable meta-regression. There may be other predictors of cognition in children with IF that we could not include in the meta-regressions. For example, changes in gut microbiota, also seen in pediatric patients with IF (70), are thought to influence cognition (71). The role of having a central venous line and other disease-specific factors of IF remain unclear in this matter.

We present the first meta-analysis on cognitive outcomes in both pediatric patients with IF and patients at risk of IF with conditions affecting the small intestine. The review’s main strengths is its adherence to a registered protocol and methodologic advantages. Our study has several limitations that need to be taken into account when interpreting the results. First, most studies were retrospective with small sample sizes and limited follow-up time. Also, only 2 studies on midgut malformations were found, and no studies concerning enteropathies or motility disorders. Second, pooling of observation data without access to individual patient data is a limitation of meta-analyses in general. Therefore, we could not separate patients with PN dependency at the time of cognitive assessment from patients without PN. Another issue concerning PN and IF is that cut-offs of PN duration used for the definition of IF often differed or were not provided. Third, we had to transform medians to means for several patient characteristics for the meta-analysis. This may have led to an overestimation or underestimation of DQ/IQ and PN dependency duration. The widespread confidence intervals of outcomes shows the heterogeneity and indicates that the pooled estimates of the current meta-analyses are less precise and should be interpreted with caution. We chose to include multiple measures for defining developmental outcome, which may explain the heterogeneity too.

Cognitive development is a child’s evolving ability to think and understand. It is important to detect alterations in cognitive functioning in an early stage, to stimulate development as soon as possible. Often, only medical predictors are evaluated but we know that also psychological factors, such as parent-child attachment and emotional functioning are associated with cognitive development (72,73). Future research should focus on gaining more insight into both medical and psychological risk and protecting factors for developing intellectual disabilities in children with and at risk of IF in order to create prevention and remediation strategies.

CONCLUSIONS

In conclusion, our systematic review and meta-analysis showed that in patients with conditions affecting the small intestine requiring PN, children with IF and surgical NEC have a higher risk of developing adverse cognitive outcomes. Those with a low gestational age, long hospitalization, and multiple surgical procedures are especially prone. As survival rates of children with IF are improving, the number of at-risk patients is increasing. Therefore, it is important to monitor cognitive development in this vulnerable patient population and explore avenues for prevention and remediation whenever possible.

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