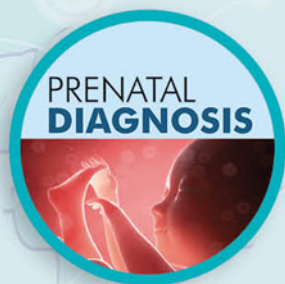




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REVIEW

Neurodevelopmental outcomes in children with isolated congenital diaphragmatic hernia: A systematic review and meta-analysis

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Abstract

Background: Congenital diaphragmatic hernia (CDH) reportedly has neurologic consequences in childhood however little is known about the impact in isolated CDH.

Aims: Herein we aimed to describe the risk of neurodevelopmental complications in children born with isolated CDH.

Materials & Methods: We systematically reviewed literature for reports on the neurological outcome of infants born with isolated CDH. The primary outcome was neurodevelopmental delay. Secondary outcomes included, motor skills, intelligence, vision, hearing, language and behavior abnormalities.

Results: Thirteen out of 87 (15%) studies reported on isolated CDH, including 2624 out of 24,146 children. Neurodevelopmental delay was investigated in four studies and found to be present in 16% (3-34%) of children. This was mainly attributed to motor problems in 13% (2-30%), whereas cognitive dysfunction only in 5% (0-20%) and hearing in 3% (1-7%). One study assessed the effect of fetal surgery. When both isolated and non-isolated children were included, these numbers were higher.

Discussion: This systematic review demonstrates that only a minority of studies focused on isolated CDH, with neurodevelopmental delay present in 16% of children born with CDH.

Conclusion: To accurately counsel patients, more research should focus on isolated CDH cases and examine children that underwent fetal surgery.

Lennart Van der Veeken and Simen Vergote shared first authorship.

#Jan Deprest and Matteo Bruschetti shared last authorship.

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1 | INTRODUCTION

Congenital diaphragmatic hernia (CDH) is a serious birth defect that occurs in 3–4/10000 fetuses (ORPHA:2140).¹ The condition is characterized by a defect in the diaphragm allowing abdominal organs to herniate into the thorax thus interfering with normal lung development. This leads to bilateral lung hypoplasia, which at birth causes respiratory insufficiency and pulmonary hypertension. Survival rates in large volume centers using standardized neonatal treatment protocols are over 70% in isolated cases.² However, survival may come at the cost of high medium-to long term morbidity rates including chronic lung disease, variable pulmonary hypertension, gastroesophageal reflux, feeding and growth problems, neurocognitive delay, hearing loss, thoracic deformations, and hernia recurrence.^{3–10}

For parents of children born with CDH, the most relevant long term morbidity may be neurodevelopmental impairment (NDI). Several studies have indicated that CDH-patients are at risk for cognitive and motoric dysfunction with numbers varying from 16% to 80%.^{11–19} Extracorporeal membrane oxygenation (ECMO), supplemental oxygen requirement beyond 30 days of life and neuromuscular hypotonicity are known (postnatal) predictors of NDI, next to prenatal predictors such as disease severity or gestational age at delivery.^{11,15,20,21} However, the majority of these studies included both isolated and nonisolated CDH cases. It is important to differentiate between these two groups as the rate of NDI is increased in children with nonisolated CDH presenting with various chromosomal and/or structural abnormalities.^{22–25} Second, the ongoing TOTAL-trial is investigating the effect of a prenatal intervention for CDH, is restricted to fetuses with isolated CDH.^{26,27} When counseling parents prenatally and evaluate if they are suitable candidates for fetal therapy, it is important to be able to present reliable data to estimate the risk of severe comorbidities, including NDI of their child.

Therefore, we aimed to systematically review the literature on the risk of NDI in fetuses and infants with CDH, either isolated or with associated structural or genetic abnormalities.

2 | METHODS

2.1 | Protocol and registration

This systematic review was conducted in accordance with the guidance on Preferred Reporting Items for Systematic reviews and Meta-analyses. The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO 2018 CRD42018115854).²⁸

2.2 | Eligibility criteria

Randomized controlled trials (RCT), cohort and case-controlled studies and case series reporting the neurologic outcomes of children

Highlights

What's already known about this topic?

- Children born with congenital diaphragmatic hernia (CDH) are at increased risk for neurodevelopmental delay
- Most published data reports on combined isolated and nonisolated CDH cases

What does this review add?

- This is the first review examining the impact of isolated CDH
- This can be used when counseling CDH patients that qualify for fetal surgery on the neurologic outcome

born with CDH were considered eligible. No date or language restrictions were applied. Systematic reviews, narrative review articles, case reports, incomplete reports, book chapters, conference abstracts, letter to the editors, and comments were excluded. Case series reporting on less than five patients were excluded.

2.3 | Search strategy

A systematic search was conducted in MEDLINE, EMBASE, and Cochrane databases using free text and Medical Subject Headings as described in Appendix S1. Subsequently, reference lists of relevant review articles were manually checked to identify relevant cross-references (snowballing). Covidence (Veritas Health Innovation Ltd) was used to eliminate duplicate articles and manage study screening. We excluded duplicates type I (among different databases) and type-II (in different journals/issues).

2.4 | Study selection

Two authors (Lennart Van der Veeke and Simen Vergote) screened all titles and abstracts independently, excluded irrelevant studies and then independently assessed the remaining full-text articles for eligibility; disagreements were resolved by consensus or if necessary by a third author (Karl Kristensen). Studies were excluded if the full text was unavailable online and the abstract contained insufficient information. Authors from studies from which data could not be extracted (e.g., composite or combined outcomes given) were contacted by e-mail for further clarification. If authors did not reply, studies were listed as “awaiting classification”. Studies containing patient cohorts which appeared to have been published previously by the same authors were excluded. In that case we opted only to include the cohort with the largest number of patients for each outcome measure. If cohorts were tested twice, we

included most recent results, that is oldest age of children at testing.

2.5 | Data extraction

Two authors independently extracted data (Simen Vergote and Lennart Van der Veeken) and entered this into a standardized Excel form (Microsoft; Appendix S2) with study and condition characteristics. Disagreements were resolved by consensus. Neurologic outcomes were categorized in eight categories: general neurologic outcome, development, cognition, motor, language, vision, hearing, and behavior. Outcomes were the number of children scoring abnormal and borderline (abnormal was defined as scoring more than two standard deviations below average on standardized tests and borderline as a score between two and one standard deviation below average). The primary outcome was neurodevelopmental delay. Secondary outcomes included, motor skills, intelligence, vision, hearing, language, and behavior abnormalities. Data were separated between isolated and nonisolated studies. The definition for isolated CDH was: (1) absence of major structural abnormalities at birth and (2) normal genetic findings. If possible, data from isolated cases was extracted from studies including both isolated and nonisolated cases. If it was not possible to distinguish the two groups, all data were considered as nonisolated.

2.6 | Quality assessment of studies

Study quality and risk of bias were analyzed using a standardized form. Randomized trials were analyzed using the Cochrane Collaboration's tool for assessing risk of bias.²⁹ Case-control studies were analyzed using the Newcastle–Ottawa Scale for assessing the quality of nonrandomized studies.³⁰ Case series were analyzed using the National Institutes of Health study quality assessment tool.³¹

2.7 | Assessment of heterogeneity

Methodological and clinical heterogeneity of data per study were evaluated. Variables were tested for statistical heterogeneity by applying the I^2 test to determine whether data could be pooled. An I^2 value less than 40% was taken to indicate heterogeneity not to be important; 30%–60% may represent moderate heterogeneity; 50%–90%: may represent substantial heterogeneity, 75% to 100% considerable heterogeneity.³²

2.8 | Meta-analysis

Meta-analysis for all outcomes was carried out using MedCalc statistical software version 15.4 (MedCalc Software). Results were expressed as proportions with 95% confidence intervals (CI) as all outcomes were categorical variables. Pooled proportions were

calculated using the random effects model as we anticipated the presence of heterogeneity among the included studies. Results from meta-analyses are presented as percentage with confidence interval, 95% (CI). Comparisons between groups are presented as risk ratios.

3 | RESULTS

3.1 | Search results

The electronic literature search (April 2020) identified 2292 study records. After deduplication, 1854 articles were screened by title and abstract, and a further 1672 were excluded as irrelevant. Snowballing identified an additional 10 records and the full texts of the remaining 192 articles were reviewed. After assessment of the full text, 102 articles were excluded: 14 did not report neurologic outcomes, 17 were not randomized trials, case-control series or case series, four studies did not report on CDH, 36 were excluded for overlapping data and for 31 studies we are at the moment of writing, still waiting for response to clarify the data (Figure 1).

3.2 | Study characteristics

Finally, 90 studies were included in this review, reporting on 24,930 children with CDH (Table S1). This included 83 case series^{15,17–21,33–110}, four cohort studies,^{16,111–113} and three randomized controlled trials.^{7,114,115} Nine studies reported only on isolated CDH cases^{7,21,52,76,85,91,104,105,109} and in four studies a differentiation was made between isolated and nonisolated cases.^{39,51,81,94}

3.3 | Risk of bias

Quality assessment of the studies is displayed in Table S2. No studies were found to have a high risk of bias or to be low quality.

3.4 | Statistical heterogeneity

Neurologic outcomes data were pooled in 40 separate meta-analyses. The results and levels of heterogeneity per outcome measure are listed in Appendix S3.

3.5 | CDH characteristics

Survival of children born with CDH was included in 44 studies.^{7,16–19,21,33–36,38,39,42–44,46,49,50,52–54,56,60,62,70,71,73,76,78,80,81,85–88,90–92,95–97,100–108,114,116} In total 60% (8301/13937) of children survived. When studies that only included ECMO patients were excluded, we observed a survival rate of 71% (4204/5959). The diagnosis of CDH was made prenatally in 48% of reported cases (7897/16569). Disease

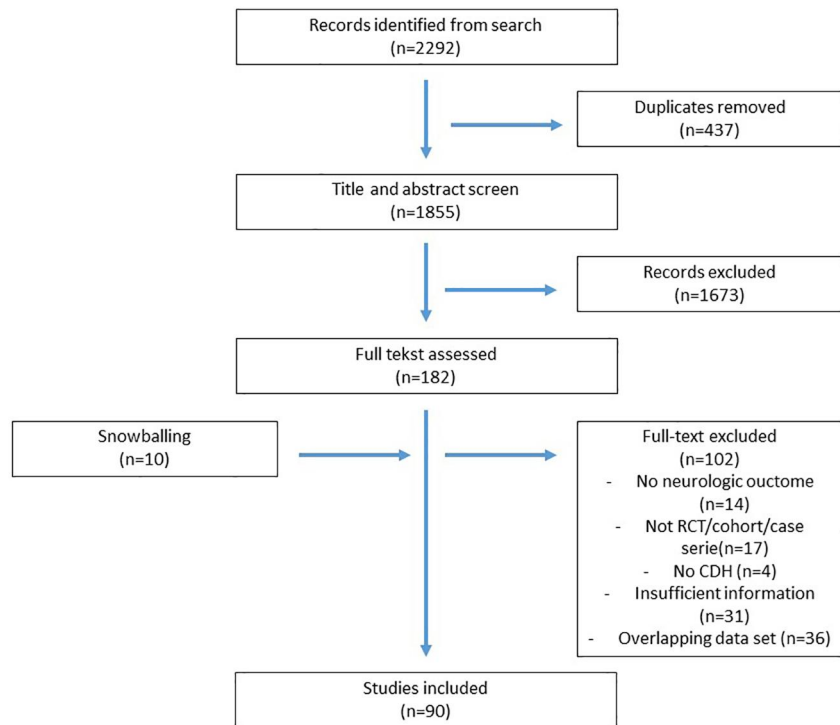


FIGURE 1 Preferred Reporting Items for Systematic reviews and Meta-analyses flow diagram

severity was mentioned in many different ways: lung-to-head ratio, observed/expected lung-to-head ratio, lung-to-thorax ratio, total lung volume or classified as “high risk” or “severe”. The side of herniation was mentioned in 41 studies (47%) and 78% of children (9906/12729) had left sided hernia.

3.6 | Isolated CDH

Of the 89 included studies, 14 studies reported only on isolated cases or distinguished isolated from nonisolated cases. A total of 2719 children were included, with the majority ($n = 2017$) being reported by a study from the CDHSG Registry. Four studies revealed that 16% of children scored abnormal on development using standardized tests; using the Bayley Scales of Infant Development (BSID) 32% (18%–47%) of patients scored abnormal^{7,21} and 7% (1%–17%) scored abnormal on the Griffith Mental Development Scales (Griffith)^{85,91} (Figure 2). Cognition was abnormal in 5% (0%–20%; Figure 3) and motor function in 13% (2%–30%). Hearing was impaired in 3% (1%–7%; Figure 4). Six studies reported on general neurologic problems, tested either by general impression of a pediatrician or by testing if the child could walk independently at two years of age.^{52,76,81,94,104,105}

4 | NONISOLATED CDH

4.1 | Development

Development using standardized tests was performed in 23 studies.^{7,16,21,46,48,58,60,67,68,71,74-76,79,85,86,88,89,91,92,95,110,114,115}

When pooled together, 18% (11%–26%) of children scored abnormally on these tests. There was a large difference between the different tests used. Only 9% (1%–23%) of children tested with Griffith scored abnormal whereas 25% (14%–37%) of children scored abnormal on the BSID.

4.2 | Cognition

Cognitive deficits were reported in 22 studies.^{7,16,17,19,33,37,38,40-42,47,63,74,75,80,83,88,94,109,111-113} In total, 10% (7%–15%) of CDH children scored abnormal. The majority of these studies used BSID and if only BSID results were analyzed, 14% (8%–20%) of children scoring abnormally.

4.3 | Motor deficit

Multiple studies reported on motoric deficits in CDH children.^{7,16,17,19,33,37,38,41,42,45,47,56,58,60,68,74,75,83,85,88,91,93,94,109,113} Numbers range from 0% to 47%. Pooling of the data demonstrated that 14% (10%–19%) of children scored abnormal on motoric tests. No differences were seen when only studies using the BSID were analyzed.

4.4 | Language

Language performance was reported in nine studies, all used the BSID^{16,17,19,38,47,74,88,109,113} or the ASQ. Abnormal scores were reported in 9% (4%–15%).

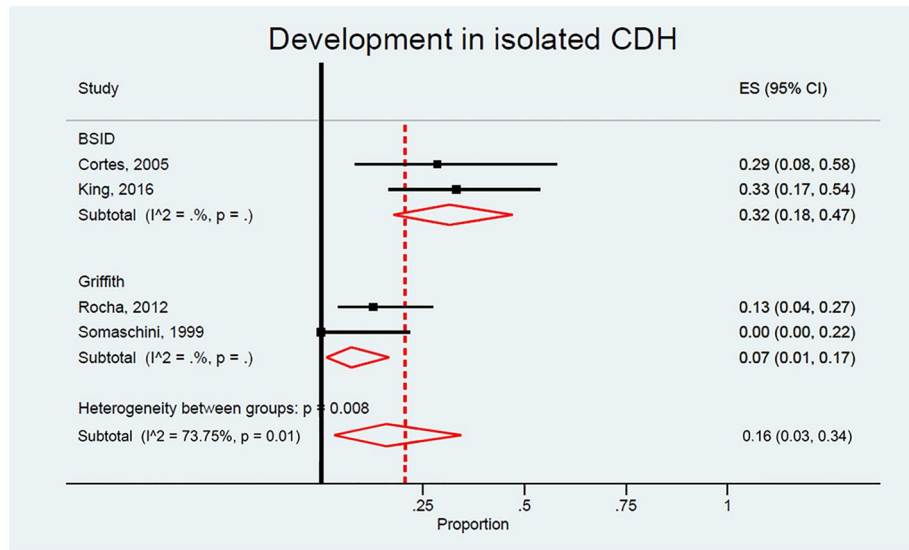


FIGURE 2 Meta-analysis of developmental delay in isolated congenital diaphragmatic hernia

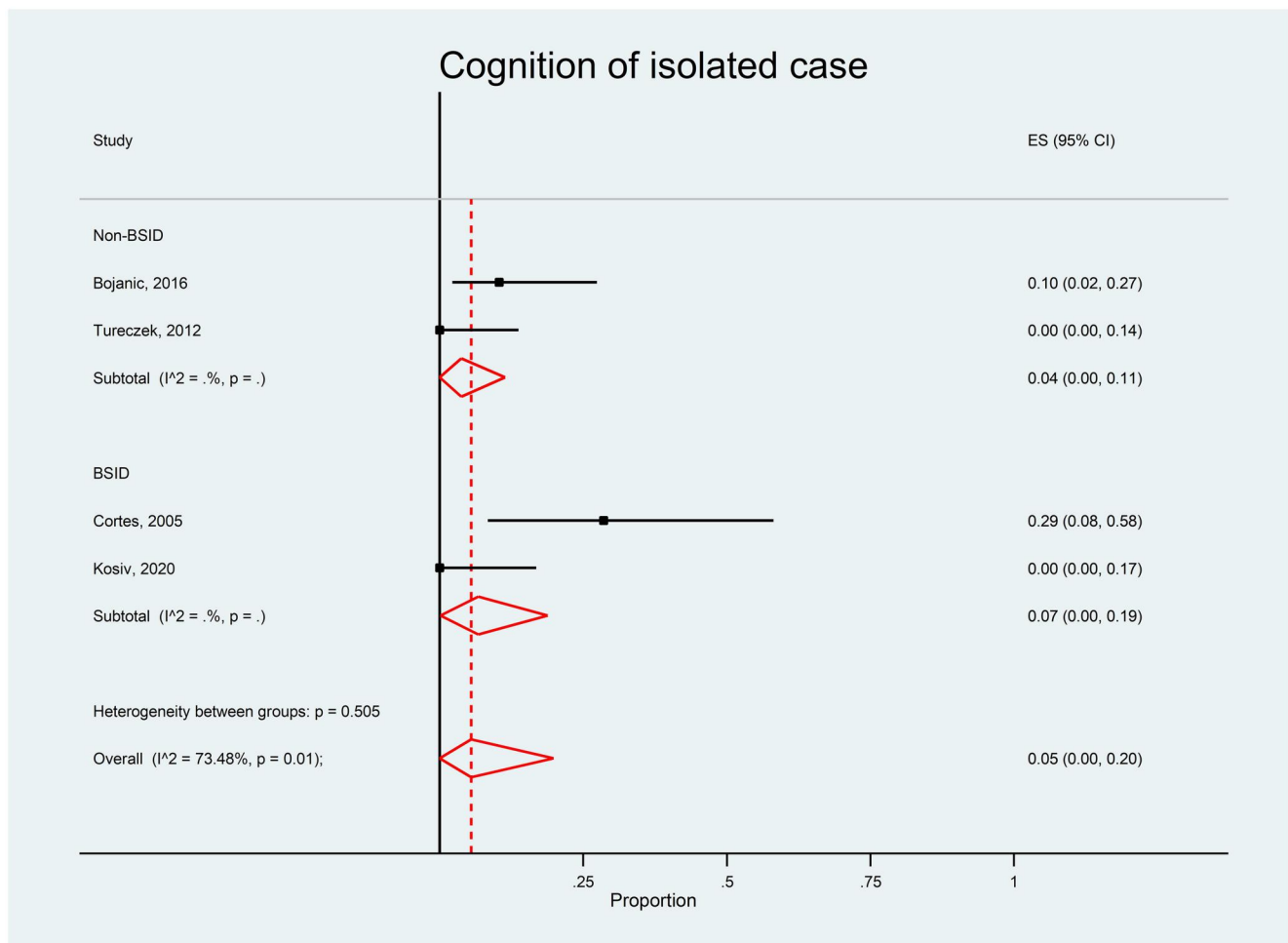


FIGURE 3 Meta-analysis of cognitive delay in isolated congenital diaphragmatic hernia

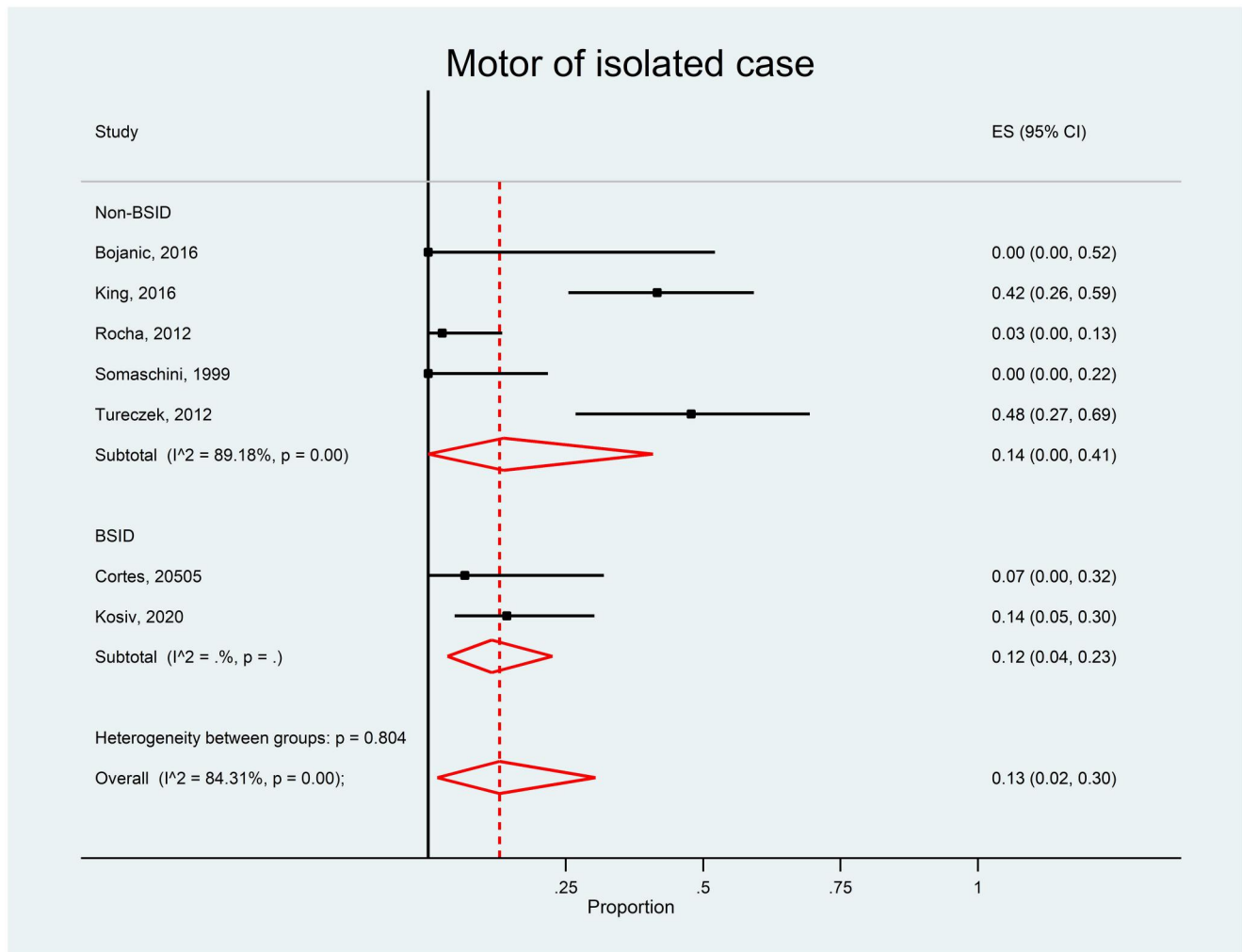


FIGURE 4 Meta-analysis of motor delay in isolated congenital diaphragmatic hernia

4.5 | Vision and hearing

Seven studies reported on visual problems using a variety of tests. Somaschini et al. reported 0/15 patients having visual problems when examined by an ophthalmologist.⁹¹ Rocha et al. reported strabismus to be present in 1/39 patients.⁸⁵ Studies using questionnaires, reported visual problems in 5%–21%.^{55,67,75,77,88}

Hearing was tested in 1 four studies by audiometry at different ages (0.5–14 years).^{51,57,62,65,67,69,70,73,79,83–85,98,107} Abnormal scores were seen in 31% (17%–47%) of children. Other tests included questionnaires or unknown methods and abnormal scores varied from 0%–44%.^{7,15,18,20,34,39,42,43,49,55,61,75,77,88,111} Four studies showed that hearing problems were more prevalent with increasing age.^{7,15,18,65}

4.6 | Behavioral problems

Behavioral problems were reported in 12 studies.^{19,40,47,55,63,68,74,75,78,80,89,111} A meta-analysis of these studies demonstrated behavioral problems in 14% (4%–26%). Half of the

studies were performed using the CBCL, with 11% (1%–28%) of children having an abnormal score.

4.7 | Neurologic morbidity nonstandardized tests

Using nonstandardized tests, neurologic development was assessed in 23 studies using a wide variety of tests ranging from physical examination to nonstandardized questionnaires. The majority of these patients were included in large series including ECMO treated patients. Due to the heterogeneity of testing methods used it was not appropriate to perform a meta-analysis on this data.

4.8 | Isolated versus nonisolated cases

Nine studies compared isolated versus nonisolated CDH or reported on the relative risk (RR).^{20,45,51,68,79,81,94,117} Putnam et al. reported a RR of 2.35 (1.33–4.14) for developmental impairment in nonisolated CDH, which was similar to Tureczek et al. (RR of 2.5). On the

cognitive level Bojanic et al. found a RR of 2.1 and Tureczek et al. found 0/30 children with isolated CDH to have impairment versus 3/8 with nonisolated CDH. On motor level a RR of 2.1 was found by Tureczek et al. whereas Church et al. found this to be 16 (7.2–24.9).^{45,94} The risk for autism was nine times higher according to Danzer et al. in nonisolated CDH. Lastly also hearing problems were more 3.8 times more prevalent in nonisolated CDH.

4.9 | Extracorporeal membrane oxygenation

The rate of NDI was compared in ECMO versus non-ECMO cases in 17 studies.^{15,17,19,20,39,41,45,54,60,68,71,77-79,81,107,118} The RR of ECMO for developmental problems was calculated in a meta-analysis of seven studies, to be 3.3 (2.8–3.8). The RR is similarly increased on the cognitive level (RR:1.8 [0.5–3.1]) as on motoric level (RR: 1.7 [0.6–2.8]).

4.10 | Severity

Six studies investigated the relationship between neurologic outcomes and severity. Church et al. described smaller lung volumes on prenatal MRI to be associated with lower fine motor scores.⁴⁵ Bojanic et al. did not see a correlation between liver status and motor scores.³⁹ The correlation between cognition and lung size was examined in five studies but none found this to be correlated.^{21,39,80,94,100}

4.11 | Prenatal diagnosis

One paper investigated the difference between pre- and postnatal diagnosed CDH. Mesas Burgos et al. found neurologic morbidity to be present in 15 % of prenatal diagnosed cases versus 11% when diagnosed postnatally.

4.12 | Fetoscopic endoluminal tracheal occlusion (FETO)

One study compared neurologic outcome in patients that were treated with FETO versus patients that were not treated prenatally.⁷ They did not detect any differences in cognition, motoric score, requirement of hearing aids or postnatal CT in both groups. A study by Deprest et al. described no neurologic morbidity in 10 patients treated with FETO.⁵²

5 | DISCUSSION

In this systematic review, we report a 16% occurrence of neurodevelopmental delay in children with isolated CDH. There was a wide variety in domains tested, as well as the methods to test these domains, leading to heterogeneity in the prevalence of NDI.

Nonetheless, we came to a motoric deficit rate of 13%, abnormal cognitive function in 5% and aberrant hearing in three %. Although earlier studies reported that associated anomalies increase the risk for NDI, we only found a slightly lower rate of developmental delay in isolated CDH. However, hearing impairment and cognitive delay were found to be less frequent in isolated CDH compared to combined isolated and nonisolated cases. The relative risk on the other hand clearly demonstrated an increased risk in case of nonisolated CDH. The findings in the nonisolated group may be an underestimation because these studies include both isolated and nonisolated cases with a variable percentage (1%–37%) of nonisolated cases.

Many studies still rely on nonstandardized assessment tools, only four out of 10 studies on NDI in isolated CDH used standardized tests, the other six varied widely in methodology and definitions. Based on these four studies, the rate of NDI was 16%. This is much higher than in the general population, which is around 4%–8%.¹¹⁹⁻¹²¹ If mild NDI is included this number is reported around 15%, and also mental health problems have been reported to be as high as 20%,¹²² however we restricted in this study to severe NDI. NDI was mainly attributed by an increased rate of motor problems, present in 13% of cases. Cognitive problems were only seen in 5%. We can only speculate on why the motor function is more often affected than the cognitive function. Possibly, the decreased exercise capacity or oxygen dependency limits the motor function and development in children with CDH. Second, these children suffer from nutritional and growth problems caused by gastrointestinal disorders which can impact motor development.¹²³ Inadequate development of brain regions that are responsible for motor function, might also play a part. Radhakrishnan et al. found a correlation between the lung volumes and cerebellar dimensions.¹²⁴ On the other hand, this might not be a consequence of the disease, but of the required postnatal surgery, anesthesia, complications, and other neonatal interventions as a motor deficit occurs also in other surgical correctable congenital anomalies.¹²⁵

It is unclear whether this impairment persists later in life due to the lack of studies reporting on the motor or cognitive outcome in adults. Four studies reporting on outcomes in adolescents found cognitive impairment to be similar to our meta-analysis which suggests that the cognitive impairment lasts at least until adolescence.^{63,80,111,112} On the other hand, self-esteem and life management ability in adults with CDH have been reported not to be affected¹²⁶ which might suggest that children catch up, or do not feel limited by these motor problems.

Subsequently we examined the rate of hearing disability, reported to be present in up to 50% of CDH children.¹²⁷ In isolated CDH, we only found this to be present in three % of cases, which is much lower compared to studies including also nonisolated CDH (31%). Perhaps this is due to the low number of studies examining hearing in isolated CDH (2 studies vs. 29 including nonisolated CDH). However, this might also be an actual difference between isolated and nonisolated CDH. Dennett et al. found that hearing loss was associated with longer length of hospital stay⁵¹ and it is likely that nonisolated CDH patients stay longer in the hospital, however this is speculative as these numbers were not reported.

Severe cases these days are offered to opt for prenatal surgery as FETO has been shown to increase survival.^{26,27} Two studies examining the effect of FETO in CDH, found no increased risk for neurologic problems however these included only 10 and 14 patients,^{52,85} so due to the small numbers, no definitive conclusions can be drawn. To properly counsel parents, we need data on prenatally diagnosed, severe isolated cases. However, no articles were restricted to severe cases. Furthermore, severity was only reported in a minority of published studies and was defined in many different ways. Although ECMO, which is linked to severity, increases the risk for NDI, a correlation between NDI and severity could not be demonstrated.^{21,39,80,94,100} Moreover, we did not find studies investigating the impact of a prenatal diagnosis. Only one paper reported numbers of pre- and postnatal diagnosed CDH separately. This is important as prenatal diagnosed cases have an improved survival, but this is often believed to come at the cost of an increase in morbidity. Amongst all included cases, only 47% of diagnoses were made prenatally which is lower than commonly reported rates in literature (59%–68%).^{128,129}

5.1 | Strengths and limitations

This study has limitations. First the quality of a systematic review highly depends on the published data and our effort to provide a tool for counseling fetal surgery patients is therefore compromised by the poor quality of the primary data. In this review, only three RCTs and four cohort studies were included, all other studies did not include a control group. A second limitation is that we pooled data to report on a single number for each outcome in the absence of clinical and statistical homogeneity. Another limitation is that although we tried to identify studies only including isolated cases, some studies included additional anomalies, though minor, that were of unknown nature. Lastly, although we checked for overlapping data, it is possible the same children were included in multiple studies, reporting on different neurologic domains which increases the risk for over estimation. Therefore, to avoid double counting, we did not report on an overall rate of neurologic complications.

This study also has some strengths. We performed a systematic search according to current guidelines for systematic reviews and included all articles reporting on neurologic outcome in CDH. Because we included case series, we maximized the number of cases included. Secondly, by analyzing neurologic domains separately, we were able to report impairment rates different outcomes. Thirdly, we are, to our knowledge the first to focus on outcome in isolated CDH which is important for counseling of fetal surgery candidates.

6 | CONCLUSION

Children with CDH seem to be at increased risk for neurodevelopmental delay, mainly attributed to abnormal motor function whereas cognition and hearing are less frequently affected. Only a minority of published data deals with isolated CDH fetuses. The

outcomes of these were better. In view of the potential of antenatal management and its complications, it would be interesting to determine the relationship of the severity of pulmonary hypoplasia, the gestational age at delivery, and conduct studies on the difference between isolated and nonisolated cases. This systematic review highlights the current need for standardized core outcomes for CDH patients (<https://ern-ernica.eu/>).

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CONFLICT OF INTEREST

The authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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