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Catarina Leite Baía Soares

Neurodevelopment outcomes in the first five years of the life of children with Transposition of the Great Arteries surgically corrected in the neonatal period

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TÍTULO DISSERTAÇÃO/~~MONOGRAFIA~~ (riscar o que não interessa)

Neurodevelopment outcomes in the first five years of the life of children with transposition of the great arteries surgically corrected in the neonatal period

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ASSINALE APENAS UMA DAS OPÇÕES:

É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
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Faculdade de Medicina da Universidade do Porto, 4 / 3 / 2023

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Dedicatória

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Neurodevelopment outcomes in the first five years of the life of children with Transposition of the Great Arteries surgically corrected in the neonatal period: a systematic review and meta-analysis

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Abstract

Congenital heart defects are the most common abnormalities at birth, resulting in many short and long-term consequences. In patients with Transposition of the Great Arteries (TGA), surgical correction may achieve definitive treatment, so a thorough knowledge of the long-term outcomes, particularly neurodevelopment outcomes, is essential. Therefore, we conducted a systematic review and meta-analysis to study the neurodevelopment outcomes in the first five years of the life of children submitted to corrective surgery for TGA in the neonatal period.

A total of 18 reports from 17 studies were included in the systematic review, assessing 809 individuals with surgically corrected TGA. The neurodevelopmental outcomes were assessed with the Bayley Scales of Infant and Toddler Development (BSID) and the Wechsler Intelligence Scale for Children (WISC). Mean Mental Development Index (MDI) and Psychomotor Development Index (PDI) were within the average values from 1 to 3 years of age, and mean full-scale global IQ, verbal IQ and performance IQ scores, from four to five years, were within the reference range.

This study revealed no major impairments in global neurodevelopment scores until five years of age in children submitted to corrective surgery for TGA in the neonatal period. Further studies are needed to identify specific risk factors and early markers of later impairment to guide the establishment of early interventions.

Keywords: Neurodevelopment, Transposition of the Great Arteries, neonatal period, arterial switch operation, five years

Statements and Declarations

Competing Interests: Authors have no conflicts of interest to disclose.

1. Introduction

Congenital heart defects (CHD) are the most common congenital abnormalities, affecting 6 to 8 per 1000 live births [1]. CHD are responsible for 3% of all infant deaths and for 46% of deaths from all congenital malformations [2]. Among CHD, transposition of the great arteries (TGA) accounts for approximately 5% of all congenital heart diseases, with an incidence of 1 in 2300 to 1 in 5000 live births[3,4].

Surgical correction may achieve definitive treatment of TGA. The current gold standard is the arterial switch operation (ASO), first performed by Jatene in 1975[5-7]. Although surgical correction performed early in the neonatal period, ideally in the first two weeks of life [8], leads to improvements in the quality of life and development of newborns with TGA as well as reduced mortality rates [9-11]. However, neurodevelopment impairments in patients with TGA have been reported during childhood [12,13], as TGA has been associated with impairments in psychomotor, mental, learning, memory and language development, leading to social-cognitive and social-communication deficits [14-17]. A wide variety of factors have been associated with adverse neurodevelopment outcomes in patients with TGA, such as the presence of brain lesions detected by MRI before and/or after surgery[18-21], as well as the timing of surgery, the surgical technique and conditions: intraoperative hyperglycemia, hypothermic circulatory arrest versus low-flow cardiopulmonary bypass [22-24].

Many studies have assessed the impact of surgical correction of TGA in the neonatal period on neurodevelopmental outcomes, but results are conflicting [25-27]. Additionally, although a systematic review on this matter has been previously published [28], this systematic review assessed a more selective population, showed some methodological limitations and was performed using a single database. Additionally, no quantitative synthesis was performed. As a result, we set off to perform a systematic review and meta-analysis on the neurodevelopment outcomes in the first five years of the life of children with TGA surgically corrected in the neonatal period.

2. Methods

This study is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [29].

2.1 Literature search

We conducted a systematic literature search in 3 electronic databases: Medline via OVID, Scopus and Web of Science. The last search was performed in April 2022. We screened the reference list of included studies and relevant reviews for potentially eligible studies. We did not apply restrictions based on language or publication date. The search query for each database is available in Supplementary Tables 1,2 and 3.

2.2 Study selection

We included all prospective studies assessing the neurodevelopmental outcomes (assessed through Bayley Scales of Infant and Toddler Development (BSID) and Wechsler Intelligence Scale for Children (WISC)), until five years of age, in children with TGA surgically corrected during the neonatal period.

After eliminating duplicate results, two reviewers independently screened article titles and abstracts. Two reviewers independently read and analyzed the full texts of articles not excluded in the screening phase. Attempts were made to contact the authors of articles not accessible by other means. In any phase, disagreement between reviewers was solved by the decision of a third independent reviewer. All efforts were made to identify published articles assessing one same group of participants; in such cases, non-duplicate data (e.g. data on the outcome assessment at different periods in time) were retrieved from the articles.

2.3 Data extraction

We collected the following information, whenever available: (1) study characteristics – year of publication, study design, setting (number of centers and countries involved in the study), inclusion and exclusion criteria, sampling method, method of randomization (if adequate), and follow-up duration; (2) participant number (total and per group) and characteristics, including demographic data (gestational age and sex), data before surgery (gestational age, birth weight), surgical information (age at surgery, type of procedure, duration of deep hypothermic circulatory arrest and total bypass time), data after surgery (duration of hospital stay); (3) neurodevelopment outcomes - cognitive, gross and/or fine motor, speech, language and behaviour outcomes and time of assessment. Regarding neurodevelopment outcomes, we extracted mean scores and standard deviations (SD), as well as the proportion of children whose score was more than one SD below the normative mean; when data on proportions were not available, we modelled a normal distribution using the reported mean and standard deviation to estimate the number of children whose score was below one SD from the normative mean. In some cases, times at which neurodevelopment was assessed were clustered; namely, assessments performed at the age of 1.5 years, 2.5 years, 3.5 years and 4.5 years were considered along with those performed at the age of 2, 3, 4, and 5 years, respectively. When results were reported separately by subgroups, and no aggregate data could be obtained from the authors, data from different groups were combined as recommended by Cochrane [30].

Data were independently collected by two reviewers into a prespecified form. When data were only available in graphic form, and no additional information was obtained from the authors, Plot Digitizer 2.6.9 was used to estimate raw data, as previously done in other systematic reviews [31-33].

2.4 Quality Assessment

Two reviewers independently performed quality assessment of the included articles using Cochrane's RoB 2 Tool for randomized control trials [34] and Cochrane's ROBINS-I Tool for nonrandomized studies [35].

2.5 Quantitative Synthesis

We performed random effects meta-analyses weighted by the inverse variance (using the method of DerSimonian and Laird [36]). For each outcome and time point, weighted averages were calculated with the respective 95% confidence intervals (95% CI). Heterogeneity was evaluated using I^2 and Cochran *Q* statistics — an $I^2 > 50\%$ and a Cochran *Q* test *p* value < 0.10 were considered to represent severe and significant heterogeneity, respectively. In the presence of significant/severe heterogeneity, subgroup analyses based on clinical criteria were planned to be performed. All statistical analyses were performed using the meta package for R [37].

3. Results

3.1. Search Results

Our search in electronic bibliographic databases returned a total of 3260 results (Figure 1). After duplicate removal and selection by title and abstract screening, we obtained 86 articles. 68 reports were excluded after full-text reading. A list of reports excluded, with reasons, can be found in Supplementary Table 4. Overall, 18 reports from 17 studies were included in our systematic review [8,14-18,24-26,38-46].

3.2. Quality assessment

Risk of bias summaries are shown in Supplementary Figure 1. Nonrandomized studies (n=13) had an overall moderate risk of bias [8,14-18,25,26,40-43,46], except for one study with serious risk of bias [41]. Confounding and selection of the reported results were the main cause of bias. Confounding was mainly due to the multiple factors assessed in the different studies, making it difficult to establish an association between corrective TGA surgery in the neonatal period and neurodevelopment. Nevertheless, all known important confounding domains were appropriately measured and controlled for, except for one study [41] where the reliability of the measurement of important domains was low enough, potentially allowing for residual confounding. Regarding the selection of the reported results, in the majority of the studies, the outcome measurements and analyses were consistent with an *a priori* plan, except for one study[41] where assessment by a speech-language pathologist was not possible at all sites, which may affect the outcome. Risk of bias was low mainly in the classification of the interventions and deviations from intended interventions.

For randomized controlled trials (n=4) [24,38,39,44,45], we found some concerns mainly due to missing outcome data and to selection of reported results. Outcome data were only available for some, or nearly all, randomized participants. Therefore, there is a risk of bias due to missing outcome data, primarily due to losses to follow-up.

3.3 Characteristics of included studies

The demographic characteristics of included studies are depicted in table 1. The included studies were published from 1983 to 2020, assessing populations mainly from North America and Europe as well as South Korea and Japan. The included publications assessed a total of 809 individuals with TGA (from 10[14] to 158[45] participants per study). The majority of the patients (n=652) were submitted to the arterial switch operation (ASO), but there were some exceptions [16,18,43,46]: Mackie et al.[46] included 36 patients submitted to ASO, 26 submitted to the Norwood procedure and 21 submitted to other types of procedures (not specified); Freed et al.[43] reported that 52 patients were submitted to ASO and 22 were submitted to ASO with ventricle septal defect repair, but other complex types of procedures were performed in 14 patients; similarly, Mendoza et al.[16] reported that 30 patients were submitted to ASO and 3 were submitted to ASO and ventricle septal defect repair. Additionally, Peyvandi et al. [18] did not specify how many patients were submitted to ASO or other types of surgery. Gestational age, on average, ranged from 38 weeks [43] to 40 weeks [17] and mean weight at birth was within reference values for gestational age, ranging from 3116g [14] to 3740g [43]. Eight studies [8,15,25,26,38,39,44,46] did not report sex distribution of participants. Age at surgery was, in most cases, within the first two weeks of life (mean: 9.37 days). Concerning surgical characteristics, the total bypass time mean of the overall studies ranged from 106.96 minutes[45] to 268 minutes[14] and the deep hypothermic circulatory arrest time was only reported in four studies ranging from 7.4[46] to 16.8[42] minutes. The mean length of stay was variable from 8[38] days to 34.3[40] days. All included articles assessed neurodevelopment either with BSID [8,14,16-18,24-26,38-41,43,44,46] or WISC [15,42,45].

3.4. Meta-analytic results

3.4.1. Neurodevelopment assessment at 1 year of age

Overall, nine studies [14,17,18,24,25,38-40,44] assessed neurodevelopment outcomes at one year of age, including a total of 390 children. The BSID-II and III were used to assess neurodevelopment in included studies at one year of age (Figure 2). The results from studies [14,17,18,24,38,44] using BSID-II are depicted in Figures 2a, 2b, 2c, 2d. The estimated mean Psychomotor Development Index (PDI) was 91.2 (95% CI 86.2-96.3), albeit with important heterogeneity (I^2=87%, p < 0.01). Similar results, with high heterogeneity, were also found when we restricted the meta-analysis to studies in which all patients (total of 382) had been submitted to the arterial switch operation (ASO) [14,17,24,38,44] (mean PDI = 93.2 [95% CI 88.8-97.6], I^2=71% [p < 0.01]). Regarding the Mental Developmental Index (MDI) score of the studies included in the meta-analysis[14,17,18,24,38,44], mean MDI was 96.2 (95% CI 88.5-104.0), with high and significant heterogeneity (I^2=95%, p<0.01) (Figure 2c), even when restricting the analysis to studies in which all patients (total of 382) had been submitted to the arterial switch operation (ASO) [14,17,24,38,44] (mean MDI = 97.0 [95% CI 87.6-106.3], I^2=94% [p < 0.01]). Figures 2e and 2f depict the results from studies using BSID-III [25,39,40]. The estimated mean motor composite score was 93.6 (95% CI 90.3-96.9) (Figure 2e) and the cognitive composite score was 106.7 (95% CI 103.2-110.2) (Figure 2f), both analyses showing no heterogeneity (I^2=0%, p =0.80).

In table 2, we summarize meta-analytical results of percentage of children scoring more than one SD below the normative mean. At 1 year of age, 33.7% (95% CI = 22.0-48.0) of children scored less than 85 at PDI and 27.2% (95% CI = 17.8-39.1) also scored less than 85 at motor composite score. This significantly differs from the proportion of children scoring less than 85 in the general population.

3.4.2. Neurodevelopment assessment at 2 years of age

Overall, five studies [8,16,41,43,46] assessed neurodevelopment at two years of age, including a total of 293 children. At two years of age, both BSID-II and III were used to assess neurodevelopment outcomes in the included studies (Figure 3). The results from studies using BSID-II [16,43,46] are shown in Figures 3a, 3b, 3c, 3d. The estimated mean PDI was 89.2 (95% CI 83.7-94.6), but heterogeneity was substantial (I^2=83%, p < 0.01) (Figure 3a). Importantly, heterogeneity was reduced after restricting the analysis to studies in which all patients had been submitted to the arterial switch operation (ASO)[16,43,46] (mean PDI = 91.5 [95% CI 89.1-93.8], with heterogeneity I^2=0% [p=0.83]) (Figure 3b). Mean MDI was 90.8 (95% CI 82.8-98.8), with high and significant heterogeneity (I^2=76%, p=0.02) (Figure 3c), even after restricting the analysis to those studies in which all patients had been submitted to the arterial switch operation (ASO) [16,43,46] (mean MDI = 91.4 [95% CI 84.8-98.0], I^2=62% [p=0.07]) (Figure 3d). Figures 3e, 3f and 3g show the results from studies using BSID-III [8,41]. The estimated mean motor composite score 101.1 (95% CI 96.2-105.9), with high heterogeneity (I^2=69%, p=0.07) (Figure 3e). The mean cognitive composite score was 100.8 (95% CI 92.9-108.7), also with high heterogeneity (I^2=91%, p<0.01) (Figure 3f). Finally, the mean language composite score was 94.1 (95% CI 90.0-98.2), with moderate heterogeneity (I^2=35%, p=0.21) (Figure 3g).

At 2 years of age, 41.7% (95% CI = 29.9-54.5) of children scored less than 85 at PDI, 35.1% (95% CI = 21.7-51.4) scored less than 85 at MDI and 29.7% (95% CI = 20.0-41.7) also scored less than 85 at language composite score (Table 2). This significantly differs from the proportion of children scoring less than 85 in the general population.

3.4.3. Neurodevelopment assessment at 3 years of age

Three studies [14,18,26] assessed neurodevelopment at three years of age, including a total of 30 children. Studies assessing neurodevelopment outcomes of patients with surgically corrected TGA at three years of age used the BSID-II [14,18,26] (Figure 4). The mean PDI was 95.5 (95% CI 90.1-100.9), with moderate heterogeneity (I^2=46%, p=0.16) (Figure 4a), which was reduced by performing subgroup analysis on those studies [14,26] including only patients (total of 30 patients) submitted to ASO (mean PDI = 98.9 [95% CI 92.7-105.1], with low heterogeneity [I^2=0%, p=0.56])) (Figure 4b). The estimated mean MDI was 95.3 [95% CI 92.1-98.6], with low heterogeneity (I^2=0%, p=0.89) (Figure 4c). Similar results were found on subgroup analysis restricting for studies [14,26] reporting that all patients (total of 30 patients) had been submitted to ASO (mean MDI = 96.6 [95% CI 90.2-102.9], I^2=0% [p=0.83]) (Figure 4d).

At 3 years of age, 28.2% (95% CI = 19.3-39.2) of children scored less than 85 at PDI and 25.5% (95% CI = 17.1-36.3) scored less than 85 at MDI (Table 2). This significantly differs from the proportion of children scoring less than 85 in the general population.

3.4.4. Neurodevelopment assessment from 4 to 5 years of age

Three studies [15,42,45] assessed neurodevelopment from 4 to 5 years of age, including a total of 264 children. From 4 to 5 years of age, neurodevelopment was assessed with WISC, including full-scale global, verbal, and performance intelligence quotient (IQ) scores (Figure 5). Regarding the global IQ score, the mean from three studies [15,42,45] was 97.5 (95% CI 90.0-104.9), with severe and significant heterogeneity (I^2=94%, p<0.01) (Figure 5a). Two studies reported on the performance IQ score [15,45]. Its mean was 92.9 (95% CI 89.7-96.2), with severe heterogeneity (I^2=54%, p=0.14) (Figure 5b). Finally, the mean verbal IQ score estimated from two studies [15,45] was 95.1 (95% CI 93.0-97.2), with low heterogeneity (I^2=0%, p=0.97) (Figure 5c).

From 4 to 5 years of age, 22.3% (95% CI = 12.1-37.4) of children scored less than 85 at IQ (Table 2). This does not significantly differ from the proportion of children scoring less than 85 in the general population.

4. Discussion

In our study, a meta-analysis of 809 patients with surgically corrected TGA during the neonatal period, we show that these patients do not display significant impairments in mean neurodevelopment scores in the first five years of life. Indeed, cognitive, motor and language scores were within average values, although, except for the latter, heterogeneity was found to be significant. Overall, MDI and PDI were within the average values (mean between 90-109) [47] from 1 to 3 years of age. However, from 1 to 3 years of age, the proportion of children scoring less than 85 in studied population in scores as PDI, MDI, motor and language composite scores was significantly higher than in the general population. From 4 to 5 years, full-scale global, verbal, and performance IQ scores were within the reference range and the percentage of children scoring more than one SD below the normative mean did not significantly differ from the general population. These results suggest that TGA surgically corrected in the neonatal period does not seem to significantly impact early neurodevelopment components, namely cognitive, motor and language development scores. However, it is important to notice that even if these scores are within the reference range, they may be in the low end of this interval, particularly until 3 years of age, which may still impact on the neurodevelopment of these children and have implications to their follow-up. Heterogeneity was high for most of our meta-analytical results, which may be partially due to the heterogeneous designs of the studies included in this systematic review. Importantly, in an attempt to reduce heterogeneity, we performed subgroup analyses, including only those studies in which all the patients with TGA had been submitted to ASO. However, except for neurodevelopment outcomes at three years of age, heterogeneity remained high.

We should notice that there are some conflicting results between studies. For instance, the majority of the studies show no impact on language development, confirmed by our meta-analysis, but one study suggests poor language development at two years of age, highlighting the need for focused post-operative early language interventions [41]. However, in the referred study, assessment by a speech-language pathologist was not possible at all sites, which may have affected the outcome.

The American Heart Association, in its 2015 statement, recommends that surveillance should be performed in all children with CHD, placing children with TGA requiring open heart surgery in the neonatal period at high risk for development disorders and disabilities, namely in the areas of intelligence, academic achievement, executive functioning, language, and fine and gross motor skills[12]. Indeed, TGA is one of the most studied CHD with regard to neurodevelopment outcomes and previous reviews have shown neurodevelopment impairment in these patients during their lifespan. However, our results are consistent with a recently published review [28] which showed a low rate of adverse outcomes until five years of age and a rate of adverse outcomes at school age twice the rate at age 5. Additionally, in adolescents with dextro-TGA, lower than anticipated scores were found in academic achievements, visuo-spatial skills, memory, psychosocial, and executive functions. Another literature review [48] also reported that early development was characterized by mild to moderate neurodevelopment delays, but more recent reports showed improvement in these early outcomes. However, the authors found impairment in later cognitive outcomes, particularly executive functioning.

We did not assess the prevalence of autism spectrum disorders, but it is essential to notice that deficits in social cognition have been reported [48], and other studies [15] reported higher rates of autism among TGA patients below five years of age.

Additionally, some of the reports included in our systematic review addressed interesting associations. For instance, one study shows that pre and post-operative white matter injuries detected by magnetic resonance imaging are associated with a lower score in MDI and PDI at three years [18]. Additionally, brain hypoxia seems to negatively affect the PDI score at one and three years[14,38,40], which suggests that better neurodevelopment outcomes may be achieved by improving O_2 cerebral saturation and blood flow velocity during the early neonatal period in patients with TGA. This draws attention to the importance of pre-natal diagnosis [49], which may allow for the optimisation of surgical conditions. However, while some studies showed that neurocognitive deficits were more prevalent and more severe in children with a post-natal diagnosis[49], this finding was not consistent in the literature and Bartlett *et al.* found that, although infants with TGA with and without pre-natal diagnosis differ among perinatal and perioperative variables, their development at one year of age was similar[50]. The surgical techniques may also play an important role in outcomes, as circulatory arrest as the predominant support strategy seems to be associated with a higher risk of delayed motor development at both 1 and 4 years of age than with surgery with a low-flow bypass strategy [24,45]. Given the heterogeneity between studies, we were unable to perform a meta-analysis comparing these variables.

This is, to our knowledge, the first systematic review of the literature with meta-analysis on the neurodevelopment outcomes in pre-school age children with TGA, adding, therefore, additional insight on this crucial issue. According to these results and considering the studies addressing school-age

children and adolescents, we would emphasize that assessments in infancy and school-aged children with TGA, while important to plan early intervention programs, should be regarded with caution as they might not adequately predict long-term outcomes.

This study has some limitations, mostly due to the characteristics of the primary studies included in this systematic review. Heterogeneity between studies was substantial, including in their designs and characteristics of assessed populations. As previously mentioned, some studies assessed the association between brain lesions and neurodevelopment [18], while others assessed the impact of surgical conditions, such as hypoxia [14,26,38,40], pH [44] and support strategies [24,39,45]. However, we were unable to perform a meta-analysis comparing these variables, as they were not consistently reported across studies. It should be highlighted that not all the components of children neurodevelopment were assessed in this systematic review, such as visual-motor integration, executive functions, preacademic skills, adaptive skills, and social, emotional and behavioural functioning, due to heterogeneity in reported outcomes in the included studies. However, we aimed to assess crucial and global neurodevelopment components such as mental, psychomotor, performance, language and verbal components. Furthermore, while most of the studies assessed all different components of neurodevelopment [8,15,16,25,42,43], one only assessed language development [41]. Additionally, some of the included studies assessed a small sample [14,17,25] and, for some studies, the surgical approach was not reported [18,39,42]. Furthermore, most studies did not directly report on the proportion of children scoring more than one SD from the normative mean, so we estimated this proportion assuming a normal distribution of the scores with the reported mean and SD. Despite this, some strengths can be pointed out. We attempted to maximize study inclusion by performing a thorough search of the literature in three different databases, with no language or date restrictions, checking the reference lists of included studies and relevant reviews, and contacting authors when data needed to be clarified. Additionally, overall included studies did not show a high risk of bias. Finally, this is the first meta-analysis to attempt to aggregate the results from several studies to estimate the proportion of children scoring more than one SD below the normative mean.

5. Conclusion

This systematic review and meta-analysis provides an overview of neurodevelopment outcomes up to five years of age in patients with TGA surgically corrected during the neonatal period. Overall, from one to five years of age, cognitive, motor and language scores were within average value, although from 1 to 3 years of age the proportion of children scoring less than one SD from the normative mean significantly differed from the general population. However, heterogeneity between studies was high limiting the evaluation of other specific components of the neurodevelopment. Additionally, these early outcomes may not adequately predict long-term outcomes. Further well-designed studies are needed to gather more consistent evidence of risk factors for neurodevelopment outcomes and early markers of later impairment to guide the establishment of early interventions.

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Table 1 Demographic characteristics of included studies

Study	*N* participants	Male *N* (%)	Gestational age — Mean (SD)	Weight at birth — Mean (SD)	Age at surgery — Mean (SD)	VSD — *N* (%)	Total bypass time — Mean (SD)	Deep hypothermic circulatory arrest time — Mean (SD)	Length of stay — Mean (SD)
Mendoza *et al.*, 1991[16]	33	24 (72.7)	39.8 (0.9)	3476.0 (512)	NA	6 (18.2)	144 (NA)	NA	NA
Bellinger *et al.*, 1995/1999[24,45]	158	119 (75.3)	39.8 (1.2)	3537.2 (435.8)	9.8 (11.4)	36 (22.8)	106.96 (32.6)	NA	NA
Bellinger *et al.*, 2001 [44]	80	NA	NA	NA	5 (3)	NA	NA	NA	NA
Toet *et al.*, 2005[26]	20	NA	NA	3290 (NA)[a]	NA	3 (15)	139 (NA)	NA	NA
Freed *et al.*, 2006[43]	88	56 (63.6)	38.8 (1.9)	3740 (620)	9.9 (6.5)	22 (25)	140.8 (69.8)	16.8 (19.2)	26.8 (22.7)
Park *et al.*, 2006[17]	16	9 (56.3)	40 (NA)	3200 (NA)	13 (NA)	0 (0)	137 (NA)	NA	NA
Neufeld *et al.*, 2008[15]	65	NA	NA	NA	NA	19 (29.2)	NA	NA	NA
Gaynor *et al.*, 2010[42]	41	26 (63.4)	39.1 (1.6)	3284 (486)	4.7 (5.4)	NA	114.3 (55.5)	10.3 (18.2)	10.0 (5.3)
Andropoulos *et al.*, 2012[25]	30	NA	38.9 (1.2)	3420 (563)	8 (6-9)[a]	7 (23.3)	208 (187-271)	NA	20.7 (5.4)
Ibuki *et al.*, 2012[14]	10	5 (50)	39.0 (1.2)	3115.9 (409.5)	NA	NA	268 (24)	NA	NA
Mackie *et al.*, 2012[46]	36	NA	38.9 (1.3)	NA	12.3 (8.2)	NA	141 (50)	7.4 (4.5)	23 (13.6)
Andropoulos *et al.*, 2013[39]	21	NA	NA	NA	NA	NA	NA	NA	NA
Cheng *et al.*, 2014[38]	43	NA	39.0 (1.5)	3500 (500)	5 (2-23)[a]	NA	NA	NA	8 (5-43)[a]
Hicks *et al.*, 2016[41]	91	61 (67.0)	39 (1.8)	3367.6 (569)	11.5 (14.8)	31 (34.1)	120.6 (39.8)	NA	19.1 (8.4)
Peyvandi *et al.*,	NA[b]	NA	NA	NA	NA	NA	NA	NA	NA

2018[18]									
Lim *et al.*, 2019[8]	45	NA	NA	NA	11.1 (9.8)	11 (24.4)	NA	0	NA
Di Silvestro *et al.*, 2021[40]	32	23 (71,9)	39.5 (1.2)	3404.2 (425.2)	14.4 (5.8)	NA	189.3 (46.6)	NA	34.3 (11.8)

TGA- Transposition of the great arteries; VSD- ventricle septal defect; NA- not available; [a]Median (range); [b] No data at baseline (84 at 12 months and 56 at 30 months).

Table 2 Meta-analytical results of percentage of children scoring more than one standard-deviation below the normative mean.

Outcome	***N* studies**	**Children scoring less than 85 — % (95% CI), I^2**
1 year		
BSID-I		
PDI	6	33.7 (22.0; 48.0), I^2 = 79.6% (*)
MDI	6	18.9 (9.5; 34.1) I^2 = 82.0%
BSID-II		
Cognitive Composite Score	3	7.6 (3.2; 17.1), I^2 = 0%
Motor Composite Score	3	27.2 (17.8; 39.1), I^2 = 0% (*)
Language Composite Score	1	25.8 (13.5; 43.7)†
2 years		
BSID-I		
PDI	3	41.7 (29.9; 54.5), I^2 = 65.4% (*)
MDI	3	35.1 (21.7; 51.4), I^2 = 77.3% (*)
BSID-II		
Cognitive Composite Score	2	10.4 (5.0; 20.5), I^2 = 13.5%
Motor Composite Score	2	10.4 (5.0; 20.5), I^2 = 13.5%
Language Composite Score	2	29.7 (20.0; 41.7), I^2 = 22.7% (*)
3 years		
BSID-I		
PDI	3	28.2 (19.3; 39.2), I^2 = 0% (*)
MDI	3	25.5 (17.1; 36.3), I^2 = 0% (*)
4-5 years		
WISC IQ	3	22.3 (12.1; 37.4), I^2 = 75.7%

BSID-I - Bayley Scales of Infant and Toddler Development version I; BSID-II - Bayley Scales of Infant and Toddler Development version II; PDI- Psychomotor Development Index; MDI- Mental Development Index; WISC- Wechsler Intelligence Scale for Children (WISC); IQ- intelligence quotient; N- number of studies. * Marks outcomes in which the proportion of children scoring less than 85 in studied population significantly differs from the proportion of children scoring less than 85 in the general population (16%).

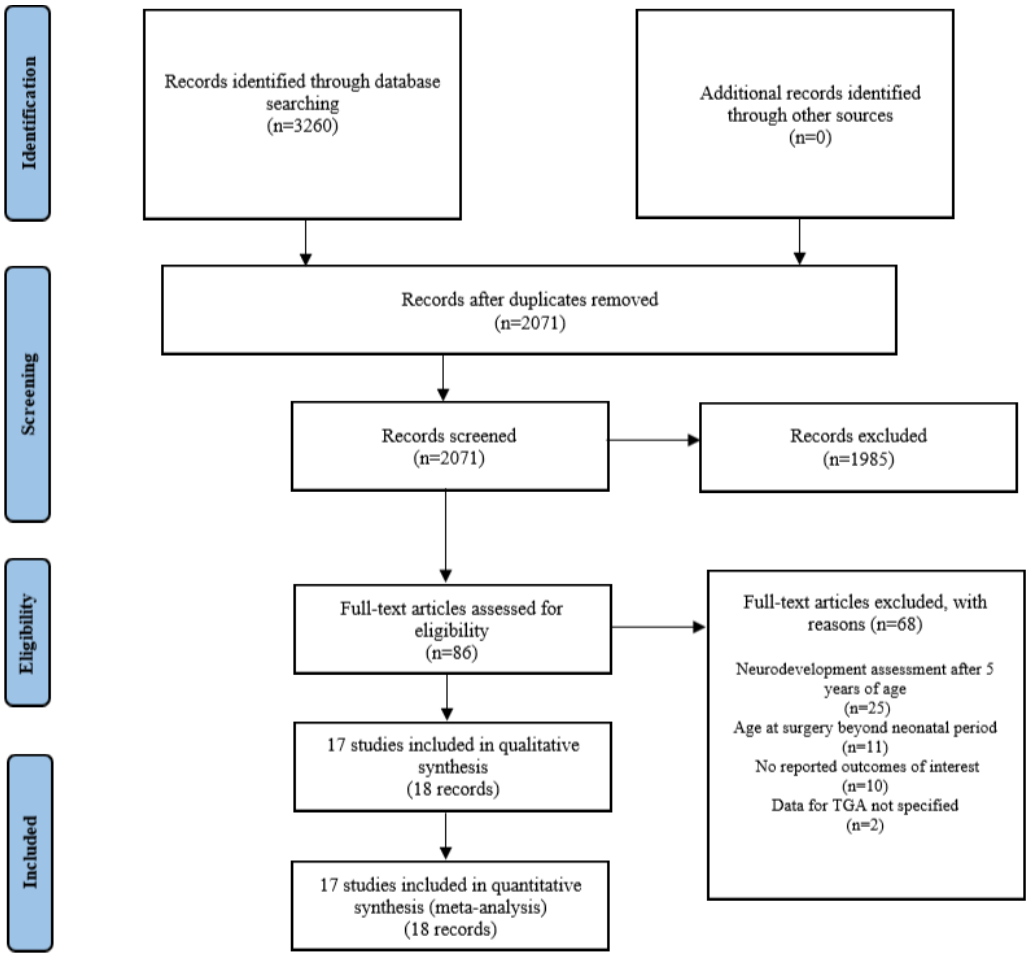


Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram illustrating the studies' selection process

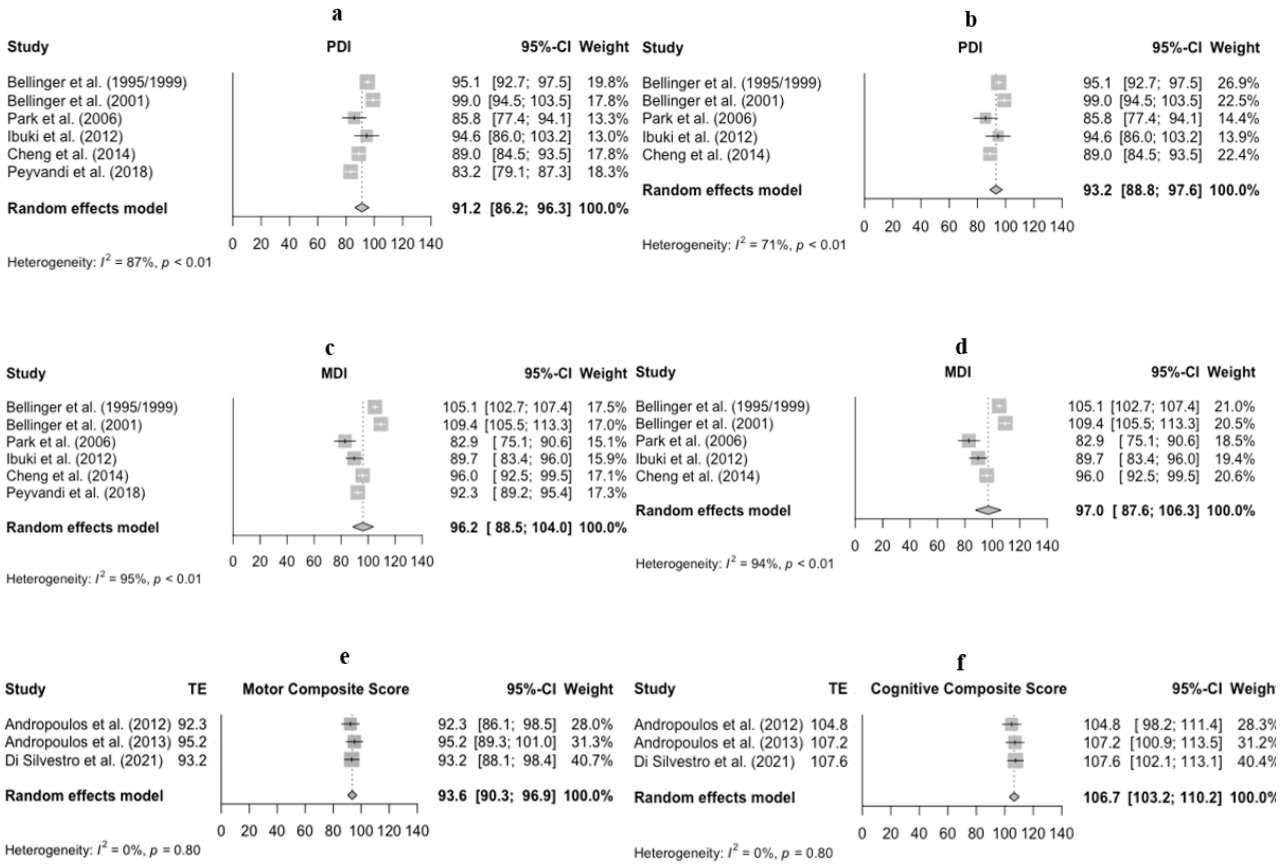


Fig. 2 Neurodevelopment assessment at 1 year of age with BSID-II and III: a- PDI score (BSID-II), b- PDI score for ASO patients only (BSID-II), c- MDI score (BSID-II), d- MDI score for ASO patients only (BSID-II), e- Motor Composite Score (BSID-III), f- Cognitive Composite Score (BSID-III)

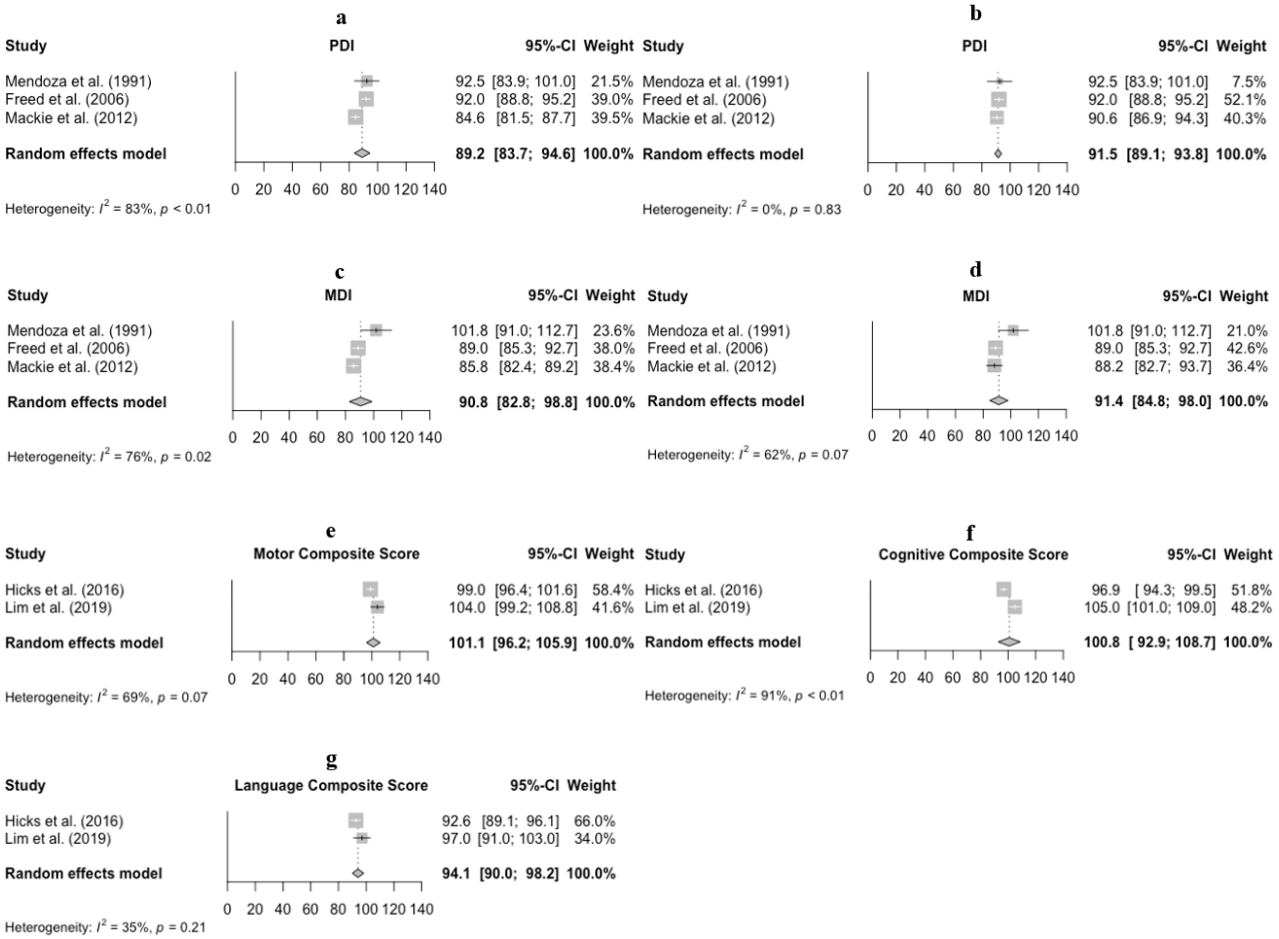


Fig. 3 Neurodevelopment assessment at 2 years of age with BSID-II and III: a- PDI score (BSID-II), b- PDI score for ASO patients only (BSID-II), c- MDI score (BSID-II), d- MDI score for ASO patients only (BSID-II), e- Motor Composite Score (BSID-III), f- Cognitive Composite Score (BSID-III), g- Language Composite Score (BSID-III)

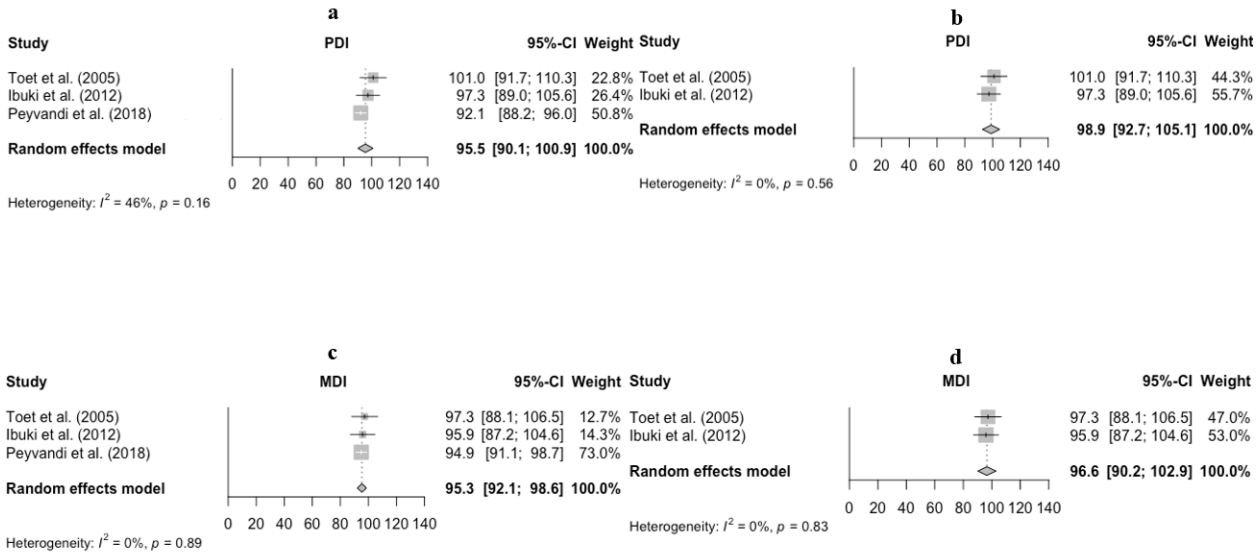


Fig. 4 Neurodevelopment assessment at 3 years of age with BSID-II: a- PDI score (BSID-II), b- PDI score for ASO patients only (BSI-D-II), c- MDI score (BSID-II), d- MDI score for ASO patients only (BSID-II)

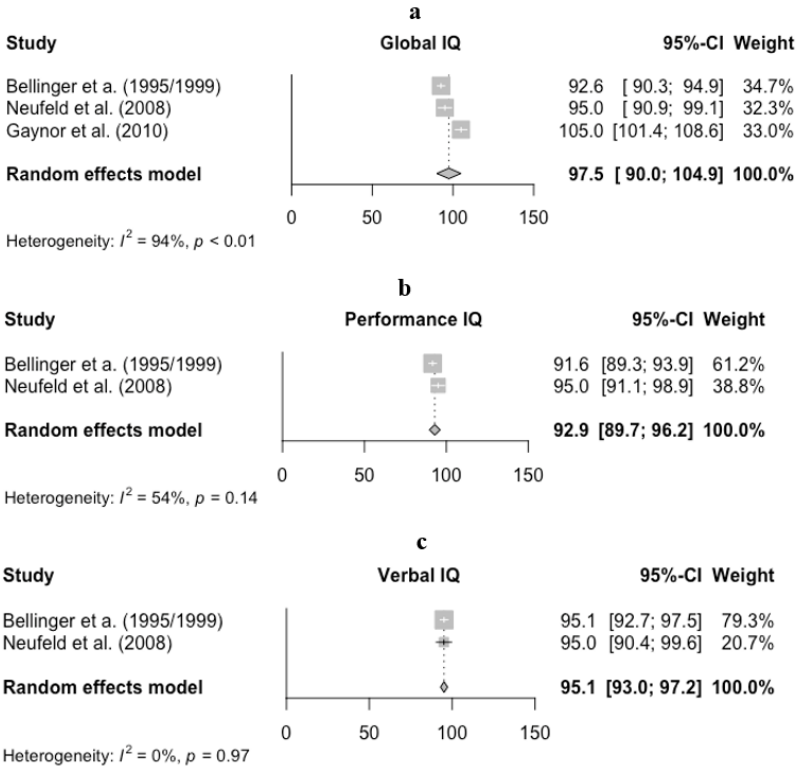


Fig. 5 Neurodevelopment assessment from 4 to 5 years of age with WISC: a- Global IQ score, b- Performance IQ score, c- Verbal IQ score

7. Supplementary Documents

Supplementary Table 1 Medline via OVID

Number	Query	Search results
#1	exp Transposition of Great Vessels/	8081
#2	(Complete and transpos* and "great arter*").mp.	943
#3	(complete adj3 (malposition or transposition) adj5 (arter* or vessel*)).mp.	688
#4	((D or dextro) adj1 transpos* adj5 arter*).mp.	805
#5	("TGA" or "TOGA" or "dextro?TGA" or "d?TGA").mp.	16406
#6	(arter* adj2 switch adj2 operation*).mp.	1650
#7	(arter* adj2 switch adj2 procedure*).mp.	231
#8	(Jatene adj2 procedure).mp.	41
#9	(transposition adj2 "great arter*").mp.	898
#10	(transposition adj2 "great vessel*").mp.	7495
#11	exp Child Development/	65128
#12	exp Neurodevelopmental Disorders/	199548
#13	(neurological adj3 (outcome or sequel*)).mp.	12742
#14	(neurodevelopment* disorder* or neurodevelopment* outcome* or neurodevelopment* disabilit*).mp.	22026
#15	neurodevelopment*.mp.	44544
#16	child* develop*.mp.	69373
#17	(neurocogniti* or neuropsych* or cogniti* or motor* or movement or psychomotor or intell*).mp.	1638112
#18	exp Neuropsychological Tests/	188946
#19	exp Psychomotor Performance/	119612
#20	(neurologic and (outcome* or examination*)).mp.	63545
#21	(developmental adj3 (outcome or sequel*)).mp.	1895
#22	developmental delay.mp.	14616
#23	(gross motor or fine motor or neuromotor).mp.	13150
#24	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	24438
#25	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23	1936462
#26	24 and 25	484

Supplementary Table 2 ISI Web of Science

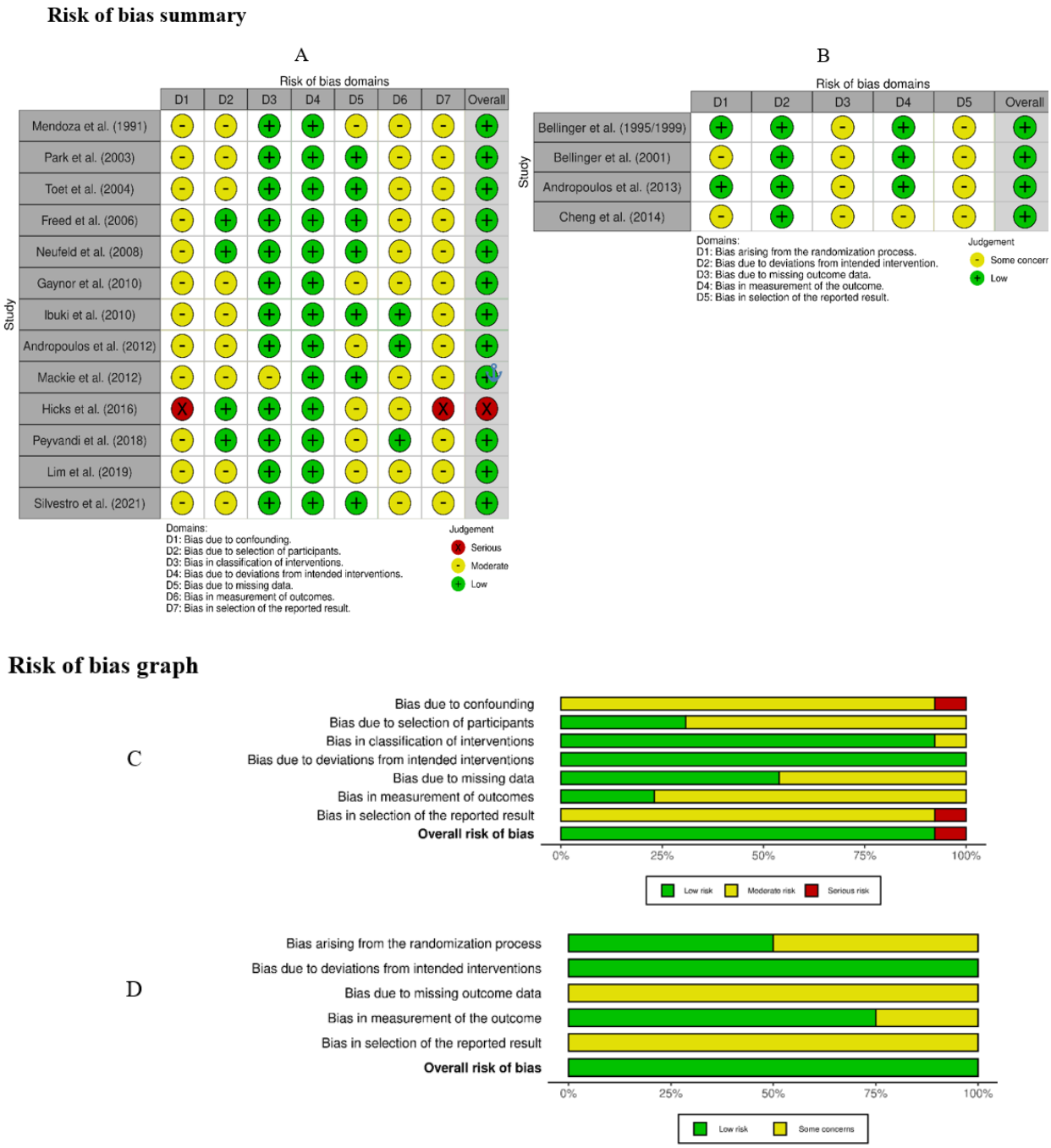
Number	Query	Search results
#1	(TS=(Complete AND transpos* AND "great arter*")) OR (TS= (complete NEAR/3 (malposition OR transposition) NEAR/5 (arter* OR vessel*))) OR (TS=(((D OR dextro) NEAR/1 transpos* NEAR/5 arter*))) OR (TS=(("TGA" OR "TOGA" OR "dextro$TGA" OR "d$TGA"))) OR (TS=((arter* NEAR/2 switch NEAR/2 operation*))) OR (TS=((arter* NEAR/2 switch NEAR/2 procedure*))) OR (TS=(Jatene NEAR/2 procedure)) OR (TS=(transposition NEAR/2 "great arter*")) OR (TS=(transposition NEAR/2 "great vessel*"))	94711
#2	(TS=(neurological NEAR/3 (outcome or sequel*))) OR (TS=(neurodevelopment* disorder* OR neurodevelopment* outcome* OR neurodevelopment* disabilit*)) OR (TS=neurodevelopment*) OR (TS=(child* develop*)) OR (TS=(neurocogniti* OR neuropsych* OR cogniti* OR motor* OR movement OR psychomotor OR intell*)) OR (TS=(neurologic AND (outcome* OR examination*))) OR (TS=(developmental NEAR/3 (outcome OR sequel*))) OR (TS=(developmental delay)) OR (TS=(gross motor or fine motor or neuromotor))	3136966
#3	#1 AND #2	997

Supplementary Table 3 Scopus

Number	Query	Search results
#1	((TITLE-ABS-KEY (complete AND transpos* AND "great arter*")) OR (TITLE-ABS-KEY (complete PRE/3 (malposition OR transposition) PRE/5 (arter* OR vessel*))) OR (TITLE-ABS-KEY (((d OR dextro) PRE/1 transpos* PRE/5 arter*))) OR (TITLE-ABS-KEY (("TGA" OR "TOGA" OR "dextro$TGA" OR "d$TGA"))) OR (TITLE-ABS-KEY ((arter* PRE/2 switch PRE/2 operation*))) OR (TITLE-ABS-KEY ((arter* PRE/2 switch PRE/2 procedure*))) OR (TITLE-ABS-KEY (jatene PRE/2 procedure)) OR (TITLE-ABS-KEY (transposition PRE/2 "great arter*")) OR (TITLE-ABS-KEY (transposition PRE/2 "great vessel*"))) AND ((TITLE-ABS-KEY (neurological PRE/3 (outcome OR sequel*))) OR (TITLE-ABS-KEY (neurodevelopment* AND disorder* OR neurodevelopment* AND outcome* OR neurodevelopment* AND disabilit*)) OR (title-abs-keyneurodevelopment*) OR (TITLE-ABS-KEY (child* AND develop*)) OR (TITLE-ABS-KEY (neurocogniti* OR neuropsych* OR cogniti* OR motor* OR movement OR psychomotor OR intell*)) OR (TITLE-ABS-KEY (neurologic AND (outcome* OR examination*))) OR (TITLE-ABS-KEY (developmental PRE/3 (outcome OR sequel*))) OR (TITLE-ABS-KEY (developmental AND delay)) OR (TITLE-ABS-KEY (gross AND motor OR fine AND motor OR neuromotor)))	1779

Supplementary Table 4 Reasons for study exclusion

Study	Reason to exclude
[1-25]	Neurodevelopment assessment beyond 5 years of age
[26-36]	Age at surgery beyond neonatal period
[37-46]	No neurodevelopment assessment No reported outcomes of interest
[47]	Fetal period
[48,49]	Data for TGA not specified



Supplementary Fig. 1 Risk of bias summary and risk of bias graph for included studies. A- Risk of bias summary of non-randomized studies; B- Risk of bias summary of randomized studies; C- Rick of bias graph of non-randomized studies; D- Risk of bias graph of randomized studies.

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8. Apêndices

a. Reporting Guidelines

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page and paragraph/ table #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both. **- MANDATÓRIO**	Sim. Página 6 "Neurodevelopment outcomes in the first five years of the life of children with Transposition of the Great Arteries surgically corrected in the neonatal period: a systematic review and meta-analysis."
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. **– SEGUIR RECOMENDAÇÕES DA REVISTA**	Sim. Página 7 "Congenital heart defects are the most common abnormalities at birth, resulting in many short and long-term consequences. In patients with Transposition of the Great Arteries (TGA), surgical correction may achieve definitive treatment, so a thorough knowledge of the long-term outcomes, particularly neurodevelopment outcomes, is essential. Therefore, we conducted a systematic review and meta-analysis to study the neurodevelopment outcomes in the first five years of the life of children submitted to corrective surgery for TGA in the neonatal period. A total of 18 reports from 17 studies were included in the systematic review, assessing 809 individuals with surgically corrected TGA. The neurodevelopmental outcomes were assessed with the Bayley Scales of Infant and Toddler Development (BSID) and the Wechsler Intelligence Scale for Children (WISC). Mean Mental Development Index (MDI) and Psychomotor Development Index

			(PDI) were within the average values from 1 to 3 years of age, and mean full-scale global IQ, verbal IQ and performance IQ scores, from four to five years, were within the reference range. This study revealed no major impairments in global neurodevelopment scores until five years of age in children submitted to corrective surgery for TGA in the neonatal period. Further studies are needed to identify specific risk factors and early markers of later impairment to guide the establishment of early interventions.”
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. **– MANDATÓRIO** ***O rationale corresponde à justificação da importância da revisão sistemática***	Sim. Página 9. Parágrafos 1 e 2 da introdução “Congenital heart defects (CHD) are the most common congenital abnormalities, affecting 6 to 8 per 1000 live births [1]. CHD are responsible for 3% of all infant deaths and for 46% of deaths from all congenital malformations [2]. Among CHD, transposition of the great arteries (TGA) accounts for approximately 5% of all congenital heart diseases, with an incidence of 1 in 2300 to 1 in 5000 live births[3,4].” “Surgical correction may achieve definitive treatment of TGA. The current gold standard is the arterial switch operation (ASO), first performed by Jatene in 1975[5-7]. Although surgical correction performed early in the neonatal period, ideally in the first two weeks of life [8], leads to improvements in the quality of life and development of newborns with TGA as well as reduced mortality rates [9-11]. However, neurodevelopment impairments in patients with TGA have been reported during childhood [12,13], as TGA has been associated with impairments in psychomotor, mental, learning, memory and language development, leading to social-cognitive and social-communication deficits [14-17]. A wide variety of factors have been associated with adverse neurodevelopment outcomes in patients with TGA, such as the presence of brain lesions detected

			by MRI before and/or after surgery[18-21], as well as the timing of surgery, the surgical technique and conditions: intraoperative hyperglycemia, hypothermic circulatory arrest versus low-flow cardiopulmonary bypass [22-24]."
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). **- MANDATÓRIO**	Sim. Página 9. Parágrafo 3 da introdução "Many studies have assessed the impact of surgical correction of TGA in the neonatal period on neurodevelopmental outcomes, but results are conflicting [25-27]. Additionally, although a systematic review on this matter has been previously published [28], this systematic review assessed a more selective population, showed some methodological limitations and was performed using a single database. Additionally, no quantitative synthesis was performed. As a result, we set off to perform a systematic review and meta-analysis on the neurodevelopment outcomes in the first five years of the life of children with TGA surgically corrected in the neonatal period."
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. **– FACULTATIVO**	Sim. Página 9. Parágrafo Métodos "This study is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines"
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. **– MANDATÓRIO** ***É altamente recomendado, de acordo com as boas práticas da Cochrane, que não***	Sim. Página 9 e 10. Parágrafos 2.1. , 2.2. "We conducted a systematic literature search in 3 electronic databases:

		sejam aplicados critérios de exclusão baseados na língua e/ou data de publicação dos estudos.	Medline via OVID, Scopus and Web of Science. The last search was performed in April 2022. We screened the reference list of included studies and relevant reviews for potentially eligible studies. We did not apply restrictions based on language or publication date. The search query for each database is available in Supplementary Tables 1,2 and 3." "We included all prospective studies assessing the neurodevelopmental outcomes (assessed through Bayley Scales of Infant and Toddler Development (BSID) and Wechsler Intelligence Scale for Children (WISC)), until five years of age, in children with TGA surgically corrected during the neonatal period. After eliminating duplicate results, two reviewers independently screened article titles and abstracts. Two reviewers independently read and analyzed the full texts of articles not excluded in the screening phase. Attempts were made to contact the authors of articles not accessible by other means. In any phase, disagreement between reviewers was solved by the decision of a third independent reviewer. All efforts were made to identify published articles assessing one same group of participants; in such cases, non-duplicate data (e.g. data on the outcome assessment at different periods in time) were

			retrieved from the articles.”
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. **– MANDATÓRIO** ***Em consonância com as boas práticas da Cochrane, é mandatório que se verifique pesquisa em pelo menos duas bases de pesquisa bibliográfica (idealmente, deverão ser pesquisadas duas bases generalistas e uma específica da área). No caso de revisões sistemáticas de estudos experimentais/ensaios clínicos aleatorizados, é altamente recomendado que uma das bases pesquisadas corresponda à CENTRAL ou a bases de ensaios clínicos como a ClinicalTrials.gov.*** ***Estudos de revisão da literatura em que a pesquisa decorra numa única base de dados não serão classificados como revisões sistemáticas.***	Sim. Página 9 e 10. Parágrafos 2.1. , 2.2. “We conducted a systematic literature search in 3 electronic databases: Medline via OVID, Scopus and Web of Science. The last search was performed in April 2022. We screened the reference list of included studies and relevant reviews for potentially eligible studies. We did not apply restrictions based on language or publication date. The search query for each database is available in Supplementary Tables 1,2 and 3. “We included all prospective studies assessing the neurodevelopmental outcomes (assessed through Bayley Scales of Infant and Toddler Development (BSID) and Wechsler Intelligence Scale for Children (WISC)), until five years of age, in children with TGA surgically corrected during the neonatal period. After eliminating duplicate results, two reviewers independently screened article titles and abstracts. Two reviewers independently read and analyzed the full texts of articles not excluded in the screening phase. Attempts were made to contact the authors of articles not accessible by other means. In any phase, disagreement between reviewers was solved by the decision of a third independent

			reviewer. All efforts were made to identify published articles assessing one same group of participants; in such cases, non-duplicate data (e.g. data on the outcome assessment at different periods in time) were retrieved from the articles."
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. **– MANDATÓRIO** ***A query de pesquisa deve ser obrigatoriamente disponibilizada. A utilização de filtros de pesquisa da InterTASC é altamente recomendada (https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/home)***	Sim. Página 9 e 10. Parágrafos 2.1. , 2.2. "The search query for each database is available in Supplementary Tables 1,2 and 3." As tabelas suplementares encontram-se nas páginas 29 e 30 nos documentos suplementares.
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). **– MANDATÓRIO** ***As fases de selecção dos estudos primários devem ser descritas. Em consonância com as boas práticas da Cochrane, é mandatório que o processo de selecção envolva duas fases (fase de rastreio, em que os registos são seleccionados por título e abstract, e fase de inclusão, na qual se procede à leitura integral dos full texts). Em cada uma destas fases, o processo de selecção deve mandatoriamente envolver dois investigadores actuando de forma independente.***	Sim. Página 10. Parágrafo 2.2. "After eliminating duplicate results, two reviewers independently screened article titles and abstracts. Two reviewers independently read and analyzed the full texts of articles not excluded in the screening phase. Attempts were made to contact the authors of articles not accessible by other means. In any phase, disagreement between reviewers was solved by the decision of a third independent reviewer. All efforts were made to identify published articles assessing one same group of participants; in such cases, non-duplicate data (e.g. data on the outcome assessment at different periods in time) were retrieved from the articles."

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. **– MANDATÓRIO** ***Trata-se de descrever de que forma se procedeu à extracção de dados dos estudos primários. Em consonância com as boas práticas da Cochrane, tal processo deverá envolver dois investigadores de forma independente.***	Sim. Página 10. Parágrafo 2.2. e 2.3. "After eliminating duplicate results, two reviewers independently screened article titles and abstracts. Two reviewers independently read and analyzed the full texts of articles not excluded in the screening phase. Attempts were made to contact the authors of articles not accessible by other means. In any phase, disagreement between reviewers was solved by the decision of a third independent reviewer. All efforts were made to identify published articles assessing one same group of participants; in such cases, non-duplicate data (e.g. data on the outcome assessment at different periods in time) were retrieved from the articles." "We collected the following information, whenever available: (1) study characteristics – year of publication, study design, setting (number of centers and countries involved in the study), inclusion and exclusion criteria, sampling method, method of randomization (if adequate), and follow-up duration; (2) participant number (total and per group) and characteristics, including demographic data (gestational age and sex), data before surgery (gestational age, birth weight), surgical information (age at surgery, type of procedure, duration of deep hypothermic circulatory arrest and total bypass time), data after

			surgery (duration of hospital stay); (3) neurodevelopment outcomes - cognitive, gross and/or fine motor, speech, language and behaviour outcomes and time of assessment. Regarding neurodevelopment outcomes, we extracted mean scores and standard deviations (SD), as well as the proportion of children whose score was more than one SD below the normative mean; when data on proportions were not available, we modelled a normal distribution using the reported mean and standard deviation to estimate the number of children whose score was below one SD from the normative mean. In some cases, times at which neurodevelopment was assessed were clustered; namely, assessments performed at the age of 1.5 years, 2.5 years, 3.5 years and 4.5 years were considered along with those performed at the age of 2, 3, 4, and 5 years, respectively. When results were reported separately by subgroups, and no aggregate data could be obtained from the authors, data from different groups were combined as recommended by Cochrane [30]. Data were independently collected by two reviewers into a prespecified form. When data were only available in graphic form, and no additional information was obtained from the authors, Plot Digitizer 2.6.9 was used to estimate raw data, as previously done in other

			systematic reviews [31-33].”
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. **– MANDATÓRIO** ***Trata-se de descrever as variáveis para as quais foi obtida informação.***	Sim. Página 10. Parágrafo 2.3. “We collected the following information, whenever available: (1) study characteristics – year of publication, study design, setting (number of centers and countries involved in the study), inclusion and exclusion criteria, sampling method, method of randomization (if adequate), and follow-up duration; (2) participant number (total and per group) and characteristics, including demographic data (gestational age and sex), data before surgery (gestational age, birth weight), surgical information (age at surgery, type of procedure, duration of deep hypothermic circulatory arrest and total bypass time), data after surgery (duration of hospital stay); (3) neurodevelopment outcomes - cognitive, gross and/or fine motor, speech, language and behaviour outcomes and time of assessment. Regarding neurodevelopment outcomes, we extracted mean scores and standard deviations (SD), as well as the proportion of children whose score was more than one SD below the normative mean; when data on proportions were not available, we modelled a normal distribution using the reported mean and standard deviation to estimate the number of children whose score was below one SD from the

			normative mean. In some cases, times at which neurodevelopment was assessed were clustered; namely, assessments performed at the age of 1.5 years, 2.5 years, 3.5 years and 4.5 years were considered along with those performed at the age of 2, 3, 4, and 5 years, respectively. When results were reported separately by subgroups, and no aggregate data could be obtained from the authors, data from different groups were combined as recommended by Cochrane [30]. Data were independently collected by two reviewers into a prespecified form. When data were only available in graphic form, and no additional information was obtained from the authors, Plot Digitizer 2.6.9 was used to estimate raw data, as previously done in other systematic reviews [31-33]."
Risk of bias in individual studies / Risk of bias across studies	12/ 15	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 this information is to be used in any data synthesis. **– MANDATÓRIO** ***Em todas as revisões sistemáticas, deverá existir um processo de avaliação da qualidade dos estudos primários. No caso de revisões sistemáticas de estudos experimentais/ensaios clínicos aleatorizados, a aplicação dos critérios de risco de viés (Risk of Bias) da Cochrane é altamente recomendada. No caso de revisões sistemáticas de estudos observacionais, poderão ser seguidos os critérios ROBINS ou os critérios dos National Institutes of Health (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools).***	Sim. Página 10. Parágrafo 2.4. "Two reviewers independently performed quality assessment of the included articles using Cochrane's RoB 2 Tool for randomized control trials [34] and Cochrane's ROBINS-I Tool for nonrandomized studies [35]."
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). **–**	Sim. Página 11. Parágrafo

		FACULTATIVO. APENAS NECESSÁRIO SE FOR FEITA META-ANÁLISE	2.5. "We performed random effects meta-analyses weighted by the inverse variance (using the method of DerSimonian and Laird [36]). For each outcome and time point, weighted averages were calculated with the respective 95% confidence intervals (95% CI). Heterogeneity was evaluated using I^2 and Cochran *Q* statistics — an $I^2 > 50\%$ and a Cochran *Q* test *p* value < 0.10 were considered to represent severe and significant heterogeneity, respectively. In the presence of significant/severe heterogeneity, subgroup analyses based on clinical criteria were planned to be performed. All statistical analyses were performed using the meta package for R [37]."
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. **– FACULTATIVO. APENAS NECESSÁRIO SE FOR FEITA META-ANÁLISE**	Sim. Página 11. Parágrafo 2.5. "We performed random effects meta-analyses weighted by the inverse variance (using the method of DerSimonian and Laird [36]). For each outcome and time point, weighted averages were calculated with the respective 95% confidence intervals (95% CI). Heterogeneity was evaluated using I^2 and Cochran *Q* statistics — an $I^2 > 50\%$ and a Cochran *Q* test *p* value < 0.10 were considered to represent severe and significant heterogeneity, respectively. In the presence of significant/severe heterogeneity, subgroup analyses based on clinical criteria were planned to be performed. All statistical analyses were performed using the meta package for R [37]."
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. **– FACULTATIVO. APLICÁVEL**	Sim. Página 11 parágrafo 2.5. "In the presence of significant/severe heterogeneity,

		APENAS SE FOR FEITA META-ANÁLISE	subgroup analyses based on clinical criteria were planned to be performed." Páginas 12-14 Parágrafos 3.4.1, 3.4.2, 3.4.3. "…which was reduced by performing subgroup analysis on those studies [14,26] including only patients (total of 30 patients) submitted to ASO…"
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. **– MANDATÓRIO**	Sim. Página 11-Parágrafo 3.1. Página 24-Figura 1 "Our search in electronic bibliographic databases returned a total of 3260 results (Figure 1). After duplicate removal and selection by title and abstract screening, we obtained 86 articles. 68 reports were excluded after full-text reading. A list of reports excluded, with reasons, can be found in Supplementary Table 4. Overall, 18 reports from 17 studies were included in our systematic review [8,14-18,24-26,38-46]."
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. **– MANDATÓRIO**	Sim. Página 12-Parágrafo 3.3. Página 20 e 21- tabela 1. "The demographic characteristics of included studies are depicted in table 1. The included studies were published from 1983 to 2020, assessing populations mainly from North America and Europe as well as South Korea and Japan. The included publications assessed a total of 809 individuals with TGA…"
Risk of bias within and across studies	19/ 22	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). **– MANDATÓRIO**	Sim. Página 11- Parágrafo 3.2. Página 31-figura suplementar 1. "Risk of bias summaries are shown in Supplementary Figure 1.

			Nonrandomized studies (n=13) had an overall moderate risk of bias [8,14-18,25,26,40-43,46], except for one study with serious risk of bias [41]. Confounding and selection of the reported results were the main cause of bias. Confounding was mainly due to the multiple factors assessed in the different studies, making it difficult to establish an association between corrective TGA surgery in the neonatal period and neurodevelopment. Nevertheless, all known important confounding domains were appropriately measured and controlled for, except for one study [41] where the reliability of the measurement of important domains was low enough, potentially allowing for residual confounding. Regarding the selection of the reported results, in the majority of the studies, the outcome measurements and analyses were consistent with an *a priori* plan, except for one study[41] where assessment by a speech-language pathologist was not possible at all sites, which may affect the outcome. Risk of bias was low mainly in the classification of the interventions and deviations from intended interventions. For randomized controlled trials (n=5) [24,38,39,44,45], we found some concerns mainly due to missing outcome data and to selection of reported results. Outcome data were only available

			for some, or nearly all, randomized participants. Therefore, there is a risk of bias due to missing outcome data, primarily due to losses to follow-up.”
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. **– FACULTATIVO. APLICÁVEL APENAS SE FOR FEITA META-ANÁLISE**	Sim. Páginas 12 a 14- Parágrafos 3.4.1. a 3.4.4. Páginas 25 a 28- figuras 2 a 5 “Overall, nine studies [14,17,18,24,25,38-40,44] assessed neurodevelopment outcomes at one year of age, including a total of 390 children. The BSID-II and III were used to assess neurodevelopment in included studies at one year of age (Figure 2).” “The estimated mean Psychomotor Development Index (PDI) was 91.2 (95% CI 86.2-96.3), albeit with important heterogeneity (I_2=87%, $p < 0.01$). Similar results, with high heterogeneity, were also found when we restricted the meta-analysis to studies in which all patients (total of 382) had been submitted to the arterial switch operation (ASO) [14,17,24,38,44] (mean PDI = 93.2 [95% CI 88.8-97.6], I_2=71% [$p < 0.01$]).”
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency. **– FACULTATIVO. MANDATÓRIO APENAS SE FOR FEITA META-ANÁLISE**	Sim. Páginas 12 a 14- Parágrafos 3.4.1. a 3.4.4. Páginas 25 a 28- figuras 2 a 5 “Overall, nine studies [14,17,18,24,25,38-40,44] assessed neurodevelopment outcomes at one year of age, including a total of 390 children. The BSID-II and III were used to assess neurodevelopment in included studies at one year of age (Figure 2).” “The estimated mean Psychomotor Development Index (PDI) was 91.2 (95% CI 86.2-96.3), albeit with important heterogeneity (I_2=87%, $p < 0.01$). Similar results, with high heterogeneity, were also found when we restricted the meta-analysis to studies in which all patients (total of 382) had been submitted to the arterial switch operation (ASO) [14,17,24,38,44] (mean PDI = 93.2 [95% CI 88.8-97.6], I_2=71% [$p < 0.01$]).”
Additional	23	Give results of additional analyses, if done	Sim. Página 11 parágrafo

analysis		(e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). **– FACULTATIVO. APLICÁVEL APENAS SE FOR FEITA META-ANÁLISE**	2.5. "In the presence of significant/severe heterogeneity, subgroup analyses based on clinical criteria were planned to be performed.". Páginas 12-14 Parágrafos 3.4.1, 3.4.2, 3.4.3. "…which was reduced by performing subgroup analysis on those studies [14,26] including only patients (total of 30 patients) submitted to ASO…"
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). **– MANDATÓRIO**	Sim. Página 14 a 16- Parágrafo 4. "In our study, a meta-analysis of 809 patients with surgically corrected TGA during the neonatal period, we show that these patients do not display significant impairments in mean neurodevelopment scores in the first five years of life. Indeed, cognitive, motor and language scores were within average values, although, except for the latter, heterogeneity was found to be significant. Overall, MDI and PDI were within the average values (mean between 90-109) [47] from 1 to 3 years of age. However, from 1 to 3 years of age, the proportion of children scoring less than 85 in studied population in scores as PDI, MDI, motor and language composite scores was significantly higher than in the general population. From 4 to 5 years, full-scale global, verbal, and performance IQ scores were within the reference range and the percentage of children scoring more than one SD below the normative

			mean did not significantly differ from the general population. These results suggest that TGA surgically corrected in the neonatal period does not seem to significantly impact early neurodevelopment components, namely cognitive, motor and language development scores. However, it is important to notice that even if these scores are within the reference range, they may be in the low end of this interval, particularly until 3 years of age, which may still impact on the neurodevelopment of these children and have implications to their follow-up. Heterogeneity was high for most of our meta-analytical results, which may be partially due to the heterogeneous designs of the studies included in this systematic review. Importantly, in an attempt to reduce heterogeneity, we performed subgroup analyses, including only those studies in which all the patients with TGA had been submitted to ASO. However, except for neurodevelopment outcomes at three years of age, heterogeneity remained high."
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). **– MANDATÓRIO**	Sim. Página 16. "This study has some limitations, mostly due to the characteristics of the primary studies included in this systematic review. Heterogeneity between studies was substantial, including in their designs and characteristics of assessed populations. As previously

			mentioned, some studies assessed the association between brain lesions and neurodevelopment [18], while others assessed the impact of surgical conditions, such as hypoxia [14,26,38,40], pH [44] and support strategies [24,39,45]. However, we were unable to perform a meta-analysis comparing these variables, as they were not consistently reported across studies. It should be highlighted that not all the components of children neurodevelopment were assessed in this systematic review, such as visual-motor integration, executive functions, preacademic skills, adaptive skills, and social, emotional and behavioural functioning, due to heterogeneity in reported outcomes in the included studies. However, we aimed to assess crucial and global neurodevelopment components such as mental, psychomotor, performance, language and verbal components. Furthermore, while most of the studies assessed all different components of neurodevelopment [8,15,16,25,42,43], one only assessed language development [41]. Additionally, some of the included studies assessed a small sample [14,17,25] and, for some studies, the surgical approach was not reported [18,39,42]. Furthermore, most studies did not directly report on the proportion of children scoring more than one SD

			from the normative mean, so we estimated this proportion assuming a normal distribution of the scores with the reported mean and SD. Despite this, some strengths can be pointed out. We attempted to maximize study inclusion by performing a thorough search of the literature in three different databases, with no language or date restrictions, checking the reference lists of included studies and relevant reviews, and contacting authors when data needed to be clarified. Additionally, overall included studies did not show a high risk of bias. Finally, this is the first meta-analysis to attempt to aggregate the results from several studies to estimate the proportion of children scoring more than one SD below the normative mean."
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research. – **MANDATÓRIO**	Sim. Página 16. Parágrafo 5. "This systematic review and meta-analysis provides an overview of neurodevelopment outcomes up to five years of age in patients with TGA surgically corrected during the neonatal period. Overall, from one to five years of age, cognitive, motor and language scores were within average value, although from 1 to 3 years of age the proportion of children scoring less than one SD from the normative mean significantly differed from the general population. However, heterogeneity between studies was high limiting the evaluation of other

			specific components of the neurodevelopment. Additionally, these early outcomes may not adequately predict long-term outcomes. Further well-designed studies are needed to gather more consistent evidence of risk factors for neurodevelopment outcomes and early markers of later impairment to guide the establishment of early interventions."
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. **– SEGUIR RECOMENDAÇÕES DA REVISTA**	Não.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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- Book chapter

Brown B, Aaron M (2001) The politics of nature. In: Smith J (ed) The rise of modern genomics, 3rd edn. Wiley, New York, pp 230-257

- Online document

Cartwright J (2007) Big stars have weather too. IOP Publishing PhysicsWeb. http://physicsweb.org/articles/news/11/6/16/1. Accessed 26 June 2007

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• This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of University B (Date.../No. ...).

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• The questionnaire and methodology for this study was approved by the Human Research Ethics committee of the University of D (Ethics approval number: ...).

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Summary of requirements

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Written informed consent was obtained from the parents.

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The authors affirm that human research participants provided informed consent for publication of the images in Figure(s) 1a, 1b and 1c.

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