

Cognitive, Motoric, and Linguistic Impairment in Children Born at Term in Association with Fetal Growth Restriction and Small for Gestational Age: A Systematic Review and Meta-analysis

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Received on: 22 April 2024; Accepted on: 21 June 2024; Published on: 19 November 2024

ABSTRACT

Aims and background: Fetal growth restriction (FGR) poses a risk for neurodevelopmental impairment in the fetus. Hence, a literature review is essential to understand the correlation between cognitive, motoric, and linguistic impairments in term-born children who are appropriate for gestational age (AGA), particularly concerning FGR and small for gestational age (SGA) conditions.

Materials and methods: Studies were reviewed through medical databases: PubMed, Science Direct, Google Scholar, and Research Gate. The keywords used were FGR and cognitive and motoric and language following Boolean operator rules. The written study was analyzed and synthesized through qualitative and quantitative approaches. The study quality was analyzed for presence of bias; non-randomized studies were evaluated and scored using the methodological index for non-randomized studies (MINORS).

Results: There were 5 studies with a total sample of 550. Fetal growth restriction are significant influencing impairment in cognitive [MD -0.37 (-0.55, -0.18); 95% CI; $z = 3.91$; $p < 0.0001$], motoric [MD -3.53 (-4.63, -2.43); $z = 6.29$; $p < 0.00001$], linguistic [MD -8.02 (-14.77, -1.26); 95% CI; $z = 2.32$; $p = 0.02$] compared with AGA. Overall, the included non-randomized studies had an average MINORS score of 18–22.

Conclusion: Children born at term with FGR exhibited significant impairments in cognitive, motoric, and linguistic development compared with children born with AGA.

Clinical significance: Development impairment in cognitive, motoric and linguistic are found to be significant in children born at term.

Keywords: Fetal growth restriction, Small for gestational age, Motoric impairment cognitive impairment, Linguistic impairment.

Journal of South Asian Federation of Obstetrics and Gynaecology (2024): 10.5005/jp-journals-10006-2529

INTRODUCTION

Fetal growth restriction (FGR) is a condition determined when the result of estimated fetal weight (EFW) is below the 10th percentile which can cause multiple complications and one of the most severe cases are stillbirth.^{1,2} Pregnancy cases with FGR is identified with 3–7%.³ With the most common occurrence affected infants in Asia, as the make up to 75% total from all cases.³ The frequency of occurrences differs based on factors such as the population under study, fetus gestational age and the occurrence for small for gestational age (SGA) are take into consideration.⁴ In cases of children with FGR there is known to have multiple long-term complications, whether it's reproductive problems, cardiovascular related diseases, hypertension, insulin impaired resistance, and impairment of cognitive skill and other neurodevelopmental problems.⁵ It is important to keep an eye on cognitive and psychomotor development and refer for an early intervention when necessary.⁵ In this study aims to investigate neurodevelopmental impairment in term-born children with FGR and those born SGA in comparison to children who were born AGA. Specifically, it focuses on cognitive, motor, and linguistic abilities.

MATERIALS AND METHODS

Search Strategy

On February 28, 2024, a systematic review was reviewed through medical databases: PubMed, Science Direct, Google Scholar, and Research Gate. The focus was on exploring the association between FGR and neurodevelopmental impairment, specifically in terms of

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How to cite this article: Simanjuntak TP, Punia IMDAM, Vighneshwara D. Cognitive, Motoric, and Linguistic Impairment in Children Born at Term in Association with Fetal Growth Restriction and Small for Gestational Age: A Systematic Review and Meta-analysis. *J South Asian Feder Obst Gynae* 2024;16(6):756–760.

Source of support: Nil

Conflict of interest: None

cognitive, motoric, and language abilities. This investigation utilized MeSH keywords as outlined in Table 1. The search for articles was not limited by a specific time frame, but it excluded inaccessible research articles. Any disagreements are discussed to reach an agreement (Fig. 1).

Eligibility Criteria

In this study the following criteria are needed to be able to be employed for analysis in our systematic reviews meta-analysis: (1) The journal types are either cohort study designs, case report articles or case series article that study the relation between FGR and impairment in neurodevelopment in cognitive, motoric, and

Table 1: Keywords of this systematic review

| Databases | Keywords | Hits |
|----------------|---|------|
| PubMed | FGR OR Intrauterine Growth Restriction OR Fetal Growth Restriction AND Cognitive AND Language AND Motoric | 14 |
| Science Direct | FGR OR Intrauterine Growth Restriction OR Fetal Growth Restriction AND Cognitive AND Language AND Motoric | 23 |
| Research Gate | FGR OR Intrauterine Growth Restriction OR Fetal Growth Restriction AND Cognitive AND Language AND Motoric | 2 |
| Google Scholar | FGR OR Intrauterine Growth Restriction OR Fetal Growth Restriction AND Cognitive AND Language AND Motoric | 979 |

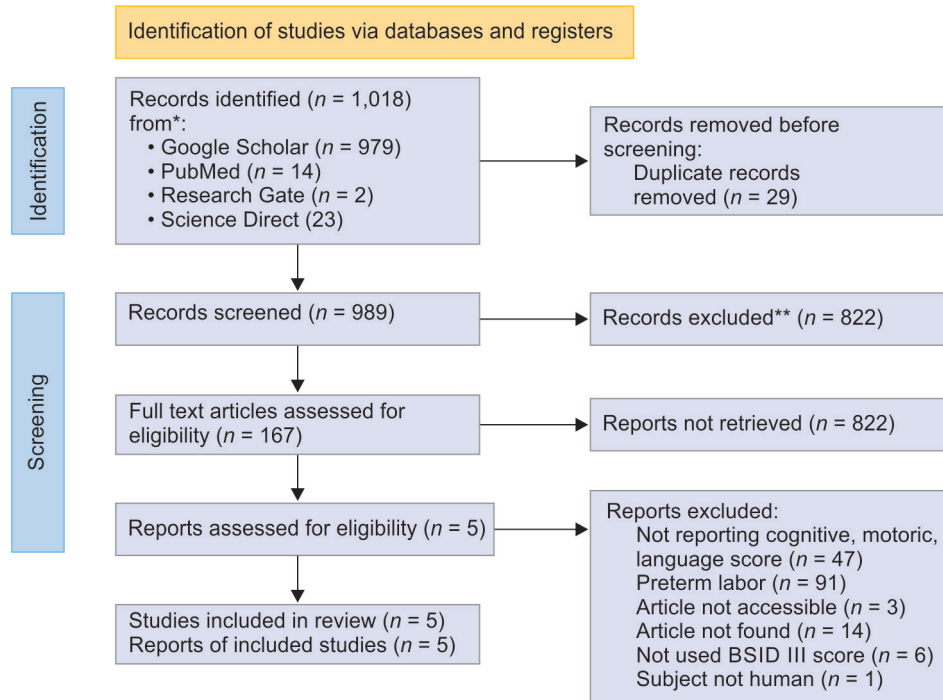


Fig. 1: PRISMA flow

linguistic skills. (2) Journals contains subjects at term (>37 weeks). (3) Assessing the impairment of cognitive, motoric and linguistic problems in FGR children. (4) Journals that are accessible to the open public. Exclusion criteria for this study composed of (1) Narrative articles and Reviews. (2) Journals related and using non-human subject. (3) Articles and Journals not written in English.

After eliminating duplicate sources using EndNote 20 software, the identified articles underwent screening of titles and abstracts by the research team, aligning with the inclusion and exclusion criteria. Subsequent to the initial screening, the researcher proceeded to conduct a full-text assessment and extract pertinent data from the chosen articles.

Data Extraction and Quality Assessment

The data that are taken from other studies include: (1) Authors of Journals or Articles, (2) Years of the publications, (3) Location or area of the study, (4) Types of design of studies, (5) Neonates with FGR, (6) Measurement of the effect of neurodevelopment, (7) Outcomes of cognitive impairment in children, (8) Motoric skills in children, (9) Developmental of linguistic abilities in children.

After extraction of the data above, an analysis in undergo using meta-analysis and proportion test. This process involved for calculation of the confidence interval (CI) and if the result of $p < 0.05$ could be considered a significant result of association between FGR and the neurodevelopmental problems in the sector of cognitive, motoric, and linguistic.

Preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines are used in our current research study to ensure the qualities of the result of this systematic reviews and meta-analysis. For assessing the quality of our source article albeit case series or case report, we employed Methodological Quality and Synthesis of Case Series and Case Reports Quality Scales to ensure the quality of our study.

Assessment of Bias

In our current research, we are employing the methodological index for non-randomized studies (MINORS) risk of bias instrument as a critical tool for evaluating the quality of non-randomized studies. This instrument allows us to systematically assess various methodological aspects, including the study’s design, controls, and the appropriateness of statistical analyses, among others. By utilizing the MINORS instrument, we aim to ensure proper reliability in our assessment of non-randomized studies, therefore enhancing the validity of our research findings. This meticulous approach enables us to identify potential biases and limitations within the included studies, ultimately strengthening the overall integrity and credibility of our research outcomes.

Statistical Analysis

Meta-analysis was performed using Review Manager 5.4 software (Cochrane Collaboration, Oxford, UK). The outcomes of data processing were visually represented through forest plot graphics.

Table 2: Characteristic of studies

| Study | Design study | Characteristic | Sample | | Outcome assessment | |
|--------------------------------|--------------|--|--------|-------------|--------------------|-----------|
| | | | SGA | AGA/Control | Measure | Age (yrs) |
| Castro JR et al. ⁶ | Cohort | SGA babies were confirmed by presenting a birthweight <10th percentile. GA >37 weeks | 51 | 67 | BSID-III | 2 |
| Batalle D et al. ⁷ | Cohort | IUGR: EFW below 10th percentile. GA: EFW between the 10th and 90th percentile | 42 | 41 | BSID-III | 1.75 |
| Simões RV et al. ⁸ | Cohort | Birthweight above or below the 10th percentile | 40 | 30 | BSID-III | 1.9 |
| Mazarico E et al. ⁹ | Case control | Non-IUGR: EFW and birth weight between 10th and 90th percentile. IUGR: birth weight <10th percentile | 31 | 25 | BSID-III | 2 |
| Savchev S et al. ¹⁰ | Cohort | SGA confirmed birth weight < 10th percentile. GA: 10th and 90th percentiles | 112 | 111 | BSID-III | 2 |

AGA, appropriate for gestational age; BSID-III, Bayley scale for infant development; EFW, estimated fetal weight; PI, pulsatility index; SGA, small for gestational age

To assess the degree of heterogeneity between studies, statistical analysis was utilized. Statistical heterogeneity was calculated using the I^2 method (<25% was considered low heterogeneity, 25–50% moderate heterogeneity, and >50% high heterogeneity). If high heterogeneity is found in the meta-analysis, additional analysis will be conducted using a random effect model. Study heterogeneity of $I^2 > 50%$ was considered significant. $p < 0.05$ was considered statistically significant.

RESULTS

We scanned a total of 1,018 articles retrieved from four databases, comprising 14 articles from PubMed, 23 from Science Direct, 2 from Research Gate, and 979 from Google Scholar. The selection of journals followed the PRISMA methodology and was guided by the predefined inclusion criteria (Fig. 1; PRISMA flow diagram, Supplementary).

After checking for duplicate articles, it was found that there were 29 duplicates. Subsequently, out of the remaining 989 articles, Relevance for titles and abstracts were screened with the result out of 982 articles, 822 were excluded for the various following reasons:¹ About 763 Journals and article were founded to not report any FGR and impairment in cognitive motoric or linguistic sector.² And 50 Journals were neither articles nor literature and,³ 9 articles were not written and published in English.

The subsequent phase entailed meticulous screening, evaluation, and discerning selection from a pool of 167 full-text journals. Out of this comprehensive review, 162 journals were excluded due to various reasons:¹ About 91 focused on preterm populations, three were inaccessible,² 47 lacked assessments of motoric and linguistic abilities,³ 6 did not incorporate the BSID-III score,⁴ 14 proved untraceable, and⁵ 1 involved non-human subjects. Ultimately, five journals that impeccably fulfilled all inclusion criteria were incorporated into this systematic review. Consequently, these same five journals constituted the definitive selection for inclusion in the subsequent meta-analysis.

By the end of screening and evaluation process, we found five articles and journals that match our inclusion criteria and were selected to be included in our research. These journals are the final selection in our study of systematic review and meta-analysis.

According to the findings presented in Table 2, which includes the five selected articles, Castro Conde JRC et al.,⁶ Simões RV et al.,⁸ Batalle et al.,⁷ and Savchev S et al.¹⁰ reported a significant cognitive

impairment between FGR and SGA. However, Mazaricco et al.⁹ found cognitive impairment present but not statistically significant.

For motoric results based on research by Batalle et al.⁷ and Savchev S et al.¹⁰ reported there's a significant motoric impairment between FGR and SGA. Based on Castro Conde JRC et al.⁶ research found that SGA full-term neonates showed high rates of immature EEG patterns. Low birthweight and immaturity EEG both correlated with low development scores.⁶ Simões RV et al.⁸ and Mazaricco et al.⁹ show no significant relation with motoric impairment.

Regarding linguistic outcomes, Simões et al.⁸ and Batalle et al.⁷ reported significant linguistic impairment. However, Savchev S et al.¹⁰ found lower scores in FGR and SGA children compared with AGA children, though not statistically significant. Castro Conde et al.⁶ indicated that SGA children tended to exhibit a poorer understanding of language. In contrast, Mazaricco et al.⁹ found no significant relation with linguistic impairment. Overall, the included non-randomized studies had an average MINORS score of 18–22 (Fig. 2).

There were five studies comparing cognitive outcomes in the SGA/FGR group with the AGA group. There was a statistically significant association [MD -0.37 (-0.55, -0.18); 95% CI; $Z = 3.91$; $p < 0.0001$]. Children with SGA/FGR had more cognitive impairment than children with AGA. Furthermore, homogeneous data were obtained ($I^2 = 0%$; $p = 0.56$) (Fig. 3).

There were five studies comparing motoric outcomes in the SGA/FGR group with the AGA group. There was a statistically significant association [MD -3.53 (-4.63, -2.43); $Z = 6.29$; $p < 0.00001$]. Children with SGA/FGR had more motoric impairment than children with AGA. Furthermore, heterogeneous data were obtained ($I^2 = 92%$; $p < 0.00001$) (Fig. 4).

There were five studies comparing linguistic outcomes in the SGA/FGR group with the AGA group. There was a statistically significant association [MD -8.02 (-14.77, -1.26); $Z = 2.32$; $p = 0.02$]. Children with SGA/FGR had more motoric impairment than children with AGA. Furthermore, heterogeneous data were obtained ($I^2 = 91%$; $p < 0.00001$).

DISCUSSION

Fetal growth restriction, which is a pathological is linked to notable neonatal health challenges and a higher risk of mortality.¹¹ Additionally, structural and morphology of the brain are believed to be altered in children with FGR.¹² Moreover, it is thought to affect the development of brain in matters of morphology and structural as well.¹² Children born with SGA tend to exhibit lower scores in

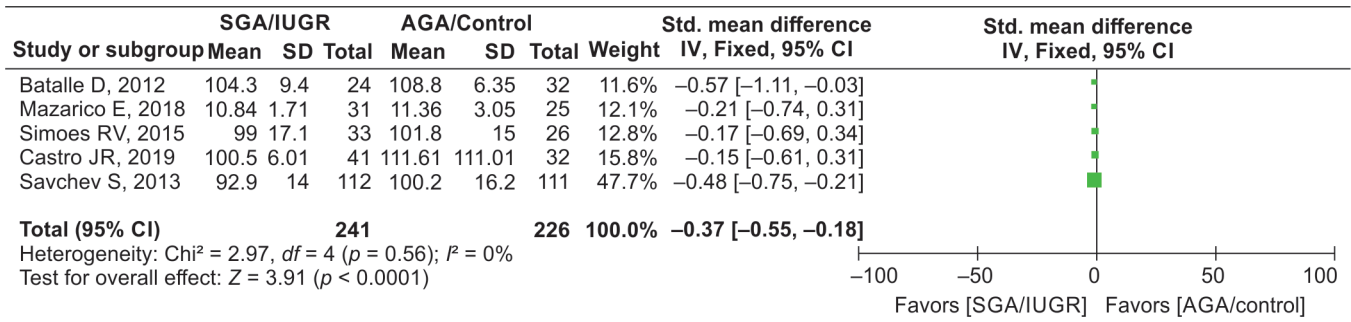


Fig. 2: Meta-analysis of cognitive comparison in SGA group with AGA group

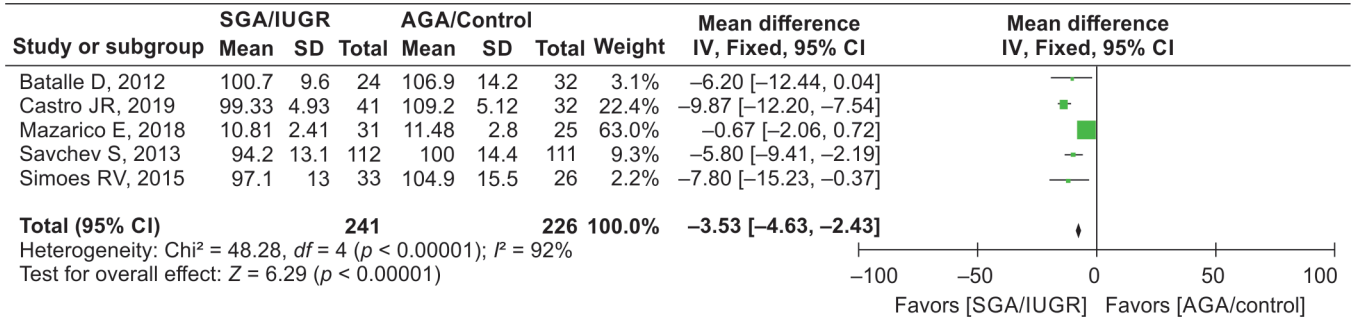


Fig. 3: Meta-analysis of motoric comparison in SGA group with AGA group

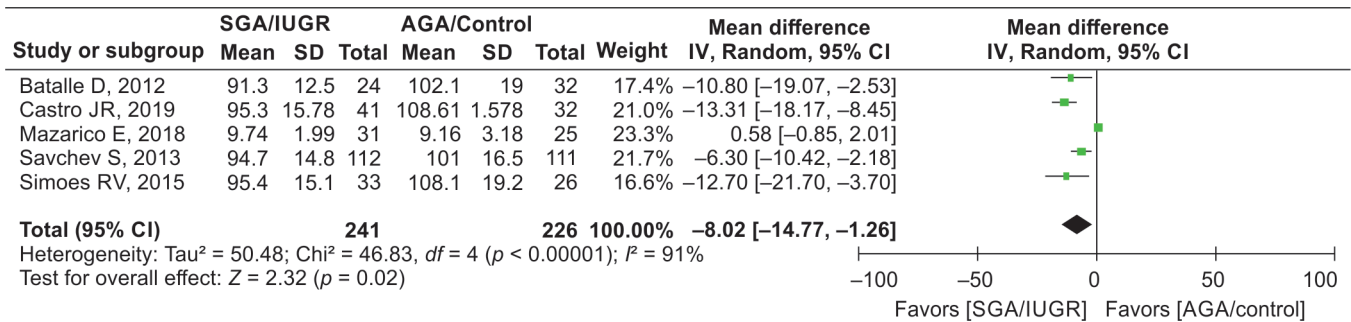


Fig. 4: Meta-analysis of linguistic comparison in SGA group with AGA group

cognitive, motor, and academic performance, and they often score higher on behavioral assessments, pointing to potential issues.¹³ And language development in children with FGR have poorer language outcomes with difficulties with language comprehension, content, structure, and vocabulary size.¹⁴

This study is in line with that conducted by Sacchi et al. that the former had considerably poorer cognitive scores than the latter.¹⁵ These findings indicate a connection between SGA, and long-term neurological consequences.¹⁵ Research by Hartkopf J et al. found that there was no significant relationship in the Psychomotor Development Index (PDI) between the FGR, SGA, and AGA groups. This contrasts with our findings, possibly because we assessed fetal brain responses to visual and sound stimulation before birth.¹² The study conducted by Šimić Klarić A et al. revealed notable differences between the IUGR group and the AGA group.¹⁴ Specifically, significant variations were observed in areas such as language comprehension, total expressive language (including vocabulary, structure, and content), naming ability, and word repetition.¹⁴

It is understood that several proteins in the hippocampus play a role in the mechanism of cognitive impairment in FGR. These proteins include phosphorylation of protein kinase B (PKB or Akt),

glycogen synthesis kinase 3 beta (GSK3β), N-methyl- D-aspartate (NMDA), and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors, brain-derived neurotrophic factor (BDNF), calcium calmodulin-dependent kinase II (CaMKII), extracellular regulated kinase ½ (ERK½), and cAMP-response element-binding protein (CREB).¹⁶ Their decreased presence in the hippocampus leads to compromised memory function and affects the regulation of the learning process.¹⁶

In cases of FGR, a greater proportion of the parietal component was linked to reduced motor skills at 22 months old.¹⁷ Regarding the noted connection between higher relative gray matter volume in the occipital and parietal cortex and lower motor and cognitive abilities, one possible explanation might be disparities in how gray and white matter mature in tandem.¹⁷ Previous research has demonstrated that when gray matter expands comparatively more in FGR fetuses, it tends to coincide with a decrease in nearby white matter.¹⁷

Fetal growth restriction children have lower brain mass and size, lower white matter volume and lower gray matter volumes which are responsible for developing new skills such as learning language and speaking.¹⁸ Reduced size of the left superior temporal gyrus (STG) is observed as it contains Hersch’s gyrus and Wernicke’s

area as well as the left planum temporale, which is responsible for auditory processing and comprehension.¹⁹ The underdeveloped Broca's area is also another possibility as to why there is a gap in linguistic ability.¹⁹ The lack of development of this part of the brain will cause children to have poor vocal speaking language or transmitting words they read into words they speak. This also affects how they perceive the words they hear.²⁰

Children born at term with FGR tend to fall behind their peers in terms of working memory and processing speed. These difficulties typically do not improve with age and persist into school age and beyond. Furthermore, infants with FGR are at a higher risk of developing metabolic disorders and behavioral issues in adulthood compared with infants with AGA.²¹ Keeping a close watch on the cognitive, motor, and linguistic development of children with FGR is crucial. These challenges may not surface immediately and could become more noticeable once the child starts school.²¹

Absolutely, fetal maturation is crucial, yet neurodevelopment is a multifaceted and ongoing process influenced by numerous factors.²² Implementing interventions is essential to mitigate the risk of FGR, which can be achieved by minimizing maternal stressors and ensuring a healthy maternal diet.²¹

The results of this meta-analysis have limitations, because this study did not use the same method, and the sample of studies that conducted research was low. The strength of this meta-analysis study is the important conclusion about neurodevelopment impairment in FGR. It is recommended to conduct further long-term research.

CONCLUSION

Children born at term with FGR exhibited significant impairments in cognitive, motoric, and linguistic development compared with children born with AGA.

Clinical Significance

Development impairment in cognitive, motoric, and linguistic are found to be significant in children born at term.

SUPPLEMENTARY MATERIALS

All the supplementary materials are available on the website www.jsafog.com

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