The Journal of Maternal-Fetal & Neonatal Medicine

ISSN: 1476-7058 (Print) 1476-4954 (Online) Journal homepage: www.tandfonline.com/journals/ijmf20

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To cite this article: Ashwini Rao, Renuka Suvarna, Vijetha Shenoy Belle, Padmanabha Udupa E. G. & Leslie Edward S. Lewis (2025) Neurodevelopmental outcomes in Intrauterine Growth-Restricted children – an umbrella review, The Journal of Maternal-Fetal & Neonatal Medicine, 38:1, 2577243, DOI: 10.1080/14767058.2025.2577243

To link to this article: https://doi.org/10.1080/14767058.2025.2577243

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THE JOURNAL OF MATERNAL-FETAL & NEONATAL MEDICINE
2025, VOL. 38, NO. 1, 2577243
https://doi.org/10.1080/14767058.2025.2577243

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REVIEW ARTICLE

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Neurodevelopmental outcomes in Intrauterine Growth-Restricted children – an umbrella review

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ABSTRACT

Objective: Optimal neurodevelopment during pregnancy is crucial for healthy brain functioning for a lifetime, which can prevent the risk of adverse outcomes like autism, Attention-deficit hyperactivity disorder (ADHD), mental health issues, or learning disabilities. Intrauterine Growth Restriction (IUGR) is one of the conditions leading to adverse neurodevelopmental outcomes in the newborn. This umbrella review aimed to synthesize the existing evidence on neurodevelopmental outcomes in children with IUGR and highlight critical knowledge gaps, emphasizing the need for long-term standardized studies.

Methods: A systematic literature search was conducted across Medline/PubMed, Embase, and Scopus up to June 2025 as per the eligibility criteria, including systematic reviews on neurodevelopmental outcomes in IUGR children diagnosed as per the Delphi criteria. The extracted articles underwent study selection and data extraction processes, with discrepancies resolved by consensus. The eligible articles were synthesized qualitatively and presented.

Results: Eight eligible studies were included in this review; two included meta-analyses, and six had only qualitative synthesis. Qualitative narrative synthesis was conducted for these eight studies. The included studies were of moderate quality and consistently reported that IUGR children exhibited significantly lower cognitive, motoric, and linguistic scores than their Appropriate for Gestational Age (AGA) peers. Some noted specific impairments included reduced Intelligence Quotient (IQ), fine and gross motor delays, and language comprehension deficits. While some studies showed insignificant differences in behavioral or language outcomes, others linked biomarkers like S100B, Neuron Specific Enolase (NSE), and tau proteins to substandard neurodevelopment. Adverse neurological outcomes and neurodevelopmental impairment were associated with IUGR. Protective brain-sparing effects might pose benefits early in life, which may not persist throughout.

Conclusion: IUGR children are at an elevated risk for adverse neurodevelopmental outcomes, specifically in cognitive and motor domains. While language and behavioral findings vary, early life impairments are notable. The heterogeneity in the methodologies across the included primary studies highlights the need for standardized research, diagnostic criteria, and longitudinal studies to extract definitive conclusions. Extensive neurodevelopmental monitoring, timely interventions, and further exploration of predictive biomarkers are essential to optimize outcomes and mitigate long-term adverse effects in this vulnerable population.

ARTICLE HISTORY
Received 21 July 2025
Revised 14 October 2025
Accepted 14 October 2025

KEYWORDS
Intrauterine Growth Restriction; Fetal Growth Restriction; neurodevelopmental outcomes; children; umbrella review

Introduction

Intrauterine Growth Restriction (IUGR), synonymized with Fetal Growth Restriction (FGR), describes a condition where the developing fetus fails to achieve its genetically determined growth potential, primarily diagnosed when the Estimated Fetal Weight (EFW) lies below the 10th percentile for the gestational age [1,2].

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/14767058.2025.2577243.

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Appropriate fetal brain development plays a crucial role, as it is the essential groundwork for lifelong cognitive, motor, and socio-emotional functioning throughout life, and childhood and adulthood development could be significantly affected by IUGR [2]. A study by Marra et al. [3] has evaluated fetal cortical development through ultrasound, which is characterized by a significant increase in the depth of key brain cortical structures like Sylvian, Parieto-occipital, and Calcarine fissures with advancing gestational age. After 28 weeks of gestation, gender-related differences arise in this development, with male fetuses showing significantly deeper fissures than female fetuses [4]. Late-onset fetal growth-restricted fetuses show smaller midline structures and shallower Sylvian, Parieto-occipital, and Calcarine fissures as diagnosed by ultrasound. These changes are markedly evident in FGR cases, indicated with abnormal uterine doppler findings, highlighting a crucial link between altered brain maturation and impaired utero-placental circulation due to chronic hypoxemia [5,6].

The neurological outcome of a newborn is associated with prenatal exposure and environment. IUGR is most often accompanied by placental insufficiency or undernutrition, which may lead to neural changes having consequences on the developing fetus, including motor and sensory neurodevelopmental deficits, cerebral palsy, etc [7,8]. The consequences of IUGR continue beyond the fetal and neonatal period and might have an intense impact on child development [9]. Children affected by IUGR/FGR frequently exhibit distinct neurodevelopmental profiles compared to their Appropriate for Gestational Age (AGA) peers. This involves altered brain growth and a higher risk of cognitive and motor dysfunction and behavioral issues, like a heightened risk of autism spectrum disorders and speech difficulties [10,11].

Despite extensive research, significant gaps remain in understanding these issues in depth and the long-term effects of impaired neurodevelopment in IUGR children. While some systematic reviews and meta-analyses have attempted to consolidate the findings, the evidence remains fragmented and variable in scope. Hence, the present umbrella review aims to synthesize the existing evidence on neurodevelopmental outcomes in IUGR children to highlight critical voids, or the need for long-term standardized studies across the relevant neurodevelopmental outcomes.

Method

This review was performed per *a priori*-designed protocol, which was preregistered with the PROSPERO (ID: CRD420251072435).

Search strategy

A systematic literature search was done on electronic databases, which included Medline/PubMed, Embase, and Scopus, utilizing a search strategy developed using a combination of the following MeSH terms and their variants: “Intrauterine Growth Restriction,” “Fetal Growth Restriction,” “IUGR,” “FGR” AND “Neurodevelopment,” “Neurodevelopmental Disorders” AND “Systematic Review” OR “Meta-analysis.” The search was conducted up to June 2025 and was restricted to English articles.

Eligibility criteria

This review included studies based on the PICOS criteria. The target population included children born from IUGR pregnancies (diagnosed during pregnancies as per the Delphi criteria) [12] who are followed up for their neonatal period or beyond. There is no intervention. The comparator includes pregnancies used for comparison with the IUGR group in the systematic reviews. The outcome involves neurodevelopmental outcomes assessed in the IUGR and/or comparator groups in the neonatal period and beyond. The study designs include systematic reviews with/without meta-analyses.

This umbrella review excluded studies that included non-human models or in which neurodevelopmental outcomes were not measured. Studies that assessed neurological impairments/injuries were

eliminated. Primary studies/original research articles, umbrella reviews, narrative reviews, scoping reviews, and unpublished articles were excluded from the study. Non-English articles were excluded from the review. Additionally, articles where the definition of IUGR were not clearly distinguished from Small for Gestational Age (SGA) were also excluded from the review.

Study selection and data extraction

Studies from the designated databases were exported to Rayyan, where two authors independently screened titles and abstracts, blinded to each other's decisions. Duplicates were removed, and discrepancies were resolved through discussion with additional authors to ensure accuracy. A full-text screening was performed, following which two authors extracted the data from the eligible articles, which mainly included authors' names and publication details, primary study designs included in each systematic review, quality assessment tools used, sample sizes, outcomes, and their measurement models, as well as the results/conclusions. For systematic reviews with meta-analysis, meta-analysis model (random effect/fixed effect models), effect measure models (i.e. standardized mean difference (SMD), odds ratio (OR), hazard ratio (HR), etc.) with their 95% Confidence Interval (CI) and significance value, heterogeneity measure and its significance were also documented along with the other details. The types of neurodevelopmental outcomes were categorized and tabulated (cognitive, motor, behavioral, etc.) for the systematic reviews without meta-analysis.

Quality assessment

The methodological quality of each systematic review included in the study was assessed using A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2) tool, which evaluated and classified the quality of evidence into four categories: "critically low," "low," "moderate," and "high" based on the critical domains of the tool. Two authors independently screened the studies for the overall confidence of each included review, based on the sixteen domains of the tool. Discrepancies were resolved through a discussion among the first three authors, while the other authors provided additional input wherever applicable.

Statistical analysis and data synthesis

The anticipated quantitative synthesis of the meta-analyses included in this review couldn't be implemented, as only one of the two studies had meta-analysis results reported in their articles. Hence, a qualitative narrative synthesis of the obtained outcomes was conducted, along with the studies that did not involve meta-analyses. The outcomes were tabulated as explained in the data extraction step, and the direction of effects was analyzed and reported in the review.

Results

The electronic databases search extracted 1840 systematic reviews. Of these reviews, 237 duplicates were removed, and a total of 1603 articles were eligible for the first-stage screening. A total of 1562 articles were excluded for various reasons, and 41 reviews underwent a second-stage screening. After a comprehensive evaluation, 27 articles were excluded for various reasons. Subsequently, 6 additional articles were excluded because they did not meet the Delphi criteria for diagnosing IUGR. A total of 8 reviews were finalized for the umbrella review. Of these, 2 reviews underwent meta-analyses, and the remaining 6 articles were qualitative syntheses only. The study selection is depicted in Supplementary Figure 1.

Study characteristics

The overview and results of the studies included in this review are depicted in Tables 1 and 2.

IUGR was diagnosed in the included studies using the following criterias, which accord with the Delphi criteria for IUGR diagnosis, though they were not distinguished as early or late-onset IUGR: EFW <10th centile for GA confirmed by ultrasound, along with the EFW crossing centiles >2 quartiles on growth centiles [13]; Abdominal Circumference (AC) <10th centile along with Absent or Reverse End Diastolic Flow (AREDF) in the umbilical artery (UA) [13,14]; EFW <10th centile for GA confirmed by ultrasound, along with UA-PI (pulsatility index) >95th centile [9,13–15]; EFW <5th or 10th centile along with abnormal UA Doppler indices [9,15–18]; EFW <3rd centile [19]; EFW <10th centile along with Uterine Artery (UtA-PI) >95th centile or Cerebroplacental ratio (CPR) <5th centile [15,19]; AC <10th centile with UA-PI >95th centile with/without AREDF [17]; UA-AREDF [14] EFW <10th centile with UA-PI >95th centile [14].

To summarize, we broadly classified the neurodevelopmental outcomes from the studies into cognitive, motoric, language, behavioral/social-emotional, neurological, adaptive/global/psychological outcomes (Table 3). These outcomes were measured using the models/tools mentioned in Tables 1 and 2.

Study quality

The detailed AMSTAR 2 assessment for the 8 included studies is depicted in Supplementary Table 1. Of these, one study [18] had a critically low quality, two studies [9,13] had low quality, two studies [14,15] were of moderate quality, and three studies [16,17,19] had high quality. The main contributing factors for reduced confidence in the studies were the absence of pre-registered protocols, the absence of an extensive literature search strategy, and the lack of justification for the exclusion of some studies. Based on the findings, the studies included in this review were of moderate quality.

Systematic reviews with quantitative synthesis

Of the 8 studies included in the review, 2 studies [13,18] included a quantitative synthesis, the outcomes of which are tabulated in Table 1. The study by Sacchi et al. [13] included 17 studies on the IUGR group and 43 on the SGA group, which were compared with the AGA group for cognitive scores and borderline intellectual impairment. It revealed that the cognitive scores were lower in preterm and term IUGR groups as compared to the AGA group, estimated using the random effects model at 95% CI: preterm IUGR [SMDH: −0.36 (−0.55, −0.18) $p = 0.01$]; term IUGR children [SMDH: −0.58 (−0.82, −0.35) $p = 0.08$]; and preterm IUGR children who were SGA were more likely to have borderline intellectual impairment than preterm children with AGA [OR: 1.69 (1.06, 2.69) $p = 0.02$]. The second study by Arcangeli et al. [18] included 28 studies on SGA and three with FGR, which compared neurodevelopmental outcomes in these groups with normal controls. They referred to a book and an article for the quality assessment. The study reported that meta-analysis was not carried out due to the limited number of FGR babies and controls, but the effect sizes at 95% CI were reported. It was concluded that small fetuses born with or without growth restriction were associated with lower neurodevelopmental scores than controls, and the results for the FGR population were imprecise.

Systematic reviews with qualitative synthesis

Six of the 8 studies included in this review [9,14–17,19] have included exclusively qualitative data synthesis; the summary of the outcomes from all 6 studies is shown in Table 2. The studies by Benítez-Marín et al. [19] and Musco et al. [16] estimated S100B, neuron-specific enolase (NSE), and tau protein levels in cord blood at birth, maternal venous blood, fetal umbilical artery, and newborn urinary nerve growth factor, and correlated them with neurodevelopmental outcomes. S100B and NSE had an inverse relationship with adaptive behavior, cognitive test, fine motor development, socio-emotional development, and expressive communication in FGR children. Tau proteins were lower in FGR children. The urinary nerve growth factor was reduced in preterm FGR newborns

Table 1. Basic characteristics of studies with meta-analysis.

Study (year)	Databases searched	Design of primary studies included	Number of studies included in SR	Number of studies included in the MA	Quality assessment and/or risk of bias tool used	Number of participants		Age for follow-up	Outcomes	Measuring models*	Analysis model	Effect measure			Heterogeneity		Results/Conclusions
						Cases	Controls					Model	Value (95% CI)	p-value	I^2	p-value	
Sacchi et al. [13]	Scopus PubMed Web of Science Science Direct PsycInfo ERIC	Prospective Cohort Prospective case control Retrospective cohort	60	60	Not Reported	1157	1933	0.16 – 11.6 years	Cognitive scores in preterm IUGR Cognitive scores in term IUGR Borderline Intellectual impairment in IUGR	WAIS FSIQ WISC-IV WPPSI BSID-II BSID-III MDI GMDS DQ K-ABC CMP WISC RAKIT WISC-R	Random effects model	SMDH SMDH OR	−0.36 [−0.55, −0.18] −0.58 [−0.82, −0.35] 1.69 [1.06, 2.68]	$p = 0.01$ $p = 0.08$ $p = 0.02$	58.3% 50% 60.7%		• Preterm and term IUGR groups had lower cognitive scores than the AGA group. • Preterm IUGR children who were SGA were more likely to have BII than preterm children with AGA.
Arcangeli et al. [18]	Medline/ PubMed Embase	Prospective case control	3	(Cited) [20,21]		119	49	Not Reported	–	Griffiths scale Bayley's DQ WPPSI	Limited number of FGR babies and controls, so meta-analysis was not done.	–	–	–	–	–	Growth-restricted/ normal growth small fetuses born at term were associated with lower neurodevelopmental scores than controls. The results for the FGR population were imprecise.

*Abbreviations: ASQ, Ages and Stages Questionnaire; BAS, British Ability Scales; BAIT, Behavioral Assessment of Infant Temperament; Bayley-II, Bayley Scales of Infant Development, Second Edition; Bayley-III, Bayley Scales of Infant and Toddler Development, Third Edition; BBDS, Brief Behavioral Distress Scale; BRS, Behavior Rating Scale; Brown's ADD Scales, Brown Attention-Deficit Disorder Scales; BSID-II, Bayley Scales of Infant Development, Second Edition; BSID-III, Bayley Scales of Infant Development, Third Edition; BSITD-III, Bayley Scales of Infant and Toddler Development, Third Edition; CBCL, Child Behavior Checklist; CAT, Cognitive Abilities Test; CLAMS – Clinical Linguistic and Auditory Milestone Scale; CMP, Child Monitoring Protocol; DHS, Difficulties and Handicaps Schedule; ECBQ, Early Childhood Behavior Questionnaire; FTII, Family Temperament and Interaction Inventory; FSIQ, Full Scale Intelligence Quotient; FSS, Functional Status Scale; GMDS DQ, Griffiths Mental Development Scales – Developmental Quotient; HINE, Hammersmith Infant Neurological Examination; IBQ, Infant Behavior Questionnaire; IBQ-R, Infant Behavior Questionnaire –Revised; ICQ, Infant Characteristics Questionnaire; ITSEA, Infant-Toddler Social and Emotional Assessment; K-ABC, Kaufman Assessment Battery for Children; M-CHAT, Modified Checklist for Autism in Toddlers; MABS, Motor Assessment Battery for Children; MDI, Mental Development Index; MIDI, MacArthur Inventory of Developmental Indicators; NBAS, Neonatal Behavioral Assessment Scale (Brazelton); PAIT, Parent-Adult Interaction Tool; PCIS, Parent-Child Interaction Scale; PSS, Perceived Stress Scale; QNST, Quick Neurological Screening Test; RAKIT, Revised Amsterdam Kinder Intelligent Test; RITQ, Revised Infant Temperament Questionnaire; SFS, Social Functioning Scale; SDQ, Strengths and Difficulties Questionnaire; TTQ, Toddler Temperament Questionnaire; TTS, Toddler Temperament Scale; VADS, Visual-Auditory Digit Span Test; VIQ, Verbal Intelligence Quotient; VEP, Visual Evoked Potentials; WAIS, Wechsler Adult Intelligence Scale; WISC, Wechsler Intelligence Scale for Children; WISC-IV, Wechsler Intelligence Scale for Children – Fourth Edition; WISC-R, Wechsler Intelligence Scale for Children – Revised; WISC-R95, Regional variant of the WISC-R; WPPSI, Wechsler Preschool and Primary Scale of Intelligence; and WPPSI-R, Wechsler Preschool and Primary Scale of Intelligence – Revised.

Table 2. Basic characteristics of studies without meta-analysis.

Study (year)	Databases searched	Design of primary studies included	Number of studies included in SR	Quality assessment and/or risk of bias tool used	Number of participants		Age for follow-up	Outcomes	Measuring models*	Matrix for biomarkers	Results/Conclusions
					Cases	Controls					
Benítez-Marín et al. [19]	PubMed Embase	Longitudinal case-control Prospective observational Prospective Cohort	5	Quality Assessment Tool for Quantitative Studies	233	272	2 years	S100B Neuron-specific enolase Urinary nerve growth factor Tau protein Hyperkinesia Hypokinesia Apathy Syndrome Hyperexcitability syndrome Cognitive impairment Motoric Impairment Linguistic impairment	Griffiths' scales of child development, third edition Bayley scales of infant and toddler development, third edition Prechtl's general movements assessment	Cord blood at birth and urine from the newborn within the first month of life	• S100B, neuron-specific enolase, C-reactive protein, and IL were increased in FGR. • S100B had an inverse relationship with the development of adaptive behavior. • Neuron-specific enolase negatively correlated with cognitive, fine motor, and socio-emotional development. • Nerve growth factor, BDNF, and Tau were decreased in FGR. • Urinary nerve growth factor was significantly decreased in preterm FGR newborns compared with full-term references. • Tau proteins were lower in children with FGR and adverse neurodevelopmental outcomes. • No differences were found between the groups for neurodevelopmental outcomes at 2 years old.
Musco et al. [16]	CINAHL Embase Web of Science	Prospective case-control	1	QUADAS-2	31	25	2 years	S100B NSE Adaptive behavior test Language composite score values Fine motor subset Social-emotional test	BSITD-III	Maternal venous blood and fetal umbilical arterial blood	• S100B in maternal serum showed an inverse relationship with the adaptive behavior test. • S100B in umbilical cord blood showed an inverse relationship with cognitive, fine motor, social-emotional, and expressive communication subtests. • At 2 years of age, neurodevelopmental outcomes and blood biomarkers showed an inverse relationship.

(*Continued*)

Table 2. Continued.

Study (year)	Databases searched	Design of primary studies included	Number of studies included in SR	Quality assessment and/or risk of bias tool used	Number of participants		Age for follow-up	Outcomes	Measuring models*	Matrix for biomarkers	Results/Conclusions
					Cases	Controls					
Benítez-Marín et al. [17]	PubMed Embase	Prospective Longitudinal Retrospective	12	Quality Assessment Tool for Quantitative Studies	1125	739	40 weeks to 8 years	Habituation, motor, social-interactive, and attention areas Gross motor development Lower IQ scores Behavioral problems at young age	ASQ Bayley scales of infant and toddler development Wechsler Intelligence Scale Neuropsychological task NBAS VEP RAKIT test HINE		• FGR group with abnormal CPR values had significantly lower mean scores in ASQ and Bayley scales than in the SGA group. • FGR group with normal CPR values had significantly lower mean scores than the SGA group in gross and fine motor development. • The FGR group had lower scores than the AGA group for WISC-IV. • Motor scores in the Bayley scales significantly differed between the FGR groups. • The FGR group had significantly more social and attention problems than the normal group. • Habituation, motor, social-interactive, and attention scores were significantly lower in the FGR group than in the AGA group.
Levine et al. [15]	PubMed Embase PsycINFO CINAHL	Case control (not mentioned)	24	(Cited) [22]	1051	896	1 to 4 years	Adaptive behaviors Autism Less approaching behaviors Psychological development Behavior rating scale scores	NBAS BSID-III IBQ PCIS FTII DHS FSS SFS BAIT PAIT ICQ BSID-II Griffiths' mental development scales for infants McCarthy's scales of children's abilities CBCL RITQ TTQ ECBQ ITSEA TTS ASQ M-CHAT SDQ PSS		Poorer adaptive behavior and increased risk of autism in the IUGR group.

(*Continued*)

Table 2. Continued.

Study (year)	Databases searched	Design of primary studies included	Number of studies included in SR	Quality assessment and/or risk of bias tool used	Number of participants		Age for follow-up	Outcomes	Measuring models*	Matrix for biomarkers	Results/Conclusions
					Cases	Controls					
Levine et al. [9]	PubMed Embase PsycINFO Maternity and Infant Care CINAHL	Prospective cohort Retrospective	16	Guidelines for Assessing Quality in Prognostic Studies ISPOR for retrospective study	1639	3048	6 months to 3 years	Neuromotor and neurologic abnormalities Neuromotor function Neurobehavioral scores Neurodevelopmental delays Motor delays Cognitive delays Language delays	Bayley-II NBAS Bayley-III Motor score Stanford-Binet Intelligence Scale		• IUGR children had higher rates of neuromotor and neurological abnormalities than controls at 1 year. • The IUGR group scored significantly lower on the Bayley Scales of Infant Development scores than controls. • Preterm infants with asymmetric IUGR showed significantly lower scores in habituation, motor function, social interaction, and attention on the Neonatal Behavioral Assessment Scale at 40 weeks, compared to both healthy controls and those with symmetric IUGR. • Bayley-II revealed cognitive, linguistic, and motor deficits in the IUGR group. • Bayley-III showed lower scores on the adaptive behavior subscale in the IUGR group. • IUGR children had developmental delay at 3 years as compared to controls. • 11 studies found motor delay, eight found cognitive delay, and 7 found language delay. • Preterm IUGR children had lower verbal IQ and full-scale IQ test scores at 5 to 8 years in a study than preterm or term AGA children.

(*Continued*)

Table 2. Continued.

Study (year)	Databases searched	Design of primary studies included	Number of studies included in SR	Quality assessment and/or risk of bias tool used	Number of participants		Age for follow-up	Outcomes	Measuring models*	Matrix for biomarkers	Results/Conclusions
					Cases	Controls					
Murray et al. [14]	Medline CINAHL PsycInfo Scopus	Case control Cohort	38	GATE (Cited) [21]	15400	15558	3 months to 11 years	Neurodevelopmental impairment Shorter attention span and motor hyperactivity Personal-social scores Adaptive behavior Minor/major neurological sequelae Perceptual performance Problem-solving scores Social and self-help abilities General cognitive index Conceptual ability Motor coordination Abnormality of neurological function Gross and fine motor skills	Conner's symptoms of ADHD Griffith's test ASQ MABS MIDI IBQ-R BRS CBCL SDQ Brown's ADD scales BSID-III Stanford Binet WISC-R95 K-ABC VADS McCarthy scales WPPSI RAKIT BSID-II WISC BAS VIQ CAT CLAMS HINE QNST Zurich neuromotor test BBDS		• IUGR children born at ≥35 weeks of gestation were specifically impaired in domains of cognitive and behavioral development. • IUGR children born at <35 weeks of gestation were specifically impaired in domains of cognitive, behavioral, and hearing development. • IUGR children born at <35 weeks of gestation experienced a higher level of impairment across all neurodevelopmental domains compared to IUGR children born at ≥35 weeks. • The IUGR group had: Shorter attention span and motor hyperactivity Lower personal-social scores Impaired adaptive behavior Lower perceptual performance Lower problem-solving scores Delayed social and self-help abilities Hyperactive Lower general cognitive index Lower conceptual ability Lower motor coordination Lower muscle tone Increased abnormality of neurological function Lower gross and fine motor skills

*Abbreviations: ASQ, Ages and Stages Questionnaire; BAS, British Ability Scales; BAIT, Behavioral Assessment of Infant Temperament; Bayley-II, Bayley Scales of Infant Development, Second Edition; Bayley-III, Bayley Scales of Infant and Toddler Development, Third Edition; BBDS, Brief Behavioral Distress Scale; BRS, Behavior Rating Scale; Brown's ADD Scales, Brown Attention-Deficit Disorder Scales; BSID-II, Bayley Scales of Infant Development, Second Edition; BSID-III, Bayley Scales of Infant Development, Third Edition; BSITD-III, Bayley Scales of Infant and Toddler Development, Third Edition; CBCL, Child Behavior Checklist; CAT, Cognitive Abilities Test; CLAMS – Clinical Linguistic and Auditory Milestone Scale; CMP, Child Monitoring Protocol; DHS, Difficulties and Handicaps Schedule; ECBQ, Early Childhood Behavior Questionnaire; FTII, Family Temperament and Interaction Inventory; FSIQ, Full Scale Intelligence Quotient; FSS, Functional Status Scale; GMDS DQ, Griffiths Mental Development Scales – Developmental Quotient; HINE, Hammersmith Infant Neurological Examination; IBQ, Infant Behavior Questionnaire; IBQ-R, Infant Behavior Questionnaire –Revised; ICQ, Infant Characteristics Questionnaire; ITSEA, Infant-Toddler Social and Emotional Assessment; K-ABC, Kaufman Assessment Battery for Children; M-CHAT, Modified Checklist for Autism in Toddlers; MABS, Motor Assessment Battery for Children; MDI, Mental Development Index; MIDI, MacArthur Inventory of Developmental Indicators; NBAS, Neonatal Behavioral Assessment Scale (Brazelton); PAIT, Parent-Adult Interaction Tool; PCIS, Parent-Child Interaction Scale; PSS, Perceived Stress Scale; QNST, Quick Neurological Screening Test; RAKIT, Revised Amsterdam Kinder Intelligent Test; RITQ, Revised Infant Temperament Questionnaire; SFS, Social Functioning Scale; SDQ, Strengths and Difficulties Questionnaire; TTQ, Toddler Temperament Questionnaire; TTS, Toddler Temperament Scale; VADS, Visual-Auditory Digit Span Test; VIQ, Verbal Intelligence Quotient; VEP, Visual Evoked Potentials; WAIS, Wechsler Adult Intelligence Scale; WISC, Wechsler Intelligence Scale for Children; WISC-IV, Wechsler Intelligence Scale for Children – Fourth Edition; WISC-R, Wechsler Intelligence Scale for Children – Revised; WISC-R95, Regional variant of the WISC-R; WPPSI, Wechsler Preschool and Primary Scale of Intelligence; and WPPSI-R, Wechsler Preschool and Primary Scale of Intelligence – Revised.

Table 3. Classifications of the neurodevelopmental outcomes assessed in the studies.

Study (year)	Cognitive outcomes	Motor outcomes	Language outcomes	Behavioral/ social-emotional outcomes	Neurological outcomes	Adaptive/ global/ psychological outcomes
Sacchi et al. [13]	Cognitive scores, borderline intellectual impairment	–	–	–	–	–
Arcangeli et al. [18]	–	–	–	–	–	–
Benítez-Marín et al. [19]	Cognitive impairment	Hyperkinesia, Hypokinesia, Motoric impairment	Linguistic impairment	Hyperexcitability Syndrome, Apathy Syndrome	–	–
Musco et al. [16]	–	Fine motor subset	Language composite score	Social-emotional test	–	Adaptive behavior
Benítez-Marín et al. [17]	Lower IQ	Motor development, Habituation	–	Social-interactive, Attention	–	–
Levine et al. [15]	Psychological development	–	–	Less approaching behavior	–	Adaptive behavior, Autism
Levine et al. [9]	Cognitive, Neurodevelopmental delays	Motor delays, Neuromotor function	Language delays	–	Neurologic abnormalities	–
Murray et al. [14]	General cognitive index, Conceptual ability, Problem solving	Gross & fine motor skills, Motor coordination	–	Hyperactivity, Shorter attention span, Behavior, Motor hyperactivity, personal-social scores	Neurological abnormality	Adaptive behavior, Social & self-help abilities

compared to the full-term references. The neurodevelopmental outcomes assessed in these studies were broadly classified as cognitive, motoric, language, behavioral/social-emotional, neurological, adaptive/global/psychological outcomes.

Cognitive outcomes

Six studies [9,13–15,17,19] evaluated cognitive outcomes in the IUGR/FGR population, which included cognitive impairment, cognitive scores, borderline intellectual impairment, IQ, cognitive delay, psychological impairment, conceptual ability, and problem-solving skills. Children born with preterm or term IUGR/FGR have consistently shown poorer cognitive development when compared to AGA groups. Verbal and performance IQ are significantly lower in the IUGR group. Brain sparing effects are seen in FGR fetuses, which may lead to adverse cognitive outcomes in these children, though the degree of impairment varies. Cerebral redistribution has also been linked with lower IQ scores and poor cognitive functioning in early childhood (up to 8 years). Follow-up studies have also highlighted the increased risk of cognitive delays and impairments in IUGR children, with lower scores in the cognitive domain of neurodevelopmental assessments.

Motor outcomes

Five studies [9,14,16,17,19] evaluated motor outcomes in the IUGR/FGR population, which included motoric impairment, hyper/hypokinesia, fine motor subset, gross and fine motor development, motor development, habituation, motor delays, neuromotor function, and motor coordination. Children with IUGR/FGR showed significantly greater motor impairments compared to AGA children, with a higher incidence and prevalence of motor difficulties also seen in them, particularly between 6 months and 3 years. Motor delay was specifically observed in these studies, which covered the major part of the overall adverse neurodevelopmental outcomes. Specific motor deficits, including lower Psychomotor Development Index (PDI) scores, were frequently reported. At 1 year, IUGR is the best predictor of neurologic impairment, though mild, but seemingly more frequent than in controls, particularly affecting the motor function. Fine motor skills are also significantly impacted, but age-related

variations are observed. The findings were heterogeneous, and some of these studies have highlighted the need for consistent IUGR diagnostic methods and control of confounding factors to better understand motor outcomes in IUGR children.

Language outcomes

Three studies [9,16,19] evaluated language outcomes, which included linguistic impairments, language problems, language composite scores, and language delays. FGR children have poorer language development and linguistic impairments than AGA children. Multiple primary studies have shown statistically significant deficits in language outcomes, specifically in comprehension, content, vocabulary size, and structural use. However, these findings aren't consistent across all the primary studies. Supporting this, the study by Musco et al. [16] reported no significant difference in language skills between FGR and AGA infants. Contrarily, Benítez-Marín et al. [19] have reported that FGR children may face difficulties in language and communication, specifically associated with lower levels of specific biomarkers. Additionally, language delays have been observed frequently in IUGR children than AGA children.

Behavioral/social-emotional outcomes

Five studies [14–17,19] evaluated behavioral/social-emotional outcomes, which included hyperexcitability syndrome, Apathy syndrome, social-emotional tests, behavioral problems, social-interactive and attention problems, approaching behaviors, hyperactivity, shorter attention span, and personal social scores. Children with IUGR have shown significant behavioral differences as compared with AGA children. Behavioral assessments have shown that IUGR is associated with elevated risks of behavioral issues by 11 years of age as compared to the general population. While brain-sparing effects were associated with better behavioral outcomes at 4 years of age, these effects do not seem to persist in later childhood. Parents of FGR children have reported heightened attention and social problems, irrespective of brain sparing. At 11 years old, no significant difference was found in behavior between the FGR and AGA children, suggesting that early behavioral benefits may decline over time. SGA children portrayed significant psychological differences, whereas IUGR children showed poorer long-term outcomes. Behavioral impairments are evidently noted in IUGR children as early as 3 and 6 months of age, with significant beta coefficients pointing to the degree of impact. However, these associations tend to weaken after adjustment for the confounding variables.

Neurological outcomes

Two studies [9,14] evaluated neurological outcomes, which involved neurodevelopmental impairment and neurological abnormalities. A history of any adverse pregnancy outcomes, like IUGR, has been associated with a heightened risk of poorer neurodevelopmental outcomes through early and late childhood, affecting multiple domains. It was observed that asymmetric IUGR is particularly associated with poorer neurodevelopmental outcomes compared to normal fetal growth. Even in term pregnancies with optimal management throughout the pregnancy, 1/3rd of the IUGR fetuses had neurological damage. The risk is pronounced in preterm infants; those born before 35 weeks with IUGR show a significant neurodevelopmental impairment of approximately 0.7 SD compared to those born at or after 35 weeks of gestation. Also, Fetal Circulatory Redistribution (FCR) was associated with additional neurological impairment ranging from 0.50 SD to 0.76 SMD, particularly affecting cognitive and behavioral domains.

Adaptive/global/psychological outcomes

Three studies [14–16] evaluated adaptive/global/psychological outcomes, which included adaptive behavior, developmental delays, autism, and social and self-help abilities. These studies have indicated that IUGR children, specifically those with fetal circulatory redistributions, have exhibited more

pronounced impairments in adaptive functioning, attention, and personal-social behavior, reflecting significant psychological challenges. SGA children have shown an increased risk of poor psychological outcomes compared to AGA children. It included altered mother-infant interactions, heightened infant reactivity and temperament issues, mood disturbances, attention problems, adaptive behavior deficits, autistic-like symptoms, and increased internalizing behaviors, which are seen in IUGR populations as well. While no significant differences were observed in the BSITD-III subtests between FGR and AGA infants, indicating comparable performance in these assessments, the broader evidence suggests ongoing psychological and adaptive challenges for growth-restricted children. The variability in neurodevelopmental evaluations, contributed by differing assessment tools and varying ages of evaluation, adds to the complexity of interpreting these outcomes. Early psychological difficulties may persist in the later developmental stages, emphasizing the need for continuous monitoring. The current literature reveals a significant lack of evidence linking placental insufficiency to early psychological outcomes, indicating an essential gap in understanding this relationship.

Discussion

In this umbrella review, the studies with meta-analyses have reported lower cognitive scores, lower neurodevelopmental scores, and intellectual impairment in IUGR children as compared to their AGA peers. The qualitative results have supported these findings, highlighting the associations between biomarkers such as S100B, NSE, and tau proteins and poorer neurodevelopment. The study by Mazarico et al. [23] has a similar finding where elevated maternal serum levels of S100B protein correlate with poor adaptive behavior in IUGR children. Elevated cord blood concentrations correlate with reduced cognitive scores and impaired expressive communications. The study by Aisa et al. [24] has concluded that, along with cerebral volumes and NGF, urinary S100B and tau protein are significant parameters for early detection of future risk of neurodevelopmental abnormalities.

Multiple studies have shown significantly lower cognitive scores in IUGR groups, including reduced IQ and increased risk of borderline intellectual functioning. Several studies have identified fine motor delays and gross motor skills in IUGR children, which aligns with the literature [1,25] and linguistic delays, including vocabulary and language comprehension deficits. Studies by Benítez-Marín et al. (2024) and Musco et al. (2024) have also explored the correlation between neurodevelopment and biomarkers, showing the potential for early identification of at-risk infants. Some studies did not find significant differences in language or behavioral outcomes, possibly due to variability in the findings based on methodology and assessment tools. The prevalence of ADHD did not significantly vary between the IUGR and AGA groups. At 11 years of age, the behavioral differences were no longer significantly different. This finding goes with the study by Vollmer et al. [26], which has reported that brain sparing was not an independent risk factor for the behavioral outcomes at 11 years. Psychological and neurological outcomes were evaluated using various tools at different developmental stages, which reduced the scope for comparability and generalizability of the obtained findings.

The key takeaways from this review are that IUGR children suffer significant neurodevelopmental impairments, specifically in cognitive and motor domains. They also face a higher risk of impairments across these domains in addition to language, behavioral, and adaptive outcomes, notably in the early years of life. Early neurodevelopmental assessments and biomarker studies may pave the way for identifying at-risk infants early in life and for timely interventions, minimizing long-term impairments.

This study has several limitations that impact the interpretation of its findings. It includes studies with diverse primary designs and statistical methods, contributing to methodological heterogeneity. Longitudinal studies with consistent methodologies are needed to track neurodevelopmental outcomes into adulthood. Future research should explore the roles of placental health, cerebral blood flow, and predictive biomarkers in shaping outcomes. Additionally, investigating protective factors such as nutrition, early stimulation, and social support may help mitigate developmental disparities and improve outcomes in children affected by IUGR. Future studies should also be well-designed to adhere to standardized reporting frameworks, such as the Delphi criteria, to ensure that there is no overlap between the definitions of SGA and IUGR, thereby increasing the reliability of the findings.

The implications of these studies call for the early identification and monitoring of IUGR infants, particularly those with additional risk factors, such as prematurity or abnormal MCA findings. Routine screening for neurodevelopment is essential to reduce the long-term deficits.

Conclusion

This umbrella review highlights that IUGR children are at an increased risk of adverse neurodevelopmental outcomes. The evidence consistently suggests cognitive and motor development deficits, with variable findings in language and behavior outcomes. Protective effects, such as brain sparing, may offer benefits early in life but may not persist later in childhood. The heterogeneity found highlights the need for standardized methodologies and adherence to standardized diagnostic criteria in future research. A significant gap exists in understanding the psychological findings and the mechanisms associated with these adverse outcomes. Comprehensive neurodevelopmental monitoring, timely interventions, and evidence-based follow-up strategies are crucial for optimizing outcomes and minimizing long-term adverse effects in this vulnerable population.

Author contributions

CRediT: **Ashwini Rao**: Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing; **Renuka Suvarna**: Methodology, Project administration, Supervision, Validation, Writing – review & editing; **Vijetha Shenoy Belle**: Conceptualization, Formal analysis, Methodology, Supervision, Validation, Visualization; **Padmanabha Udupa E. G.**: Methodology, Supervision, Validation, Visualization; **Leslie Edward S. Lewis**: Methodology, Supervision, Validation, Visualization.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

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Data availability statement

Additional information can be found in the supplementary material provided with this article.

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