Cognitive and Behavioral Outcomes of Intrauterine Growth Restriction School-Age Children

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abstract

CONTEXT: Children who experienced intrauterine growth restriction (IUGR) may be at increased risk for adverse neurologic developmental outcomes during the school-age years of life.

OBJECTIVE: To estimate the effect of IUGR on cognition and behavior in school-aged children.

DATA SOURCES: Medline, Embase, and PsycINFO were searched for English-language articles published after 1980.

DATA SELECTION We included case-control studies reporting cognitive and/or behavioral data of children who had IUGR and were evaluated afterfifth birthday.

DATA EXTRACTION: Cognitive data from 15 studies and behavioral data from 6 studies were selected with a total of 1559 cases and 1630 controls. The cognitive scores and behavioral outcomes were extracted.

RESULTS: The controls had significantly higher cognitive scores than the children with IUGR (standardized mean difference [SMD] −0.38, 95% confidence interval [CI] −0.51 to −0.25, $P <$ .00001). The IQ scores of the IUGR group were not significantly correlated with mean birth weight and gestational age ($P > .05$). Five trials were included in the behavioral outcomes trial, the behavior scores were significantly different between the groups with and without IUGR (SMD 0.31, 95% CI 0.13 to 0.48, $P = .001$). The incidence of attention-deficit/hyperactivity disorder (ADHD) was not significantly different between 2 groups ($P = .11$).

LIMITATIONS: The number of studies that assessed behavioral and ADHD outcome is small.

CONCLUSIONS: The findings demonstrate that IUGR is associated with lower cognitive scores in school-age children. However, further large-scale trials are needed to assess the effects of IUGR on the outcome of behavioral disorder and ADHD.

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Dr P. Chen conceptualized and designed the study, and reviewed and revised the manuscript; Dr J. Chen carried out the initial analyses, and drafted the initial manuscript; Drs Bo and Luo collected data, and critically reviewed the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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In humans, fetal development is a critical period that influences adult phenotypes, and a relevant marker of fetal development is intrauterine growth restriction (IUGR). IUGR is defined as a significant reduction in fetal growth rate that results in a birth weight in the lowest 10th percentile for gestational age.[1] IUGR is estimated to occur in 5% to 7% of all pregnancies. The most common identifiable cause of IUGR is placental-vascular insufficiency.[2] Fetuses affected by IUGR form a subset of cases of small for gestational age (SGA) infants, 2 terms are often used interchangeably.

By 2 to 3 years after birth, infants with IUGR will undergo catch-up growth of both the body and head[3]; however, approximately 10% of IUGR cases do not achieve catch-up growth and exhibit persistent growth delay.[4] Many studies have shown that IUGR is associated with increased neonatal morbidity and mortality as well as cardiovascular disease, insulin resistance, diabetes mellitus type 2, dyslipidemia, and end-stage renal disease in adulthood. In addition, numerous large-scale follow-up studies have shown that IUGR is associated with significant neurodevelopmental impairment across a range of outcomes in children.[5–7]

The effects of IUGR persist beyond the neonatal period and may have a profound impact on childhood development. To date, neurodevelopment in school-age children with IUGR has received comparatively little attention. Here, we present a meta-analysis and systematic review investigating the associations between IUGR and neurodevelopmental outcomes in school-age children. This review has the following aims: (1) to meta-analytically chart the cognitive and behavioral outcomes of children with IUGR; and (2) to examine the relationships among age at assessment, birth weight (BW), and gestational age (GA) and to determine their effect sizes with regard to the indices of cognitive functioning.

METHODS

Inclusion Criteria

The guidelines for reporting meta-analyses of observational studies published by Stroup et al[8] were taken into account in the design, performance, and report of this meta-analysis. The following search terms were used: intrauterine growth restriction, intrauterine growth retardation, small for gestational age, child development, neurodevelopment, cognition, intelligent, behavior and behavioral disorder, attention-deficit/hyperactivity disorder (ADHD). We searched the Medline, Embase, PsycINFO, and CINAHL databases for the period from 1980 to June 2015. The reference lists of the relevant published articles were used to identify other relevant articles for inclusion in this meta-analysis. The search was limited to English-language publications. The following inclusion criteria were used: (1) published in 1980 or later; (2) examined children with IUGR or children with SGA; (3) case-control design; (4) evaluations performed after the fifth birthdays of the enrolled subjects; and (5) reported cognitive data, behavioral data, or both. Studies were excluded if they did not meet all of these inclusion criteria. If multiple studies were published describing the same cohort of subjects at different ages, only the last published report was included (unless the cognitive and behavioral data were published separately, in which case both reports were included).

Data Extraction

The following data were entered into a customized database created for this meta-analysis: study design, attrition rate, demographic variables, geographic location, socioeconomic status, and detailed information on the cognitive and behavioral evaluations performed. The data from each study were reviewed twice to minimize the chance of data-entry errors.

Quality Assessment

We also performed quality assessment for each study included in the analysis by using existing checklists (Supplemental Table 6).[9] The quality rating scale assessed the likelihood of bias in 5 methodological domains: the participant sample (eg, population sample), the study design (prospective longitudinal follow-up), the quality of the data assessment (eg, gender and demographic data), the statistical analysis of the data (eg, the extent of control for potential confounding variables, such as maternal socioeconomic status), and the thoroughness of the results reported (eg, the presentation of neurologic outcomes). For the purposes of the subgroup analysis, studies that scored ≥8 were considered to have high quality, and studies scoring <8 were considered to have low quality.

Statistical Analysis

Statistical calculations were performed by using the computer programs SPSS version 16.0 (IBM SPSS Statistics, IBM Corporation, Chicago, IL) and Stata 12 statistical software (Stata Corp, College Station, TX). For dichotomous data, we presented the results as odds ratio (OR) with 95% confidence intervals (95% CIs). Data were combined for the meta-analysis to calculate a pooled estimate of the treatment effect for each outcome. For continuous data, we reported the standardized mean difference (SMD). Summary estimates of SMDs were obtained by using a random effects model. The I^2 statistic and Galbraith plots were used to assess

heterogeneity between trials, and heterogeneity was determined by using a random effects model. If substantial heterogeneity was found between trials (I^2 >50%), subgroup analyses of the main outcomes were performed. Potential publication bias was assessed by using the Egger test. A 2-sided $P < .05$ was regarded as significant for all analyses. The SMDs and trend lines were plotted graphically, with the size of each point representing the sample size of that study. Mean effect sizes were calculated for each domain, and overall effects (pooled across domains) were also calculated.

Pearson's correlation coefficients (r) were calculated to test the impact of mean BW, mean GA, and mean age at assessment on the strength of the studies' effect sizes for all indices of cognitive achievement and behavioral problems.

RESULTS

Cognition

Fifteen case-control studies (including 1499 cases and 1570 controls) that assessed children after their fifth birthdays were originally included in our study. Of the included studies, 3 and 12 assessed the neurodevelopmental outcomes of children with IUGR born at <35 and ≥35 weeks of gestation, respectively. Control subjects were matched with case subjects in ≥1 demographic features in all studies. In all 15 studies originally included in our study, the diagnosis of IUGR was made by abnormal Doppler velocimetry of the umbilical and middle cerebral arteries in the final assessment before birth and was confirmed by a BW <10th percentile for GA at birth.

Details on the studies included are provided in Table 1. The standardized cognitive tests that were used in these studies all had identical normative scales with age- and grade-based standard scores, such as Wechsler Preschool and Primary Scale of Intelligence, Revised Wechsler Intelligence Scale for Children, and Third Wechsler Intelligence Scale for Children. One[10] of the originally included studies did not present SDs and, thus, could not be included in the meta-analysis. Demographic data, such as gender, race, and socioeconomic status, were found in most studies. The results of the quality analysis are shown in Table 1; most studies were of high to medium quality (quality score >5).

IQ is used to test cognitive outcomes in children with IUGR. A random-effects meta-analysis showed that the SMD between the mean cognitive scores of the cases and controls was −0.38 (95% CI −0.51 to −0.25, $P < .00001$), indicating a significant difference between the 2 groups. However, the I^2 test for heterogeneity was significant (I^2 = 58.1%, $P = .003$). The results of the 14 studies included in the meta-analysis are shown in Fig 1. A Galbraith plot to assess study heterogeneity showed that the 2 studies[14,17]with the lowest SMD were the cause for this heterogeneity. Frisk et al[14] showed the lowest SMD between the cases and controls, which is possibly explained by the fact that the populations of the cases group (included many preterm infants) were different from controls (all term infants).Similarly, the populations of the cases group in Leitner et al[17] also included many extremely preterm infants with IUGR. Thus, heterogeneity (I^2 = 12.8%, $P = .32$) was no longer significant after excluding the data of these 2 studies; the SMD for remaining studies was −0.28 (95% CI −0.36 to −0.19, $P < .00001$). We assessed the possibility of publication bias by using the Egger test and did not find significant publication bias ($P = .903$).

The IQ test generates scores for both verbal IQ and performance IQ. Table 2 presents the sample sizes, number of studies, and 95% CI for effect sizes pertaining to verbal IQ and performance IQ. The scores of verbal IQ and performance IQ were available for 8 trials. Compared with the control group, the verbal IQ and performance IQ in the IUGR group were both significantly reduced. The combined SMD for verbal IQ was −0.26 (95% CI −0.36 to −0.16, $P < .00001$, heterogeneity: I^2 = 0%, $P = .44$), and the combined SMD for performance IQ was −0.36 (95% CI −0.46 to −0.25, $P < .00001$, heterogeneity: $I^2 = 0$, $P = .089$). Formal statistical testing showed no evidence of publication bias for the outcome of verbal IQ (Egger test, $P = .84$) and performance IQ (Egger test, $P = .38$).

Behavior Outcomes

Five publications met the inclusion criteria for the analysis of behavior outcomes, and they compared the incidence of behavioral problems between 237 SGA cases and 257 appropriate for gestational age (AGA) cases. The behavior function tests used in these studies included the Conner Abbreviated Parent Rating Scale, Strengths and Difficulties Questionnaire, Child Behavior Check List tests, and mean reaction time. The demographic features and behavioral data from these studies are summarized in Table 3. When data from all studies were combined, the overall SMD was 0.31 (95% CI 0.13 to 0.48, $P = .001$, heterogeneity: I^2 = 0%, $P = .58$). This indicated that a significant difference between the 2 groups (Fig 2).

Four publications (including 206 cases and 194 controls) used formally defined criteria to diagnose ADHD in cases and controls (eg, ADHD Rating Scale-IV, Brown Attention Deficit Disorder scale), and the details of these assessments are shown in Table 4 and Fig 2. These studies were selected for a random-effects meta-analysis to calculate the OR of ADHD in children with IUGR (Fig 3). The cases had a pooled

TABLE 1 Studies That Reported on Cognitive Data in Children With IUGR

Studies	No. Participants	Year of Birth	Birth Weight (SD),g	Gestational Age (SD), wk	Age at Evaluation, y	Type of Test	Mean Score (SD)	Quality Score
Westwood et al, [10]1983	SGA 33	1960–1966	NA	NA	13–19	WISC	103.6	7
	AGA 33						108.7	
McCarton et al, [11]1996	SGA 85	1975–1987	1196 (321)	32.5 (2.6)	5–6	WPPSI-R	85.4 (14.5)	9
	AGA 206		1645 (425)	32.5 (2.4)			91.4 (16.5)	
Strauss and Dietz, [12] 1998	SGA 154	1959–1976	2260 (290)	NA	7	WISC	91 (13)	8
	AGA 154		3000 (320)				92.4 (13.6)	
Sommerfelt et al, [13] 2000	SGA 338	1986–1988	NA	NA	5	WPPSI-R	106 (15)	6
	AGA 335						110 (15)	
Frisk et al,[14] 2002	SGA 71	1984–1987	NA	21–41wk	7–9	WISC- III	97.5 (12.6)	8
	AGA 16			>37 wk			112.4 (10.5)	
Hollo et al,[15] 2002	SGA 106	1985	2452	38 (5)	10	WISC-	90.8 (12.4)	5
	AGA 105		3378	37.5 (4.9)		R	94.2 (10)	
Kulseng et al,[16] 2006	SGA 60	1986–1988	2920 (210)	39.5 (1.1)	14	WISC- III	94.1 (14.3)	9
	AGA 83		3690 (458)	39.6 (1.2)			97.1 (14.3)	
Leitner et al,[17] 2007	SGA 123	1992	1842 (411)	36.9 (2.4)	10	WISC-R	98.39 (12.9)	6
	AGA 63		2826 (755)	37.6 (3.4)			107.5 (10.4)	
Tideman et al,[18] 2007	SGA 19	1982–1985	NA	38 (4)	18.1	WAIS-	94.5 (15.3)	6
	AGA 23			40		III	101.7 (13.3)	
Geva et al,[19] 2008	SGA 138	1992–1995	1839 (339)	36.9 (2.4)	10	WISC-	101.1 (13.8)	9
	AGA 64		2812 (755)	37.6 (3.4)		R	107.1 (10.8)	
Geva et al,[20] 2009	SGA 20	1992–1995	2.47 (2.53)	36.6 (2.3)	6	WPPSI	105.1 (13.85)	7
	AGA 19		51.6 (25.37)	38.7 (1.9)			115.3 (13.85)	
Martinussen et al, [21] 2009	SGA 49	1986-	2915 (216)	39.5 (1.1)	15	WISC- III	95 (15)	7
	AGA 57	1998	3714 (486)	39.6 (1.1)			98 (15)	
Theodore et al,[22] 2009	SGA 241	1995–1996	NA	NA	7	WISC- III	108.6 (13)	9
	AGA 350						110.7 (13.6)	
Morsing et al,[23] 2011	SGA 34	1998–2004	642	31.5 (5.4)	5–8	WISC-	78.9 (16.6)	10
	AGA 34		1015	30.3 (6.6)		R	90.1 (14.2)	
Tanis et al,[24] 2012	SGA 28	2000–2001	888	29.7	8.6	WISC- III	93.2 (10.6)	9
	AGA 28		1163	29.4			97.5 (12.9)	

NA, indicates data were not reported or not extractable; WISC, Wechsler intelligence scale for children; WISC-R, revised Wechsler intelligence scale for children; WISC-III, third Wechsler intelligence scale for children; WPPSI, Wechsler Preschool and Primary scale of intelligence; WPPSI-R, revised Wechsler Preschool and Primary scale of intelligence.

OR of 2.36 (95% CI 0.78 to 7.11) compared with the controls ($P = .11$). There were no significant differences between the 2 groups. Heterogeneity was not significant between these studies ($P = .304$).

However, the number of studies that have assessed behavioral ($n = 5$) and ADHD ($n = 4$) outcome is too small to make the results of these tests reliable.

Relationship Between Effect Sizes for IQ Score and Age at Assessment, BW, and GA

Table 5 displays the Pearson correlation coefficients for the relationships between the mean age at assessment, BW, GA, and the studies' effect sizes for cognitive outcomes. The correlation coefficients for the relationships between the effect sizes for IQ scores and mean BW, and IQ scores and mean GA were all small and nonsignificant (all r values >0.5; all $P > .05$).

The correlation coefficients for the relationships between the effect sizes for performance IQ scores and mean BW, performance IQ scores and mean GA, and verbal IQ scores and mean BW were all small and nonsignificant (all r values >0.4; all $P > .05$). Mean age was not correlated with IQ scores, verbal IQ scores, and performance IQ scores (all r values <0.2; all $P > .05$).

DISCUSSION

Our meta-analysis shows that IUGR birth is associated with lower cognitive scores in school-age children than in AGA-born controls. Lower cognitive scores for the cases were noted in all of the studies selected for this meta-analysis, highlighting the developmental vulnerability of the IUGR brain.

TABLE 2 Studies That Reported on Verbal IQ Score and Performance IQ Score Data in Children With IUGR

Studies	No. Participants	Verbal IQ Score[a]	Verbal IQ SMD (95% CI)	Performance IQ Score[b]	Performance IQ SMD (95% CI)
McCarton et al,[11] 1996	SGA 85	85.2 (15)	−0.30 (−0.55 to −0.04)	88.1 (14.4)	−0.40 (−0.65 to −0.14)
	AGA 206	90.1 (17.1)		94.3 (16)	
Sommerfelt et al,[13] 2000	SGA 338	102 (15)	−0.20 (−0.35 to −0.05)	108 (15)	−0.28 (−0.43 to −0.12)
	AGA 335	105 (15)		112 (14)	
Frisk et al,[14] 2002	SGA 71	103.9 (13.2)	−0.40 (−0.94–0.15)	107.7 (16)	−0.44 (−0.99–0.11)
	AGA 16	108.9 (8.7)		114.6 (13.8)	
Hollo et al,[15] 2002	SGA 106	90.8 (12.4)	−0.30 (−0.57 to −0.03)	94.9 (12.8)	−0.46 (−0.73 to −0.19)
	AGA 105	94.2 (10)		100.8 (12.8)	
Tideman et al,[18] 2007	SGA 19	94.5 (15.3)	−0.51 (−1.12–0.11)	98.0 (16.1)	−0.62 (−1.24–0.00)
	AGA 23	101.7 (13.3)		107.7 (15.2)	
Martinussen et al,[21] 2009	SGA 49	92 (17)	−0.06 (−0.44–0.32)	95 (20)	−0.31 (−0.69–0.08)
	AGA 57	93 (16)		101 (19)	
Morsing et al,[23] 2011	SGA 34	83.8 (17.3)	−0.76 (−1.26 to −0.27)	79.3 (16.0)	−0.48 (−0.96–0.01)
	AGA 34	96.0 (14.5)		87.2 (17.2)	
Tanis et al,[24] 2012	SGA 28	95 (13.6)	−0.15 (−0.68–0.37)	92.1 (15.1) 98.6 (12.4)	−0.46 (−0.99–0.07)
	AGA 28	97.2 (15.1)			
Total	SGA 730		−0.26 (−0.36 to −0.16)		−0.36 (−0.46 to −0.25)
	AGA 804				
P			<.0001		<.0001

[a] Values are expressed as mean (SD).
[b] Values are expressed as mean (SD).

Further large-scale trials are needed to adequately assess the effects of IUGR on the behavior and outcome of ADHD, because the number of studies that have assessed these outcomes is small.

Children with lower GA and BW may be more prone to cognitive and behavior problems than infants with higher GA and BW. As we know, human brains with lower GA are more vulnerable; and GA at birth clearly plays an important role in long-term outcomes with regard to brain. According to increasing evidence, extremely premature infants with IUGR carry a significantly higher risk for long-term cognitive sequelae compared with term infants with IUGR.[29–32] Many studies were included in the correlational analyses, and significant results were also obtained.[33,34] BW was shown to be specifically correlated with hippocampal volume and, to a lesser extent, with total cortical gray matter volume at term-equivalent ages. A similar inverse relationship was previously demonstrated for the incidence of major disabilities in very preterm children in multiple meta-analyses, and was also found to

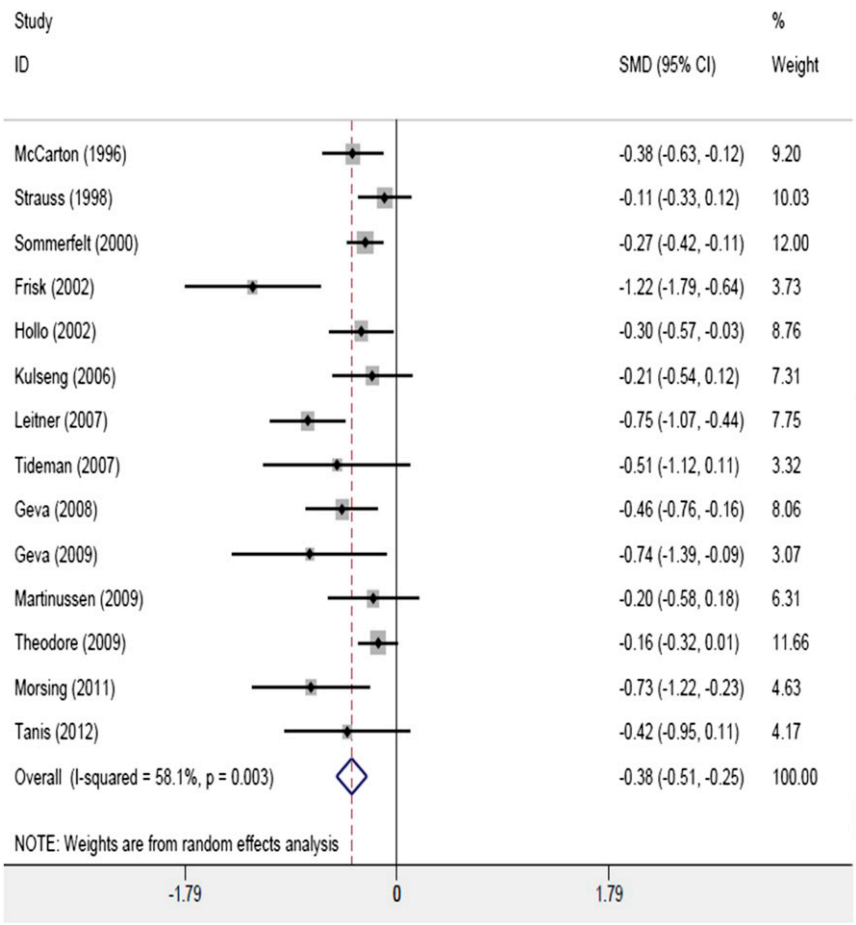

FIGURE 1
Random-effects meta-analysis comparing cognitive test scores between control groups and IUGR groups. The test for heterogeneity was significant (I^2 = 58.1%, P = .003); the test scores between 2 groups were significantly different (P < .00001).

TABLE 3 Studies That Reported on Behavior Data in Children With IUGR

Studies	No. Participants	Year of Birth	Birth Weight (SD), g	Gestational Age (SD), wk	Age at Evaluation, y	Type of Test	Mean Score (SD)
Hollo et al,[15] 2002	SGA 105	1985	2452	38 (5)	10	CPRS	8.8 (5.7)
	AGA 102		3378	37.5 (4.9)			6.9 (2.9)
Indredavik et al,[25] 2010	SGA 60	1986–1988	2921 (211)	39.5	14	CBCL	3.0 (4.7)
	AGA 83		3691 (459)	39.6			2.0 (2.7)
Morsing et al,[23] 2011	SGA 34	1998–2004	642	31.5 (5.4)	5–8	SDQ	9.6 (5.1)
	AGA 34		1015	30.3 (6.6)			7.8 (4.9)
Tanis et al,[24] 2012	SGA 28	2000–2001	888	29.7	8.6	CBCL	32 (15)
	AGA 28		1163	29.4			30 (18)
Reveillon et al,[26] 2013	SGA 10	NA	1038 (292)	30.7 (2.8)	6–7	Mean reaction time	652.9 (52.1)
	AGA 10		1273 (478)	29.4 (3.5)			664.5 (29.4)

CBCL, Child Behavior Check List; CPRS, Conner Abbreviated Parent Rating Scale; NA, indicates data were not reported or not extractable; SDQ, Strengths and Difficulties Questionnaire.

be related to the risk of disruption of neurobehavioral development and brain connectivity, which increases with decreasing BW.[9,35,36] These findings underline the importance of BW and GA as predictors of later neural development. The correlation coefficients for the relationships between the effect sizes for IQ scores and both BW and GA were not significant in our study, and we hypothesize that this finding was due to differences in the test methods used between the included studies. Thus, many large-scale studies are needed to confirm the relationships between GA (and BW) and cognitive outcomes among children with IUGR.

The key factors associated with the neurodevelopmental outcome of IUGR after birth include socioeconomic status, gender, and race. Studies have also shown that socioeconomic status factors are strongly related to the developmental outcomes of children with IUGR.[37,38] Children with IUGR born SGA and reared in poorer environments demonstrate significantly lower professional attainment and income than those reared in more stimulating environments; thus, childhood intelligence is associated with later academic achievement and occupational status. The difference in the association of IUGR with poor neurodevelopmental outcome between girls and boys is not well

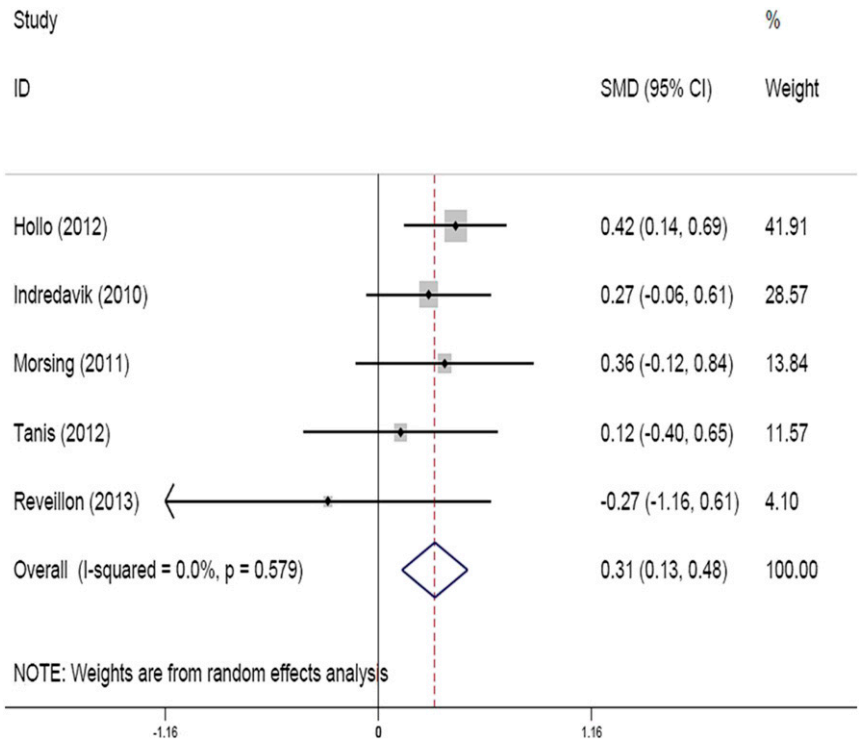

FIGURE 2
Random-effects meta-analysis comparing behavior test scores between control groups and IUGR groups. The test for heterogeneity was not significant (I^2 = 0%, P = .579); the test scores between 2 groups were significantly different (P = .001).

understood. Others have also found that brain development in boys is more vulnerable to the effects of IUGR than that in girls.[39,40] Most studies included in our meta-analysis featured cases and controls that were matched for ≥1 demographic variables, so effect of these factors on final outcomes may be negligible. The age of the children at the time of assessment in each included study was variable. Our study showed that there was no significant correlation between age and IQ values, but the conclusions of other experiments were the opposite.[41] At the same time, studies of neurodevelopmental assessments of infants with IUGR in adulthood are lacking. Thus, further large-scale studies are needed to

TABLE 4 Studies That Reported on ADHD Data in Children With IUGR

Studies	No. Participants	Year of Birth	Birth Weight (SD),g	Gestational Age (SD), wk	Age at Evaluation, y	Type of Test	The Ratio of ADHD
Indredavik et al,[27] 2004	SGA 60	1986–1988	2921(211)	39.5	14	ADHD Rating scales IV	2/60
	AGA 83		3691(459)	39.6			1/83
Morsing et al,[23] 2011	SGA 68	1998–2004	642	31.5(5.4)	5–8	Brown's ADD scales	13/68
	AGA 34		1015	30.3(6.6)			2/34
Klaric et al,[28] 2012	SGA 50	2002–2004	NA	40	6	NEPSY	0
	AGA 50			40			3/50
Tains et al,[24] 2012	SGA 28	2000–2001	888	29.7	8.6	Dutch ADHD Q	6/28
	AGA 27		1163	29.4			2/27

ADD, attention-deficit disorder; Dutch ADHD Q, Dutch ADHD questionnaire; NA, indicates data were not reported or not extractable; NEPSY, Developmental Neuropsychological Assessment.

confirm the relationships between age and cognitive outcomes among children with IUGR.

IUGR is associated with an increased risk for behavioral disorders or their symptoms and poorer neurobehavioral outcomes in early childhood.[42–44] However, the number of studies that have assessed behavioral and ADHD outcomes is insufficient, and further large-scale trials are needed to adequately assess the effects of IUGR on the outcome of behavior and ADHD among school-age children.

Examining the perinatal course of these children may shed some light on the mechanisms underlying these differences. In most cases, SGA status with abnormal fetal Doppler ultrasound finding represents pathologic smallness due to placental insufficiency. The fetal response includes slowing of growth, elevated resistance of the umbilical artery flow, and increased blood flow to the brain.[45] Some studies had shown that children who were SGA showed reduced cerebral cortical gray matter volume and cerebellar white matter volumes, reduced basal ganglia volumes, and reduced overall cortical surface areas compared with premature infants born AGA.[46,47] In humans, IUGR also is associated with a severe reduction in cortical growth and a significant decrease in cell number in the future cortex.[48] At the same time, IUGR neonates are at higher risk of postnatal complications, such as intraventricular hemorrhage, premature birth, and sepsis.

TABLE 5 Pearson Correlation Coefficients Between Cognitive Outcome Measures and Age, BW, and GA

	n	Age		BW		GA	
		P	*r*	*P*	*r*	*P*	*r*
Total IQ	15	0.564	0.162	0.103(10)	0.546	0.133(10)	0.509
VIQ	8	0.944	0.030	0.497 (5)	0.406	0.517 (6)	0.334
PIQ	8	0.849	0.081	0.127 (5)	0.771	0.143 (6)	0.673

Number of included studies is indicated in parentheses.
n, the number of included studies; PIQ, performance IQ; VIQ, verbal IQ.

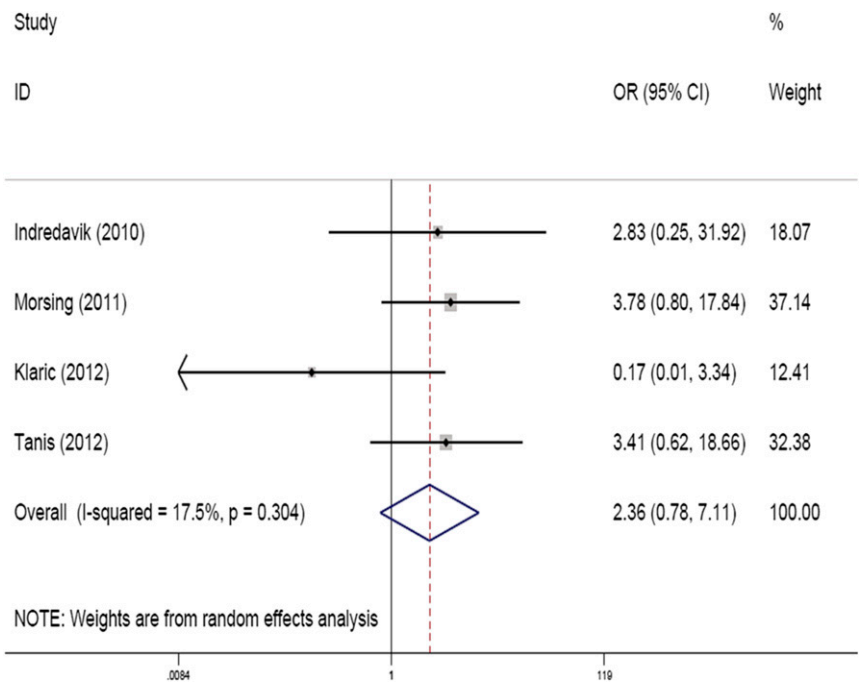

FIGURE 3
Random-effects meta-analysis comparing the incidence of ADHD between control groups and IUGR groups. The test for heterogeneity was not significant (I^2 = 17.5%, P = .304); the incidence of ADHD between 2 groups was not significantly different (P = .11).

Similarly, increased incidences of neurocognitive and behavioral abnormalities were found to be

correlated with MRI abnormalities in the brains of 14-year-old children who had IUGR.[49] Therefore, these findings showed that the disturbance in brain structure of IUGR possibly accounted for the abnormality of cognition and behavior.

There are some limitations to this meta-analysis. First, the cognitive and behavioral outcome assessments used across studies varied, which restricted the power of the meta-regression analyses used to investigate developmental influences. Second, we limited our search to English-language literature because of practical difficulties in abstracting data from articles published in other languages; however, our meta-analysis still contained studies from many countries, and no significant differences in cognitive outcomes were observed between studies conducted in the United States and those conducted elsewhere. Because of the limited information contained in each abstract, we cannot state whether these studies fulfilled all of the inclusion criteria of our meta-analysis. Third, the number of included trials that examined the effects of IUGR on behavioral outcomes was very small; only 4 of the included trials evaluated the association of ADHD with IUGR. Fourth, the most common criteria used to diagnose ADHD are those of the Diagnostic and Statistical Manual of Mental Disorders, Third Edition or the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, but criteria used in our study were variable, which may have affected the results.

Because IUGR was found to be associated with neurodevelopmental impairments in childhood, it is important that infants with IUGR are identified by obstetricians for in-depth neurodevelopmental assessment during infancy and early childhood. Effective interventions during this time may be necessary, as previous research has demonstrated that they may promote early neurodevelopment, and reduce academic failure and behavioral difficulties.[50–52] However, many studies need to be conducted, and more focused therapeutic interventions should be developed to decrease or prevent these long-term impairments after IUGR.

CONCLUSIONS

According to our meta-analysis, IUGR birth is associated with lower cognitive scores in school-age children than in AGA-born controls. The IQ scores of the IUGR group were not significantly correlated with mean BW, GA, and age; so further follow-up studies were needed to investigate whether GA at birth or other factors have any influence on the outcomes among children with IUGR. The number of studies that have assessed behavior and ADHD outcome is insufficient, and further large-scale trials are needed to adequately assess the effects of IUGR on the outcome of behavioral disorders and ADHD.

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ABBREVIATIONS

ADHD: attention-deficit/hyperactivity disorder
AGA: appropriate for gestational age
BW: birth weight
CI: confidence interval
GA: gestational age
IUGR: intrauterine growth restriction
OR: odds ratio
SGA: small for gestational age
SMD: standardized mean difference

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