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# Intrauterine Growth and Neuropsychological Performance in Very Low Birth Weight Preschoolers

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**Abstract**

In this study we examined the association between intrauterine growth, indexed either as a categorical variable or continuous dimension, and neuropsychological outcome, in a very low birth weight (VLBW) sample of 143 preschoolers. When the commonly used split at the 10th percentile rank was applied to classify intrauterine growth restriction (IUGR), we found that the growth restricted group ($n = 25$) exhibited significantly poorer performance in the global motor domain, but not on any other neuropsychological measure. In contrast, when adequacy of intrauterine growth was indexed by standardized birth weight, a continuous dimension, this early risk factor explained a unique portion of the variance in global cognitive abilities and visuospatial skills, as well as in global, fine, and gross motor skills. These findings are consistent with recent magnetic resonance imaging data disclosing global neurodevelopmental changes in the brains of preterm infants with IUGR. When cases classified with IUGR (<10th percentile) were excluded, the relationship between adequacy of intrauterine growth and global cognitive abilities remained significant despite range restriction. Hence, an association between appropriateness of intrauterine growth and global intellectual outcome may be observed even within the population of VLBW preschoolers with adequate standardized birth weight. (*JINS*, 2012, *18*, 200–211)

**Keywords:** Preterm birth, Intrauterine growth retardation, Preschool children, Intelligence tests, Motor skills, Language tests

## INTRODUCTION

Intrauterine growth restriction (IUGR) is a major risk factor for fetal death (Silver, 2007), accounting for 52% of unexplained cases of still births (Froen, Gardosi, Thurmann, Francis, & Stray-Pedersen, 2004). A newborn whose birth weight for gestational age falls below the 10th centile is typically classified as growth restricted or "small for gestational age" (SGA). Thus, the newborn population is artificially split into those with, and those without, IUGR, based on birth weight data that are stratified by gestational age. The latter newborn group has also been labeled "appropriate for gestational age" (AGA). The 10th percentile is the most commonly applied threshold for IUGR, yet other cutoffs have been used, ranging from the stringent cutoff at -2 standard deviations (e.g., Bergvall et al., 2006; Ley, Tideman, Laurin, Bjerre, & Marsal, 1996), to the lenient cutoffs at the 15th (e.g., Hu, Simonet, & Luo, 2010; Kronenberg, Raz, & Sander, 2006) or even the 20th (Guellec et al., 2011) percentile ranks. Although the term SGA has been used extensively as a proxy for restricted fetal growth in both term and preterm neonates, IUGR, a construct connoting a pathological process, more adequately captures the phenomenon in the very preterm birth population. This is because SGA babies delivered at term could be constitutionally small, rather than growth restricted, as biological variation in fetal size is largely a third trimester occurrence (Ananth & Vintzileos, 2009).

The etiology of IUGR is multifactorial and may include maternal/uterine, fetal, placental, and external factors. It is associated not only with increased perinatal morbidity and mortality, but also with long-term outcome risk (Rizzo & Arduini, 2009). Because placental metabolism and transport are often affected in IUGR in humans (Marconi, & Paolini, 2008), the condition often necessitates weighing the hazard of continuing *in utero* fetal life under adverse conditions (chronic hypoxemia and restricted nutrient supply), versus the risk of induced (very) preterm birth (Mandruzzato et al., 2008). In an earlier investigation on a largely middle class

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sample of children of mothers with pregnancy induced hypertension, we found that suboptimal intrauterine growth was associated with neuropsychological skill deficits, while the severity of maternal hypertension—the etiological factor that had apparently led to growth restriction in the first place—was not (Kronenberg et al., 2006).

The results of studies published in the last decade suggest that preschool and school age, as well as early adulthood, neuropsychological outcome is adversely affected by IUGR in term, or mostly term, birth samples in comparison to AGA controls (e.g., Bergvall, Iliadoum Johansson, Tuvermo, & Cnattingius, 2006; Bergvall et al., 2006; Frisk, Amsel, & Whyte, 2002; Geva, Eshel, Leitner, Fattal-Valevski, & Harel, 2008; Larroque, Bertrais, Czernichow, & Leger, 2001; Leitner et al., 2000, 2007; Ley et al., 1996; Lundgren, Cnattingius, Jonsson, & Tuvmo, 2003; O'Keeffe, O'Callaghan, Williams, Najman, & Bor, 2003; Paz et al., 2001; Sommerfelt et al., 2000; Tideman, Marsal, & Ley, 2007). Studies on preterm-birth (or mostly preterm) children with history of IUGR, who were compared to their AGA counterparts, also yielded similar findings (e.g., Bergvall et al., 2006; Bergvall et al., 2006; Kronenberg et al., 2006; Valcamonico, 2004).

In addition to differences in the samples' chronological and gestational age ranges, or the threshold selected for IUGR classification, the studies varied in the extent of consideration given to the presence of neuromotor handicaps and perinatal brain lesions. The birth period, whether during the pre-surfactant or surfactant era, and the level of adjustment for perinatal confounds, also differed between investigations.

Eleven studies focused on IUGR in very preterm (VPT; gestational age $<32$) or very low birth weight (VLBW; birth weight $<1500$ g) infants, populations for which intrauterine growth indices are likely to reflect nongenetic pathological processes (Ananth & Vintzileos, 2009). The studies differed in the participants' age range, focusing on infancy (Latal-Hajnal, von Siebenthal, Kovari, Bucher, & Largo, 2003; Procianoy, Koch, & Silveira, 2009; Sung, Vohr, & Oh, 1993), the preschool years (Gutbrod, Wolke, Soehne, Ohrt, & Riegel, 2000; Kok et al., 1998), school age (Hutton, Pharoah, Cooke, & Stevenson, 1997; Kan et al., 2008; Kok et al., 1998; Guellec et al., 2011), or young adulthood (Weisglas-Kuperus et al., 2009). A single study (Monset-Couchard, de Bethmann, & Relier, 2004) focused on multiples, discordant for IUGR, with a wide age range (3–17 years). Three of the eight studies that had followed children beyond infancy reported significant group differences between VLBW and/or VPT participants with and without IUGR in the frequency of visual abnormalities, speech problems, and behavioral disturbance (Monset-Couchard et al., 2004), in the frequency of gross motor and minor neurological dysfunction, cognitive dysfunction, and special education placement (Kok et al., 1998), and in the frequency of minor cognitive dysfunction and inattention/hyperactivity (Guellec et al., 2011). Hutton et al. (1997) reported that a ratio of actual to expected intrauterine growth was linearly related to IQ at 8 or 9 years of age, while Weisglas-Kuperus et al. (2009) reported that intelligence was more strongly associated with IUGR when both birth weight and head circumference were $\leq -2$ *SD*s below the mean for the infant's gestational age. However, 5 of the 11 above listed studies (Gutbrod et al., 2000; Kan et al., 2008; Latal-Hajnal et al., 2003; Procianoy et al., 2009; Sung et al., 1993) were unable to document a relationship between intrauterine growth and neurodevelopmental outcome within the VPT /VLBW population.

With the exception of the early school investigation by Kan et al. (2008) and the infant study by Procianoy et al. (2009), both with negative findings, as well as the school and preschool-age study by Guellec et al. (2011), the eight remaining above mentioned VPT/ VLBW studies included children who had received Neonatal Intensive Care Unit (NICU) services before the availability of surfactant treatment. Hence, in addition to multiple differences on variables associated with improvements in the standard of care between the presurfactant and surfactant periods (e.g., Hack, Friedman, & Fanaroff, 1996), studies including samples of children born before surfactant availability could not adequately represent the lower end of the gestational age spectrum. These infants, with extremely low birth weight or gestational age, were unlikely to survive at the time.

The dearth of preschool or school age outcome data pertaining to VLBW children born during the surfactant era and classified with IUGR provided the initial impetus for our investigation. We expected IUGR classification to be linked to poorer neuropsychological performance in a VLBW preschool cohort receiving current critical care. We used the commonly applied partitioning of the natural continuum of intrauterine growth data at the 10th centile rank into IUGR (SGA) *versus* adequate growth (AGA) for three reasons. First, to provide continuity with the bulk of the available body of literature and with clinical practice; second, since there is no known threshold with biological interpretability to justify a binary split in the first place; and third, because of sampling constraints (a more stringent cutoff would have yielded too few subjects for analyses). A suburban, middle class sample was used to reduce confounding influences linked to biological and social risk factors thought to be more commonly associated with lower socioeconomic status (SES) (Hjern & Thorngren-Jerneck, 2008). Thus, in weighing the trade-off between internal and external validity, we opted to enhance the former, albeit at the expense of the latter.

Artificial categorization of individual differences data that is inherently continuous, in medical research and practice, involves treatment of individuals within group as if they are identical with respect to the attribute in question (Maxwell & Delaney, 1993) and is primarily driven by need for simplification. Yet the grouping of continuous variables into $\geq 2$ categories is not without considerable cost, as it leads to substantial loss of power and incomplete correction for confounding factors (Naggara et al., 2011; Pedhazur, 1982) as well as to spurious main effects and interactions not evident in continuous variable analysis (Kang & Waller, 2005; MacCallum, Zhang, Preacher, & Rucker, 2002; Maxwell & Delaney, 1993). In this investigation, we expected that treating intrauterine growth as a continuous dimension will allow us to demonstrate a corresponding neuropsychological performance gradient that cannot be tapped using the common split at the 10th percentile of birth weight stratified by gestational age. To examine our predictions, we used a sample of VLBW preschoolers whose birth weight covered a broad range (1st–91st percentile), yet did not include extremely large for gestational age cases (Hu et al., 2010) at increased medical risk (e.g., Kaymak et al., 2011).

In contrast with earlier IUGR investigations, an additional objective of the current study was the examination of neuropsychological correlates of intrauterine growth within the VLBW population with appropriate intrauterine growth (growth for gestational age $\geq$10th percentile). We hypothesized that linear relationships between intrauterine growth and neuropsychological outcome will prove to be robust, hence amenable to detection when the range of the former variable is restricted to cases with adequate growth. Finally, in accord with MRI studies reporting global cerebral morphological changes in preterm-birth children with IUGR (Dubois et al., 2008; Tolsa et al., 2004), we expected to document associations between adequacy of intrauterine growth and multiple neuropsychological skills. Yet because evidence also exists for greater structural changes in posterior (occipital), relative to anterior, brain regions in the VLBW IUGR population (Thompson et al., 2007), we also expected to observe salient relationships between growth and visuospatial skills. Such results would be commensurate with our earlier findings of visuospatial, but not verbal, deficits in growth restricted preterm-birth children born to hypertensive mothers (Kronenberg et al., 2006).

## METHOD

### Participants

Outcome data were available from 155 VLBW preschoolers (81 males, 74 females), graduates of the William Beaumont Hospital (WBH) Neonatal Intensive Care Unit (NICU) at Royal Oak MI. At WBH NICU, resuscitation is attempted for all infants with an estimated gestational age $\geq$ 23 0/7 weeks (Batton, DeWitte, & Pryce, 2011). The children were born between 1996 and 2001 and evaluated between July 2002 and July 2007. Twelve children were removed from the sample: Three with cerebral palsy (CP), four with intracranial hemorrhage (ICH) grade >2 (a single untestable case also with autistic-like symptoms), three with both CP and ICH grade >2, one with right porencephaly, and one with hydrocephalus. We excluded moderate or severe CP and ICH as such pathologies may involve distinct causal mechanisms (e.g., Truwit, Barkovich, Koch, & Ferriero, 1992) with independent effects on neuropsychological functioning (e.g., Hou et al., 2010; Raz et al., 1995) that may, in turn, confound the hypothesized effects of IUGR. Altogether, 143 cases (69 boys and 74 girls) were included, approximately 25% of the relevant hospital cohort. Gestational age ranged from 23 0/7 to 34 6/7; the mean ($\pm$ *SD*) was 28.65 $\pm$ 2.65 weeks. Gestational age was determined by maternal dates and confirmed by early prenatal ultrasound in >95% of cases. Birth weight ranged from 365 to 1495 g, while mean birth weight ($\pm$ *SD)* was 1075 $\pm$ 282 g.

The catchment area of WBH NICU includes primarily middle class strata, residing in suburban Detroit. Approximately 85% of admissions were covered by private medical insurance whereas 15% were insured through Medicaid. These data are consistent with our sample's composition, where the median Hollingshead (1975) socioeconomic status (SES) score was 51.5 on a scale with an upper limit of 66. The 1996–2001 NICU cohort (<1500 g, gestational age <35 weeks) was comprised of 8.7% African Americans, 51.05% males, and 41.72% multiples, while our sample included 8.4% African Americans ($\chi^2[1] = .00$, not significant [n.s.]), 48.25% males ($\chi^2[1] = .27$, n.s.), and 42.65% multiples ($\chi^2[1] = .01$, n.s.). The average gestational age (mean $\pm$ *SD* = 28 $\pm$ 2.8 weeks) or birth weight (1044 $\pm$ 294 g) of the cohort was almost identical to the sample average.

Of the 143 subjects, 106 were recruited through a follow-up study of preterm children in the preschool years (26 with IUGR *vs.* 80 without), whereas 37 of the children were recruited through a related concurrent study on the preschool outcome of mild ICH (2 with IUGR *vs.* 35 without). Thus, the proportion of IUGR cases relative to cases without IUGR differed by recruitment mechanism/study (Fisher exact $p = .0145$), with a significantly lower proportion of IUGR cases ascertained through the ICH study. Presumably, this association is partly explained by the reduced rate of IUGR in VLBW children with documented ICH, compared to those without (e.g., Amato, 1992; Amato, Konrad, Huppi, & Donati, 1993). We reasoned that, if anything, an increase in ICH frequency in our comparison group should mitigate against our hypotheses. IUGR classification was assigned when birth weight, stratified by gestational age at delivery, was <10th percentile according to norms by Kramer et al. (2001). Age range at recruitment and participation rates differed somewhat between the studies (4–6 years for the prematurity follow-up and 3–5 years for the ICH study, participation rates of 64% and 56% of contactable families, respectively).

According to maternal report, none of the cases sustained a head injury with loss of consciousness. In eight cases the family reported seizure history (One with IUGR *vs.* seven without), yet only one of the children (without IUGR) had received antiseizure medication, for petit mal, in the past. A single mother reported drinking one glass of wine per day and 18 mothers reported cigarette smoking during pregnancy (see Table 2).

Detailed information about each child's sociodemographic characteristics, pre-, peri-, and neonatal backgrounds, as well as exposure to diagnostic and treatment procedures, was obtained from hospital charts and electronic data bases (see Tables 1–3). The tables provide a comparison of a group of 25 children with IUGR (birth weight <10th centile or $z < -1.28$ *SD*) with a comparison group of 118 children with standardized birth weight $\geq$10th centile, that is, appropriate intrauterine growth (AIUG).

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**Table 1.** Group Comparisons of Demographic and Sociofamilial Characteristics[a]

| Characteristics | Appropriate growth comparison group $n = 118$ | Intrauterine growth restriction $n = 25$ |
|---|---|---|
| Adjusted age (mo) | 58.14 ± 9.81 | 59.93 ± 8.45 |
| Gender (M:F)[b*] | 51 : 67 | 18 : 7 |
| Multiples | 53 | 8 |
| Race (W : O)[c] | 95 : 24 | 21 : 4 |
| SES[d] | 50.21 ± 11.93 | 49.41 ± 11.08 |
| Parental VIQ[e] | 105.08 ± 12.18 (103) | 105.56 ± 9.30 (23) |
| Mother's education (yrs) | 15.63 ± 2.47 (117) | 16.48 ± 2.58 |
| Father's education (yrs) | 15.45 ± 2.83 (116) | 16.04 ± 3.06 |

*Note.* $^*p < .05$. Frequencies are reported for discrete data, means and standard deviations for continuous data. Group differences examined *via t* test (continuous data), $2 \times 2$ $\chi^2$ with Yates correction (discrete data), or Fisher exact probability test (less than five cases per cell).
[a] All comparisons between Intrauterine Growth Restriction (intrauterine growth *z* score $< -1.28$ *SD* or 10th percentile) and Comparison group (intrauterine growth *z* score $\geq -1.28$).
[b] M = male, F = female.
[c] W = White, O = Other (12 African Americans, 1 African American/Asian, 5 Asian/Caucasian, 1 African American/Caucasian, 1 Indian/Asian, 1 Indian/African American, 7 Hispanic/Caucasian).
[d] Hollingshead's (1975) Four Factor Index of Social Status.
[e] Prorated parental IQ based on three subtests (Vocabulary, Similarities, and Information) of the Wechsler Adult Intelligence Scale-III (Wechsler, 1997); Testing was completed on the biological mothers in all cases except for 11 cases where the mother was unavailable and the father was tested instead (2 cases in the IUGR group and 9 cases in the AIUG group).

Table 1 reveals no significant differences between the group with IUGR and the AIUG (comparison) group on any of the variables, with the exception of the male to female ratio. Table 2 presents the ante-, peri-, and neonatal characteristics of both groups. The table shows a significantly increased frequency of chorioamnionitis in the comparison group, while the IUGR group, not surprisingly, showed an increased rate of maternal hypertension—a leading cause of IUGR (Kronenberg et al., 2006)—and related Cesarean section. The table reveals that the IUGR group had a significant advantage in gestational age, averaging approximately three additional weeks, while the less mature AIUG group showed an increased overall rate of neonatal complications, associated with elevated rates of hyaline membrane disease, patent ductus arteriosus, and apnea. Finally, Table 3 presents ante-, peri-, or neonatal treatment and diagnostic procedures. The table reveals an increased frequency of surfactant treatment in the AIUG group, while treatment to control maternal hypertension was required at a higher rate in the IUGR group. Additionally, peak supplemental oxygen requirement was significantly higher in the AIUG group, compared to the IUGR group, though there were no significant group differences in the number of ventilation or oxygenation days.

## Neuropsychological Assessment

Children were evaluated in one or two sessions, depending upon the child's attention span. The examiners were graduate students trained extensively in developmental neuropsychological assessment. To prevent bias in administration and scoring, they were kept unaware of the child's perinatal status. All testing and perinatal background data included in this manuscript were obtained in compliance with the regulations of the Human Investigation Committees of Wayne State University and WBH. Intellectual functioning was assessed using the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R; Wechsler, 1989). Due to time constraints, four of the five subtests from the Verbal (VIQ) subscale (Information, Similarities, Vocabulary, and Comprehension) and four of the five subtests from the Performance IQ (PIQ) subscale (Geometric Design, Mazes, Block Design, and Picture Completion) were administered to each child. Motor skills were assessed using the Peabody Developmental Motor Scales (PDMS-2; Folio & Fewell, 2000). This instrument has precise scoring criteria and is normed on a large, stratified sample (Maring & Elbaum, 2007). The PDMS-2 is a comprehensive, standardized measure of gross and fine motor skills that yields Total, Gross, and Fine Motor (TM, GM, and FM, respectively) scales. The GM subtests are appropriate for preschoolers and include Stationary (equilibrium and balance), Locomotion (crawling, walking, running, hopping, and jumping) and Object Manipulation (catching, throwing, and kicking). The FM subtests include Grasping (from one hand grasp to bilateral manipulation) and Visual-Motor Integration (reaching and grasping, building with blocks and copying designs). We used the Preschool Language Scale (PLS-3; Zimmerman, Steiner, & Pond, 1992) to assess language skills. The PLS-3, an extensively standardized instrument, includes tasks assessing linguistic skills in the areas of semantics, morphology, syntax, integrative language and pre-literacy competencies. The test provides scores for Total Language (TL), and two subscales assessing receptive and expressive language: Auditory Comprehension (AC) and Expressive Communication (EC).

## General Statistical Considerations

Intrauterine growth, our predictor of interest, was indexed either as a binary variable (<10th percentile cutoff for IUGR),

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**Table 2.** Antenatal Perinatal and Neonatal Factors by Group[a]

| Risk factors | Appropriate growth comparison group $n = 118$ | Intrauterine growth restriction $n = 25$ |
|---|---|---|
| Antenatal factors | | |
| Abruption of the placenta | 9 (117) [7.69%] | 1 (25) [4.00%] |
| Chorioamnionitis (histological)** | 35 (117) [29.91%] | 1 (24) [4.16%] |
| Diabetes[b]* | 16 [13.56%] | 0 [0.00%] |
| HELLP syndrome[c] | 5 [4.24%] | 2 [8.00%] |
| Hypertension in pregnancy*** | 24 [20.34%] | 13 [52.00%] |
| Intrauterine growth ($z$ score)[d]*** | $-.15 \pm .62$ | $-1.77 \pm .27$ |
| Membranes ruptured > 12 hrs[e] | 17 [14.41%] | 1 [4.00%] |
| Mother's age at delivery (yrs) | $31.44 \pm 4.39$ | $32.16 \pm 5.20$ |
| Mother's height (inch) | $64.74 \pm 2.52$ (103) | $64.63 \pm 2.45$ (23) |
| Oligohydramnios | 1 [.84%] | 2 [8.00%] |
| Parity | $.34 \pm .68$ | $.48 \pm .87$ |
| Smoking during pregnancy[f] | 12 [10.17%] | 6 [24.00%] |
| Vaginal bleeding (abnormal) | 36 [30.51%] | 4 (24) [16.67%] |
| Total antenatal complications[g] | $1.77 \pm .96$ | $1.50 \pm .83$ (24) |
| Perinatal factors | | |
| Abnormal presentation[h] | 50 [42.37%] | 9 [36.00%] |
| Birth weight (g) | $1074 \pm 271$ | $1075 \pm 333$ |
| Cesarean section* | 76 [64.41%] | 22 [88.00%] |
| Forceps | 2 [1.69%] | 0 [0.00%] |
| General anesthesia | 3 [2.54%] | 9 [36.00%] |
| Gestational age (weeks) [i]*** | $28.14 \pm 2.28$ | $31.08 \pm 2.96$ |
| Nuchal Cord | 16 [13.56%] | 4 [16.00%] |
| 1 minute Apgar | $5.95 \pm 1.83$ | $6.52 \pm 1.78$ |
| 5 minute Apgar | $8.02 \pm 1.01$ | $8.24 \pm 0.83$ |
| Total perinatal complications[j] | $1.52 \pm 1.06$ | $1.64 \pm 0.90$ |
| Neonatal factors | | |
| Anemia at birth[k] | 16 [13.56%] | 2 [8.00%] |
| Apnea*** | 109 [92.37%] | 11 [44.00%] |
| Days in NICU | $71.51 \pm 36.10$ | $54.96 \pm 49.51$ |
| Hyaline membrane disease (HMD)[l]*** | 105 [88.98%] | 15 [60.00%] |
| Hyperbilirubinemia[m] | 0 [0.00%] | 2 [8.00%] |
| Hypermagnesemia | 9 [7.63%] | 2 [8.00%] |
| Hypotension[n] | 4 [3.39%] | 0 [0.00%] |
| Intracranial hemorrhage[o] | 28 [23.72%] | 5 [20.00%] |
| Meconium aspiration | 2 [1.69%] | 1 [4.00%] |
| Necrotizing enterocolitis (NEC)[p] | 5 [4.24%] | 0 [0.00%] |
| Patent ductus arteriosus (PDA)[q]* | 66 [55.93%] | 7 [28.00%] |
| Peak bilirubin (mg/dl) | $8.39 \pm 1.66$ | $8.05 \pm 1.93$ |
| Persistent pulmonary stenosis (PPS) | 8 [6.78%] | 0 [0.00%] |
| Pneumothorax | 6 [5.08%] | 0 [0.00%] |
| Retinopathy of prematurity (ROP)[r]* | 41 [34.74%] | 3 [12%] |
| Sepsis (initial or acquired)[s] | 25 [21.19%] | 5 [20.00%] |
| Thrombocytopenia | 10 [8.47%] | 5 [20.00%] |
| Total neonatal complications[t]** | $4.02 \pm 2.13$ | $2.48 \pm 2.50$ |
| Total nonrespiratory neonatal complications[u] | $1.23 \pm 1.45$ | $1.04 \pm 1.48$ |
| Total complications | $7.38 \pm 2.87$ | $6.66 \pm 2.94$ |

* $p < .05$, ** $p < .01$, *** $p < .001$. Frequencies are reported for discrete data, means and standard deviations for continuous data. Group differences examined *via t* test (continuous data), $2 \times 2$ $\chi^2$ with Yates correction (discrete data), or Fisher exact probability test (less than five cases per cell). In the case of missing data, number of subjects used in calculating group means and *SD*s is provided in parentheses.
[a]All comparisons between Intrauterine Growth Restriction (intrauterine growth $z$ score $< -1.28$ *SD*, i.e., the 10th percentile) and Comparison group (intrauterine growth $z$ score $\geq -1.28$).
[b] Includes both gestational diabetes and diabetes mellitus.
[c] Hemolysis, elevated liver enzymes and low platelets.
[d] A $z$ score expressing the deviation of an infant's birth weight from the mean weight of his/her gestational age group, at delivery, according to norms published by Kramer et al. (2001).

*(footnote continued on next page)*

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[e] Time from spontaneous or artificial rupture of membranes to delivery.
[f] Smoking behavior details: 9 cases .5–10 cigarettes, 5 cases 15–20 cigarettes, and 4 cases no details.
[g] Total antepartum complications includes maternal hypertension, chorioamnionitis, maternal diabetes, HELLP syndrome, membranes ruptured >12 hours, multiple gestation, smoking during pregnancy, abnormal vaginal bleeding, and placental abruption (IUGR excluded to avoid duplication with group membership).
[h] Includes various atypical presentations such as breech or transverse lie.
[i] As determined by obstetrician; >95% of cases were corroborated by antenatal ultrasound.
[j] Total perinatal complications include abnormal presentation, C section, forceps, general anesthesia, nuchal cord, and fetal tachycardia.
[k] Hematocrit <40%.
[l] Based on a chest roentgenogram and clinical evaluation.
[m] Peak bilirubin ≥ 12 mg/dl
[n] Requiring treatment
[o] Documented on the basis of serial cranial ultrasound. Comparison group: 21 with Grade I and 7 with grade II. IUGR group: 5 with grade I and none with Grade II (A single child from the Comparison group, without ICH, had mild spastic diplegia).
[p] Documented by radiographic changes, positive stool guiacs and abdominal distention.
[q] Diagnosed by clinical manifestations and echocardiographic information.
[r] Comparison Group:.5 with Grade I, 19 with Grade II, 3 with Grade III, 12 with Grade III+, 2 with Grade IV. IUGR group: 1 with Grade II, 1 with Grade III, 1 with Grade III+.
[s] Established by positive blood culture.
[t] Total neonatal complications includes anemia, apnea, hyaline membrane disease, bronchopulmonary dyslplasia (BPD), hyperbilirubinemia, hypermagnesemia, hypotension, ICH, necrotizing enterocolitis, PDA, persistent pulmonary stenosis, pneumothorax, retinopathy of prematurity, sepsis, and thrombocytopenia.
[u] Total nonrespiratory complications includes anemia, hypotension, ICH, meconium aspiration, NEC, ROP, initial or acquired sepsis, thrombocytopenia.

or as a continuum reflected by standardized growth scores. The *z* score was computed as the deviation of an infant's birth weight from the mean weight of his/her gestational age group, at delivery (see Kramer et al., 2001). To examine the outcome data from the sample of VLBW preschoolers, we used multiple regression analyses (with several continuous or categorical predictors that may be conceptualized as covariates).

In selecting covariates for statistical analyses, we reasoned that, in addition to basic demographic measures, early risk variables on which the IUGR and AIUG groups differed significantly should be examined for inclusion. We, therefore, considered gestational age, for inclusion as a covariate, in addition to sex, SES (Holingshead, 1975), and age of testing adjusted for prematurity.

Individual variables on which the AIUG group exhibited a significant disadvantage (e.g., antenatal complications such as vaginal bleed and chorioamnionitis, or neonatal complications such as respiratory distress, patent ductus arteriosus, ROP and apnea) were not included in order to reduce the number of predictors. To alleviate multicollinearity, variables that correlated highly with selected predictors (e.g., Pearson's r [141] = .80, .80 and .79, all $p$ values <.001, between gestational age and days on $O_2$, between gestational age and birth weight, and between gestational age and neonatal complications, respectively) were excluded. Diagnosis of maternal hypertension (associated with an elevated frequency of Cesarean section) was not included as it is a known etiological factor in the occurrence of suboptimal intrauterine growth (e.g., Kronenberg et al., 2006). The WPPSI-R PIQ, and VIQ were dependent variables in analyses of intellectual outcome, the PDMS-2 Fine and Gross Motor (FM, and GM, respectively) quotients were dependent variables in analyses

**Table 3.** Antenatal and neonatal diagnostic and intervention procedures by group[a]

| Diagnostic and intervention procedures | Appropriate growth comparison group $n = 118$ | Intrauterine growth restriction $n = 25$ |
|---|---|---|
| Antenatal magnesium sulfate[b] | 72 | 12 |
| Antenatal steroids[c] | 107 | 22 |
| Antenatal steroid doses | 2.43 ± 2.87 | 2.56 ± 1.92 |
| Hypertension medications (m)* | 5 | 14 |
| Neonatal cranial ultrasound | 118 | 25 |
| Neonatal steroids | 27 | 3 |
| Surfactant administration** | 75 | 7 |
| Days respiratory support [d] | 50.22 ± 46.86 | 29.84 ± 56.70 |
| Days ventilation | 19.15 ± 26.22 | 8.93 ± 17.68 |
| Highest percentage $O_2$* | 70.99 ± 31.37 | 53.96 ± 33.43 |
| Home on $O_2$ | 25 | 3 |

Note. * $p < .05$, ** $p < .01$, *** $p < .001$. Frequencies are reported for discrete data, means and standard deviations for continuous data. The *t*-tests were used to test continuous data; 2 × 2 chi-square with Yates correction were used for discrete data, and Fisher's exact probability test were used for discrete data with less than five cases per cell. In the case of missing data, number of subjects used in calculating group means and *SD*s is provided in parentheses.
[a] All comparisons between Intrauterine Growth Restriction (intrauterine growth *z* score < −1.28 *SD*) and Comparison group (intrauterine growth *z* score ≥ −1.28 *SD*).
[b] Magnesium sulfate, administered to inhibit preterm labor and/or control seizures in preeclampsia.
[c] Betamethasone, to promote fetal lung maturation.
[d] Including mechanical ventilation continuous positive airways pressure (CPAP), nasal cannulae, and oxyhood.

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**Table 4.** Unadjusted and adjusted (± *SEM*)[a] group means by outcome domain

| Domain | Appropriate growth comparison group $n = 118$ | Intrauterine growth restriction $n = 25$ | *t (df) /F (df)* | Effect size (with Hedges' correction) |
|---|---|---|---|---|
| FSIQ | 101.88 ± 1.46 (118) | 99.16 ± 3.86 (25) | $t$ (141) = −.75 | .16 |
| | 101.65 ± 1.52 (118) | 96.75 ± 3.65 (25) | $F$ (1,139) = 1.53[b] | .30 |
| VIQ | 100.98 ± 1.35 (118) | 99.36 ± 3.78 (25) | $t$ (141) = −.48 | .10 |
| | 100.69 ± 1.42 (118) | 96.59 ± 3.40 (25) | $F$ (1,139) = 1.23[c] | .26 |
| PIQ | 102.39 ± 1.49 (118) | 98.64 ± 3.63 (25) | $t$ (141) = −1.03 | .23 |
| | 102.90 ± 1.49 (117)[d] | 98.59 ± 3.25 (25) | $F$ (1,139) = 1.42 | .26 |
| TM | 95.46 ± 1.01 (114) | 90.46 ± 2.18 (24) | $t$ (136) = −2.06* | .46 |
| | 95.93 ± 0.93 (112)[e] | 91.08 ± 2.03 (24) | $F$ (1,133) = 4.63* | .45 |
| FM | 98.82 ± 1.24 (117) | 93.75 ± 2.73 (24) | $t$ (139) = −1.68 | .38 |
| | 98.35 ± 1.21 (117) | 92.69 ± 2.93 (24) | $F$ (1,137) = 3.19[f] | .42 |
| GM | 93.94 ± 0.92 (114) | 89.08 ± 2.45 (24) | $t$ (136) = −2.11*[h] | .47 |
| | 94.14 ± .88 (113)[g] | 91.13 ± 1.96 (23) | $F$ (1,133) = 1.93 | .29 |
| TL | 101.76 ± 0.90 (118) | 96.04 ± 1.67 (25) | $t$ (141) = −1.65 | .36 |
| | 101.50 ± 1.45 (118) | 96.90 ± 3.18 (25) | $F$ (1,140) = 1.69 | .29 |
| EC | 99.90 ± 1.43 (118) | 95.92 ± 3.66 (25) | t (141) = −1.13 | .25 |
| | 99.73 ± 1.49 (118) | 96.46 ± 3.27 (25) | $F$ (1,140) = .82 | .20 |
| AC | 103.06 ± 1.35 (118) | 97.84 ± 2.66 (25) | $t$ (141) = −1.64 | .36 |
| | 103.21 ± 1.27 (117)[d] | 98.75 ± 2.77 (25) | $F$ (1,139) = 2.09 | .31 |

Note. *$p < .05$. FSIQ = WPPSI-R Full Scale IQ, VIQ = Verbal IQ, PIQ = Performance IQ, TM = Peabody Developmental Motor Scales (PDMS-2) Total Motor, FM = Fine Motor, GM = Gross Motor, TL = Preschool Language Scale (PLS-3) Total Language, EC = Expressive Communication, AC = Auditory Comprehension, SES = socioeconomic status. Parentheses: number of subjects per group.
[a]Unadjusted group means (upper row) and group means adjusted for 'sex' (lower row).
[b]The full model including sex by group effect was used because of a trend for an interaction (F[1,139] = 3.31, $p < .08$).
[c]The full model including sex by group effect was used because of a significant interaction (F 1,139) = 5.29, $p < .05$. Direction could not be reliably interpreted because of small subgroup size (only 7 females with IUGR).
[d]A single outlier identified by SYSTAT was removed from the comparison group.
[e]Two outliers identified by SYSTAT were removed from the comparison group.
[f]The full model including sex by group effect was used because of a trend for an interaction (F [1,137] = 3.82, $p < .06$.
[g]Two outliers identified by SYSTAT, one per group, were removed.
[h]Group differences computed with Bonferroni correction for multiple comparisons ($p < .025$ for the VIQ vs PIQ, FMQ vs GMQ, and ACS vs ECS) were not significant for the uncorrected GM means.

of motor outcome, and the PLS-3 Auditory Comprehension (AC), and Expressive Communication (EC), scale scores were dependent variables in analyses of language outcome. In computation of each dependent measure score, age corrected for extent of prematurity, rather than chronological age, was used.

Before conducting statistical analyses, interactions between the categorical and continuous predictors were examined. No significant interactions were evident when intrauterine growth was treated as a continuum, indexed by a *z* score (all *p* values ≥.10); thus the reduced model with a predictor of interest and four covariates was used. However, inclusion of the covariates in analyses of group differences, between those with and without IUGR, resulted in multiple, apparently spurious, interactions between predictors. Therefore, we retained "sex" (the single demographic factor on which group differences were evident), as the only "covariate" in statistical analyses where intrauterine growth was indexed as a binary variable.

## RESULTS

Table 4 shows means ± *SE*s for the IUGR and AIUG groups on various outcome measures with, and without, adjustment for "sex". The comparison yielded significant group differences on two of nine uncorrected measures, TM and GM. Yet after correction for "sex", only differences on TM remained significant.

Table 5 shows the results of two series of multiple regression analyses in which the intrauterine growth *z* score was the variable of interest. In the first group of analyses, we used the total sample of 143 VLBW children to examine the relationships between adequacy of intrauterine growth and preschool outcome. Examination of the table reveals significant relationships between the intrauterine growth *z* score and the FSIQ ($\eta p^2 = 4.8\%$). Further examination of the two components of the FSIQ, revealed that only the PIQ, but not the VIQ was significantly associated with the *z* score ($\eta p^2 = 5.78\%$), yet the difference between the two statistical

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**Table 5.** Intrauterine growth *z* score[a] and neuropsychological outcome

| Outcome | Source | *F(df)*[b] | *F(df)*[c] |
|---|---|---|---|
| FSIQ | Intrauterine growth *z* score | 6.70 (1,137)** **[ηp² = 4.80%]** | 5.53 (1,112)* **[ηp² = 4.71%]** |
| | SES | 13.97 (1,137)*** | 17.29 (1,112)*** |
| | Sex | 0.04 (1, 137) | 2.00 (1,112) |
| | Age at testing (adj) | 1.71 (1,137) | 1.26 (1,112) |
| | Gestational age | 6.19 (1,137)* | 2.12 (1,112) |
| VIQ | Intrauterine growth *z* score | 3.64 (1,137) **[ηp² = 2.59%]** | 3.77 (1,112) **[ηp² = 3.26]** |
| | SES | 11.41 (1,137)*** | 14.36 (1,112)*** |
| | Sex | .39 (1,137) | 3.69 (1,112)* |
| | Age at testing (adj) | .11 (1,137) | .013 (1,112) |
| | Gestational age | 4.01 (1,137)* | 1.38 (1,112) |
| PIQ | Intrauterine growth *z* score | 8.42 (1,137)** **[ηp² = 5.78%]** | 4.71 (1,112)*[d] **[ηp² = 4.03%]** |
| | SES | 10.69 (1,137)** | 12.49 (1,112)** |
| | Sex | .02 (1,137) | .49 (1,112) |
| | Age at testing (adj) | 6.48 (1,137)** | 5.84 (1,112)** |
| | Gestational age | 6.36 (1,137) | 2.26 (1,112) |
| TM | Intrauterine growth *z* score | 11.73 (1,132)** **[ηp² = 8.16%]** | 2.10 (1,108) **[ηp² = 1.90%]** |
| | SES | 6.46 (1,132)** | 9.89 (1,108)** |
| | Sex | 2.03 (1,132) | 2.165 (1,108) |
| | Age at testing (adj) | 1.88 (1,132) | 4.43 (1,108)* |
| | Gestational age | 15.13 (1,132)*** | 16.38 (1,108)*** |
| FM[e] | Intrauterine growth *z* score | 7.30 (1,135)** **[ηp² = 5.12%]** | 2.92 (1,111) **[ηp² = 2.56%]** |
| | SES | 5.98 (1,135)* | 5.70 (1,111)* |
| | Sex | 4.65 (1,135)* | 6.41 (1,111)** |
| | Age at testing (adj) | 1.19 (1,135) | 3.18 (1,111) |
| | Gestational age | 9.05 (1,135) | 8.96 (1,111)** |
| GM[f] | Intrauterine growth *z* score | 7.95 (1,131)[g]** **[ηp² = 5.72%]** | 0.57 (1,108) **[ηp² = .52%]** |
| | SES | 5.34 (1,131)* | 8.41 (1,108)** |
| | Sex | .01 (1,131) | .002 (1,108) |
| | Age at testing (adj) | 2.01 (1,131) | 2.67 (1,108) |
| | Gestational age | 18.34 (1,131)*** | 15.40 (1,108)*** |
| TL | Intrauterine growth *z* score | 1.20 (1,137) **[ηp² = .87%]** | .55 (1,111)[d] **[ηp² = .49%]** |
| | SES | 8.95 (1,137)** | 11.24 (1,111)*** |
| | Sex | 4.12 (1,137)* | 4.30 (1,111)* |
| | Age at testing (adj) | 0.02 (1,137) | .09 (1,111) |
| | Gestational age | .01 (1,137) | .00 (1,111) |
| AC | Intrauterine growth *z* score | 1.58 (1,136)[g] **[ηp² = 1.14%]** | .21 (1,111)[g] **[ηp² = .19%]** |
| | SES | 8.17 (1,136)** | 10.35 (1,111)** |
| | Sex | 5.50 (1,136)* | 5.21 (1,111)* |
| | Age at testing (adj) | .54 (1,136) | .64 (1,111) |
| | Gestational age | .01 (1,136) | 0.00 (1,111) |

*(Continued)*

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**Table 5.** Continued

| Outcome | Source | $F(df)^{b}$ | $F(df)^{c}$ |
|---|---|---|---|
| EC | Intrauterine growth $z$ score | .97 (1,137) **[$\eta p^2$ = .70%]** | .63 (1,112) **[$\eta p^2$ = .56%]** |
| | SES | 7.61 (1,137)** | 7.43(1,112)* |
| | Sex | 1.56 (1,137) | 3.12 (1,112) |
| | Age at testing (adj) | .13 (1,137) | .035 (1,112) |
| | Gestational age | .01 (1,137) | .00 (1,112) |

*Note.* * $p < .05$, ** $p < .01$, *** $p < .001$. FSIQ = WPPSI-R Full Scale IQ, VIQ = Verbal IQ, PIQ = Performance IQ, TM = Peabody Developmental Motor Scales (PDMS-2) Total Motor, FM = Fine Motor, GM = Gross Motor, TL = Preschool Language Scale (PLS-3) Total Language, EC = Expressive Communication, AC = Auditory Comprehension, SES = socioeconomic status.
[a]Intrauterine growth $z$ score defined as birth weight stratified by gestational age according to norms provided by Kramer et al. (2001).
[b]Total sample.
[c]Subsample of children without IUGR (defined as birth weight stratified by gestational age < $10^{th}$ percentile).
[d]Effect computed with Bonferroni correction for multiple comparisons ($p < .025$ for the VIQ vs PIQ, FM vs GM, and AC vs EC) was not significant for the PIQ following correction.
[e]Two cases could not be included because the family could not be rescheduled to complete testing.
[f]Three cases could not be rescheduled to complete testing, one case was not tested because of mild spastic diplegia, and one child refused to cooperate on the Gross Motor testing.
[g]A single multivariate outlier detected by SYSTAT removed from analyses.

effects was not significant (Steiger Z* = .54; $p = .59$). The $z$ score was also significantly associated with the TM quotient ($\eta p^2 = 8.16\%$), and with its FM and GM components ($\eta p^2 = 5.12\%$ and 5.72%, respectively). None of the language performance measures was significantly associated with the growth $z$ score.

In the second group of analyses we removed the 25 children with IUGR classification from the sample to determine whether the observed relationships between intrauterine growth and neuropsychological outcome were detectable in a subsample of 116 preschoolers with adequate intrauterine growth (stratified birth weight > 10th centile). As Table 5 shows, in the second series of analyses the significant relationship between the intrauterine growth $z$ score and the FSIQ was maintained ($\eta p^2 = 4.71\%$; $p \leq .02$). Yet the relationships between the intrauterine growth $z$ score and either the PIQ or VIQ ($\eta p^2 = 4.03\%$ and 3.26%, respectively) were not significant following Bonferroni adjustment for multiple comparisons at $p < .025$ per subscale. The relationships between the $z$ score and either motor or language outcomes were not significant in the subsample of preschoolers with adequate intrauterine growth.

## DISCUSSION

Neuropsychological performance of VLBW preschoolers with, and without, IUGR was examined in the current study. After adjustment for "sex", significant group differences in favor of the latter group were found on one out of nine outcome measures, an index of global motor performance (Table 4). The motor skills disadvantage for the IUGR group does not appear to be associated with economic status, as no significant group differences were observed on demographic variables other than "sex" (Table 1). Furthermore, the more complicated neonatal status of the comparison group (Table 2), should mitigate, if anything, against detection of the observed group differences in motor skills.

The documented group differences in motor skills are incompatible with the negative findings from the investigation of Procianoy et al. (2009) of VLBW cases born during the surfactant era (2003–2005) and followed up until 24 months of age. These investigators found no differences on infant intellectual, or motor, skills measures between the 41 AGA and 55 SGA cases. Whether discrepancies in age or outcome measures account for the discrepant findings is unknown.

Our examination of the link between a continuous index of adequacy of intrauterine growth and neuropsychological performance yielded significant associations with intellectual measures that could not be observed when the growth continuum was artificially dichotomized at the 10th percentile rank. As Table 5 ([b]) shows, linear relationships were found between the intrauterine growth $z$ score and five neuropsychological performance measures, the FSIQ, PIQ, TM, FM, and GM. This finding reflects (in accord with our prediction), a relatively generalized decrease in the quality of neuropsychological performance with increasing growth deficit, in the total sample. These relationships were established after adjusting for demographic factors and for gestational age. Interestingly, despite truncation of the range of intrauterine growth (following exclusion of VLBW children with IUGR from the analyses; Table 5 [[c]]), the relationships between the growth $z$ score and the FSIQ remained significant. Therefore, even within the restricted range of *adequate* intrauterine growth (stratified birth weight > 10th percentile), growth variability explained a unique portion of the variance in global intellectual skills in VLBW preschoolers. In contrast, the observed relationship between intrauterine growth and global motor abilities (TM) was dependent upon inclusion of growth values < 10th percentile (Table 5b,c).

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Similar results were obtained in a Swedish investigation of term-birth cases (Yang, Bergvall, Cnattingius, & Kramer, 2010). The authors used large nationwide data bases to study young Swedish men (37–41 weeks gestation) to tap a "cleaner" effect of gestational age in a more homogeneously "normal" birth cohort (born 1973–1981). After adjustment for multiple covariates, they documented a linear relationship between gestational age or fetal growth (i.e., birth weight stratified by gestational age) and adult height, blood pressure, and general cognitive ability.

Two recent studies were able to document an association between adequacy of intrauterine growth and cognitive outcome in VLBW children, although intrauterine growth was treated as a categorical variable, rather than a continuous dimension. Morsing et al. (2011) found that the intellectual performance of 34 VP children (24–29 weeks gestation) with high-risk IUGR was significantly lower than performance of a matched VP group without IUGR (age 4–8 years). The children in the IUGR group were actively delivered because of absent or reversed end-diastolic blood flow (using Doppler ultrasound velocimetry); thus, the relative risk to this sample appears greater than that observed in our sample. Guellec et al. (2011) reported minor cognitive (and behavioral) difficulties in preschool and school-age VP children (29–32 gestational weeks) with birth weight for gestational age <20th percentile. In contrast with our sample, children with CP, severe brain damage (PVL or grades III and IV ICH), and vision and hearing impairments were apparently not excluded in the two abovementioned studies.

Our findings are inconsistent with results reported by Kan et al. (2008), who studied a cohort of extremely preterm birth children born during the surfactant era. The authors were unable to demonstrate a link between the intrauterine growth $z$-score and performance on cognitive, academic, and motor tests at 8 years of age in children who were free from either chromosomal and genetic abnormalities, or CP. Methodological differences between our study and the study by Kan and colleagues included a substantially wider gestational age range in the current sample (23–34 6/7 weeks), compared to the limited gestational age range (23–27 weeks) studied by Kan et al. (2008). Additionally, over half the mothers in a study by Kan et al. had <12 years of education, while in the current investigation only two mothers did not complete high school. It is unclear whether, and to what extent, sample characteristics contributed to the differences in the results. At any case, in a recent study of extreme preterm birth (Raz et al., 2010), where sample selection criteria for gestational age were more similar to those of Kan et al. (2008), we reported an incidental finding of significant relationships between the intrauterine growth $z$ score and cognitive skills. In our study of VPT children, with and without bronchopulmonary dysplasia (Newman, Debastos, Batton, & Raz, 2011), we documented a similar trend. Perhaps a lower level of social-environmental risk and increased socioeconomic homogeneity facilitate detection of associations between intrauterine growth and neuropsychological outcome.

An important, yet often overlooked difference between investigations is sample composition: VLBW *vs.* VP cases. The study of VLBW involves arbitrary restriction of birth weight to <1500 g. Consequently, gestational age tends to have a moderate *negative* correlation ($r = -.43$; $p < .000$ in our sample) with birth weight standardized for gestational age. The inverse relationships occur because the heavier of the more gestationally mature infants are excluded from the sample, while the lighter ones are retained. Hence more mature children are also more likely to have poorer growth rate and to be growth restricted or, conversely, infants with poorer intrauterine growth tend to have an advantageous neonatal status associated with their higher gestational age. Thus, when the sample selection criteria are based on the cutoff for VLBW (<1500 g), rather than VP birth (<32 weeks), the study of relationships between intrauterine growth rate and outcome is likely to be more rigorous. Using the latter cutoff, the outcome effects of inadequate intrauterine growth are increasingly confounded with the outcome effects of lower gestational age and its associated complications.

The hypothesis of an enhanced visuospatial deficit in this population may seem partially supported. As Table 5 ([b]) reveals, in addition to global intellectual indices, the PIQ, a measure of visuospatial skills, was significantly associated with the intrauterine growth $z$ score in the total sample of 143 VLBW preschoolers, while measures of verbal skills (e.g., the VIQ) were not. Yet as reported above, the two statistical effects were not significantly different.

In summary, the results of the current study suggest that intrauterine growth should not be viewed merely as a dichotomy, but as a continuum that is associated with global cognitive development throughout the naturally occurring range of birth weight (for gestational age) values. In fact, even within the limited range of values reflecting "adequate" birth weight, a direct linear relationship between appropriateness of intrauterine growth and global intellectual outcome may be observed in preschoolers with history of VLBW.

Of interest, the findings from the group comparisons (Table 4) as well as the linear regression models on the total, but not partial, sample (Table 5) provided support to the notion that intrauterine growth restriction is associated with decline in global motor performance. Though dichotomization of continuous data is a contentious issue, dichotomization may preserve performance of models when it has a biological interpretation (Baneshi & Talei, 2011). Perhaps the 10th centile cutoff approximates the boundaries of influence of an underlying antenatal biological threshold, not yet specified, that adversely affects motor skill development.

The limitations of the current study include retrospective review of neonatal and obstetric data, the use of participants from two studies, a relatively small IUGR group, and the absence of a term birth control group. The latter would have facilitated determination of the extent to which the VLBW group as a whole is deviant from baseline expectations; yet this was not the focus of our investigation. As our sample was representative of middle class strata, it will also be useful to determine whether our results generalize to low SES samples. Finally, neuroimaging studies in VLBW preschoolers may be instrumental in enhancing our understanding of the CNS changes mediating the association between increasing intrauterine growth deficit and decline in cognitive and motor performance. Indeed, two studies reveal changes in "global" cortical morphology (Dubois et al., 2008), and cerebral anatomy (Tolsa et al., 2004) associated with IUGR classification in preterm-birth samples. Yet further investigation is required to explore the CNS changes mediating the relationship between adequacy of intrauterine growth and global intellectual performance, within the population of VLBW children classified as AIUG.

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