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Cognitive ability in adolescents born small for gestational age: Associations with fetal growth velocity, head circumference and postnatal growth

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ABSTRACT

Background: Small size at birth may be associated with impaired cognitive ability later in life.
The aim of this study was to examine the effect of being born small for gestational age (SGA), with or without intrauterine growth restriction (IUGR) on cognitive ability in late adolescence.
Study design: A follow-up study of a former cohort included 123 participants (52 males); 47 born SGA and 76 born appropriate for gestational age (AGA). Fetal growth velocity (FGV) was determined by serial ultrasound measurements during the third trimester. A control group matched for age and birthplace was included. The original Wechsler Adult Intelligence Scale (WAIS) was administered, and verbal, performance and full-scale Intelligence Quotient (IQ) scores were calculated.
Results: There was no difference in IQ between adolescents born SGA and AGA. FGV or IUGR during the third trimester did not influence cognitive ability in late adolescence. Full-scale IQ was positively related to head circumference (HC) in adolescence (B: 1.30, 95% CI: 0.32–2.28, $p = 0.01$). HC at birth and three months was positively associated with full-scale IQ. Catch-up growth in the group of SGA children was associated with a significantly increased height, larger HC, increased levels of insulin-like growth factor-I (IGF-I) and increased full-scale IQ compared to those born SGA without catch-up growth.
Conclusion: SGA and IUGR may not be harmful for adult cognitive ability, at least not in individuals born at near-term. However, known risk factors of impaired fetal growth may explain the link between early growth and cognitive ability in adulthood.

1. Introduction

Intrauterine growth restriction (IUGR) during critical periods of brain development may deprive the brain of nutrients required for normal growth and development [1]. Being born small for gestational age (SGA) has been found to influence intelligence in the offspring and these effects seem to be associated with the severity of fetal growth restriction. In addition, prematurity is also an independent risk factor for suboptimal cognitive development [2–4]. This may explain why studies on term-born SGA children found no difference in IQ compared to term-born children appropriate for gestational age (AGA) [5,6]. SGA is generally considered an indicator of impaired fetal growth, but birth weight is a physical dimension measured at a given time, whereas IUGR is a dynamic process of changes in size during pregnancy. Thus, SGA and IUGR are not necessarily the same entity.

Large cohort studies of IQ tests administered to military conscripts have found associations between smaller size at birth and lower IQ in early adulthood [2,3,7]. In a study of more than 300,000 young men at military conscription, lower weight, length and head circumference (HC) at birth was independently associated with a lower cognitive ability in adolescence when adjusted for maternal and socioeconomic factors [4]. These large cohort studies corroborate the hypothesis that fetal growth *per se* influences cognitive ability later in life. However, the effect sizes of the differences in IQ scores between SGA and AGA children are small, which may partly explain the lack of IQ difference reported in smaller studies [5,6,8].

Positive correlations between intelligence and growth in childhood, adult height and adult head circumference have been reported [9–11]. Thus, in a nationwide population-based Swedish study, the males born SGA ($n = 4{,}585$) had an increased risk for subnormal performance in all four dimensions of the IQ test when compared to the males born

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AGA ($n = 157{,}876$) [12]. The same study concluded that among males born SGA, those who had smaller head circumference at birth (<−2 SDS) and those with lower adult stature (height < −2 SDS) had lower intelligence scores compared to those born SGA, but with normal head circumference at birth and normal adult height [12]. Lack of linear catch-up growth in SGA children was also associated with decreased cognitive ability in large cohorts of healthy males [3]. Furthermore, there is a well-known association between head circumference and IQ which is thought to reflect the relation between brain size and IQ [13]. These associations were confirmed in large cohorts of healthy males where small head circumference at birth was an independent risk factor for subnormal cognitive ability [4,12].

To our knowledge, only one previous study has explored the associations between size at birth and intelligence later in life including evaluation of intrauterine growth by ultrasound measurement. This study concluded that IQ scores were lower in SGA children which was related to IUGR [14]. The aim of the present study was to examine the associations between early pre- and postnatal growth including measurements of fetal growth and intelligence in adolescence.

2. Subjects and methods

2.1. Participants

In a follow-up study of a larger study on fetal growth, we included 123 (52 males) adolescent offspring (participation rate, 45%) (Details on the primary study and selection of the cohort have been reported earlier [15–17]). The baseline data were collected in 1985–1987 on pregnant women who had one or more risks factors for giving birth to an SGA child (i.e. smoking in pregnancy, previous birth to a SGA child, previous pre-eclampsia). Data on third trimester fetal growth velocity determined by repeated ultrasound measurements, birth anthropometrics and perinatal complications were collected (reported in detail earlier [18,19]). The children were examined at birth and at 3, 6 and 12 months of age as part of the primary study, and the children were then invited to participate in the follow-up study in adolescence at the ages of 16–18. Furthermore, a healthy control group ($N = 21$, 7 males) was selected from a birth registry of children born at the same hospital in the same time period who had a birth weight between the 25th and the 75th percentile and no maternal risk factors. There was no information on third trimester fetal growth velocity in the control group. Only term-born children were invited to participate. In total, 144 children were participating in the study.

2.2. Fetal growth velocity and birth anthropometrics

Calculations of third trimester fetal growth velocity (FGV) were based on repeated ultrasound measurements every three weeks (on average, 4 measurements were available, range 3–9) from week 28 until birth. A linear regression analysis was performed to calculate the changes in estimated fetal weight SDS per 28 days with a standard error (SE) of 0.22 SDS/28 days. These calculations were used to evaluate fetal growth restriction (IUGR) during third trimester using the 10th percentile (equivalent to −0.39 SDS/28 days) of normal third trimester FGV as cutoff [20].

Birth weight (BW) was measured with a calibrated electronic scale and birth length (cm) was measured by means of a Harpenden infantometer and head circumference (cm) with a calibrated measuring tape. BW (SDS) was calculated using a normal reference [21]

The cohort was divided into infants born appropriate for gestational age (AGA) or SGA using the 10th percentile for BW (equivalent to −1.28 SDS) as cutoff value based on the previously published reference data [20]. Furthermore, they were divided into those with or without IUGR defined as a FGV below the 10th percentile. In the follow-up study, these measurements made it possible to divide the cohort into five groups; AGA (+/− IUGR), SGA (+/− IUGR) and the control group (Fig. 1). Postnatal weights and lengths were expressed as SDS based on national reference data [22].

2.3. Clinical evaluation at follow-up in adolescence (age 16–19 years, $n = 144$)

Height (cm) was measured to the nearest 0.1 cm using a calibrated wall-mounted stadiometer (Force Institute, Denmark) and weight (kg) was measured on a digital weight scale with a precision of 0.01 kg (Lindeltronic 8000, Denmark). Standard deviation scores (SDS) for height and weight were calculated based on a Danish national reference material [22].

Serum IGF-I was determined by radioimmunoassay. Briefly, serum was extracted by acid-ethanol and cryoprecipitated in order to remove interfering IGF binding proteins [23]. Inter- and intra-assay coefficients of variations (CV) were 9% and 6%, respectively. IGFBP-3 was determined by a radioimmunoassay previously described [24]. Reagents for the assay were obtained from Mediagnost GmbH (Tübingen, Germany). Sensitivity was 0.29 ng/ml (3 SD above zero standard). Inter- and intra-assay CV were 10.7% and 7.6%, respectively [25].

2.4. Assessment of intelligence

Of the participants, 143 completed the six verbal and five performance subtests of the original version of the Wechsler Adult Intelligence Scale (WAIS). This test provides three IQs including Verbal IQ, Performance IQ and Full-scale IQ. The WAIS was administered by two of the authors and was supervised by a trained neuropsychologist. Selected test protocols were checked, but no systematic difference in test scoring was found between the two testers. One subject was excluded from the test because of mental retardation.

Standard procedures were used to calculate IQ. The raw scores were converted to scaled scores and the sums of scaled scores were converted to IQ using a normal reference population of 200 men and women with a mean age of 23 years [26].

2.5. Covariates

Parental socioeconomic status (SES) was derived from a questionnaire completed by the parents concerning total number of completed school years, occupational training and employment. The participants also provided information on total number of completed school years and occupational training, but the majority of Danish young men and women are still in school at the age of 16–19. Maternal age and smoking status was recorded in the baseline study.

2.5.1. Statistics

The variables were analysed for normal distribution and were log-transformed or square root-transformed to approximate a normal distribution if necessary (GA, weight, IGF-I). Differences between those born AGA and SGA +/− IUGR were compared using ANOVA with Bonferroni correction. Multiple linear regression analyses were used to evaluate associations between IQ scores and anthropometric measurements adjusting for gender, age and target height. The adjusted models included predictors and potential predictors of IQ as covariates (sex, age, social status, smoking in pregnancy, BW and FGV) was performed.

Statistical analyses were performed using the statistical package PASW (version 18; SPSS Inc., Chicago, IL).

2.5.2. Ethical aspects

The study was performed according to the Helsinki II declaration and approved by the local Ethical Committee (KF 01-229/02 and KF 01-065/03) and The Danish Data Protection Agency. Written informed consent was obtained from all participants and also from the parents/guardians of the participants under 18 years of age.