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Neurodevelopmental delay in small babies at term: a systematic review

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KEYWORDS: developmental delay; fetal growth restriction; infant; meta-analysis; small-for-gestational age; systematic

ABSTRACT

Objective *Being small for gestational age (SGA) or having fetal growth restriction (FGR) may be associated with poorer neurodevelopmental outcomes compared to being appropriate for gestational age (AGA). The aim of this paper was to evaluate the existence and magnitude of decrease in neurodevelopmental scores in SGA and FGR infants born at term from a systematic review of the existing literature.*

Methods *Studies of neurodevelopment in SGA/FGR babies were identified from a search of the internet scientific databases. Studies that included preterm births and those that did not define absolute indices of standardized cognitive outcome were excluded. SGA was defined as birth weight below the 10th centile for gestation and FGR as the same birth-weight standard with abnormal umbilical artery Doppler ultrasound or evidence of abnormal placentation on pathology specimen studies. Effect size was calculated as the standardized mean difference between neurodevelopment scores of controls and SGA/FGR children.*

Results *There were 28 studies of SGA, with a total of 7861 SGA and 91 619 control AGA babies, and three studies of FGR, with a total of 119 FGR and 49 control AGA babies. Data synthesis showed that standardized neurodevelopmental scores in SGA babies were 0.32 SD (95% CI, 0.25–0.38) below those for normal controls, though with heterogeneity between studies ($I^2 = 68.3\%$). Insufficient data were available for FGR babies.*

Conclusion *The findings of the study demonstrate that among babies born at term, being SGA is associated with lower scores on neurodevelopmental outcomes compared to AGA controls. A trial designed to evaluate the effects of intervention in small fetuses born at term in order to improve the neurodevelopmental outcome is urgently needed. Copyright © 2012 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Small fetal size is known to be a risk factor for perinatal morbidity and mortality[1–4]. Birth weight lower than the 5th or 10th centile of the population-adjusted standard is often called small for gestational age (SGA)[5,6]. Fetal growth restriction (FGR) is a concept that describes a condition in which the baby has failed to reach its growth potential. Although not all small babies are growth restricted, there is a general consensus that small fetuses exhibiting elevated resistance in the umbilical artery, and reduced resistance in the fetal middle cerebral artery, indicate placental insufficiency[7–9]. Over the last two decades, several papers have examined the impact of fetal size on neurodevelopmental outcome. Fetal response to placental dysfunction may be protective of the development of the brain, but this protection may not be complete.

The group of small babies almost certainly contains many that are not pathologically small. There are several reasons for being small[10–12]; gestational age at birth, ethnicity, parental stature, presence of fetal abnormalities, fetal exposure to alcohol or drugs and maternal diseases are some of the factors involved[13–17]. At least some of these, such as prematurity, are associated with morbidity in its own right. Chromosomal/genetic abnormalities and fetal infections are expected to lead to suboptimal neurodevelopment.

There is no systematic review exploring whether motor and cognitive development of babies born small at term (with or without abnormal fetal Doppler ultrasound) is any inferior than it is in those born with a normal weight.

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We undertook such a review and quantified the magnitude of any possible difference in neurodevelopment in these groups.

METHODS

We developed a protocol using recommended methods for review of observational studies to guide our work. Databases were searched to identify all studies that investigated the developmental outcome of term SGA/FGR babies and the results reported according to accepted guidelines[18].

Identification of the literature

We combined search terms for the two concepts of interest. For the first concept we included: 'cognitive development' OR 'neurodevelopment*' OR 'developmental disability' OR 'developmental disabilities' OR 'development* delay' OR 'learning disabilities' OR 'learning disability' OR 'learning disorders' OR 'learning disorder' OR 'child development' OR 'intelligent*' OR 'Bayley test' OR 'Wechsler' OR 'Stanford Binet*' OR 'Bayley' OR 'outcome' OR 'outcome*' OR 'language development' and expanded the following thesaurus terms: 'developmental disabilities' OR 'child development' OR 'cognition disorders' OR 'intelligence' OR 'language developmental disorders' OR 'Wechsler scales' OR 'Stanford Binet test' OR 'learning disorders' OR 'mental retardation'.

The second concept included: 'small for gestational age' OR 'SGA' OR 'growth restriction' OR 'IUGR' OR 'growth retardation' OR 'birthweight' OR 'term' OR 'gestational age' OR 'born' OR 'newborn*' OR 'birth' and expanded thesaurus terms: 'infant, small for gestational age' OR 'fetal growth retardation' OR 'gestational age' OR 'birthweight'. The two main concepts were combined using 'AND'. The last search was run on 25th August 2010. Two independent researchers carried out the search in MEDLINE, PubMed and EMBASE.

We limited our query to studies published between January 1980 and August 2010 in English. Easy availability of ultrasound in pregnancy would have been unlikely before this period, and it is possible that gestational age assessment was uncertain, leading to accidental inclusion of preterm babies. All the authors agreed to the search strategy. The reference lists of the articles identified were used to find other potentially relevant studies on these topics.

We only included babies born at term. Exclusion of preterm births eliminated the effect of morbidity related to prematurity and its complications. We included studies where the neurological assessment was carried out up to 10 years of age. Environmental factors also play a role in the intellectual development of the baby[19–21]. A longer follow-up would lead to significant confounding owing to differential environmental factors in the neurodevelopment of the two groups of small and normally grown babies. When different follow-up periods were given we chose the closest to 3 years, as most developmental tests are more reliable at that time. The controls were children born with birth weight appropriate for gestational age (AGA).

We excluded studies without validated developmental assessment and/or evaluation carried out without a control group. Wherever possible, studies were chosen in which the same test to assess neurodevelopment was applied to the study (small babies) and control (normal babies) groups. Studies that analyzed the same population in several papers were considered only once.

Several manuscripts reported on subscales of neurodevelopment, which may crudely be categorized as motor, cognitive and behavioral. The differences in the subscales may be different in the study and control groups. For example, the study group may have very low scores in one of the three categories, but relatively higher scores in the remaining two. In order to take this into account, we created two groups of outcome: the highest and the lowest scores in subscales for each study were pooled. Considering the lowest score from the subscale and comparing it with that of controls would give the largest effect size, and considering the highest score from the subscale and comparing it with that of controls would yield the smallest effect size. Pooled highest subscale scores and pooled lowest subscale scores compared with controls yielded the pooled smallest and largest effect size, respectively.

Quality assessment

We also performed quality assessment for each study included in the analysis, done according to existing checklists[22,23]. We considered the study of high/medium/low quality regarding effectiveness of the study design in reducing bias in various aspects, such as population selection, performance, measurement of the outcomes and attrition.

Statistical analysis

Where a study reported a continuous outcome as well as a binary one we used the continuous one, as this should estimate differences with greater precision. Where results for SGA babies and/or control babies were reported in different subgroups (e.g. late-onset SGA and early-onset SGA), we calculated overall summaries as if the groups had not been subdivided. For studies with a continuous outcome reported in an SGA group and a control group, effect size was calculated as the standardized mean difference. For studies with a continuous outcome reported in an SGA group that was compared to a reference standard rather than a control group, effect size was calculated as the difference between the SGA mean and its expected value in a healthy population, divided by the SD of the SGA. For studies with a binary outcome, the log odds ratio was converted to an effect size by dividing by 1.81[24]. If a study did not report enough information to calculate an effect size and SD, it was excluded. Effect sizes and standard errors from all studies were pooled

using a random effects meta-analysis[25]. I^2 (a function that describes the percentage of variation across studies that is due to heterogeneity rather than chance) was used to summarize heterogeneity between studies[26]. Analysis was carried out using Stata v. 11 (Stata Corporation, College Station, TX, USA), using the 'metan' command[27].

RESULTS

We identified 3556 studies from MEDLINE and 5519 studies from EMBASE with this search strategy. We examined the relevance of these articles, and 176 publications were selected for detailed review after screening of title and abstract.

After applying the exclusion criteria detailed in the methods section, there were 31 studies remaining. Two were excluded because they did not include sufficient information for the meta-analysis[28,29], leaving 29 studies (Figure 1). There were 26 studies of SGA only, two of SGA and FGR and one of FGR only. This comprises the population of 28 studies on SGA and three on FGR from 29 studies (full details given in Table S1 online).

The 28 studies of SGA were pooled, giving a total of 7861 SGA fetuses and 91 619 controls. Three studies of fetuses with growth restriction were pooled, giving 119 fetuses with growth restriction and 49 controls.

Some studies used standard scores for developmental assessment where the population distribution of the test scores is known[30–56]. We included studies with population reference as controls[34,35], as the test for neurodevelopmental assessment was validated for the population, and the expected population distribution of scores had previously been confirmed. In some studies there was an inability to divide developmental scores of preterm from term babies[57–63], or to extract mean developmental scores and their SDs, thereby leading to an inability to calculate the odds ratio[11,64–66]. These were excluded. Several studies analyzed the same population in different papers[49,51,67–79]. These were included only once.

The results of the quality analysis are shown in Figure 2; the majority of the studies were of high to medium quality.

Definitions of smallness used in published studies

We used the same definition for SGA as that used in the primary study. The most commonly used criteria were birth weight less than the 5th or 10th centile. We considered the fetus to be growth restricted if umbilical artery Doppler indices were abnormal in addition to the birth weight being below the 10th centile. One study defined growth restriction on the basis of an abnormal postnatal ponderal index[51]. The baby was considered to be in the SGA group but not in the FGR group if the size was small but fetal Doppler ultrasound results were normal. Although some authors termed babies as 'growth restricted' based only on birth weight $< 5^{th}$ centile[46] or < 2500 g[39], we considered these to be SGA babies.

The reported assessment of neurodevelopment involved the use of a large and heterogeneous variety of tests. Some of the reported tests classify a cut-off score below which the individual is classified as abnormal (Bayley Scales of Infant Development score). Others used a scoring system developed specifically for the study[80,81]. Such studies reported a mean score and SD of the distribution.

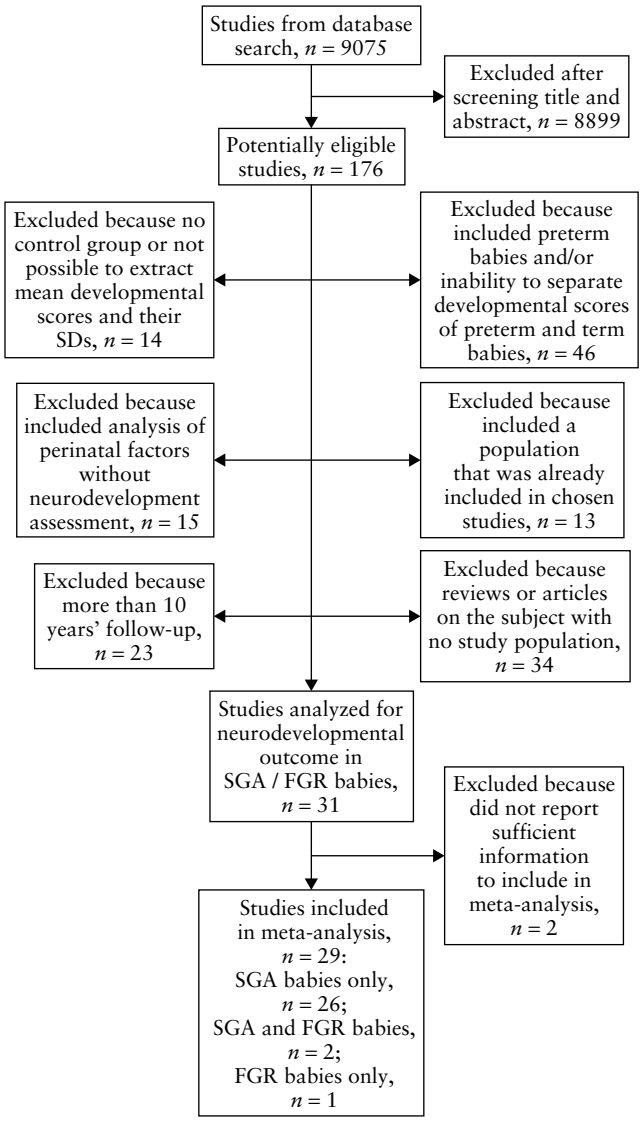

Figure 1 Flowchart of studies identified for meta-analysis. FGR, fetal growth restriction; SGA, small-for-gestational age.

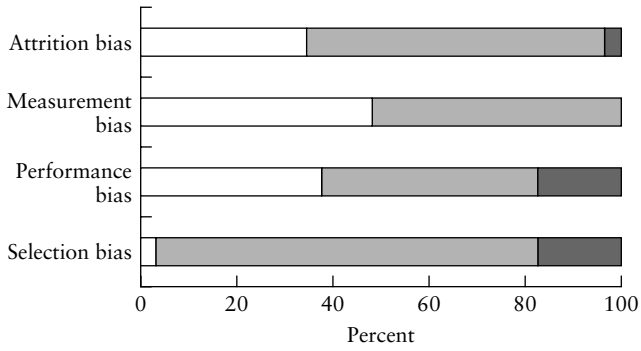

Figure 2 Quality analysis diagram of 29 studies identified for meta-analysis, indicating high (□), medium (▒) and low (■) quality.

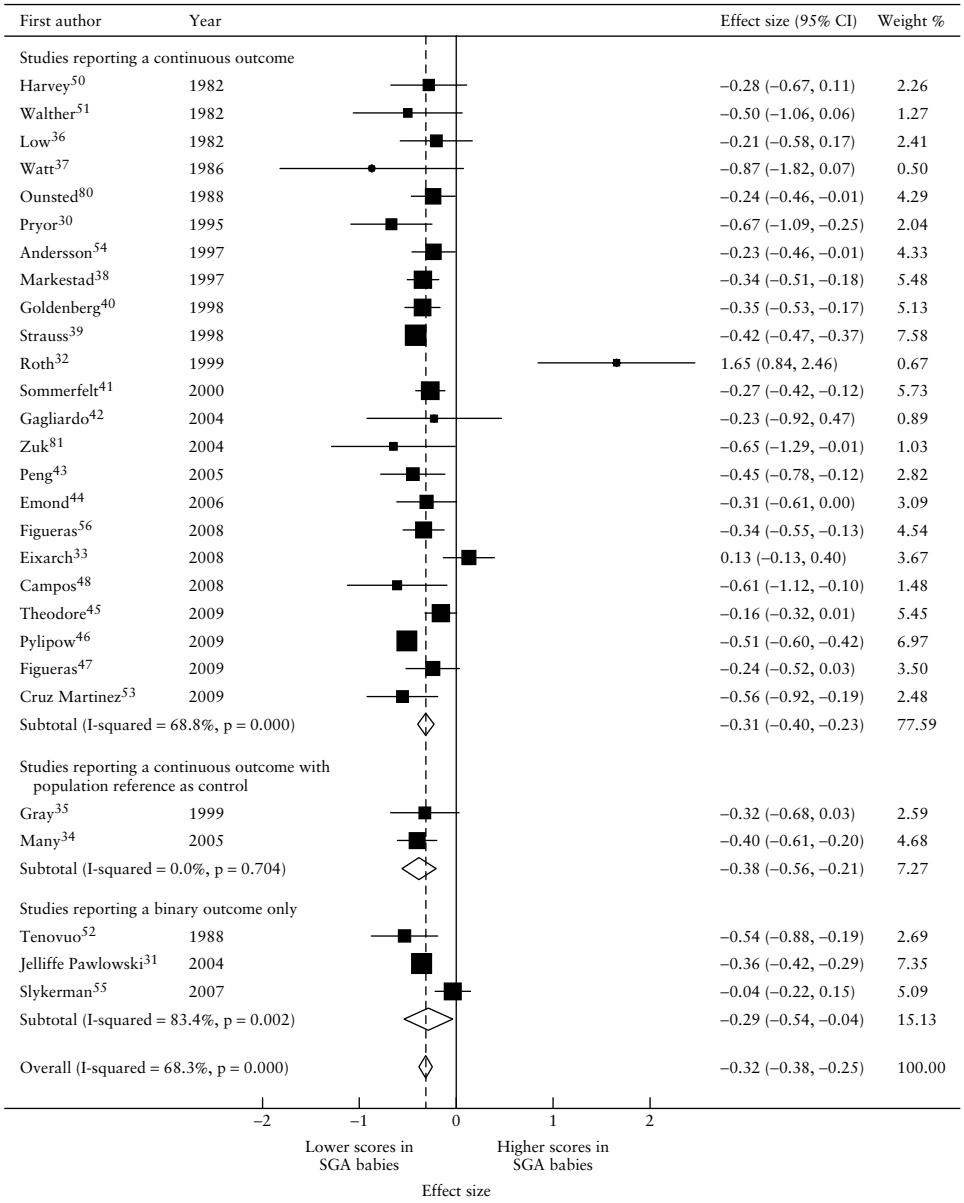

Figure 3 Largest effect size, expressed as multiples of its SD, in meta-analysis of studies of small-for-gestational-age (SGA) babies. Weights are from random effects analysis.

The largest and the smallest effect sizes and their SD are shown in Figures 3 and 4 for SGA babies. Owing to the limited number of growth-restricted babies and controls, a meta-analysis was not carried out. The results of three studies are shown in Table 1. Standardized neurodevelopmental scores in SGA (smallest effect size) and FGR babies were 0.31 SD (95% CI, 0.25–0.38) and 0.32 SD (95% CI, 0.65 to −0.01) below those for normal controls, respectively.

There was evidence of significant heterogeneity between studies in the effect size between SGA and control babies ($I^2 = 67.2\%$; $P < 0.001$). The most divergent result was found in the study by Roth *et al.*[32], but even without this study there was still heterogeneity ($I^2 = 57.5\%$; $P < 0.001$) and the pooled estimate of effect was only slightly greater (0.33 SD).

DISCUSSION

This study shows that small fetuses born at term with or without growth restriction are associated with lower neurodevelopmental scores than are normal controls. In particular, small babies showed significantly higher odds of lower scores in formal neurodevelopmental assessment. The results for FGR babies were imprecise.

Assessing cognitive and motor development is not an easy task. It is particularly difficult to assess the prevalence of 'abnormal' neurodevelopment in a 'normal' population. However, if the same test is used in cases and controls at a similar age, it is possible to compute the odds of exhibiting lower/abnormal scores or the difference in the scores for the particular test between study and control groups. Despite a wide range of variability in assessing neurodevelopment, the neurodevelopmental scores of the

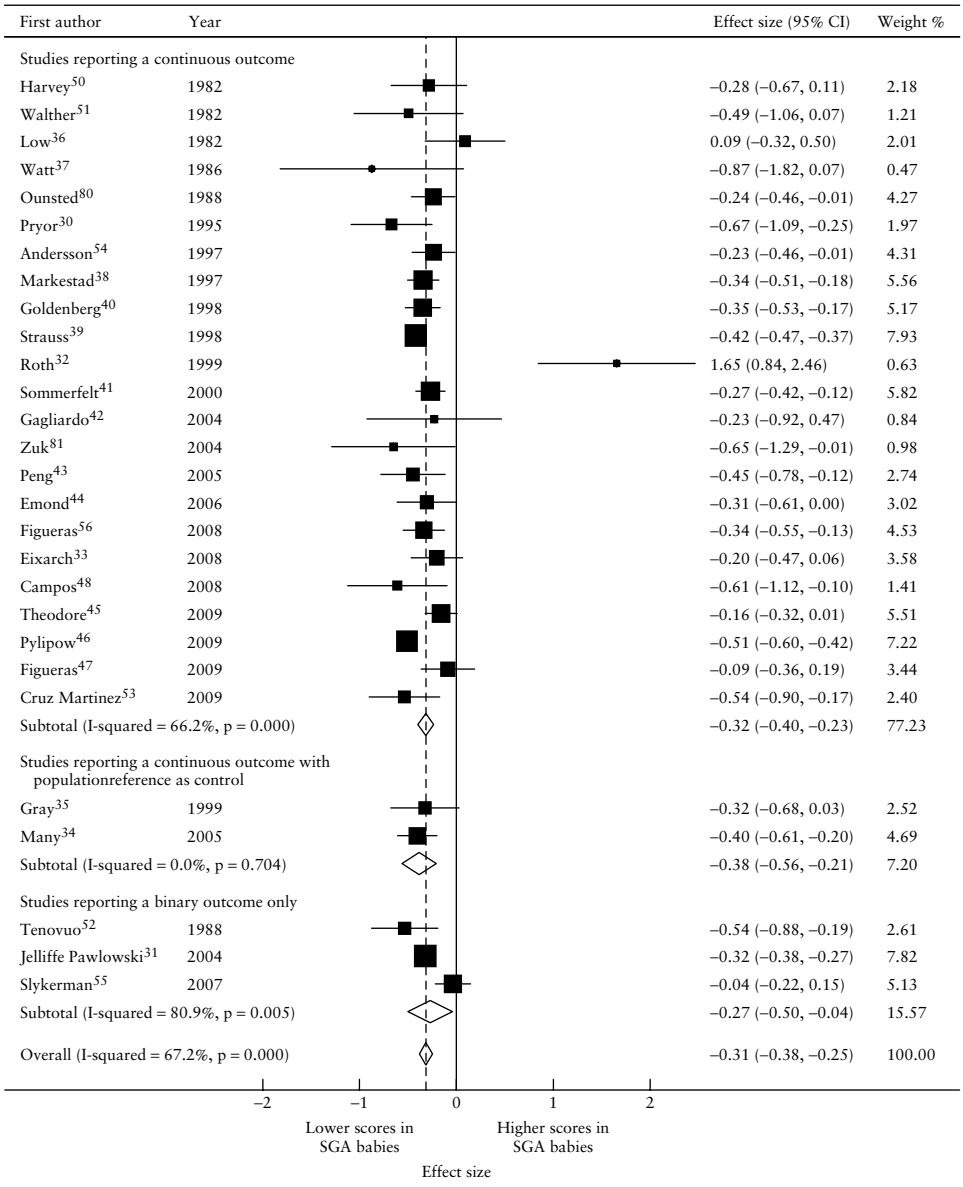

Figure 4 Smallest effect size, expressed as multiples of its SD, in meta-analysis of studies of small-for-gestational-age babies. Weights are from random effects analysis.

SGA group are consistently lower than those of controls, but the effect size is variable.

This finding of lower scores in small fetuses born at term fits well with the already-known increased risk of stillbirth, asphyxia and perinatal death[2,6,82]. The 95% CIs for the effect size in the FGR group crossed unity. This reflects the relative imprecision of the difference caused by a limited sample size.

The following are put forward as possible explanations for the observed findings:

1. Lower neurodevelopmental scores in small fetuses could be the result of placental dysfunction. In general, it is accepted that the sequence of events in fetal growth restriction due to placental insufficiency follows a predictable pattern, and smallness precedes fetal response, as evidenced by changes in fetal Doppler. It follows that small fetuses not showing changes in fetal Doppler parameters are less severely affected, and should show a smaller difference between the mean summary statistic of this group and controls as compared to that between small fetuses with Doppler changes and controls. The result of this meta-analysis has failed to demonstrate this, possibly because of the limited sample size in the growth-restriction group. This may also be due to the fact that most studies on small fetuses did not give information on the fetal Doppler findings. Many small fetuses included in the SGA group may have had abnormal Doppler findings unknown to the examiners.
2. The association between placental dysfunction and low neurodevelopmental scores may not be causative but may be due to confounding. For example, it is possible that fetal growth restriction is caused by factors such as smoking. As a group, smoking mothers may have lower neurodevelopmental scores than do non-smokers and

they may pass on the responsible genes or addictive behavioral pattern.

3. Poor neurodevelopmental scores may have nothing to do with placental dysfunction, but may be related to smallness. There are previous publications exploring the correlation of height with intelligence in the adult literature, and this shows a weak positive correlation[83–86]. In a large study of 76 111 Danish men, Teasdale *et al.*[86] reported a positive correlation between height and intelligence test scores ($r = 0.244$) and height and educational level ($r = 0.264$). A similar point estimate between small fetuses with or without abnormal fetal Doppler parameters supports this theory.
4. SGA fetuses may contain a subgroup of fetuses with conditions like chromosomal abnormality, genetic syndromes, intrauterine infections such as cytomegalovirus or Rubella infection, while intrauterine fetal exposure to substances such as alcohol or narcotic drugs can also lead to smallness. Suboptimal neurodevelopment is highly likely in such cases owing to the insult to the developing brain, thereby worsening the outcome only of that group.

Formal testing of the meta-analysis results showed significant heterogeneity. The most divergent results were those reported by Roth *et al.*[32]. Even with this study excluded there was evidence of heterogeneity of effects between studies. This may be due to heterogeneity in the populations that were studied, and the outcomes that were assessed. The direction of effect is consistent in the vast majority of the manuscripts (except Roth *et al.*[32] and Low *et al.*[36] for smallest effect size, and Roth *et al.*[32] and Eixarch *et al.*[33] for largest effect size). It is the effect size that shows heterogeneity.

The strength of the review is that inclusion of nearly 10 000 children born small was sufficient to give a precise estimation of the effect size for the SGA fetuses. An explicit search strategy with predefined search criteria means that it is unlikely that any important study has not been identified. A weakness of the study is an imprecise differentiation between SGA fetuses and those with FGR. Information about prenatal umbilical artery Doppler was not always available in the studies of SGA fetuses. The effect size for growth-restricted fetuses is estimated with relative imprecision owing to their limited number.

An SGA fetus with abnormal fetal Doppler ultrasound is evidence of pathological smallness due to placental insufficiency. Placental insufficiency can lead to smallness, and the sequence of events in the fetal response has been well characterized. There is slowing of growth, elevated resistance in the umbilical artery flow and increased blood flow to the brain. This fetal response is thought to be protective against long-term damage. Small fetuses with normal fetal Doppler ultrasound are a difficult group to manage. Almost certainly, the group contains some normally grown fetuses and others with early placental insufficiency where fetal Doppler ultrasonography has not yet become abnormal. Clearly, antenatal suspected SGA is

Table 1 Details of studies reporting fetal growth restriction (FGR)

Study	*Design*	*Definition*	*Number in trial*	*Intervention*	*Cases score (SD)*	*Control score (SD)*	P
Gray *et al.* (1999)[35]	Prospective	Birth weight < 2 SD below mean and abnormal placenta (infarcts and accelerated villous maturation)	FGR, $n = 20$	Griffiths Infant Development Scale at 1 year	103.6 (8.0)	Population reference as controls	Not reported
Roth *et al.* (1999)[32]	Prospective	Abdominal circumference (AC) < 10th centile for gestational age and change in standard deviation score for AC (ΔAC) > −1.5	FGR, $n = 18$; Controls, $n = 8$	Structured neurological examination and developmental assessment at 1 year	Impairment 6/18	Impairment 1/8	Not reported
Leitner *et al.* (2000)[49]	Prospective	Birth weight < 10th centile and asymmetric growth restriction	FGR, $n = 81$; Controls, $n = 41$	WPPSI at 7 years	101.38 (14.1)	107.0 (13.9)	< 0.05

WPPSI, Wechsler Preschool and Primary Scale of Intelligence.

not the same as postnatally diagnosed SGA based on accurately measured birth weight, and prenatal diagnosis of small fetuses would invariably be associated with a degree of inaccuracy. In preterm FGR, prolonging the pregnancy is expected to lead to a valuable improvement in fetal maturity. At term, fetal maturity is of little concern. Continuing the pregnancy even after fetal maturity has been reached may lead to more harm than good if it means progressive impairment of neurodevelopment. Currently there is clinical acceptance of the policy of induction of labor in fetuses that are SGA at term but without any other evidence of fetal compromise. The possible adverse effects of earlier delivery on neonatal outcome will have to be kept in mind. Although birth at 37 weeks' gestation is associated with a higher risk of hyaline membrane disease (adjusted odds ratio = 3.12), the risks of meconium aspiration and macrosomia are lower[87].

The growth restriction intervention (GRIT) trial assessed the influence of early elective delivery on the outcome of growth restriction[88]. No evidence was found that short-term outcome was any different with immediate delivery than with more expectant management. The GRIT trial also reported follow-up at 2 years and long-term (6–13 years). There was no difference in the composite morbidity in either arm of the trial in both these reports[89]. The majority of fetuses in the GRIT trial were born before 36 weeks' gestation. Morbidity of prematurity may be far more important than that of placental dysfunction.

More recently, the DIGITAT trial reported short-term outcomes of fetuses with suspected growth restriction after 36 weeks[90]. This trial did not report on neurodevelopment, but no difference was found in short-term outcomes. Importantly, the rates of Cesarean section were comparable in the early-delivery group and the expectant-management group. Elective early delivery may or may not prevent lower scores, but such a policy at least does not appear to increase rates of Cesarean section or instrumental vaginal delivery. The results of this meta-analysis can be used to estimate the sample size of intervention trials designed to prevent lower scores in fetal growth restriction by early elective delivery. We can hypothesize that an intervention capable of reducing the difference in the neurodevelopmental score from 0.3 SD to 0.15 SD would be clinically meaningful. To show a difference in means of 0.15 SD, a trial with 700 participants in each arm of intervention and conservative management is needed to achieve 80% power at the 5% significance level. Even if each of the 650 participants of the DIGITAT trial were available for follow-up at 2 years or more, the trial would be underpowered if no difference in the neurodevelopmental scores was found.

Smallness at term is a common problem. An intervention capable of improving the outcome by even a small amount would be associated with a large public health impact. A trial designed at intervention in small fetuses at term in order to improve the neurodevelopmental outcome is urgently needed.

In conclusion, the results of this systematic review and meta-analysis show that that among babies born at term, being SGA is associated with lower scores on neurodevelopmental outcomes compared to AGA controls. The standardized neurodevelopmental score in SGA babies was 0.32 SD (95% CI, 0.25–0.38) below those for normal controls. Insufficient data were available for FGR babies.

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SUPPORTING INFORMATION ON THE INTERNET

Table S1 may be found in the online version of this article.

