Cognitive and academic outcomes of large-for-gestational-age babies born at early-term: a systematic review and meta-analysis

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Abstract

ABSTRACT (250 words) Background: Early induction of labour (38 $^{+0}$-38 $^{+4}$ weeks) in large-for-gestational-age (LGA) babies may reduce risks such as shoulder dystocia but may increase another risk of reduced cognitive abilities in offspring. **Objectives**: To evaluate the cognitive and academic outcomes of LGA children born at early-term (combined exposures or independently) in the light of existing research. **Search Strategy:** 5 databases were searched from inception to March 2023 without language restrictions. **Selection Criteria:** Studies reporting on cognitive or academic outcomes either focusing on children born at early-term or LGA. **Data Collection and Analysis:** Besides narrative synthesis, we conducted meta-analyses where possible. **Main Results:** Out of 1592 identified articles, no study investigated the effect of early-term delivery in LGA babies on cognitive or academic outcomes. 68 articles investigated the cognitive effects of early-term delivery and LGA independently. Children born at 37 weeks (SMD, -0.13; 95% CI, -0.21 – -0.05) but not at 38 weeks (SMD, -0.04; 95% CI, -0.08 – 0.002) have lower cognitive scores than at 40 weeks. LGA children had slightly higher cognitive scores than AGA children (SMD, 0.06; 95% CI, 0.01 – 0.11). Syntheses results using cognitive impairment or academic performance as outcomes were similar. **Conclusions:** There is no existing study that investigated early-term delivery in LGA babies and their cognitive scores. Early-term delivery has a small detrimental effect on cognitive scores, whereas LGA may have a small benefit. Evidence from RCTs or observation studies is needed. **Fundings**: University of Warwick; UKRI (EP/X023206/1) **Keywords**: cognitive, intelligence, academic performance, early-term delivery, large-for-gestational-age, macrosomia, meta-analysis, systematic review

Title Page

Cognitive and academic outcomes of large-for-gestational-age babies born at early-term: a systematic review and meta-analysis

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Shortened running title : Cognitive outcomes in LGA babies born at early-term

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Introduction (400 words)

Large-for-gestational-age (LGA) is variously defined as weighing over 4000 grams, 4500 grams, or over the 90th customized weight for gestational age centile[1, 2]. It affects about 10% of all pregnancies.[3] Birth of LGA foetuses has a greater risk of complications including birth trauma, to the foetus specifically, from shoulder dystocia which can lead to fractures, brachial plexus injury, perinatal asphyxia, and death, and to the mother of vaginal tears, haemorrhage, and caesarean section.[2]A Cochrane review shows that compared with expectant management, early induction reduces the risk of shoulder dystocia and fractures.[4] A large clinical trial of LGA foetuses underway in the United Kingdom is also actively exploring whether early induction of labour starting at 38 weeks will provide perinatal benefits to the foetus and mother.[5]

However, there is emerging evidence showing that early-term birth (37^{+0}-38^{+6} gestational weeks) may be associated with reduced cognitive abilities or increased learning problems in childhood.[6-10] Sixteen to 31% of the population are delivered between 37 to 39 gestational weeks,[11, 12] and a high number of special education needs (SEN) cases may be attributed to early-term birth. Even small decreases in cognitive scores can have a marked impact on a child's ability to learn and perform academically at school,[13]and the effects can persist into adulthood,[14, 15]bringing with them issues of work status and income-earning capacity.[16, 17] The latest UK NHS guidance (2019) warns of increasing amounts of SEN attributed to early-term births.[18]

Considering the adverse effects on cognitive abilities may be confined to children born with growth restriction, an established risk factor for cognitive impairment from childhood into adulthood[19], in LGA babies, it is still unclear whether by avoiding one risk (e.g. shoulder dystocia) we may increase another risk for reduced cognitive or academic abilities. To date, there are no systematic reviews assessing the association between LGA babies born at early-term and cognitive or academic abilities. Existing systematic reviews exploring the effects of only early-term births on cognitive or academic outcomes do not provide estimation for each specific week of pregnancy, which is crucial to induction timing selection.[6-10, 20]

We aimed to systematically review the available evidence on the cognitive effects of early-term delivery in LGA babies. However, if we are unable to find enough existing studies, then instead we will review the effects of early-term birth and LGA on outcomes independently.

Methods

This systematic review and meta-analysis was conducted according to reporting guidelines[21] and using a prospective protocol.[22]

Information source and search strategy

X.Z. performed the search in 5 databases (PubMed, EMBASE, PsycINFO, Web of Science, and Scopus) from inception to 13th March 2023. We used Medical Subject Headings (MeSH) and text words for the concepts: 1) early-term delivery, 2) LGA, and 3) cognitive and/or academic outcomes. No date and language restrictions were applied. If the published language was not English, we used an AI translator (DeepL. SE, Germany) to perform the translation. Full search strategies are shown in Appendix S1.[22] In addition, X.Z. performed a hand search based on relevant systematic reviews on 21st September 2023. All references were imported in EndNote 20 (Clarivate, London, United Kingdom).

Selection process and eligibility criteria

Two reviewers (X.Z. and A.P.) independently screened titles and abstracts using self-designed Excel spreadsheets. After that potentially eligible studies were retrieved for full-text screening. Two reviewers (X.Z. and A.P.) independently performed a second eligibility check for the studies retrieved. Any disagreements were fully discussed until consensus was obtained, and if any uncertainty was left, a third reviewer was consulted (D.W.).

We included studies that evaluated the association of LGA babies born at early-term and cognitive or academic outcomes, or those evaluated the independent effects of early-term birth or LGA on cognitive or academic outcomes. We excluded animal studies, reviews, case reports, editorials, comments, conference abstracts and studies that targeted populations defined by specific health conditions.

Risk of bias assessment

A risk of bias assessment was performed by 2 reviewers (X.Z. and M.S.). It was evaluated according to the Newcastle-Ottawa Scale, which consists of 8 items with a maximum of 9 stars. Studies judged [?]7 stars were considered as low risk, [?]5 as relatively low risk, and [?] 4 as high risk. High risk on assessment was not a reason for exclusion.

Data extraction

We collected data on author, year, study design, sample size, method of assessing LGA, intervention (induction, spontaneous, caesarean delivery or not specified), age at follow-up, cognitive or academic outcome, and confounders. The primary data extraction was performed by one reviewer (X.Z.) and checked for accuracy by a second reviewer (M.S.). Any disagreements were fully discussed until a consensus was reached. Corresponding authors of included papers were contacted by email to provide further details if data were insufficient or missing.

To perform meta-analyses, for continuous variables, we extracted the mean, standard deviation (SD), and total sample size (N), or mean difference, lower/upper limit, and total N, for the exposed and control groups in the cognitive assessment scores. For the dichotomous variables, we extracted the 2*2 table or Odds Ratio and lower/upper limit.

There were two types of reference groups for comparison of early-term infants; one type of study compared early-term infants (37-38 weeks) with full-term infants (39-41 weeks), in which case we used full-term infants (39-41 weeks) as the reference group. The second of studies showed results for 37, 38, 39, 40, and 41 weeks GA separately, in which case we used 40 weeks as the reference group to examine 37w vs 40w and 38w vs 40w GA.

Any measure of cognitive function was considered for inclusion. When results were reported as both an overall test score (e.g. Intelligence Quotient; IQ) and a domain-specific score (e.g. receptive vocabulary delay), we chose the overall one in data synthesis. When results were only reported as domain-specific scores within the same study population, we calculated the mean score across domain-specific tests. Where multiple cognitive or academic outcomes were reported, we selected the one that provided the most reliable information for analysis (e.g. IQ test vs. school grade). Studies with follow-up of at least 6 months were eligible. When the outcomes were measured more than once at different ages for the same study population, we selected the oldest age group with the most reliable cognitive assessment. If multiple multivariable models were reported, we extracted data from the model with the most confounder-adjusted model (e.g. adjusted by education and sex vs. adjusted by sex).

We extracted data according to three primary outcomes as follows. Cognitive outcomes were based on cognitive scores (e.g., Bayley Scale of Infant and Toddler Development Mental Developmental Index,[23-27] and Wechsler Abbreviated Scale of Intelligence,[28]) or cognitive impairment (e.g., Wechsler Intelligence Scale for Children-full scale IQ below average defined as scores below 85 or one standard deviation below the mean[29]). Academic outcomes were based on low academic performance (e.g. special education needs defined as children in Scottish schools 2005 census requires special education provision, which comprises both children with learning disabilities, such as dyslexia and dyspraxia, and children with physical disabilities that affect learning[30]). See Appendix S2 for full details of outcome definitions.

To allow comparability of primary outcomes harmonization was required using the extracted data: (a) If the study reported a cognitive test T score, percentile or Z score, we converted it into intelligence quotient (IQ with mean: 100; SD: 15); (b) if the direction of a study's outcome was inconsistent with others (e.g., receiving a longer education rather than shorter), we converted it to a same-direction outcome; (c) if an LGA-related study defined LGA not in terms of percentiles but in terms of SD or absolute values, we converted it to percentiles using the World Health Organization foetal growth calculator (unknown foetal sex).[31]

Data synthesis

Meta-analyses were used to describe findings in the present review when data extracted could be used to calculate the standardized mean difference or risk ratios. We employed Comprehensive Meta-Analysis (CMA) software (version 4, professional, Biostat Inc. USA) to analyse the data. Random effect models were used in all the analyses. We used standardized mean difference (SMD) and their 95% confidence intervals (CIs) for continuous data. When the measurement only supplied dichotomous options, such as cognitive impairment or not, we used the Odds Ratio (OR) and their 95% CIs instead. Pooled random-effects 95% prediction intervals and heterogeneity statistics were calculated for meta-analysis where at least three studies were included. Heterogeneity was evaluated by I^2, Tau^2, and Q statistics and their p-values. When $I^2 > 75\%$, we conducted a series of subgroup meta-analyses by splitting data according to participants' characteristics (such as sex and age at follow-up) or study characteristics (such as outcome measurement scale) to examine the source of heterogeneity. Forest plots were created to provide a graphical overview of the individual studies and syntheses.

To assess publication bias, we employed a random-effect model to generate funnel plots for meta-analyses. In addition, Duval and Tweedie's trim and fill were used to estimate the number of missing studies that may exist and the effect that these studies might have had on their outcome.[32]

Two reviewers (X.Z. and M.S.) independently graded evidence according to the GRADE handbook[33] . The strength of evidence was initially set as low and was rated up for 1) large effect sizes (Relative risk <0.5 or >2, and SMD<-0.25 or >0.25), 2) where a dose-response relationship was shown, and 3) effect of plausible residual confounding (such as parental education level)[34] was considered. The strength of evidence was classified as very low, low, moderate, or high quality.

Results

Study selection

Among 1592 unique studies (1572 from databases and 20 from hand-searching) identified from our search, there were no studies that met the exact criteria of our primary aim that investigated the effects of early-term birth on cognitive or academic outcomes in LGA babies. For our secondary aim, a total of 68 articles were considered eligible and included in this systematic review after two-stage screening, as shown in Figure 1. Among the final included studies that assessed cognitive or academic outcomes, 11 studies (see Table S3) only investigated the effect of LGA,[35-45] 51 studies (see Table S2) only investigated the effect of early-term delivery (37^{+0}w-38^{+6}w),[13, 23-26, 29, 46-90] and 6 studies (see Table S1) explored the effects of both exposures simultaneously but independently.[28, 30, 91-94]

Early-term delivery

Cognitive Scores

The children born at 37 weeks GA had lower mean cognitive scores than those born at 40 weeks (27 912 children; SMD, -0.13; 95% CI, -0.21 – -0.05; I^2, 54%; moderate certainty evidence; Trim and Fill, -0.09, -0.18 – -0.01), as shown in Figure 2 a). There was no significant difference between children born at 38 and 40 weeks GA (33 004 children; SMD, -0.04; 95% CI, -0.08 – 0.002; I^2, 42%; moderate certainty evidence; Trim and Fill, -0.04, -0.09 – 0.02) (Figure 2 a). The children born at early-term (37 and 38 weeks GA combined) had lower mean cognitive scores than full-term (39 to 41 weeks) born children (39 171 children, SMD, -0.14; 95% CI, -0.26 – -0.02; I^2, 95%; low certainty evidence; no publication bias) (Figure 2 a). Due to the high heterogeneity, we conducted a subgroup analysis based on the age of follow-up. The mean differences tended to be smaller in older children (see Appendix S5).

Cognitive impairment

More cognitive impairment cases were found in children born at 37 weeks (71 597 children; OR, 1.23; 95% CI, 1.13 – 1.33; I^2, 49%; moderate certainty evidence; Trim and Fill, 1.30, 1.20 – 1.42) and at 38 weeks (92 572 children; OR, 1.08; 95% CI, 1.03 – 1.12; I^2, 0%; moderate certainty evidence; no publication bias) compared to those born at 40 weeks (Figure 2 b). Cognitive impairment was more common in early-term born children than full-term (939 397 children; OR, 1.19; 95% CI, 1.13 – 1.25; I^2, 86%; low certainty evidence; Trim and Fill, 1.17, 1.11 – 1.23) (Figure 2 b). We also conducted a subgroup analysis based on age at follow-up in this synthesis, see Appendix S5. The results showed that the OR for cognitive impairment reduced with increasing age at follow-up, except for one study[55].

Low academic performance

More low academic performance happened in those born at 37 weeks GA (576 869 children; OR, 1.17; 95% CI, 1.02 – 1.35; I^2, 96%; moderate certainty evidence; Trim and Fill, 1.03, 0.91 – 1.17) and 38 weeks GA (614 005 children; OR, 1.10; 95% CI, 1.01 – 1.19; I^2, 92%; moderate certainty evidence; Trim and Fill, 1.03, 0.95 – 1.13) compared to those born at 40 weeks (Figure 2 c). Low academic performance was more common in early-term born than full-term children (2 714 784 children; OR, 1.15; 95% CI, 1.09 – 1.21; I^2, 96%; low certainty evidence; Trim and Fill, 1.05, 0.99 – 1.11) (Figure 2 c). The heterogeneity of the studies in these three data syntheses was high. We conducted subgroup analyses according to the outcome measurement scales, see Appendix S5.

Large-for-gestational-age

Seventeen (11 plus 6) studies investigated the effects of LGA on cognitive or academic outcomes. Overall, LGA children had higher cognitive scores than AGA children (16 774 children; SMD, 0.06; 95% CI, 0.01 – 0.11; I^2, 0%; low certainty evidence; Trim and Fill, 0.05, 0.01 – 0.10). The results are shown in Figure 3 b). Cognitive impairment was less common in LGA children than AGA children (417 562 children; OR, 0.94; 95% CI, 0.92 – 0.97; I^2, 0%; low certainty evidence; Trim and Fill, 0.94, 0.91 – 0.97), as was low academic performance (775 745 children; OR, 0.93; 95% CI, 0.89 – 0.97; I^2, 61%; low certainty evidence; Trim and Fill, 0.90, 0.86 – 0.95) (Figure 3b).

Discussion (1200 words)

Main findings

This systematic review and meta-analyses found that there were no studies before 13 March 2023 that had investigated cognitive scores, cognitive impairment, or low academic performance in early-term births at LGA. Existing studies have analysed the effects of LGA against AGA or early-term births (37 to 38 weeks GA) compared to full-term births (39 to 41 weeks GA) on cognitive outcomes independently, or utilized one of these exposures as a confounder to adjust for this factor in the association with cognitive outcome. Children born at early term were found to have slightly lower cognitive scores, a slightly increased risk for common cognitive impairment, and low academic performance compared to children born at full term. Within the group of early-term born those born at 37 weeks GA tended to have a slightly larger risk than those born at 38 weeks compared to those born full-term. This suggests that there may be a dose-response relationship between GA and cognitive outcome. Compared to AGA children, LGA children had slightly higher cognitive scores, less common cognitive impairment, and fewer had low academic performance in childhood. However, this latter evidence is of low certainty.

According to Cohen's D of means, a 2-point intelligence quotient (IQ) difference refers to a very small effect size[95] (e.g. -0.14 standard difference in means * 15 points = -2.10 IQ difference). When early-term deliveries were examined separately by week of gestation, only a very small clinically significant difference in IQ was found between children born at 37 weeks compared to those born at 40 weeks while no significant difference was found for those born at 38 weeks GA compared to those born full term. Considering that 16-31% of foetuses are born early term, the effect of early term on the overall population IQ may be between 0.4 to 0.7 IQ points maximum, a very small effect. LGA versus AGA birth very slightly favoured those born LGA but the difference was not clinically significant.

There was no study published before 13 March 2023 that considered both gestational age and LGA, i.e. relative birth weight for gestation and its effect on cognitive and academic outcomes. Thus, two possibilities cannot be ruled out, the first being that the small effect of early-term birth may be partly due to confounding by SGA foetuses more often delivered at early term. SGA is a known factor associated with lower cognitive outcomes.[96] Accordingly, the small benefit of LGA may be confounded by the gestational age at birth due to the diversity of LGA definitions. The second is that gestational week and weight percentile at birth have additive effects on cognitive development, so that in early-term born LGA babies the two effects may offset each other to some extent.[97]

Strengths and limitations

The present systematic review is the best available evidence of cognitive and academic outcomes in early-term born LGA babies as it is the most comprehensive meta-analysis to date exploring the association between early-term birth and cognitive outcomes, and it is also the only systematic review to investigate the association between LGA and cognitive outcomes. The strengths of this review are that we followed a pre-registered protocol to search for articles with no time or language constraints. The population sizes were large and across several countries and follow-up was carried out across childhood.

One limitation of this article is the high heterogeneity of measurements in the definition of cognitive impairment and low academic performance. Included studies that used various metrics for reporting results, and some studies with missing metrics (e.g. SD of the mean) had to be excluded from the meta-analyses. Furthermore, different definitions were utilized for LGA or full-term across studies. For example, although most studies used greater than the 90th percentile as the definition of LGA, several studies used the 80th[40] or 85th[35, 42] percentile as the definition. Although most studies used the 10-90$^{\text{th}}$ percentile as the definition of AGA, some studies used other reference groups, e.g. 20-79th percentile[40] or 85-90th percentile[43]. Even though all fall within the official definition of the 10-90th percentile, the use of different reference groups is likely to alter the effect size of the comparisons. Similarly, N. Libuy (2023)[68]'s use of births at 39^{+0}-40^{+6} weeks (rather than 39^{+0}-41^{+6} weeks) as the full-term reference group also poses a risk of bias in data synthesis. Additionally, only a few studies were stratified according to sex, so the role of sex in their impact could not be discussed in this review.

Interpretation

There is a paucity of existing studies that stratify children born at the same gestational week according to their birth weight percentile (or vice versa). Several systematic reviews[6-10, 20] that evaluated the relationship between early-term delivery and cognitive or academic outcomes are consistent with the conclusions of our review. In terms of foetal growth, although there is a systematic review and meta-analysis with good quality showing that SGA is detrimental to cognitive development,[96] we found no extant systematic reviews synthesizing evidence on cognitive development or academic performance in children with LGA. Analysis by gestational age or LGA separately is unable to answer whether these effects are additive to or moderate each other.

Firstly, observational studies are required that allow the investigation of the effect of LGA or relative birthweight at each gestational week on cognitive and academic outcomes. A new study published after March 2023 utilized four cohort studies (N: 30 643)[97] and reported that relative birthweight (birth weight percentile per gestation) and gestational week are two exposure factors that independently affect cognitive scores in childhood and are thus additive. IQ linearly increased by 4.2 points as birth weight centiles increased from the 1st to the 69th percentile before completely plateauing (i.e. no more IQ gain at larger birth weight). Above 32 weeks gestation, each GA week gained was associated with a 0.3 IQ increase similar to previous study reports.[98]Future studies are needed to report relative birthweight per gestational week and its effect on cognitive outcomes for obstetric decision-making.

Secondly, the most desirable would be to have a randomized clinical trial comparing the effect of early-term induction for LGA versus expectant delivery on shoulder dystocia with long-term follow-up of cognitive and academic outcomes on the of the child. Considering the suggested small effect sizes, this will require large participant numbers.

Conclusions

On current best evidence and considering all the provisos outlined above, we conclude that early-term birth for LGA babies, in particular at 38 weeks, is not likely to reduce cognitive outcome to a clinically significant degree at the population level. For LGA children in particular, a large RCT and/or cohort study with long-term follow-up is urgently needed to confirm whether the slight advantage of being larger in terms of cognitive development can compensate for the slight disadvantage of being born two weeks earlier. These studies will contribute greatly to helping obstetricians and parents weigh the pros and cons of making the best possible decision about the timing of labour.

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Contribution to Authorship : XZ, SQ and DW were responsible for the design and conception of the research question. XZ and DW designed the methodology. XZ and AP undertook literature search, study selection and checked by DW. XZ and MS conducted the data extraction and risk assessment. XZ did statistical analysis and designed the tables, figures and online-only supplements. The initial drafts of the manuscript were prepared by XZ and DW, with additional input from SQ, MS and AP. All authors contributed to the final version of the manuscript.

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Figure legend

Figure 1 PRISMA flow diagram. LGA, large for gestational age

Figure 2 a) Cognitive scores and early-term delivery. The figure displays for each study included in the meta-analysis in the summary statistics (mean, standard deviation, and total sample size) for the cognitive scores and early-term delivery and the standardized mean difference (SMD) and its 95% confidence interval for the continuous outcome. SD, standard deviation; CI, confidence interval

b) Cognitive impairment and early-term delivery. The figure displays for each study included in the meta-analysis in the summary statistics (number of events and total sample size) for the cognitive impairment and early-term delivery and the odds ratios (ORs) and its 95% confidence interval for the dichotomous outcome. CI, confidence interval

c) Low academic performance and early-term delivery. The figure displays for each study included in the meta-analysis in the summary statistics (number of events and total sample size) for the low academic performance and early-term delivery and the odds ratios (ORs) and its 95% confidence interval for the dichotomous outcome. CI, confidence interval

Figure 3 a) Cognitive scores and large-for-gestational-age. The figure displays for each study included in the meta-analysis in the summary statistics (mean, standard deviation, and total sample size) for the cognitive scores and LGA and the standardized mean difference (SMD) and its 95% confidence interval for the continuous outcome. LGA, large for gestational age; AGA, appropriate for gestational age; SD, standard deviation; CI, confidence interval

b) Cognitive impairment / low academic performance and large-for-gestational-age. The figure displays for each study included in the meta-analysis in the summary statistics (number of events and total sample size) for the cognitive impairment or low academic performance and early-term delivery and the odds ratios (ORs) and its 95% confidence interval for the dichotomous outcome. LGA, large for gestational age; AGA, appropriate for gestational age; CI, confidence interval

Table S1 Characteristics of studies exploring the exposures of both early-term delivery and large for gestational age on cognitive or academic outcomes

Table S2 Characteristics of studies investigating the effect of only early-term delivery on cognitive outcomes

Table S3 Characteristics of studies exploring the exposures of only large for gestational age on cognitive or academic outcomes

Appendix S1 Full searching strategy

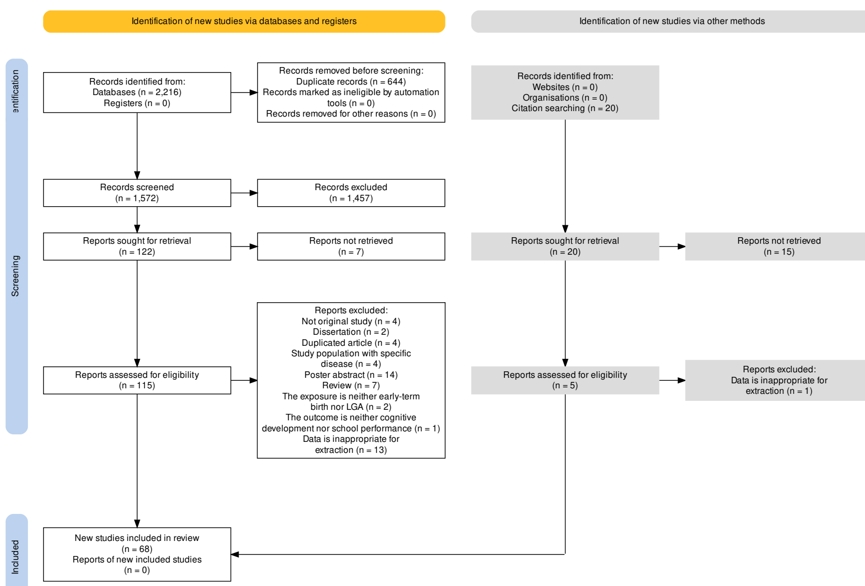
Appendix S2 Three main primary outcomes and their definitions

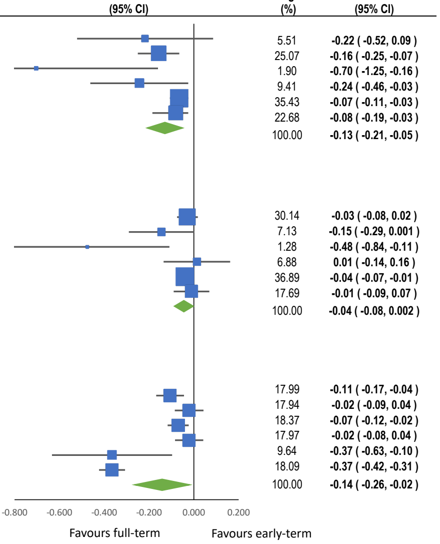
Appendix S3 Two-stages screening criteria

Appendix S4 Risk of bias in studies

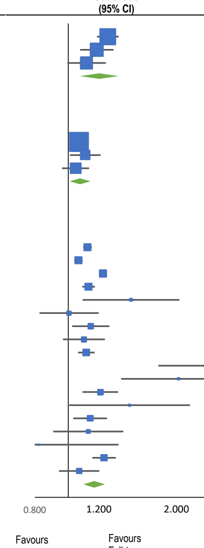
Appendix S5 Subgroup analyses

Appendix S6 ADHD and Gestational Age (early-term vs full-term)



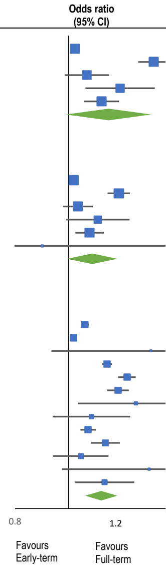


Study	Early-term Mean	Early-term SD	Early-term Total	Full-term Mean	Full-term SD	Full-term Total	Weight (%)	Standard Mean Difference (95% CI)
37w vs. 40w								
O. Rose (2013)	102.60	11	45	105.10	12	604	5.51	**-0.22 (-0.52, 0.09)**
S. Yang (2010)	-	-	469	-	-	11074	25.07	**-0.16 (-0.25, -0.07)**
E.V. Espel (2014)	-	-	17	-	-	66	1.90	**-0.70 (-1.25, -0.16)**
J. Hua (2019)	-	-	87	-	-	1152	9.41	**-0.24 (-0.46, -0.03)**
J. L. Gleason (2021)	-	-	3028	-	-	9370	35.43	**-0.07 (-0.11, -0.03)**
J.L. Richards (2016)	-	-	450	-	-	1550	22.68	**-0.08 (-0.19, -0.03)**
Pooled (Random effect model)			4096			23816	100.00	**-0.13 (-0.21, -0.05)**
Heterogeneity: τ2 = 0.004, I2 = 54%, Q(5) = 10.81 (p=0.06)								
Test of overall effect: Z = -3.30, P = 0.001								
38w vs. 40w								
O. Rose (2013)	103.40	12	260	105.10	12	604	30.14	**-0.03 (-0.08, 0.02)**
S. Yang (2010)	99.60	0.4	2100	100.00	-	11074	7.13	**-0.15 (-0.29, 0.001)**
E.V. Espel (2014)	-	-	53	-	-	66	1.28	**-0.48 (-0.84, -0.11)**
J. Hua (2019)	-	-	205	-	-	1152	6.88	**0.01 (-0.14, 0.16)**
J. L. Gleason (2021)	-	-	5570	-	-	9370	36.89	**-0.04 (-0.07, -0.01)**
J.L. Richards (2016)	-	-	1000	-	-	1550	17.69	**-0.01 (-0.09, 0.07)**
Pooled (Random effect model)			9188			23816	100.00	**-0.04 (-0.08, 0.002)**
Heterogeneity: τ^2 = 0.001, I^2 = 42%, Q(5) = 8.60 (p=0.13)								
Test of overall effect: Z = -1.88, P = 0.06								
Early-term vs. Full-term								
I. M. Zambrana (2015)	-	-	1068	-	-	15449	17.99	**-0.11 (-0.17, -0.04)**
J. L. Beauregard (2018a)	-	-	1400	-	-	2900	17.94	**-0.02 (-0.09, 0.04)**
J. L. Beauregard (2018b)	-	-	2389	-	-	6297	18.37	**-0.07 (-0.12, -0.02)**
J.L. Richards (2016)	-	-	1450	-	-	3000	17.97	**-0.02 (-0.08, 0.04)**
E. Yangin Ergon (2023)	85.35	11	109	89.97	14	109	9.64	**-0.37 (-0.63, -0.10)**
P. Shah (2016b)	93.40	0.9	1800	93.70	0.8	3200	18.09	**-0.37 (-0.42, -0.31)**
Pooled (Random effect model)			8216			30955	100.00	**-0.14 (-0.26, -0.02)**
Heterogeneity: τ^2 = 0.02, I^2 = 95%, Q(5) = 94.56 (p<0.001)								
Test of overall effect: Z = -2.32, P = 0.02								

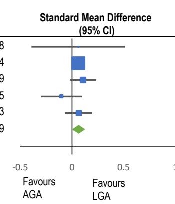


Study	Early-term Events	Early-term Total	Full-term Events	Full-term Total	Weight (%)	Odds ratio (95% CI)
37w vs. 40w						
J. P. Bentley (2016)	1021	8857	4078	44832	44.32	1.30 (1.21, 1.40)
J. L. Gleason (2021)	-	3028	-	9370	30.15	1.21 (1.08, 1.35)
L.G. Smithers (2015)	-	846	-	4664	25.53	1.13 (0.99, 1.29)
Pooled (Random effect model)		12731		58866	100	1.23 (1.13, 1.33)
Heterogeneity: τ2 = 0.003, I2 = 49% , Q(2) = 3.90 (p=0.14)						
Test of overall effect: Z = 4.91, P <0.001						
38w vs. 40w						
J. P. Bentley (2016)	2486	25608	4078	44832	62.57	1.07 (1.02, 1.13)
J. L. Gleason (2021)	-	5570	-	9370	16.34	1.12 (1.01, 1.24)
L.G. Smithers (2015)	-	2528	-	4664	21.09	1.05 (0.96, 1.15)
Pooled (Random effect model)		33706		58866	100	1.08 (1.03, 1.12)
Heterogeneity: τ^2 = 0.00, I^2 = 0% , Q(2) = 0.87						
Test of overall effect: Z = 3.49, P < 0.001						
Early-term vs. Full-term						
M. G. Eide (2009)	6849	37484	34382	209191	9.71	1.14 (1.11, 1.17)
G.K. Dhamrait (2021)	-	21107	-	32048	9.73	1.07 (1.04, 1.10)
A. Adanikin (2022)	9071	54549	31834	232865	9.78	1.26 (1.23, 1.29)
J. P. Bentley (2016)	3507	34465	7450	82783	9.35	1.15 (1.10, 1.20)
E.Roe (2022)	-	631	-	1570	1.88	1.52 (1.10, 2.10)
A. Fitzpatrick (2016)	-	2434	-	8548	3.83	1.01 (0.83, 1.23)
G. Poulsen (2013)	386	2471	1208	8789	6.11	1.16 (1.03, 1.32)
H. K. Brown (2014)	-	4333	-	9663	5.54	1.11 (0.97, 1.28)
J Hua (2022)	2131	35160	3761	69529	8.93	1.13 (1.07, 1.19)
J.J. Liang (2020)	102	374	93	713	1.96	2.50 (1.82, 3.43)
K.Baumgartel (2020)	51	453	66	1152	1.42	2.09 (1.42, 3.06)
K. Stene-Larsen (2014)	366	7109	1287	30641	6.32	1.24 (1.10, 1.40)
L.M. Reyes (2019)	-	199	-	591	1.29	1.51 (1.01, 2.25)
M.A. Quigley (2012)	900	1596	2853	5407	6.58	1.16 (1.03, 1.30)
M. Wu (2021)	125	727	258	1678	3.07	1.14 (0.90, 1.44)
M.X. Liu (2023)	-	542	-	975	0.78	0.82 (0.48, 1.40)
N. Z. Rabie (2015)	-	11527	-	24005	7.98	1.27 (1.18, 1.37)
Z. Chen (2022)	534	1288	1112	2800	5.74	1.08 (0.94, 1.23)
Pooled (Random effect model)		216449		722948	100	1.19 (1.13, 1.25)
Heterogeneity: τ^2 = 0.006, I^2 = 86%, Q(17) = 122.94 (p<0.001)						
Test of overall effect: Z = 6.80, P < 0.001						

Study	Early-term Events	Early-term Total	Full-term Events	Full-term Total	Weight (%)	Odds ratio (95% CI)
37w vs. 40w						
R. J. Burger (2023)	104433	226684	60186	132596	21.52	1.03 (1.01, 1.04)
D. F. MacKay (2010)	1217	19834	5731	130798	20.67	1.43 (1.34, 1.52)
A.K. Searle (2017)	-	946	-	6317	19.75	1.08 (0.98, 1.19)
J. L. Gleason (2021)	-	3028	-	9370	17.62	1.24 (1.07, 1.43)
K.G. Noble (2012)	1122	12152	2861	35144	20.43	1.15 (1.07, 1.23)
Pooled (Random effect model)		262644		314225	100	1.17 (1.02, 1.35)
Heterogeneity: τ^2 = 0.02, I^2 = 96% , Q(4) = 109.45 (p<0.001)						
Test of overall effect: Z = 2.21, P = 0.03						
38w vs. 40w						
R. J. Burger (2023)	99117	215882	60186	132596	22.50	1.02 (1.01, 1.04)
D. F. MacKay (2010)	2759	51569	5731	130798	21.13	1.23 (1.18, 1.29)
A.K. Searle (2017)	-	2875	-	6317	20.08	1.04 (0.98, 1.11)
J. L. Gleason (2021)	-	5570	-	9370	14.37	1.13 (0.99, 1.29)
K.G. Noble (2012)	2058	23319	2861	35135	20.30	1.09 (1.03, 1.16)
T.M. Nielsen (2021)	20	288	22	286	1.62	0.90 (0.48, 1.68)
Pooled (Random effect model)		299503		314502	100	1.10 (1.01, 1.19)
Heterogeneity: τ^2 = 0.01, I^2 = 92% , Q(5) = 62.58 (p<0.001)						
Test of overall effect: Z = 2.14, P = 0.03						
Early-term vs. Full-term						
K. Lindstroem (2007)	42367	68541	259856	431656	10.98	1.07 (1.05, 1.09)
R. J. Burger(2023)	203550	442566	172164	378493	11.07	1.02 (1.01, 1.03)
I. Kirkegaard (2006)	30	633	105	3081	1.39	1.41 (0.93, 2.14)
N. Libuy (2023)	19534	57956	47218	156291	10.92	1.17 (1.15, 1.20)
D. F. MacKay (2010)	3976	71403	13109	297000	10.54	1.28 (1.23, 1.32)
R. Wiingreen (2018) a	-	89528	-	162169	10.27	1.23 (1.18, 1.29)
A. Hedges (2021)	194	388	360	837	3.31	1.33 (1.04, 1.69)
E Chan (2014)	237	1258	745	4277	5.39	1.10 (0.94, 1.29)
M. Hanly (2017)	4654	20951	362	43199	10.66	1.09 (1.05, 1.12)
M. J. Berry (2018)	1587	131949	3399	329280	9.70	1.17 (1.10, 1.24)
N. Alterman (2022)	659	1498	2164	5064	7.18	1.05 (0.94, 1.18)
P. Shah (2016a)	-	1789	-	3717	1.74	1.40 (0.97, 2.02)
G. Poulsen (2013)	386	2471	1208	8789	6.83	1.16 (1.03, 1.32)
Pooled (Random effect model)		890931		1823853	100	1.15 (1.09, 1.21)
Heterogeneity: τ^2 = 0.006, I^2 = 96%, Q(12) = 335.10 (p<0.001)						
Test of overall effect: Z = 5.13, P < 0.001						



Study	LGA Mean	LGA SD	LGA Total	AGA Mean	AGA SD	AGA Total	Weight (%)	Standard Mean Difference (95% CI)
A. R. Bischoff (2017)	99.10	10.41	21	98.47	10.43	178	**1.05**	**0.06 (-0.39, 0.51)**
B. Yu (2017)	-	-	1436	-	-	7364	67.26	**0.06 (0.01, 0.12)**
J. F. Paulson (2014)	99.20	-	271	99.70	-	2659	13.77	**0.11 (-0.02, 0.23)**
M. M. Costantine (2021)	93.60	13.70	110	95.10	14.90	875	5.47	**-0.10 (-0.30, 0.10)**
M. Zhang (2020)	95.64	23.34	237	94.14	23.52	3623	12.45	**0.06 (-0.07, 0.20)**
Pooled (Random effect model)			2075			14699	100	**0.06 (0.01, 0.11)**
Heterogeneity: τ^2 = 0, I^2 = 0%, Q (4) = 3.11								
Test of overall effect: Z = 2.52, P = 0.01								



Study	LGA Events	LGA Total	AGA Events	AGA Total	Weight (%)	Odds ratio (95% CI)
Cognitive impairment						
A. Adanikin (2022)	4508	33944	32892	236340	65.05	0.95 (0.92, 0.98)
A. Z. Khambalia(2017)	2214	13219	18903	105543	31.20	0.92 (0.88, 0.97)
C. E. Frank (2018)	-	291	-	1374	0.10	0.10 (0.43, 2.30)
M. M. Costantine (2021)	27	110	213	875	0.34	1.01 (0.64, 1.60)
M. Zhang (2020)	94	237	1515	3623	1.01	0.92 (0.70, 1.20)
K. Tamai (2020)	145	2435	1186	19571	2.30	0.98 (0.82, 1.17)
Pooled (Random effect model)		50236		367326	100	0.94 (0.92, 0.97)
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0\%$, $Q(5) = 1.19$						
Test of overall effect: $Z = -4.49$, $P < 0.001$						
Low academic performance						
A. Z. Khambalia(2017)	3273	25158	29501	206660	24.92	0.90 (0.86, 0.93)
I. Kirkegaard (2006)	7	175	171	5020	0.28	1.18 (0.55, 2.56)
D. F. MacKay (2010)	1741	40203	15131	325867	21.49	0.93 (0.88, 0.98)
B. Yu (2017)	-	1436	-	7364	9.06	0.96 (0.86, 1.08)
K. O. Duffany (2020)	-	8634	-	99714	22.91	0.98 (0.94, 1.03)
L. G. Smithers (2019)	2279	13336	7962	42178	21.34	0.89 (0.84, 0.93)
Pooled (Random effect model)		88942		686803	100	0.93 (0.89, 0.97)
Heterogeneity: $\tau^2 = 0.001$, $I^2 = 61\%$, $Q(5) = 12.82$ ($p=0.03$)						
Test of overall effect: $Z = -3.61$, $P < 0.001$