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Investigating the association between post-term birth and long term cognitive, developmental and educational impacts: a systematic review and meta-analysis

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ABSTRACT (398 words)

INTRODUCTION: Infants who remain in-utero after their due date are exposed to increasing risk of infection, late stillbirth and delivery complications. Much of the current literature on post-term outcomes is based on short term observations and the impacts may be substantially greater in the long term. The aim of this work is to perform a systematic review and meta-analysis to quantify the cognitive or educational impacts of post term delivery.

METHODS: Systematic review was performed by the two authors using MEDLINE database (1960 to 2017). A title search was performed to identify likely relevant literature. Exposure terms were clarified to identify papers where the exposure was related to delivery after the infants' due date. Primary outcome was cognitive score. A quality assessment and data extraction proforma was completed by both reviewers for all studies deemed to satisfy the inclusion and exclusion criteria. Meta-analysis used adjusted results where available. Small-study bias was assessed visually using a funnel plot and then formally tested using Egger's regression asymmetry test.

RESULTS: MEDLINE was searched on the 12/07/2018; and produced a list of 1318 publications. Of these, 43 abstracts were screened, and of these a total of 10 full-text papers were reviewed. A further 3 papers were identified during this review and contributed to a total of 13 papers. The publications dated from 1969 to 2017. Two studies presented a binary outcome for cognitive measures and combined estimates found that the risk of a low cognitive score was higher in post-term infants compared to term infants (OR 1.06 (1.04-1.08)). Four papers presented the association with mean cognitive measures and post-term delivery, and all demonstrated a mean reduction in scores in the post-term group. A combined estimate showed strong evidence of a reduction in cognitive scores across the four studies (-1.90 (-3.50 to -0.31)). There was little evidence of heterogeneity in the studies which reported cognitive outcomes (other p-values greater than 0.2).

CONCLUSION: This meta-analysis has found that post term birth (>41+6 weeks) is associated with small but significant negative effects on cognitive outcomes when compared

with delivery at, or around term. The effect, while small, is compounded by a common exposure and appears consistent in the studies identified. Less evidence was found for a measurable impact on early developmental measures or educational outcomes. This may further help inform the debate on the timing of otherwise uncomplicated pregnancies; and further trials in this area.

Keywords: Meta-analysis; Cognition; Child development; Long term adverse effects; Term birth

INTRODUCTION

Perinatal events can have life-long impacts on the infant and their family and one high risk group of infants appears to be those who remain undelivered after their due date. While we know that significant developmental impacts are associated with birth just one or two weeks early[1,2], any long term impacts of post-term delivery are less well recognised[3,4]. Infants who remain *in-utero* after their due date are exposed to increasing risk of infection, late stillbirth and increased risks of complications such as shoulder dystocia and perinatal asphyxia[5,6], without obvious benefits to the infant. However, in contrast to preterm birth, interventions can be used to deliver the infant if the risks of continuing the pregnancy are higher than delivery: for either the mother or the infant[7]. One area of particular concern is the reported increased risk of perinatal asphyxia and encephalopathy in post-term infants[6,8–10] although results are variable[11] and the causal pathways unclear[9]. Much of the current literature on post-term outcomes is based on short term observations and, like the effect of preterm birth, the impacts may be substantially greater in the long term[12]. As such the impact, particularly on longer term measures of development and cognition are important to quantify. The aim of this work is to perform a systematic review and meta-analysis to quantify the cognitive or educational impacts of post term delivery.

MATERIALS AND METHODS

Systematic Review

Methodology was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[13]. Systematic review was performed by two authors (DO and AGW) using MEDLINE, Pubmed, EMBASE and Cochrane databases (1960 to 2017). A title search was performed (Figure 1) to identify likely relevant literature. The search strategy was piloted to ensure it identified studies already known by the authors to be relevant. Searches were limited to those with English language abstracts and for research in human subjects. Exposure terms were clarified to identify papers where the exposure was related to delivery after the infants' due date. Measures of cognition are difficult to measure in young infants, and often developmental measures are used as proxies for later cognitive development[14]. In addition, while preterm infants have both cognitive and educational impacts, the educational impact may be disproportionately higher[15]. Consequently three quantitative analyses are of

interest: i) Cognition, ii) Cognition or measures of development, ii) Educational outcomes. Outcome terms were used to identify two groups of potential consequences; poor cognition (or short term developmental proxies of), or educational achievement.

The titles obtained from database searching were sifted to exclude duplicates and those clearly not relevant to the review. Abstracts of those remaining were examined, and tested against the inclusion criteria;

- Neurodevelopmental, cognitive or educational outcome scores reported at or beyond 12 months of age.
- Summary outcomes reported for infants born at post-term ($>41^{+6}$ weeks) gestation.
- Cohort, case-control or randomised trial.
- Comparison/reference group of infants born within the range of 37^{+0} to 41^{+6} weeks of gestation

Full texts were obtained for those articles and reviewed once more. The process was performed independently by both authors (DO and AGW) and all possible papers were obtained. Where a cohort was reported in a number of papers, the most recent eligible report was used. References in the papers were checked to identify any other possible relevant studies. Data were extracted on the characteristics of the individual studies. Gestational age at birth was identified from the full text for both the reference and exposed (post-term infants). No upper gestational cut-off was defined although the where a range of ages was presented it needed to include infants at 42 weeks (post-term) gestation; where more than one 'post-term' category was reported they were combined if possible, or the group closest to 42 weeks of gestation used. Outcomes measures were identified from the full text; either as absolute measures or associations between groups. If outcome measures were defined as cognitive or educational scores by the authors then they were used as such in this work. Other measures without clear definition (or is specified as) were defined as more generic 'neurodevelopmental' measures. A quality assessment and data extraction proforma was completed by both reviewers for all studies deemed to satisfy the inclusion and exclusion criteria. Quality was assessed on five domains (sample selection, measure of gestational age, measure of outcomes, management of confounding, and management of missing data).

Meta-analysis

Where papers presented either a mean difference in scores between term and post-term groups, or give mean outcomes values for each group, these were converted to a standardised mean difference score. Measures were normalised to a mean of 100, and standard deviation (SD) of 15. Where adjusted means or adjusted mean differences were available in the paper (adjusting for potential confounding variables) these values were selected in preference to unadjusted values. Where outcomes were presented as a dichotomized value (e.g. odds of a low IQ score) the Odds Ratio (OR) of a poor outcome was derived or identified and the meta-analysis repeated for this binary outcome. The analysis was performed separately for cognitive measures, cognitive AND developmental measures, and educational measures. Small-study bias was assessed visually using a funnel plot and then formally tested using Egger's regression asymmetry test for small-study bias. All statistical analyses were carried out using Stata version 14.

RESULTS

Literature

Databases were searched on the 12/07/2018; and after removal of duplicates, produced a list of 1318 publications. Of these 43 abstracts were screened, and of these a total of 16 full-text papers were reviewed. 6 of these did not fulfil the inclusion criteria[16–21], but a further 6 likely papers were identified during this review[22–24]. These 6 additional papers were reviewed, 3 included in the analysis and three excluded[25–27]; leaving a total of 13 papers (Table 1).

Of the 9 excluded articles; one presented individual measures of educational achievement, but no summary measure for incorporation in to the meta-analysis[26], four did not report an eligible outcome of infants born at 42 weeks gestation[16,19,21,28], three did not present enough detail for summary measures to be used within the analysis[17,18,25] and one presented data only on a high risk population sub-set (small for dates infants)[20].

Eligible papers are shown in table 1; the earliest publication dates from 1969, and the most recent from 2017. A total of 5 papers reported summary measures described as measures of cognition; Record[29] reported measures of children at 11 years of age; derived from the “Eleven-plus” examination. Bergvall[30] and Eide[31] derived cognition scores from mandatory Conscript examinations at 18 years of age, Yang[32] used the Wechsler Abbreviated Scales of intelligence at 6.5 years of age, and Lagerstrom three factors from the Differential Intelligence Analysis (DBA)[33]. A total of 5 further publications reported

shorter term, or less precise, measures; Oleson reported developmental scores of infants aged 18 months of age derived from a telephone interview[34], Lovell reported scores of the Social Maturity Scale at 1 year of age[23], Slykerman reported the revised Denver Pre-screening Developmental Questionnaire (R-PDQ) at 12 months of age[24], Richards reported the cognitive ability score at 2 years old using the Bayley Short Form-Research Edition (BSF-R) Mental[35] Scale, Smithers the Australian Early Development Index (AEDI) taken at school entry on physical health and wellbeing, language and cognitive skills, emotional maturity, social competence and communication and general knowledge[26] and Heuvelman a record of intellectual disability from routine health data[36]. Finally, 2 papers have reported educational outcomes; MacKay reported the need for Special Educational ‘statementing’ for physical and cognitive reasons[37] and Ahlsson the final grades of compulsory schooling (16 years of age)[22].

The range of gestational ages assessed was clearly defined in all papers for both the comparison and the control group. Gestational age was assessed in four papers using clinical measures alone[23,24,31,33], in six using a combination of ultrasound dating and clinical measures[22,26,30,32,34,37] and in three the methods were not specific[29,35,36]. In one paper infants initially defined as post-term had a more robust examination of their likely gestational age, but initially defined ‘term’ infants did not[23]. Gestational age for the control group ranged from 37-41 weeks[30–32] to just 40 weeks[24,26,29,36,37].

Some confounding was identified and controlled in all papers but one[33]. However data for the meta-analysis needed to be derived from the unadjusted estimates in one further publication[30].

Missing data was controlled for in most papers through the use of complete case analysis, although three papers[35,37,38] used some form of multiple imputation within their analysis plan. The proportion of eligible infants included in the final (summary) measure was not always possible to precisely estimate; however some papers reported on around 50% of the population[29,34], most between 70 and 90% [24,31,32,35,37,38] and three on over 90% [22,30,33,36]. In one paper the key –frame population was not presented[23].

Study Findings

Bergvall[30], Eide[31], Lagerstrom[19] and Record[29] all present work at least in part, aiming to investigate the impact of birth weight on neurodevelopment but also present

gestational data. Bergvall's study reported on the outcome of small gestational age infants, although comprehensive population data was reported including that of post-term infants. They found some evidence for an association with a low IQ score and commented on the association between poorly grown post-term infants and a low cognitive score. Eide primarily aimed to look at the effect of birth size in their population, although again, they reported an association in all post-term infants. They report a higher risk of a low IQ score but do not expand on this in their discussion. Lagerstrom also report an association with lower mean IQ in post-term infants although, again, do not expand upon it in the discussion or conclusions. In contrast Record reported little impact of post-term birth on developmental progress and concluded that associations seen within their work were likely due to errors recording the gestation of the pregnancies and that overall impact is likely to be very small.

In contrast, Mackay[37], Richards[35], Heuvelman[36], Ahlsson[22] and Yang[32] reported studies investigating a wide range of gestational ages (not just post-term). Mackay reports a higher risk of needing special educational needs in post-term infants and comment that this effect has "been ignored in most previous studies"[37]. Richards found little evidence of an association with post-term delivery and did not discuss this group further in their paper. Yang also found little association with post-term births and later IQ, and commented that their results appeared to be consistent with other studies, reviewed here. Heuvelman was also able to identify an association between post-term delivery and worse developmental outcomes, and suggested the association may be causal and related to hypoxia or nutritional deficiencies; but that intrapartum disease was unlikely to explain the whole association[36]. Ahlsson found little association between post-term birth and educational outcomes and concluded that associations found in other studies were likely to be due to other (confounding) causes.

Lovell[23], Oleson[34] and Smithers[26,38] were papers which appear primarily designed to investigate the impact of impact of post-term delivery. Oleson found that post-term infants appeared to reach their developmental milestones at an earlier age, and discussed if this was due to bias within their study; and suggested that further studies of post-term infants was needed. Smithers reported a weak association between post-term delivery their outcome, and concluded that any effect is likely to be modest, although larger samples may help clarify this and further work was warranted. Lovell found a large association between post-term birth and developmental measures, which they hypothesise may be due to foetal hypoxia.

Finally, Slykerman aimed to identify the determinants of developmental delay in a population cohort but did not find a clear association between post-term delivery and developmental delay.

Quantitative Synthesis

Both studies that presented a binary outcome for cognitive measures found that the risk of a low cognitive score was higher in post-term infants compared to term infants (Figure 2) (Combined estimate (OR 1.06 (1.04-1.08))). In addition four papers presented the association with mean cognitive measures, and while all four demonstrated a mean reduction in scores in the post-term group (between -0.38 and -3.00 points); some showed very wide confidence intervals and only one showed a reduction in mean score at conventional levels of statistical significance (Figure 3). However a combined estimate showed strong evidence of a reduction in cognitive scores across the 4 studies (combined reduction of -1.90 (-3.50 to -0.31)). When adding in the other neuro-developmental measures to other cognitive scores the association with a poor outcome weakened slightly (OR 1.06 (1.00-1.13) (Figure 4), as did the difference in mean scores (-1.44 (-3.00 to 0.11)) (Figure 5). The risk of a low educational achievement also appeared similar between groups (OR 1.07 (0.93-1.24)) (Figure 6) although results appeared incompatible between the two studies. There was strong evidence of heterogeneity in the combined estimates for the risk of a poor educational or combined developmental/cognitive outcome (both $p \leq 0.001$), but not in any of the other analyses (other p-values greater than 0.2). No studies reported a difference in mean educational outcome. Figures 7 and 8 show the funnel plots for the risk of bias for the multiplicative and mean difference measures respectively. There was little statistical evidence for small-study effects ($p = 0.071$ and $p = 0.531$). In a sensitivity analysis restricted to papers clearly within the pseudo-95% confidence intervals, restricted analysis of binary outcomes of the two publications (Slykerman and Smithers) produced a compatible, if less precise, result to the main analysis (OR 1.14 (0.83 to 1.58), $p = 0.539$). Analysis of continuous outcomes were unchanged.

DISCUSSION

Twelve papers were found to be eligible for analysis after testing against the inclusion criteria and quality assessment. The papers examined have investigated a range of developmental, cognitive and educational outcomes in participants ranging from 1-18 years of age. Consistent with the well recognised association between post-term delivery and perinatal

events; this work suggests a small reduction in cognitive scores, and a higher risk of a low cognitive score in infants born post-term compared to term infants. There was insufficient evidence to suggest that small-study bias was a substantial problem.

The evidence for a reduction in cognitive scores appeared relatively consistent across the studies that reported it. While the effect was relatively small (around 2 IQ points), the high frequency of post term delivery and the likely prevention of any causal effect through earlier delivery, make this a potentially important for population health. Consistent with other work in this area, it is likely a small mean difference derives from a substantially higher risk of a significantly lower score in small number of children who suffer consequences[39] and this is consistent with the apparently bigger impact in the odds ratio seen in the studies which looked at risk of cognitive impairment. In contrast to cognitive measures, when assessing developmental scores the results appear much more heterogeneous; perhaps consistent with the wider range of measures and earlier assessments used to derive the summary measures. Once again point estimates suggest worse outcome in post-term infants but the 95% confidence intervals were wider. All of the papers identified have used a different measure for cognition or development and while we have attempted to standardise the numerical outcomes for the quantitative analysis the underlying ability being measured is likely vary between studies. However all tests are likely to provide some distal measurement of underlying mental ability[40]. In contrast, two studies have reported educational impacts in post-term infants. Education could be considered a more pragmatic measurement of function, although only one paper (Ahlsson[22]) reported educational outcomes *per se*. The other (MacKay[37]) presents the risk of needing special educational needs support which while likely correlated with a poor outcome may also be influenced by other factors (such as mobility or sensory issues). In addition both papers that have reported educational outcomes excluded any child unable to attend schooling.

Interpretation of this work, like any non-interventional analysis, is limited by the possibility of confounding and bias. Most papers made some attempt to adjust for possible confounders, but residual confounding is likely to remain and it remains an important limitation of any interpretation. Two papers used in this meta-analysis (Bergvall[30] and Lagerstrom[33]) had unadjusted measures although they produced compatible point estimates to other studies identified measuring similar outcomes. In addition, Heuvelman, used sibling matched pairs to try to correct for unmeasured/unknown confounders. In addition, two studies reported on only around half of the apparent eligible cohort (Record[29] and Olesen[34]), and the possibility

of selection bias further limits the interpretation of this work. However other works, often using routine data, have presented on much higher proportion of the eligible infants with compatible results. Finally, generalisability is difficult with this work. Some papers examined only a subset of the population (e.g. limited by ethnic group or sex), and infants were born over a long historical period (1950-2009). All of these limitations may well limit this work to find, or underestimate the impact of post-term delivery. Finally, we limited our work to English language abstracts, and the risk of publication bias exists; although the symmetry of the funnel plots suggests against this playing a strong role.

Conclusions

This meta-analysis has found that post term birth ($>41^{+6}$ weeks) is associated with small but significant negative effects on cognitive outcomes when compared with delivery at, or around term. The effect, while small, is compounded by a common exposure and appears consistent in the studies identified. Less evidence was found for a measurable impact on early developmental measures or educational outcomes. This may further help inform the debate on the timing of otherwise uncomplicated pregnancies; and further trials in this area.

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Contributions

DO provided substantial contributions to the conception or the work. DO and AGW contributed to the analysis and interpretation of data for the work. DO drafted the initial manuscript. DO and AGW all revised the manuscript for important intellectual content and have given final approval of the version to be published. Both authors agree to be accountable for all aspects of the work.

Declaration of interest statement; None to make.

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Table 1. Summary results from meta-analyses

| Outcome Under Investigation | Studies Included | Summary Estimate |
|---|---|---------------------------------|
| Binary Outcomes | | OR (96% CI) |
| Risk of a low IQ score | Bergvall (2005), Eide (2007) | 1.06 (1.04 to 1.08) |
| Risk of a low IQ or developmental score | Lovell (1978), Bergvall (2005), Eide (2007), Slykerman (2007), Smithers (2014), Oleson (2015), Heuvelman (2017) | 1.04 (0.97 to 1.11) |
| Risk of low Educational achievement | MacKay (2010), Ahlsson (2015) | 1.07 (0.93 to 1.24) |
| Continuous Outcomes | | Mean Difference (95% CI) |
| Mean difference in IQ score | Record (1969), Lagerstrom (1991), Eide (2007), Yang (2010) | -1.90 (-3.50 to -0.31) |
| Mean difference in IQ or developmental score | Record (1969), Lagerstrom (1991), Eide (2007), Yang (2010), Richards (2016) | -1.44 (-3.00 to -0.11) |
| Mean difference in Educational achievement | - | - |

FIGURES

Figure 1. Association between development of a low IQ score and gestational age at birth

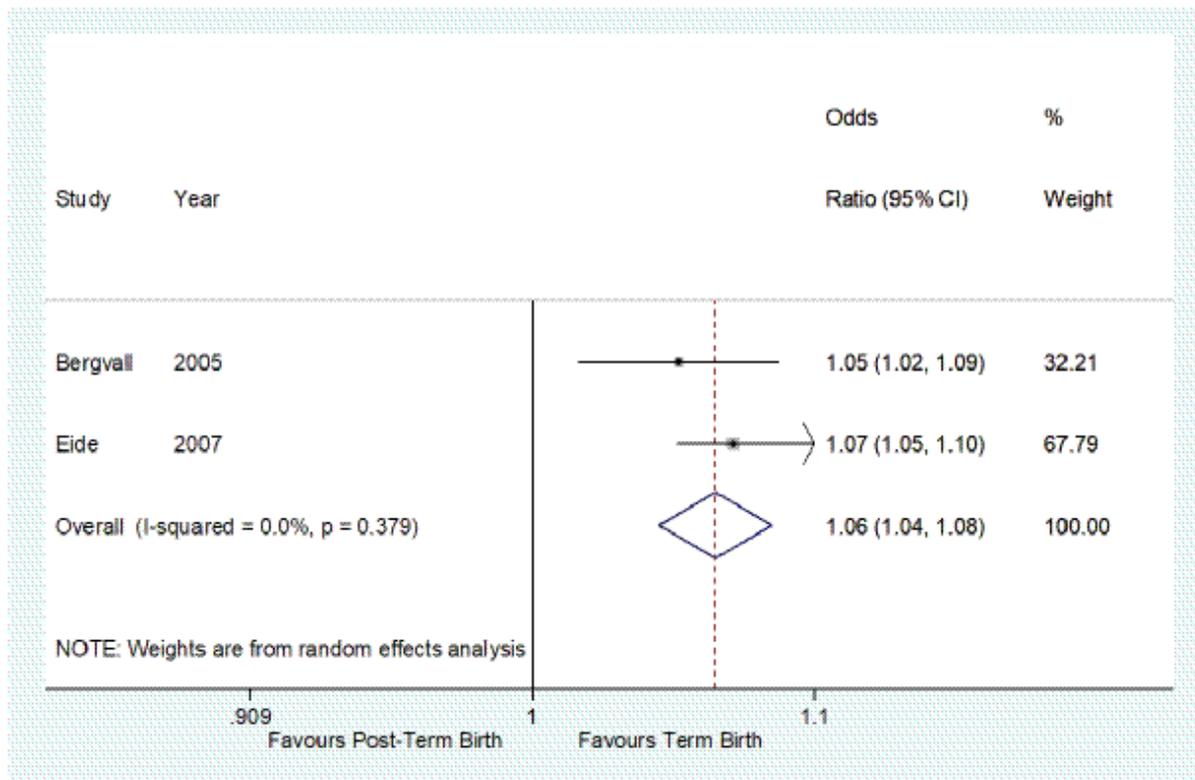
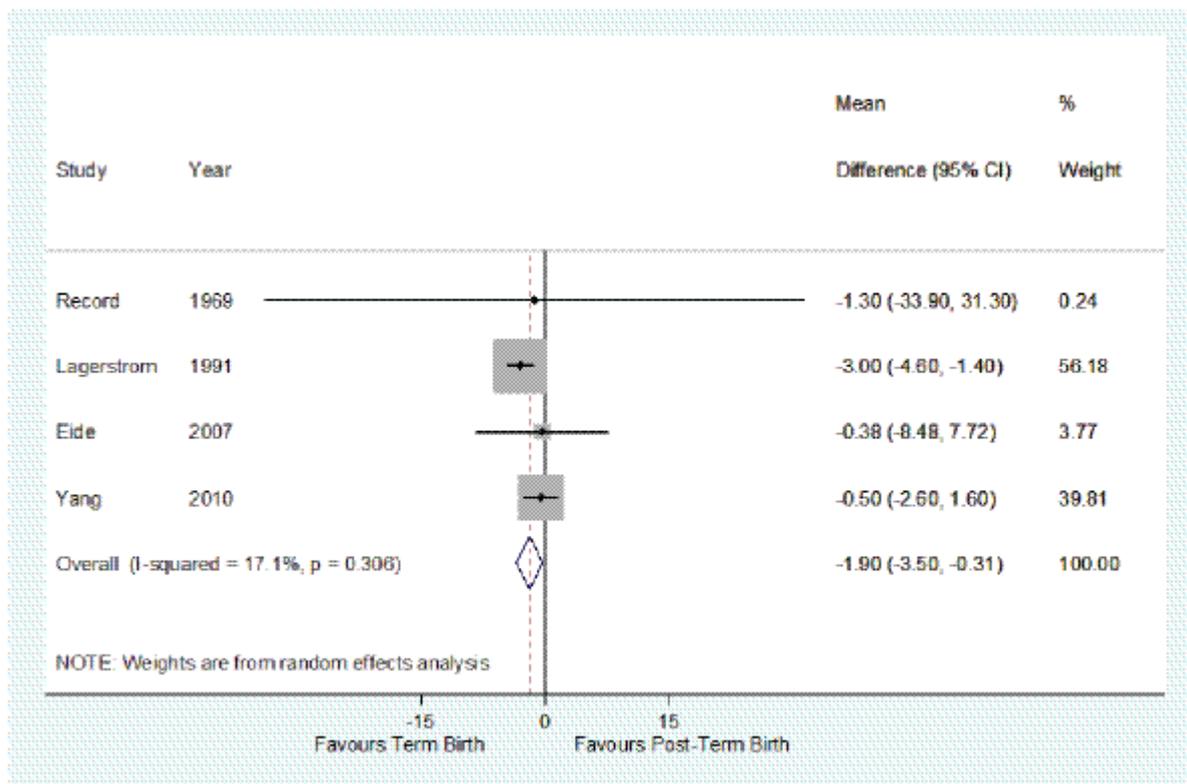


Figure 2. Association between mean IQ score and gestational age at birth



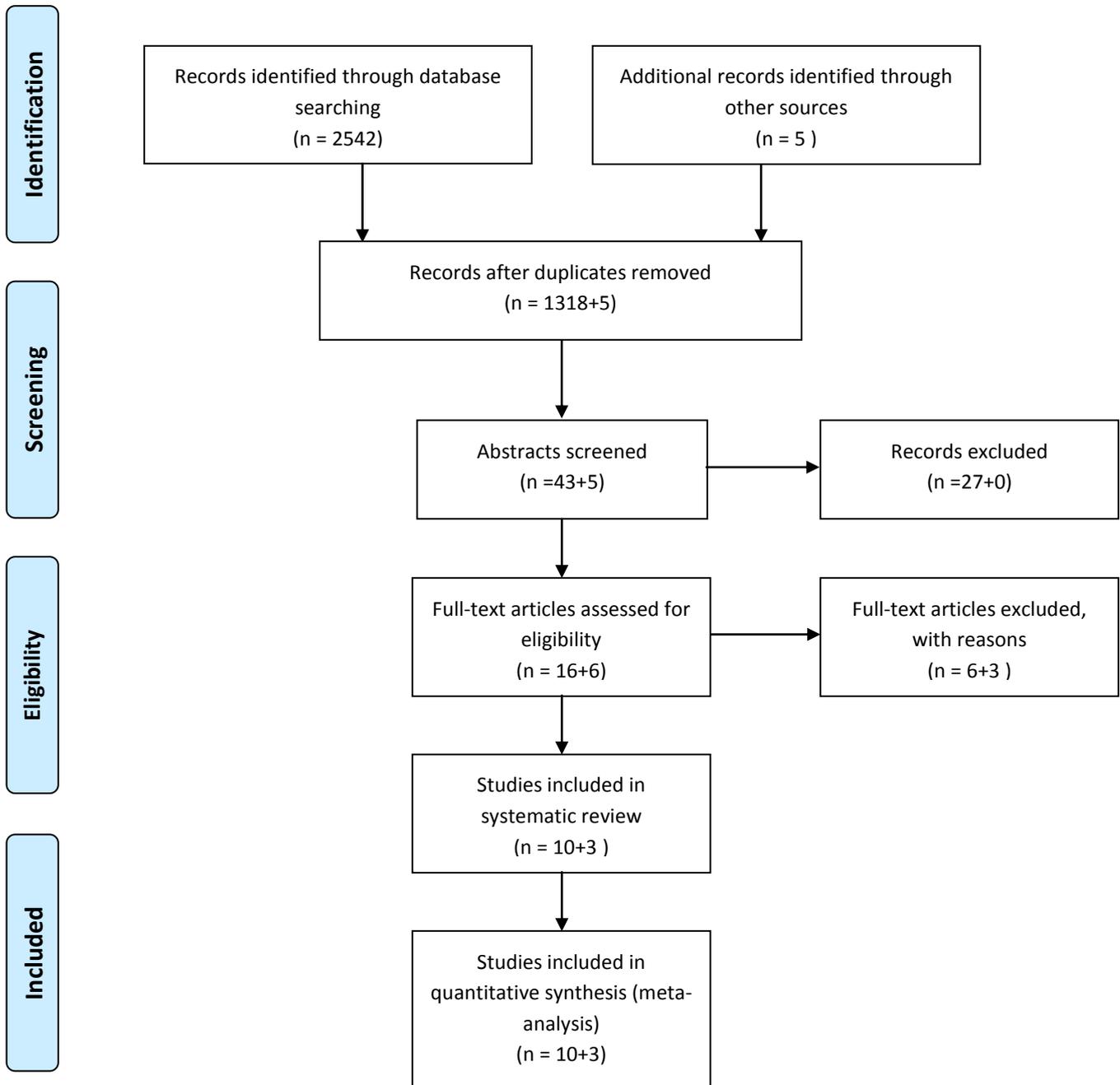
Appendix 1 – Materials and Methods

Initial search strategy (Title)

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1. "post term" OR "gestatio*" OR "date of delivery"  
2. IQ OR intelligence quotient* OR cogni* OR learning OR impair* OR  
disorder OR dysfunction* OR disab* OR delay OR outcome* OR status OR  
development* OR abilit*  
4. 1 AND 2  
5 limit 4 to (humans AND english language)
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Appendix 2 – Results

PRISMA 2009 Flow Diagram



Appendix 3. Eligible Papers

| Study | Sample and Exclusions | Exposure measures | Outcome (s) | Confounding | Missing Data |
|-------------------------------|--|--|---|--|---|
| Identified from Search | | | | | |
| Record 1969[22] | Birmingham live births from 1/1/50 to 1/9/54. Exclusions: Non specified | Gestation as recorded on the obstetric records to the nearest week according to LMP. Reference: 40 weeks gestation Post-Term: 42 weeks gestation | Verbal reasoning scores from the 11 year examinations (The Eleven-plus examination). | Standardised for sex, number of previous siblings, birth weight, duration of gestation of siblings. | Results presented for 48% of eligible cohort. Complete case analysis performed. |
| Lagerstrom 1991[26] | Children born in mid-Swedish community in 1965 Exclusions: Infants with extreme physical or mental handicaps. | Maternal Last Menstrual Period Reference: 38-41 weeks gestation Post-Term: >42 weeks gestation | Three factors from the Differential Intelligence Analysis (DBA) | Unadjusted results presented | Results presented for 92% of eligible cohort. Complete case analysis performed. |
| Bergvall 2006[23] | 1973-1981 liveborn males on Swedish Medical Birth Register Exclusions: Female infants | Gestation as recorded on Medical Birth Register. Reference: 37-41 weeks gestation Post-Term: Infants 42 or | Intellectual ability as assessed by the Swedish Conscript Register tests on logic/induction, verbal, spatial and theory/technical | Multivariate logistic-regression analysis adjusted for age at conscription, maternal characteristics, and sociodemographic | Results presented for 93% of eligible cohort. Complete case analysis performed. |

| | | 43 weeks gestation | aspects. | features. | |
|-----------------|--|--|---|--|--|
| Eide 2007[24] | 1967-1979 liveborn males on Norwegian Medical Birth Registry. Exclusions: Multiple births. Death before military draft, emigration or permanently disabled. Female infants. | Gestation as recorded on the Medical birth registry, estimated from LMP. Reference: 39-41 weeks gestation Post-Term: 42-44 weeks gestation | Intellectual ability as assessed by the National Conscript Service tests at 18 years of age on verbal analogues, number series and geometric figures. | N.B. Data for meta-analysis derived from UNADJUSTED results Adjusted for maternal age, parity, maternal education level, adult height and BMI, year of birth, marital status. | Results presented for 81% of eligible cohort. Complete case analysis performed. |
| Yang 2010[25] | 31 maternity hospital's polyclinic patients in the Republic of Belarus. Drawn from cluster randomised trial of breast feeding support (PROBIT) Exclusions: Birthweight <2.5kg, multiple births, maternal or neonatal illness, low Apgar scores, intention to formula feed | From hospital records during maternity stay (predominantly ultrasound). Reference: 39-41 weeks gestation Post-Term: 42 weeks | Wechsler Abbreviated Scales of intelligence at 6.5 years of age. | Maternal age at birth, height, smoking history, drinking during pregnancy, marital status, number of children in the household at time of birth and parental education and occupation. Birth injury, spontaneous vaginal delivery, gestation estimated by LMP. | Results presented for 81% of eligible cohort. Complete case analysis performed. Falsified outcome data excluded from one site. |
| MacKay 2010[29] | 2005 Scotland school census of children between 4 and 18 years. | Collected from the Scottish Morbidity Record; completed weeks | Need for Special Educational: need for educational | Sex, maternal age, height, marital status, parity, birth weight | Some covariates imputed using Multiple |

| | | | | | |
|-------------------|---|---|---|--|---|
| | Exclusions: Maternal height <100cm or >200cm, birth weight <400g or >5kg, gestation >43weeks or multiple birth. | of gestation. Reference: 40 weeks gestation Post-Term: | statementing for physical and cognitive reasons. | centile, induction of labour, mode of delivery, year of delivery, previous spontaneous and therapeutic deliveries and 5 min Apgar score. | Imputation by Chained Equations. 71% of initial cohort used in main analysis. |
| Olesen 2014[27] | Sample drawn from Danish National Birth cohort. Infants born 1997-2003 at estimated gestation of 39-45 weeks; whose mothers agreed to participated in a series of telephone interview. Exclusions: Second pregnancy within study period, mothers with chronic disease (including pre-eclampsia). | Combination of ultrasound and LMP measures; and recorded in registry. Reference: 39-41 weeks gestation Post-Term: | Developmental milestones by 18 (17-25) months of age. Good outcome defined as infant achieving at least 3 milestones. | Analyses were adjusted for maternal age, parity, socio-occupational status, smoking, alcohol consumption, pre-pregnancy body mass index, child's sex and age at interview. | Results presented for 51% of initial cohort. Complete case analysis performed. |
| Smithers 2015[30] | All births recorded in South Australia who were attending their first year of full-time schooling in 2009 Exclusions: Missing data | Gestation as listed in the South Australian Perinatal Statistics Collection Dept for Health and Ageing. Reference: 40 weeks gestation Post-Term: 42 weeks gestation | Australian Early Development Index (AEDI) taken at school entry on physical health and wellbeing, language and cognitive skills, emotional maturity, social competence and communication and general knowledge. | AEDI adjusted for age in years. Data also adjusted for sex, plurality, parity, birthweight z-score, maternal age at birth, smoking during second half of pregnancy, maternal relationship status and sociodemographic | Analysis performed on approximately 82% of eligible population. Missing covariates imputed using Multiple Imputation. |

| | | | | | |
|-----------------------------------|--|---|--|--|--|
| | | | | features. | |
| Richards 2016[28] | <p>Singletons born at 24-42 weeks gestational age and enrolled in the Early Childhood Longitudinal Study-Birth Cohort</p> <p>Exclusions: Multiple births</p> | <p>Clinical estimate of gestational age recorded on birth certificate.</p> <p>Reference: 39-40 weeks gestation</p> <p>Post-Term: 42 weeks gestation</p> | <p>Cognitive: Cognitive ability at 2 years old was measured using the Bayley Short Form-Research Edition (BSF-R) Mental Scale.</p> | <p>Child's age, race/ethnicity, maternal educational attainment, household poverty, child's sex, parity, and maternal age at delivery.</p> | <p>Analysis performed on approximately 82% of eligible population. Complete case analysis performed in primary outcome. Multiple imputation in sensitivity analyses.</p> |
| Heuvelman[33] | <p>Children, between 0 and 17 years old, born in Sweden before 2007, who lived for at least one year in Stockholm county between 2001 and 2011.</p> <p>Exclusions: Genetic or inborn metabolic syndromes, multiple births, improbable birth weights.</p> | <p>Gestation listed in Medical Birth Register.</p> <p>Reference: 40 weeks</p> <p>Post-Term:42</p> | <p>Routine collected data from National Patient Register, Mental Health Register, Healthcare database, psychiatric register with intellectual disability</p> | <p>Sex, parity, maternal age, gestational diabetes, hypertension or preeclampsia and birth weight. Maternal and paternal age, psychiatric history, country or birth, disposable income and educational attainment.</p> | <p>Initial analyses performed on 95.2% of eligible population. Complete case analysis performed.</p> |
| Identified from References | | | | | |
| Lovell 1973[19] | <p>Infants born at single centre, for 1 year following July 1, 1968</p> | <p>Clinical estimate based on LMP</p> | <p>Maternally asked questions from the Vineyard Social</p> | <p>Controls matched for maternal age, race, parity, method of</p> | <p>Proportion of missing cases unclear. Complete</p> |

| | | | | | |
|--------------------|--|---|--|---|---|
| | Exclusions: Uncertainty over prolonged gestational age, adoption, suboptimal antenatal care. | Reference: 40-41 weeks gestation Post-Term: 42-43 weeks gestation | Maturity Scale at 1 year of age. Low defined as 2 SD below the mean | delivery and infant's sex. | case analysis performed. |
| Slykerman 2007[20] | Drawn from the Auckland Birthweight Collaborative Study. Born 1995 to 1996. Cohort selection stratified by birth weight. Exclusions: Congenital abnormalities likely to affect development, multiple births and home deliveries. Restricted to New Zealand European mothers. | Clinical estimate based on LMP Reference: 40 weeks gestation Post-Term: 42 weeks gestation | Revised Denver Pre-screening Developmental Questionnaire (R-PDQ). Poor outcome defined as a having one, or more, developmental delay (defined as 90% of children have achieved). | Analyses weighted to account for sampling. Adjusted for gestation, infant gender, maternal education, marital status, socio-economic status, maternal age, parity and maternal smoking. | 78.6% of eligible dyads included. Only an incomplete subset (New Zealand European mothers) were analysed using complete case analysis. Some single imputation used. |
| Ahlsson 2015[21] | Swedish subjects on Medical Birth Registry from 1974-1991 Exclusions: If national registration number registered incorrectly, data not present for birth weight, birth length or gestational age, no school records or passed away before the age of 17yrs. If >4 SDs or <4 SDs away from the average weight for gestational age. | Second trimester ultrasound or on LMP as recorded on the register. Reference: 40-41 weeks gestation Post-Term: 42 weeks gestation | Grades in the final year of compulsory school (16 years of age). | Maternal age at birth, maternal and paternal education, birth order. | All subjects with missing data excluded at selection. Complete case analysis used in remaining 92.2% |

Appendix 4. Further Figures

Figure 4. Risk of low IQ or developmental score

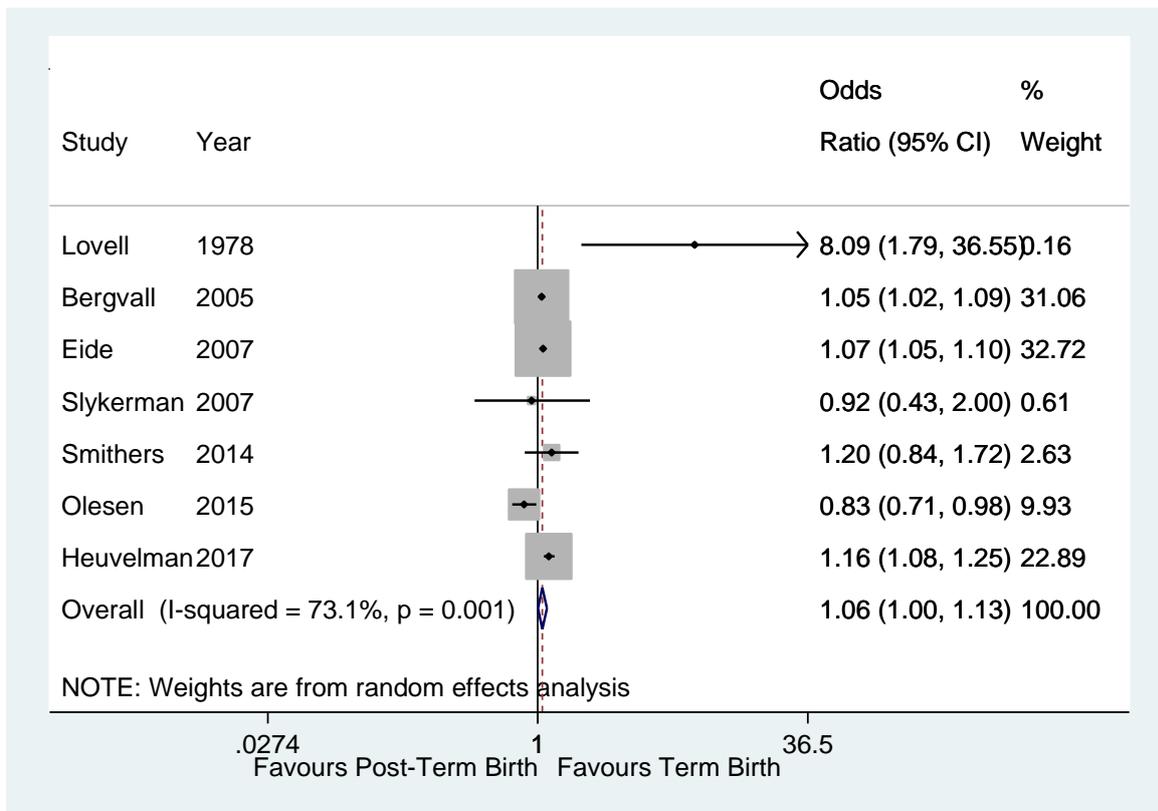


Figure 5. Mean low IQ or developmental score

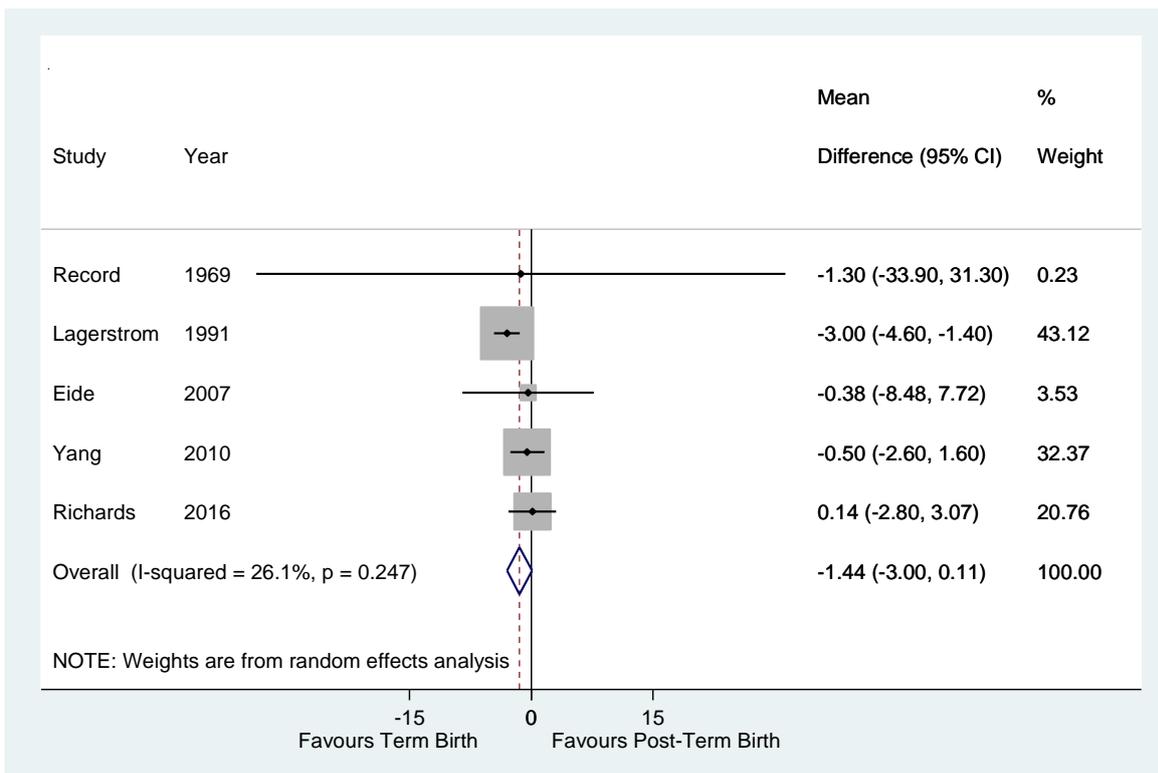


Figure 6. Risk of low Educational achievement

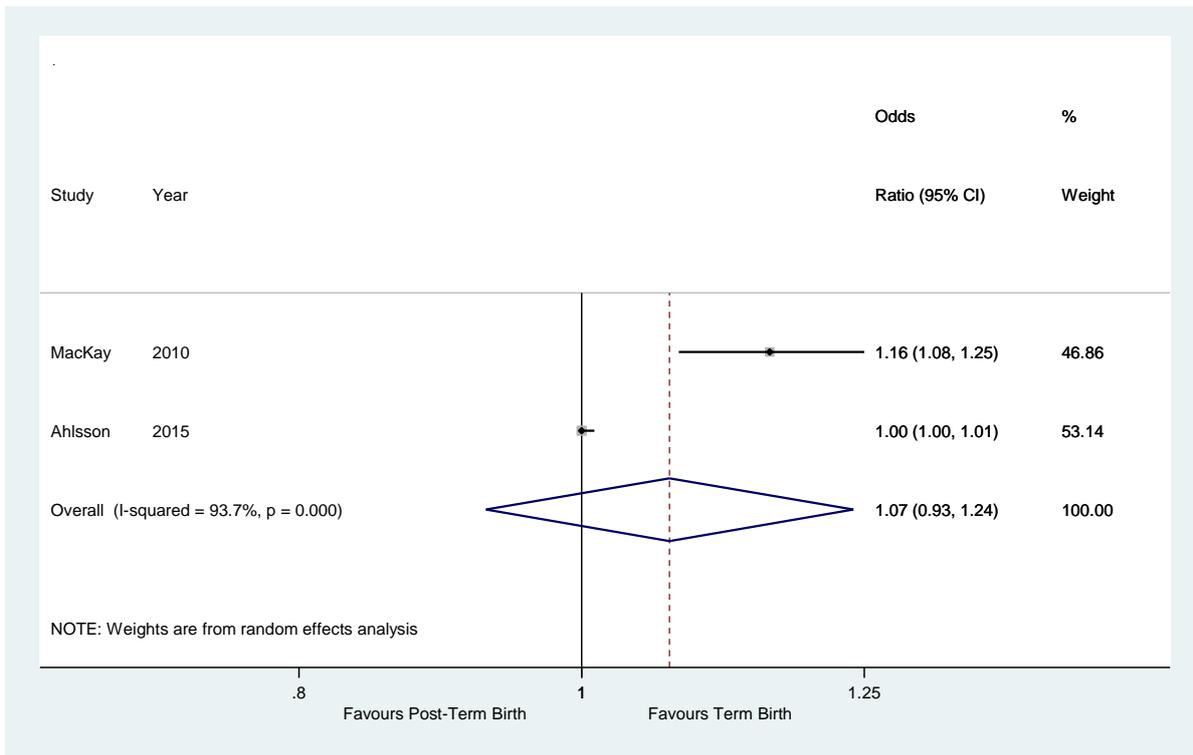


Figure 7. Funnel Plots of association between post-term delivery and cognitive/developmental/educational effect (multiplicative differences)

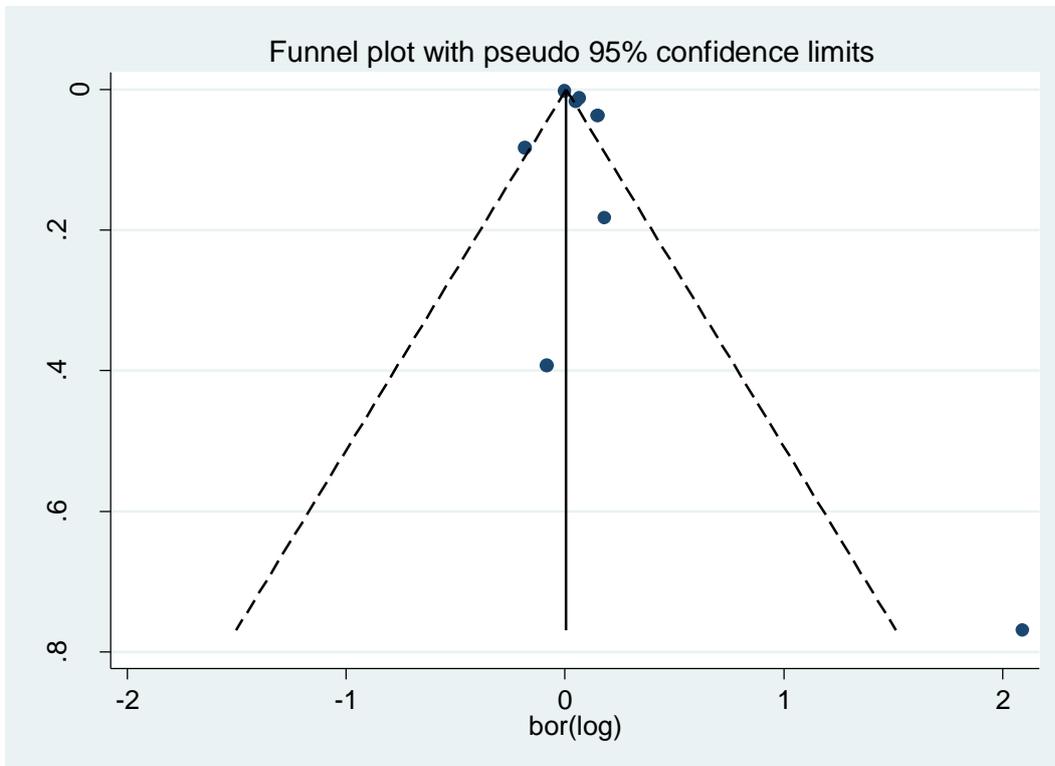


Figure 8. Funnel Plots of association between post-term delivery and cognitive/developmental/educational effect (mean differences)

