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Maternal education and cognitive development in 15 European very preterm birth cohorts from the RECAP *Preterm* platform

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ABSTRACT

Background

Studies are sparse and inconclusive about the association between maternal education and cognitive development among children born very preterm (VPT). While this association is well-established in the general population, questions remain about its magnitude among children born VPT whose risks of medical and developmental complications are high. We investigated the association of maternal education with cognitive outcomes in European VPT birth cohorts.

Methods

We used harmonised aggregated data from 15 population-based cohorts of children born <32 weeks' gestational age (GA) or <1500g from 1985 to 2013 in 13 countries with information on maternal education and assessments of general development at 2-3 years and/or IQ between 4-15 years. Term-born controls (≥ 37 weeks' GA) were available in 8 cohorts. Maternal education was classified as: low (primary/lower secondary); medium (upper secondary/short tertiary); high (bachelor's/higher). Pooled standardized mean differences (SMD) in cognitive scores were estimated (reference: high educational level) for children assessed at ages 2-3, 4-7 and 8-15 years.

Results

The study included 10 145 VPT children from 12 cohorts at 2-3 years, 8829 from 12 cohorts at 4-7 years and 1865 children from 6 cohorts at 8-15 years. Children whose mothers had low, compared with high, educational attainment scored lower on cognitive measures (pooled unadjusted SMDs: 2-3y=-0.32 (95%CI: -0.43;-0.21); 4-7y=-0.57 (-0.67;-0.47); 8-15y=-0.54 (-0.72;-0.37)). Analyses by GA subgroups (<27 versus ≥ 27 weeks), in children without severe neonatal morbidity and term controls yielded similar results.

Conclusions

Across diverse settings and regardless of degree of prematurity, low maternal education was associated with lower cognition.

KEYWORDS

Very preterm births, child development, IQ, intelligence, maternal education, cohort

KEY MESSAGE

- We found lower cognitive scores throughout childhood for children born very preterm whose mothers had low educational levels, with no difference in the effect by degree of prematurity.
- The robust nature of the association in multiple contexts provides good generalizability for our study findings.
- Understanding the association of social factors with cognitive deficit in children born very preterm is essential because these children may benefit most from early intervention

INTRODUCTION

Brain development is complex, involving genetic, physiological, and environmental influences. There is a large body of literature on the neurodevelopment of children born very preterm (VPT) (<32 weeks of gestation) demonstrating a higher risk of cognitive deficits compared to children born at term.¹⁻³ Brain injury and other neonatal morbidities (e.g. bronchopulmonary dysplasia) are strongly associated with adverse neurodevelopmental outcomes,^{3,4} but VPT children without morbidities are also at increased risk for cognitive and other neurodevelopmental impairments.⁵

It is also well established that the social environment in the family and community plays a role in determining cognitive functioning,⁶ but there is a lack of comparable evidence regarding the influence of these factors among children born VPT. There are contradictory hypotheses about how social context affects outcomes in VPT children as compared to the general population. Some have posited that social factors would have less effect because of the strong association between biological risk factors and neurodevelopment. For example, a recent study found the effect of maternal education on early language acquisition was attenuated in children with higher clinical risks (e.g. extreme prematurity <28 weeks' gestational age (GA); severe neonatal morbidities).⁷ In contrast, others hypothesise that the effect of social factors may be stronger because parental involvement plays a crucial role in enabling children to compensate for potential developmental difficulties, with results suggesting that social factors may modify the effect of preterm birth on cognitive outcomes in children.^{8,9} A final possibility is that social factors operate in similar ways regardless of underlying medical risks linked to prematurity or other pregnancy complications. Understanding and quantifying this relationship is particularly important given the impact of VPT

birth on average intelligence quotients (IQs),^{2,3} estimated at about 12 points lower than among term-born children, and the long-term consequences on school and employment outcomes.^{10,11}

Recent systematic reviews and meta-analyses have shown the complexity of synthesising existing evidence on the relationship between the social environment and cognitive development in children born VPT.²⁻⁴ First, although maternal educational level tends to be the most common indicator of social differences,^{3,12-15} other variables are also used (e.g. parental occupation, marital status, family income).¹⁵ Second, even among studies using maternal educational level, international variation in definitions makes it difficult to compare outcomes using common categories. This heterogeneity has prevented meta-analyses from deriving pooled effects of the role of maternal education on childhood cognition. Further variability also results from diversity in ages of assessment⁴ and in the domain of cognitive functioning (e.g. executive function, language, general cognition).^{7,9,15} A recent Delphi study on priorities for research on the consequences of VPT birth with clinicians, researchers, policy-makers and people with lived-experiences identified the impact of social circumstances as a top-ten theme.¹⁶

The purpose of this study is to investigate the association of maternal educational level with cognitive outcome in children born VPT, using data from population-based, prospective cohort studies in various European contexts. Based on the heterogeneous conclusions reported in the literature, we hypothesised that the association could vary by country (i.e. higher educational levels could be more protective in certain cultural contexts), key periods in childhood (i.e. with a stronger effect later in childhood), and the degree of prematurity (i.e. with a potentially attenuated effect for children born extremely preterm).

METHODS

Study population and design

This study included 23 European population-based cohorts of children born VPT (<32 weeks of gestation) or with very low birthweight (<1500g) participating in the RECAP Preterm (Research on European Children and Adults Born Preterm) platform which aims to promote research on the consequences of VPT birth.¹⁶ Cohorts were eligible if they could provide 1) information on maternal education at delivery or follow-up, and 2) an assessment of general development at 2-3 years and/or general cognitive ability between 4 and 15 years of age. Some cohorts also comprised a control population of term-born children with measures of maternal education and cognitive outcomes. Fifteen cohorts contributed data.¹⁷⁻³¹ The study used aggregated and summary data provided according to a standardised protocol. All cohorts have ethical authorisations and informed consent from families for research on the consequences of VPT birth.

Maternal educational level

Maternal educational level was the primary exposure. The preferred definition was the highest educational level at delivery, although some cohorts only had data on the number of years of schooling. For cohorts that could not provide maternal education at delivery, educational level at follow-up was used. We used the International Standard Classification of Education (ISCED)³² to create harmonised categories by mapping each cohort's educational variable into one of nine levels, which were then grouped into three categories: (1) low (ISCED 0-2; lower secondary or less), (2) medium (ISCED 3-5; upper secondary/post-secondary/short cycle tertiary), and (3) high (ISCED 6-8, bachelor degree/equivalent or more). We selected this classification, which has been used in analyses of maternal education and preterm birth in Europe,^{7,33} to maximise sample sizes in each educational category.

General development and cognitive outcomes

The primary outcome was cognitive functioning in childhood assessed by standardised tests (with normative or control samples) or validated instruments including parent-report questionnaires, which provided continuous scores (standard scores or raw scores, respectively). Cognitive tests or multi-domain tests of child general development were used across the cohorts.

Other variables

To describe the cohorts, we selected social and perinatal variables available in all cohorts and for which harmonised definitions could be specified: maternal age (≥ 35 years), cohabiting status (living in a couple), maternal country of birth (or if not available maternal nationality or ethnicity), parity, GA, birthweight, child sex, multiple pregnancy, caesarean birth, Apgar score at 5 minutes < 7 , and breastfeeding at discharge from neonatal care. Neonatal morbidities included necrotizing enterocolitis (stages II-III; NEC-II/III³⁴), intraventricular haemorrhage (stages III-IV, IVH-III/IV³⁵), cystic periventricular leukomalacia (cPVL), bronchopulmonary dysplasia (supplemental oxygen or ventilation at 36 weeks, BPD) and retinopathy of prematurity (stages III-V, ROP-III/V³⁶).

Analysis strategy

Analyses were carried out separately by age group: infancy (2-3 years), early childhood (4-7 years), later childhood (8-15 years). The drop-out rate was computed in each period by dividing the number of participants by the number of survivors at discharge from the neonatal hospitalisation. All analyses were performed on complete cases.

Descriptive tables of perinatal and sociodemographic characteristics were provided on the sample at first follow-up (i.e. two-year follow-up, if followed at two and five).

We used a meta-analytic approach based on aggregate-level data provided by each cohort following a standardised iterative protocol. First, frequencies of selected variables were collected to guide the harmonisation process. Second, harmonised variables were verified and described in summary tables. Third, cohorts provided unadjusted data on cognitive outcomes (i.e. frequencies, mean scores, standard deviations) by maternal educational level for each age group. Lastly, marginal means of cognitive scores were estimated using common multivariable regression models, adjusted for child sex and maternal age as a potential confounder.⁴ Random intercept models were specified to account for the correlation within multiple pairs when this was possible at the cohort level and also to account for clustering within countries in the European EPICE/SHIPS study.²⁹ Differential dropout was accounted for multiple imputation (EPIPAGE 2³⁷) or inverse probability weighting (EPICE/SHIPS⁷). Unadjusted and adjusted estimates were provided for children overall, stratified by severity of the VPT birth (<27 weeks, ≥27 weeks), and on the control population of term-born children when available. Estimates were also computed for children born VPT without severe neonatal morbidities (NEC-II/III, IVH-III/IV, cPVL, BPD, ROP-III/V) known to be strong predictors of cognition.³⁸ We analysed recent cohorts (births≥2000) to allow for more standardised definitions of these morbidities.

The unadjusted and adjusted estimates were pooled by random effects meta-analyses using the DerSimonian and Laird inverse-variance method.³⁹ The effect measure was expressed as the standardised mean difference (SMD, Hedges g)³⁹ in cognitive scores between groups defined by maternal educational level (reference group: high education level), making it possible to pool cognitive raw and standardised scores.³⁹ Pooled SMDs were estimated from both unadjusted and adjusted mean scores,⁴⁰ and presented with 95% confidence intervals (CI). The effect size was interpreted as small (SMD=0.2-0.4 of a SD unit), moderate (SMD=0.5-0.8), or large (SMD>0.8).⁴¹

The unadjusted SMDs were presented as the primary results as this represents the most common meta-analytical approach.^{1-3,42} Tests for sub-group differences based on random-effects models were performed. Between-cohort consistency was quantified using I^2 statistics, and we used traditional thresholds of low ($I^2 < 25\%$), modest ($I^2 = 25-50\%$) and high ($I^2 > 50\%$) heterogeneity.⁴³ Effect modification was investigated using sub-group analyses.

The leave-one-out method was applied in sensitivity analyses in meta-analyses that had high heterogeneity.⁴³ Pooled risk ratios (RRs) were also computed by random effects meta-analyses to estimate the risk of cognitive deficit (score < 1 standard deviation (SD) below the standardised mean or other established cut-offs for unstandardized tests) by maternal education level. Additional sub-group meta-analyses investigated potential biases related to the timing of maternal education measurement (birth vs follow-up), test administration mode (parent vs examiner) and type of test (cognition vs multi-domain) in infancy. The R “meta” package version 4.11-0 was used for pooled analyses.^{44,45}

RESULTS

Cohort characteristics

Fifteen cohorts from 13 countries contributed data on 22 528 live VPT births (**Table 1**). Inclusion criteria were based principally on GA, with cohorts focusing on births < 32 weeks or < 27 weeks; older cohorts used birthweight thresholds or included births at 32 weeks' GA. Cohorts covered births from 1985-1986 to 2011-2012. Follow-up rates ranged from 51.2% to 98.7%, leading to the participation of 10 145 VPT children at 2-3 years (12 cohorts), 8829 at 4-7 years (12 cohorts), and 1865 at 8-15 years (6 cohorts). In 8 cohorts, data were available for control populations of term-

born children ($GA \geq 37$ weeks, $n=2642$ in infancy and $n=1540$ in early childhood)(**Supplementary Table S1**).

Maternal educational level was collected at birth in 7 cohorts and at follow-up by the others; the proportion of mothers with high education varied from 6.1% to 47.6% (**Table 2**). In each cohort, one or more cognitive assessments were available in infancy ($n=8817$ children with complete assessment), early childhood ($n=8125$), and later childhood ($n=1660$)(**Supplementary Table S2**). Missing outcome assessments varied by cohort and period (infancy: 0-19.5%; early childhood: 3.7%-33.2%, later childhood: 9.1%-30.4%)(**Supplementary Table S3**).

Maternal and perinatal characteristics varied between cohorts (**Table 3**), such as primiparity (31.4% to 66.5%) and multiple births (12.1% to 51.1%).

Results from meta-analyses

Children whose mothers had low, compared with high, educational attainment scored lower on cognitive measures, with a small effect in infancy ($SMD=-0.32$, 95%CI -0.43 to -0.21, 12 cohorts) and a moderate effect in early ($SMD=-0.57$, 95%CI -0.67 to -0.47, 12 cohorts) and later childhood ($SMD=-0.54$, 95%CI -0.72 to -0.37, six cohorts)(**Figure 1**). Smaller effects were reported for children whose mothers had medium compared to a high educational level. Modest to high heterogeneity was observed. **Table 4** provides adjusted pooled SMDs as well as unadjusted and adjusted pooled SMDs for GA sub-groups (<27 weeks, ≥ 27 weeks), children without neonatal morbidities and controls, with corresponding forest plots in **Supplementary Figures S1-S11**. The adjusted SMDs for all VPT and by sub-groups were very close to unadjusted SMDs. No statistically significant difference in the effect size was revealed between GA sub-groups, and between VPT

and full-term controls ($p > 0.1$). The SMDs for VPT without neonatal morbidities were similar to SMDs in the group ≥ 27 weeks.

Sensitivity analyses

The pooled analysis performed using the binary outcome confirmed that a low versus a high maternal educational level was associated with an increased risk of cognitive deficit (RR infancy=1.6, 95%CI 1.3 to 1.8; RR early childhood=2.0, 95%CI 1.6 to 2.5; RR later childhood=1.4, 95%CI 1.0 to 1.9)(**Supplementary Figure S8**). The leave-one-out analysis for groups with high heterogeneity showed that no single cohort had a substantial effect on the pooled estimate (**Supplementary Figure S11**). The comparison of pooled estimates between sub-groups defined according to the timing of the measure of maternal education and the type of test did not find any difference; however, cohorts using examiner based-tests versus parent-report questionnaires in infancy had larger pooled SMD ($p < 0.01$, **Supplementary Table S4**).

DISCUSSION

This meta-analysis of major population-based European VPT cohorts spanning three decades revealed a consistent positive association between maternal educational level and cognitive test scores among VPT children, with a dose-response effect (between 0.2 and 0.3 SD for mothers with medium education, and 0.3 to 0.6 SD for mothers with low education depending on age at assessment). The effect size was less pronounced in younger children at 2 and 3 years of age, but did not differ by degree of prematurity or between VPT children and term-born controls.

These results confirm the association of maternal educational level with cognitive skills among children born VPT in a wide range of settings, previously only reported in smaller scale or single country studies.^{12,13,46-48} While there were some differences across the cohorts in effect sizes, with

modest to high heterogeneity, all but one cohort had negative SMDs for low compared to high maternal education. This cohort, EPICure-1 which included births <27 weeks of GA in the UK and Ireland in 1995, had few children with mothers in the high educational level category (8 to 16 depending on the age group), which may reflect the characteristics of families with extremely preterm children or inadequacy of the classification for describing mothers' education in that time period. In EPICure-2, a similarly defined representative sample from England in 2006, results were very similar to the pooled estimates.

We did not find any differences in the estimated pooled associations between maternal education and cognition according to the level of prematurity, in term-born controls or after excluding neonatal morbidities. Previous studies examining interactions between maternal education and perinatal risk on cognitive outcomes in VPT children have reported mixed results.^{7,9,48,49} Several studies hypothesised that disparities in outcome could be more pronounced in VPT populations, as a low educational level may negatively affect a mother's knowledge and access to resources and consequently her ability to mitigate the effects of preterm birth by acting on environmental factors known to affect cognition. These include creating stimulating and enriched learning environments,⁵⁰ lowering or managing stress, which is heightened among families with VPT children^{51,52} or breastfeeding.⁵³ Low maternal educational level is also associated with disadvantaged socioeconomic circumstances and adversity which negatively impact brain development and neurocognitive outcomes^{54,55} with a stronger detrimental effect for vulnerable children.^{9,48} Conversely, some researchers contend that the biological insults leading to poor outcomes among high-risk VPT children (e.g. with lower GA or severe neonatal morbidities) may be less amenable to change in environmental factors.⁷ Our results showing similar effect sizes for extremely preterm infants and among term controls suggest that there is not substantial effect

modification. This has been noted in studies of other outcomes after preterm birth (e.g. cerebral palsy).⁵⁶

We found an association between maternal education and cognition in all age groups, with a smaller effect at 2-3 years. At this age, children in some cohorts were assessed using tests of global development which combine an assessment of development in multiple domains, including gross and fine motor development. Moreover, cognitive tests at age 2-3 years are more heavily dependent on motor responses than tests at later ages where task completion relies more on abstract concepts. Motor development, particularly in early years, may be less affected by the social environment and contribute to a lower effect size.⁵⁷ The larger effect of maternal education on cognitive outcomes between 4 and 15 years may indicate an accumulation of environmental impact (e.g., less cognitive stimulation or sensitive parenting,⁵⁸ uptake and type of early childhood education and care services,⁵⁹ differences in school environment).

These results are important for VPT follow-up and intervention policies. First, children born VPT are more often from disadvantaged families because social factors, including maternal education, increase risks of VPT birth.^{33,60} Furthermore, lower IQ scores associated with maternal education may have more severe consequences in terms of educational and life opportunities for VPT compared to term children because of the higher baseline risks of impairment. Moreover, some studies have suggested that early intervention programs, including those focusing on parenting education,^{51,61} were associated with better cognitive outcomes in children from lower socioeconomic backgrounds only.⁶¹ Finally, given the universal effect of maternal education on cognitive outcomes in childhood suggested by our results, interventions can start early. The neonatal hospitalisation may represent a key window of opportunity for addressing social disparities by reducing financial barriers affecting parental presence,⁶² promoting breastfeeding,⁶²

and facilitating access to follow-up and early intervention programmes.⁶³ Study designs that integrate information on the families' social circumstances would ensure that research on the effectiveness of interventions targets health and developmental disparities.

Strengths of this study include pooling data using a standardised protocol from a large number of cohorts in Europe. Harmonising variable definitions, using common inclusion criteria and conducting comparable analyses minimises methodological heterogeneity,⁶⁴ which improves the accuracy of pooled estimates. Another strength is the geographic and temporal heterogeneity of the cohorts which adds to the relevance and generalisability of the findings. Study limitations include residual heterogeneity between cohorts due to diverse educational systems and outcome measurements, the small number of cohorts per country limiting investigation of country effects, the lack of some important information because of difficulties harmonising definitions, and potential bias due to attrition or missing outcome data. Countries with higher proportions of immigrants may have less reliable measures of maternal educational achievement. Moreover the underlying mechanisms are complex and some pathways, for instance genetic influences⁶⁵ or parental expectation,⁶⁶ through which maternal education may impact cognitive development, could not be examined. Lastly, our study is based on VPT cohorts, the principal research design for investigating neurodevelopmental outcomes after VPT birth, which limits causal inference because of potential collider stratification bias. To go beyond our descriptive approach, full birth cohorts are needed to investigate causality and potential mediator-interaction relationships.^{67,68}

CONCLUSION

In this meta-analysis of the principal population-based cohorts of children born VPT in Europe, we showed that maternal educational level was a consistent predictor of general development and cognitive outcomes in childhood. Further research is needed on early interventions that can mitigate

these social disparities; more broadly, equity in health and development should be included as a key outcome in all research on VPT birth.

ETHICS APPROVAL

Cohort	Local ethics committee that approved the study cohort
ACTION	Ethical approval was obtained from the Ethics Committees of the regional coordinating institutes in the participating regions.
AYLS	Ethical permission was granted by the Helsinki City Maternity Hospital, Helsinki University Central Hospital and Jorvi Hospital in Finland
BEST-BLS	Ethical approval was obtained from the University of Munich Children's Hospital and the Bavarian Health Council (Landesärztekammer Bayern) in Germany
EPIBEL	Inclusion : no ethics committee involved in 1999-2000, FU 11-15Y : 2012/27
EPIcure	NIHR South Central Southampton Research Ethics Committee [05/Q1702/126]
EPIcure-2	UCL Research Ethics Committee (reference: 10175/001) and University of Leicester Research Ethics Committee (ref: 10225)
EPIPAGE 1	The EPIPAGE study was approved by the French Data Protection Authority (Commission Nationale de l'Informatique et des Libertés)
EPIPAGE 2	Recruitment and follow-up within this study were approved by the national data protection authority (CNIL n° 911 009, 913 020, 916 212) and by the appropriate ethics committees, i.e., the advisory committee on the treatment of personal health data for research purposes (Comité Consultatif sur le Traitement de l'Information en matière de Recherche, CCTIRS reference number 10-626, 12-109 and 16-263) and the committee for the protection of people participating in biomedical research (Comité de Protection des Personnes, CPP SC 2873, CPP 3377).
EPICE/SHIPS	The European study was also approved by the French Advisory Committee on Use of Health Data in Medical Research (CCTIRS, for EPICE, N° 13.020 on 24/01/2013) and the French Expert Committee for Research, Studies and Evaluations in the field of Health (CEREES for SHIPS, TPS12460bis (16/11/2017) as well as the French National Commission for Data Protection and Liberties (CNIL) for both phases (DR-2013-194, on 10/04/2013, DR-2018-098 on 15/05/2018).
EST 02-03	151/T-23, 21.08.2006
EST 07	169/T-18, 24.03.2008 ; 5y Assessment: 214/T-20; 27.04.2012
ETFOL	All eight regional Research Ethics Committees approved the ETFOL study. Use of the data in the ETFOL cohort for this study was approved by the data protection authorities.
EXPRESS	Dnr 42/2004 and 2009/524 (Lund/Sweden)

PEP	Regional Ethics Committee (REC) Western Norway Health Authority, REC nr. 20.04 and 2009-2271
PIPARI	The PIPARI study protocol was approved by the Ethics Review Committee of the Hospital District of Southwest Finland in December 2000 and again in January 2012

AUTHOR CONTRIBUTIONS

Dr Sentenac conceptualized and designed the study, carried out the analyses at the cohort level, carried out the pooled analyses, interpreted the data, drafted the initial manuscript, and revised the manuscript.

Dr Benhammou contributed to the study concept and design, to the acquisition of cohort data, carried out the analyses at the cohort level, contributed to the interpretation of the data, and revised the manuscript.

Dr Aden, Dr Maier, and Dr Barros contributed to the acquisition of cohort data, interpretation of the data, and revised the manuscript.

Dr Ancel, Dr Boerch, Dr Cuttini, Dr Draper, Dr Halvorsen, Dr Johnson, Dr Lebeer, Pr Lehtonen, Dr Marlow, Dr Raikkonen, Dr Varendi, and Dr Wolke contributed to the acquisition of cohort data, the interpretation of the data, and revised the manuscript.

Mr Bakker and Dr Morgan contributed to conceptualize and design the study, and revised the manuscript.

Mrs Bakoy, Mrs Baumann, Mrs Funck Bilsteen, Mrs Croci, Dr Källén, Dr Land, Dr Ni, Mr Rtimi, Dr Sarrechia, Dr Vollsaeter, and Dr Ylijoki carried out the analyses at the cohort level, contributed to the interpretation of the data, and revised the manuscript.

Dr Kallen contributed to the acquisition of the cohort data, carried out the analyses at the cohort level, contributed to the interpretation of the data, and revised the manuscript.

Dr Zeitlin conceptualized and designed the study, contributed to the acquisition of the cohort data, interpreted the data, contributed to write the initial manuscript, and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DATA AVAILABILITY

No individual participant data are available. Data dictionaries are available on the RECAP Preterm platform (<https://platform.recap-preterm.eu/pub>)

SUPPLEMENTARY DATA

Supplementary Table S1 - Information on geographical coverage, inclusion criteria, and participants of term control groups by cohort and by age group

Supplementary Table S2 - Information on cognitive tests, scores and reference population by cohort and by age group

Supplementary Table S3 - IQ scores and missing data by cohort and by age group

Supplementary Table S4 – Results from sensitivity analysis

Supplementary Figure S1 – Forest plot of standardized mean differences of unadjusted mean IQ scores (SMD and 95% CI) in children born <27 weeks of gestation

Supplementary Figure S2 – Forest plot of standardized mean differences of unadjusted mean IQ scores (SMD and 95% CI) in children born ≥ 27 weeks of gestation

Supplementary Figure S3 – Forest plot of standardized mean differences of adjusted mean IQ scores (SMD and 95% CI) in all VPT children

Supplementary Figure S4 – Forest plot of standardized mean differences of adjusted mean IQ scores (SMD and 95% CI) in children born <27 weeks of gestation

Supplementary Figure S5 – Forest plot of standardized mean differences of adjusted mean IQ scores (SMD and 95% CI) in children born ≥ 27 weeks of gestation

Supplementary Figure S6 – Forest plot of standardized mean differences of unadjusted mean IQ scores (SMD and 95% CI) : subgroup VPT and term controls

Supplementary Figure S7 – Forest plot of standardized mean differences of adjusted mean IQ scores (SMD and 95% CI) in term controls

Supplementary Figure S8 – Forest plot of Relative Risk for cognitive deficit by maternal educational group (and 95% CI) in all VPT children

Supplementary Figure S9 – Forest plot of standardized mean differences of unadjusted mean IQ scores (SMD and 95% CI) in children without neonatal morbidities

Supplementary Figure S10 – Forest plot of standardized mean differences of adjusted mean IQ scores (SMD and 95% CI) in children without neonatal morbidities

Supplementary Figure S11 – Forest plots of the results of the leave-one-out sensitivity analysis (standardized mean differences of unadjusted mean IQ scores) applied when meta-analyses with high heterogeneity ($I^2 > 50\%$)

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Table 1 - Characteristics of the 15 participating cohorts

Cohort	Country, coverage, if not national ^a	Inclusion criteria (GA, BW)	Years of birth	Live birth (N)	Period 1 Age (% FU) ^b	Period 2 Age (% FU) ^b	Period 3 Age (% FU) ^b
ACTION	Italy, 5 regions ^c	<32 wks	2003-2005	2002	2 y (84.6%)	n/a	8-11 y (72.9%)
AYLS	Finland, County of Uusimaa	<32 wks	1985-1986	93	20 m (97.0%)	56 m (93.9%)	n/a
BEST-BLS	Germany, Southern Bavaria	<32 wks	1985-1986	560	20 m (97.5%)	6 y (97.3%)	8 y (97.3%)
EPIBEL	Belgium, Flanders ^d	<27 wks	1999-2000	169	3 y (81.1%)	n/a	11-15 y (55.8%)
EPIcure	UK and Ireland	<26 wks	1995	1290	2.5 y (98.1%)	6 y (76.5%)	11 y (69.5%)
EPIcure-2	England	<27 wks	2006	2034	2.5 y (55.3%)	n/a	11 y (n/a) ^e
EPIPAGE 1	France, 9 regions ^f	<33 wks	1997	2901	2 y (89.9%)	5 y (75.1%)	n/a
EPIPAGE 2	France, 25 regions	<32 wks ^g	2011	4227	2 y (83.4%)	5 y (70.3%)	n/a
EPICE/SHIPS	¹⁰ European countries ^h , 16 regions	<32 wks	2011-2012	6593	2 y (60.5%)	5 y (51.2%)	n/a
EST 02-03	Estonia	<32 wks (FU <29 wks)	2002-2003	264	n/a	5 y (81.3%) ⁱ	n/a
EST 07	Estonia	<32 wks (FU 5y: <29 wks)	2007	360	2 y (98.7%)	5 y (38.9%) ⁱ	n/a
ETFOL	Denmark	<28 wks or <1000g	1994-1995	477	n/a	5 y (90.7%)	n/a
EXPRESS	Sweden	<27 wks	2004-2007	707	2.5 y (77.4%)	6.5 y (76.2%)	n/a

PEP	Norway	<28 wks or <1000g	1999-2000	462	n/a	5 y (81.4%)	n/a
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PIPARI	Finland, Turku region	≤ 1500 g ¹	2001-2006	255	2 y (97.3%)	5 y (94.1%)	11 y (89.6%)
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Abbreviation : GA= gestational age; BW= birth weight; FU=follow-up; n/a= not available

(a) ACTION (Lazio, Marche, Tuscany, Friuli Venezia-Giulia (FVG) and Calabria) ; EPIPAGE 1 (Alsace, Franche-Comté, Lorraine, Nord-Pas de Calais, Haute Normandie, Pays de Loire, Paris-Petite couronne, Languedoc-Roussillon, Midi-Pyrénées); EPIPAGE 2 (21 regions of the 22 metropolitan regions, and all 4 overseas regions); EPICESHIPS (Flanders in Belgium; the Eastern Region of Denmark; Estonia (entire country); Hesse and Saarland in Germany; Emilia - Romagna, Lazio and Marche regions in Italy; the Central and Eastern regions of The Netherlands; Wielkopolska in Poland; the Lisbon and Northern regions of Portugal; and the East Midlands, Northern and Yorkshire and Humber regions in the UK; and the Stockholm region in Sweden)

(b) Number of participants at FU / number of survivors at discharge

(c) Two regions (Calabria and Marche) did not participate at FU at 8-11 years

(d) The original cohort is representative of whole Belgium (total: 322 born alive, of whom 303 were admitted at NICU) but only one region (Flanders) participated at the first follow-up. Non-Dutch speaking parents were excluded from the follow-up

(e) At 11 years, data were collected only among a sub-sample of 200 children

(f) Only 1 region participated at the follow up at 2-3 years

(g) children with cerebral palsy, deafness, blindness, or severe congenital brain malformations were excluded from analyses

(h) The 3 French regions were excluded of this analysis because of the overlap with EPIPAGE 2

(i) FU only among children born before <29 weeks; EST07: follow-up was restricted to specific patient selection (year of birth, birth weight, regional differences) due to financial restriction

(j) Infants with congenital anomalies and malformations were not eligible to this cohort

Table 2 – Definition and distribution of maternal educational level by cohort

Cohort ^a	Measured at ^b	N ^c	Low level (ISCED 0-2)	Intermediate level (ISCED 3-5)	High level (ISCED 6-8)	Missing data
			n (%)	n (%)	n (%)	%
ACTION	Birth	976	290 (30.1)	502 (52.1)	171 (17.8)	1.3
AYLS	Birth	58	23 (40.4)	14 (24.6)	20 (35.1)	1.7
BEST-BLS	Birth	329	108 (33.6)	184 (57.3)	29 (9.0)	2.4
EPIBEL	FU	47	3 (2.4)	19 (45.2)	20 (47.6)	10.6
EPIcure	FU	283	62 (23.6)	185 (70.3)	16 (6.1)	7.1
EPIcure-2	FU	576	41 (8.0)	295 (57.8)	174 (34.1)	6.3
EPIPAGE 1	Birth	1535	578 (37.6)	288 (18.7)	434 (28.2)	15.3
EPIPAGE 2	Birth	1884	511 (27.2)	780 (41.3)	553 (29.3)	2.1
EPICE/SHIPS	FU	3345	600 (17.9)	1374 (41.1)	1303 (39.0)	2.1
EST 02-03	FU	49	6 (16.7)	23 (63.9)	7 (19.4)	26.5
EST 07	FU	155	20 (13.1)	88 (57.5)	45 (29.4)	1.3
ETFOL	Birth	222	63 (28.8)	110 (50.2)	46 (21.0)	1.4
EXPRESS	FU	398	37 (9.7)	249 (65.5)	94 (24.7)	4.5
PEP	FU	258	19 (7.7)	114 (46.3)	113 (45.9)	4.7
PIPARI	Birth	215	28 (14.2)	87 (44.2)	82 (41.6)	8.4
Total		10 330	2389	4382	3036	

Abbreviation: FU=follow-up; ISCED= International Standard Classification of Education

(a) ACTION (Accesso alle Cure e Terapie Intensive Ostetrico Neonatali; Italy) ; AYLS (Arvo Ylppö Longitudinal Study; Finland); BEST-BLS (Bavarian Longitudinal Study Cohort; Germany); EPIBEL (Belgium); EPIcure (UK and Ireland); EPIcure-2 (England); EPIPAGE 1 and EPIPAGE 2 (Étude épidémiologique sur les petits âges gestationnels; France); EPICE/SHIPS (Effective Perinatal Intensive Care In Europe; Europe); EST 02-03 and EST 07 (Very low gestational age infants born in Estonia; Estonia); ETFOL (Treatment of extremely preterm infants: parents attitudes; Denmark); EXPRESS (Extremely Preterm Infants in Sweden Study; Sweden); PEP (Project Extreme Prematurity; Norway); PIPARI (Development and Functioning of Very Low Birth Weight Infants from Infancy to School Age; Finland).

(b) All cohorts collected data on the highest educational level achieved, except for EXPRESS where was asked about the cumulated years of education received by the mother.

(c) Number of participants at first follow-up available, except for EPIBEL (11-15 years) and EPIPAGE 1 (5 years)

Table 3 – Distribution of maternal, perinatal characteristics and neonatal morbidities by cohort

Cohort (a)	n (b)	Maternal information						Perinatal and child information						Neonatal morbidities			
		% mothers ≥ 35 years	% primiparous	% not living in couple (c)	% country-born mother (d)	GA mean/sd (range)	BW mean (sd)	% of male	% multiple births	% Apgar <7	% c-section	% breast milk at discharge	% NEC-III/IV	% IVH-III/IV	% cPVL	% BPD-III/IV	% ROP-III/IV
ACTION	976	36.7	66.5	3.3 (2)	82.9 (1)	29.0/1.9 (23-31)	1250 (347)	54.3	28.5	15.2	80.3	63.3	2.2	3.7	1.6	8.9	3.6
AYLS	58	20.7	51.7	5.3 (1)	98.3 (2)	28.7/2.1 (24-31)	1331 (375)	60.3	12.1	33.3	46.6	na	na	10.3	na	6.9	na
BEST-BLS	329	11.9	50.2	7.1 (1)	91.8 (2)	29.6/1.5 (25-31)	1306 (335)	58.4	23.4	23.5	54.4	na	na	9.4	na	60.5	na
EPIBEL	47	6.5	51.1	12.8 (2)	na	25.3/0.8 (23-26)	785 (182)	61.7	51.1	28.3	59.6	38.3	2.1	12.8	6.4	38.3	nc
EPICure	283	16.3	31.4	19.6 (2)	79.1 (3)	24.9/0.7 (22-25)	746 (113)	47.7	21.2	na	16.3	85.4	3.9	17.7	4.6	74.2	nc
EPICure-2	576	28	40.9	14.5 (2)	73.8 (3)	25.6/1.0 (22-26)	802 (149)	50.2	28.6	na	30.3	48.6	na	15.0	4.2	69.3	19.5
EPIPAGE 1	1535	15.5	44.4	7.1 (1)	86.6 (1)	29.9/2.0 (24-32)	1375 (388)	51.3	31.0	11.3	59.7	35.6	3.5	3.1	2.5	12	1.7
EPIPAGE 2	1884	23.5	38.6	6.5 (1)	79.5 (1)	29.8/2.1 (23-32)	1369 (399)	52.6	36.1	19.0	68.6	52.1	3.3	3.1	0.9	11.1	1.4
EPICE/SHIPS	3345	30.7	62.3	8.5 (2)	85.5 (1)	28.8/2.0 (23-31)	1254 (375)	53.0	32.8	14.7	71.6	66.1	4.8	4.0	3.2	14.4	4.6
EST 02-03	49	na	na	38.8 (2)	na	27.1/1.9 (23-30)	996 (228)	53.1	20.4	48.9	38.8	55.1	14.3	8.7	1.0	36.7	22.4
EST 07	155	26.8	45.8	39.4 (2)	na	28.8/2.2 (22-31)	1314 (392)	56.8	26.5	34.2	65.8	35.5	11.6	5.2	1.0	18.7	9.0
ETFOL	219	21.5	63.0	47.9 (1)	92.9 (1)	27.1/1.8 (24-32)	926 (167)	45.7	29.7	13.6	67.2	49.3	3.2	2.7	2.7	nc	3.3
EXPRESS	398	30.2	59.5	na	79.9 (1)	25.4/1.1 (22-26)	783 (169)	55.0	19.3	33.4	57.5	58.2	5.5	10.1	5.0	22.4	34.4
PEP	258	20.5	na	nc	na	26.5/1.6 (23-31)	854 (172)	55.0	24.8	21.4	67.4	74.4	nc	3.9	5.4	45.3	4.9
PIPARI	215	31.2	51.9	2.5 (1)	na	28.6/2.8 (24-35)	1143 (327)	55.8	31.2	32.7	60.9	na	nc	5.6	2.8	14.0	4.3

Abbreviations: GA= gestational age; BW= birthweight; NEC-III/IV= necrotizing enterocolitis stages III-IV; IVH-III/IV= intraventricular haemorrhage stages III-IV; cPVL=cystic periventricular leukomalacia; BPD=bronchopulmonary dysplasia; ROP-III/IV=retinopathy of prematurity stages III to V; na=not available; nc=not compatible

- (a) ACTION (Accesso alle Cure e Terapia Intensiva Ostetrico Neonatale; Italy) ; AYL5 (Arvo Ylppö Longitudinal Study; Finland); BEST-BLS (Bavarian Longitudinal Study Cohort; Germany); EPIBEL (Belgium); EPIcure (UK and Ireland); EPIcure-2 (England); EPIPAGE 1 and EPIPAGE 2 (Étude épidémiologique sur les petits âges gestationnels; France); EPICE/SHIPS (Effective Perinatal Intensive Care In Europe; Europe); EST 02-03 and EST 07 (Very low gestational age infants born in Estonia; Estonia); ETFOL (Treatment of extremely preterm infants: parents attitudes; Denmark); EXPRESS (Extremely Preterm Infants in Sweden Study; Sweden); PEP (Project Extreme Prematurity; Norway); PIPARI (Development and Functioning of Very Low Birth Weight Infants from Infancy to School Age; Finland).
- (b) Number of participants at first follow-up available, except for EPIBEL (11-15 years) and EPIPAGE 1 (5 years)
- (c) living in couple at birth (1) or at follow-up (2)
- (d) (1) country-born mother when available, or (2) with the nationality of the country, or (3) from not minor ethnicity
- (e) For the EXPRESS cohort, the % of severe bronchopulmonary dysplasia was provided

Table 4 – Unadjusted and adjusted pooled standardized mean differences (SMD) of cognitive scores by maternal educational level for all VPT infants, by gestational age sub-group and for control populations

	Infancy (2-3 years old)		Early childhood (4-7 years old)		Later childhood (8-15 years old)	
	N cohorts	Unadjusted SMD 95% CI	N cohorts	Unadjusted SMD 95% CI	N cohorts	Unadjusted SMD 95% CI
All VPT						
medium vs high	11	-0.15 (-0.23; -0.06) I ² =45%	12	-0.29 (-0.38; -0.19) I ² =48%	6	-0.14 (-0.38; 0.10) I ² =58%
Low vs high	12	-0.32 (-0.43; -0.21) I ² =52%	12	-0.57 (-0.67; -0.47) I ² =37%	6	-0.54 (-0.72; -0.37) I ² =0%
< 27 wks					6	
medium vs high	10	-0.08 (-0.20; 0.04) I ² =19%	10	-0.26 (-0.48; -0.04) I ² =63%	5	0.16 (-0.06; 0.38) I ² =0%
Low vs high	10	-0.27 (-0.44; -0.10) I ² =23%	11	-0.54 (-0.76; -0.33) I ² =33%	5	-0.24 (-0.56; 0.08) I ² =0%
≥ 27 wks						
medium vs high	8	-0.24 (-0.39; -0.10) I ² =66%	10	-0.38 (-0.56; -0.21) I ² =76%	3	-0.36 (-0.57; -0.14) I ² =24%
Low vs high	8	-0.37 (-0.52; -0.21) I ² =62%	10	-0.65 (-0.84; -0.47) I ² =69%	3	-0.70 (-1.24; -0.17) I ² =78%
Without neonatal morbidities						
medium vs high	8	-0.12 (-0.18; -0.06) I ² =0%	6	-0.34 (-0.47; -0.21) I ² =41%	na	na
Low vs high	7	-0.35 (-0.53; -0.17) I ² =68%	6	-0.67 (-0.91; -0.44) I ² =62%	na	na
Control						
medium vs high	6	-0.12 (-0.22; -0.02) I ² =6%	5	-0.43 (-0.56; -0.29) I ² =0%	na	na
Low vs high	6	-0.22 (-0.44; -0.01) I ² =58%	5	-0.55 (-0.77; -0.33) I ² =6%	na	na

Abbreviation: na= not available

Footnote: the following cohorts took into consideration clustering for multiples in the analyses : ACTION (Italy), AYL_S (Finland), BEST-BLS (Germany), EpiCure (UK and Ireland), EpiCure-2 (England), EPIPAGE 1 (France), EPIPAGE 2 (France), EPIC-SHIPS (Belgium; Denmark; Estonia; Germany; Italy; The Netherlands; Poland; Portugal; UK; Sweden), EST 02-03 (Estonia), EST 07 (Estonia), ETFOL (Denmark), EXPRESS (Sweden), PIPARI (Finland)

(a) adjusted for maternal age and child's sex

Figure 1

a) Infancy childhood (2-3 years old) (12 cohorts)

Cohort	Total (Case)	Total (High)	SMD [95% CI]	Weight
Comparison = Low vs high education				
ACTION	290	171	-0.13 [-0.32; 0.06]	14.4%
AYLS	23	20	-0.51 [-1.12; 0.10]	2.9%
BEST	108	29	-0.39 [-0.80; 0.03]	5.5%
EPIBEL	1	15		0.0%
EPIcure1	62	16	0.04 [-0.51; 0.59]	3.4%
EPIcure2	41	174	-0.46 [-0.80; -0.12]	7.2%
EPIPAGE1	173	76	-0.46 [-0.73; -0.18]	9.8%
EPIPAGE2	1099	840	-0.18 [-0.27; -0.09]	21.5%
EPICE	600	1303	-0.25 [-0.35; -0.15]	21.1%
EST07	20	45	-0.56 [-1.10; -0.03]	3.6%
EXPRESS	37	94	-0.71 [-1.10; -0.32]	6.0%
PIPARI	25	80	-0.73 [-1.20; -0.27]	4.6%
Random effect model	2479	2863	-0.32 [-0.43; -0.21]	100.0%

Heterogeneity: Tau² = 0.0128; Chi² = 20.61, df = 10 (P = 0.02); I² = 51%

Cohort	Total (Case)	Total (High)	SMD [95% CI]	Weight
Comparison = Interm. vs high education				
ACTION	502	171	-0.09 [-0.27; 0.08]	12.5%
AYLS	14	20	-0.02 [-0.70; 0.66]	1.9%
BEST	184	29	-0.36 [-0.76; 0.03]	4.8%
EPIBEL	17	15	0.22 [-0.48; 0.91]	1.8%
EPIcure1	185	16	0.57 [0.05; 1.08]	3.1%
EPIcure2	325	174	-0.14 [-0.32; 0.04]	11.9%
EPIPAGE1	76	76	-0.50 [-0.82; -0.18]	6.4%
EPIPAGE2	1315	840	-0.09 [-0.17; 0.00]	17.7%
EPICE	1374	1303	-0.10 [-0.18; -0.03]	18.3%
EST07	88	45	-0.24 [-0.60; 0.12]	5.5%
EXPRESS	249	94	-0.25 [-0.49; -0.01]	9.3%
PIPARI	85	80	-0.39 [-0.69; -0.08]	6.8%
Random effect model	4414	2863	-0.15 [-0.23; -0.06]	100.0%

Heterogeneity: Tau² = 0.0075; Chi² = 19.94, df = 11 (P = 0.05); I² = 45%

Std. Mean Difference
IV, Random, 95% CI

-1.5 -1 -0.5 0 0.5 1 1.5

Note: ACTION and EPICE/SHIPS (PARCA-R); AYLS and BEST-BLS (Griffiths Mental Development Scale); EPIBEL, EPIcure and PIPARI (BSID-II); EPIcure-2, EST 07 and EXPRESS (Bayley III); EPIPAGE 1 (Brunet-Lezine); EPIPAGE 2 (ASQ)

b) Early childhood (4-7 years old) (12 cohorts)

Cohort	Total (Case)	Total (High)	SMD [95% CI]	Weight
Comparison = Low vs high education				
AYLS	17	17	-0.13 [-0.80; 0.54]	4.2%
BEST	80	25	-0.31 [-0.76; 0.14]	7.4%
EPIcure1	50	10	0.43 [-0.25; 1.12]	4.1%
EPIPAGE1	689	487	-0.66 [-0.78; -0.54]	17.2%
EPIPAGE2	1099	840	-0.57 [-0.66; -0.47]	17.9%
EPICE	407	1180	-0.54 [-0.65; -0.42]	17.3%
EST0203	6	8	-0.88 [-2.00; 0.25]	1.8%
EST07	2	13	-0.79 [-2.32; 0.73]	1.0%
ETFOL	63	46	-0.73 [-1.12; -0.33]	8.7%
EXPRESS	28	88	-0.75 [-1.19; -0.32]	7.7%
PEP	19	113	-0.95 [-1.45; -0.45]	6.5%
PIPARI	18	76	-0.51 [-1.03; 0.01]	6.2%
Random effect model	2478	2903	-0.57 [-0.67; -0.47]	100.0%

Heterogeneity: Tau² = 0.0080; Chi² = 17.46, df = 11 (P = 0.09); I² = 37%

Cohort	Total (Case)	Total (High)	SMD [95% CI]	Weight
Comparison = Interm. vs high education				
AYLS	14	17	-0.47 [-1.19; 0.25]	3.1%
BEST	141	25	-0.43 [-0.86; 0.00]	6.5%
EPIcure1	160	10	0.95 [0.30; 1.60]	3.7%
EPIPAGE1	331	487	-0.27 [-0.41; -0.13]	13.6%
EPIPAGE2	1315	840	-0.28 [-0.37; -0.20]	14.8%
EPICE	1108	1180	-0.24 [-0.32; -0.15]	14.8%
EST0203	23	8	-0.48 [-1.30; 0.33]	2.6%
EST07	27	13	-0.85 [-1.54; -0.16]	3.3%
ETFOL	110	46	-0.21 [-0.55; 0.14]	8.1%
EXPRESS	240	88	-0.43 [-0.67; -0.18]	10.6%
PEP	114	113	-0.42 [-0.69; -0.16]	10.2%
PIPARI	72	76	-0.26 [-0.59; 0.06]	8.6%
Random effect model	3655	2903	-0.29 [-0.38; -0.19]	100.0%

Heterogeneity: Tau² = 0.0093; Chi² = 21.21, df = 11 (P = 0.03); I² = 48%

Std. Mean Difference
IV, Random, 95% CI

-1.5 -1 -0.5 0 0.5 1 1.5

Note: AYLS (CMMS, BEERY, and AWST); BEST-BLS, EPIcure, EPIPAGE 1 and EST 02-03 (K-ABC); EPIPAGE 2 (WPPSI IV); EPICE/SHIPS (ASQ); EST 07 (K-ABC 2); ETFOL, PEP and PIPARI (WPPSI-R); EXPRESS (WISC-IV)

c) Later childhood (8-15 years old) (6 cohorts)

Cohort	Total (Case)	Total (High)	SMD [95% CI]	Weight
Comparison groups: Low vs high education				
ACTION	214	130	-0.62 [-0.84; -0.40]	33.2%
BEST	79	25	-0.34 [-0.79; 0.12]	21.3%
EPIBEL	3	20	-0.19 [-1.41; 1.02]	5.4%
EPIcure1	44	8	-0.00 [-0.76; 0.75]	11.6%
EPIcure2	6	57	-0.28 [-1.13; 0.56]	9.8%
PIPARI	20	70	-0.80 [-1.32; -0.29]	18.8%
Random effect model	366	310	-0.54 [-0.72; -0.37]	100.0%

Heterogeneity: Tau² = 0; Chi² = 4.94, df = 5 (P = 0.42); I² = 0%

Cohort	Total (Case)	Total (High)	SMD [95% CI]	Weight
Comparison groups: Interm. vs high education				
ACTION	381	130	-0.20 [-0.40; 0.00]	24.9%
BEST	144	25	-0.51 [-0.94; -0.08]	16.2%
EPIBEL	19	20	0.07 [-0.56; 0.70]	10.7%
EPIcure1	146	8	0.59 [-0.12; 1.31]	9.0%
EPIcure2	83	57	0.09 [-0.24; 0.43]	19.5%
PIPARI	74	70	-0.41 [-0.74; -0.08]	19.8%
Random effect model	847	310	-0.14 [-0.38; 0.10]	100.0%

Heterogeneity: Tau² = 0.0472; Chi² = 11.77, df = 5 (P = 0.04); I² = 58%

Std. Mean Difference
IV, Random, 95% CI

-1.5 -1 -0.5 0 0.5 1 1.5

Note: ACTION and EPIcure-2 (K-ABC 2); BEST-BLS and EPIcure (K-ABC); EPIBEL (Shortened WISC III); PIPARI (WISC-IV)

Abbreviations: SMD=Standardised mean difference; ASQ= Ages & Stages Questionnaire; ; AWST=Finnish translation of the Aktiver Wortschatztest; BEERY=Beery Developmental Test of Visual-Motor Integration; BSID-II=The Bayley Scales of Infant Development – version 2; CMMS = Columbia Mental Maturity Scale; K-ABC= Kaufman Assessment Battery for Children; K-ABC 2= Kaufman Assessment Battery for Children-second edition; PARCA-R=Parent Report of Children's Abilities-Revised; Shortened WISC III= Wechsler Intelligence Scale for Children-Third edition short form; WISC-IV= Wechsler Intelligence Scale for Children-Fourth Edition; WPPSI IV= Wechsler Preschool & Primary Scale of Intelligence-Fourth edition; WPPSI-R= Wechsler Preschool & Primary Scale of Intelligence-Revised edition

SUPPLEMENTARY ONLINE MATERIALS

- Supplementary Table S1 - Information on geographical coverage, inclusion criteria, and participants of term control groups by cohort and by age group
- Supplementary Table S2 - Information on cognitive tests, scores and reference population by cohort and by age group
- Supplementary Table S3 - IQ scores and missing data by cohort and by age group
- Supplementary Table S4 – Results from sensitivity analysis
- Supplementary Figure S1 – Forest plot of standardized mean differences of unadjusted mean IQ scores (SMD and 95% CI) in children born <27 weeks of gestation
- Supplementary Figure S2 – Forest plot of standardized mean differences of unadjusted mean IQ scores (SMD and 95% CI) in children born ≥ 27 weeks of gestation
- Supplementary Figure S3 – Forest plot of standardized mean differences of adjusted mean IQ scores (SMD and 95% CI) in all VPT children
- Supplementary Figure S4 – Forest plot of standardized mean differences of adjusted mean IQ scores (SMD and 95% CI) in children born <27 weeks of gestation
- Supplementary Figure S5 – Forest plot of standardized mean differences of adjusted mean IQ scores (SMD and 95% CI) in children born ≥ 27 weeks of gestation
- Supplementary Figure S6 – Forest plot of standardized mean differences of unadjusted mean IQ scores (SMD and 95% CI) : VPT vs term controls
- Supplementary Figure S7 – Forest plot of standardized mean differences of adjusted mean IQ scores (SMD and 95% CI) in term controls
- Supplementary Figure S8 – Forest plot of Relative Risk for cognitive deficit by maternal educational group (and 95% CI) in all VPT children
- Supplementary Figure S9 – Forest plot of standardized mean differences of unadjusted mean IQ scores (SMD and 95% CI) in children without neonatal morbidities
- Supplementary Figure S10 – Forest plot of standardized mean differences of adjusted mean IQ scores (SMD and 95% CI) in children without neonatal morbidities
- Supplementary Figure S11 – Forest plots of the results of the leave-one-out sensitivity analysis (standardized mean differences of unadjusted mean IQ scores) applied when meta-analyses with high heterogeneity ($I^2 > 50\%$)

Supplementary Table S1 - Information on geographical coverage, inclusion criteria, and participants of term control groups by cohort and by age group

Cohort	Country coverage if not national ¹	Inclusion/exclusion criteria	Years of birth	Maternal educational level	Period 1 (2-3 years):		Period 2 (4-7 years):	
					IQ test and score / N participants with complete assessment	IQ test and score / N participants with complete assessment		
ACTION	FVG, Tuscany, Marche, Lazio and Calabria	Inclusion: term-born Exclusion: foreign mothers	2005-2006	Same measure than for cases	PARCA-R (Non-verbal) / n=380		Not available	
AYLS	County of Uusimaa, Finland	Inclusion: An infant born after every second hospitalized infant and without evidence of neonatal illness was identified from one of the three biggest maternity hospitals in the study area during the same period.	1985/86	Same measure than for cases	Griffiths Mental Development Scale (DQ) / n=658		Not available	
BLS	Southern Bavaria, Germany	Inclusion: Healthy infants who were cared for on the normal postnatal wards in the same obstetric hospitals	1985/86	Same measure than for cases	Griffiths Mental Development Scale (DQ) / n=916		K-ABC (MPC) / n=350	
EPIMAGE 2	France	Inclusion: selected sample from the Effe cohort of children born at or near term (≥ 37 wks) Inclusion: term healthy infant matched with the study group by sex, age and birth hospital Exclusion: Illness and intensive care requirement within 1st week of life.	2011	Same measure than for cases	Not available		WPPSI-IV (FSIQ) / n=592 (1)	
EST 07	Whole Estonia		2007	Same measure than for cases	Bayley-III (cognitive score) / n=153		Not available	
ETFOL	All Denmark	Inclusion: 36-43 completed weeks	1994-1995	Same measure than for cases	Not available		WPPSI-R (FSIQ) / n=76	

		Inclusion: singleton at-term birth with a 5-minute Apgar score greater than 3 with matching of control participants for place of living, sex, GA-adjusted day of birth +/- 14days, and maternal country of birth Exclusion: Women delivering extremely preterm but not residing in Sweden in study period. Terminations of pregnancy and infants born outside of Sweden and transferred to Sweden for neonatal care			
EXPRESS	Whole Sweden		2004-2007	Same measure than for cases	Bayley-III (cognitive score) / n=370 WISC-IV (FSIQ) / n=371
PIPARI	Finland/Turku university hospital	The parents of first boy and girl born in each week was asked to take part in the study. If they refused, the parents of next boy/girl were asked. Inclusion criteria were 1) birth weight \geq -2 SD according to age and gender specific Finnish growth charts 2) gestational age \geq 37 weeks at birth 3) the family lived inside the hospital catchment area 4) the child was not admitted to neonatal care during the first week of life 5) family was Finnish or Swedish speaking.	2001-2003	Different measure / variable has been changed in the same manner as for cases group	BSID-II (MDI) / n=165 WPPSI-R (FSIQ) / n=151 (2)

- (1) Charles MA, Thierry X, Lanoe JL, Bois C, Dufourg MN, Popa R, Cheminat M, Zaros C, Geay B. *Int J Epidemiol.* 2020 Apr 1;49(2):368-369j. doi: 10.1093/ije/dyzz227).
- (2) Munck P, Haataja L, Maunu J, Parkkola R, Rikalainen H, Lapinleimu H, & PIPARI Study Group. Cognitive outcome at 2 years of age in Finnish infants with very low birth weight born between 2001 and 2006. *Acta paediatrica.* 2010; 99(3). 359-366.

Supplementary Table S2 - Information on cognitive tests, scores and reference population by cohort and by age group

Cohort	IQ test	Infancy (2 to 3 years)			Early childhood (4 to 7 years)			Later childhood (8 to 15 years)			Information and references	
		Score (a- Age-based, scaled; b- Raw)*	Reference population (country, birth year)	Definition of cognitive delay	Score (a- Age-based, scaled; b- Raw)	Reference population (country, birth year)	Definition of cognitive delay	Score (a- Age-based, scaled; b- Raw)	Reference population (country, birth year)	Definition of cognitive delay		
ACTION	PARCA-R	non verbal cognition (0-34) (b)	None	<=22 (1)				K-ABC 2	MPI (a)	Norms (Italy, collection in 2007-2011)	<-1SD (<85)	<p>Infancy: <=2.5th percentile of the term reference group was used : Johnson, S., Evans, T. A., Draper E. S., Field, D. J., Manktelow, B. N., Marlow, N., ... & Boyle, E. M. (2015). Neurodevelopmental outcomes following late and moderate prematurity: a population-based cohort study. Archives of Disease in Childhood-Fetal and Neonatal Edition, 100(4), F301-F308. Later childhood: Valente Torre L. KABC-II. Studio italiano e norme preliminari. Giunti O.S. ed. January 2011).</p>
AYLS	Griffiths Mental Development Scale	DQ (a)	Norms (Finland, 1985)	<-1SD	Multiple tests (CMM,AWST, and BEERY)	IQ composite score (a)	Norms (Finland, 1985)	<-1SD				
BEST-BLS	Griffiths Mental Development Scale	DQ (a)	Norms (Bavaria, 1985)	<-1SD	K-ABC	MPC (a)	Norms (Bavaria, 1985)	<-1SD	K-ABC	MPC (a)	Norms (Bavaria, 1985)	<-1SD

EPIBEL	BSID-II	MDI (a)	Norms (Netherlands, 1996-1999)	<85 (<- ISD)		Shortened WISC III	Intelligence score (a) n/a)	Norms (Netherlands: n/a)	<85 (<- ISD)	<p>Infancy: van der Meulen BF, Rutter SA, Spelberg LHC, Smrkovsky M. Bayley Scales of Infant Development (BSID) – II. Nederlandse versie. Lisse, The Netherlands: Swets Test Publishers; 2002. Later childhood: Kort, W., Schittekatte, M., Dekker, P.H., Verhaeghe, P., Compaan, E.L., Bosmans, M. & Vermeir, G. (2005). WISC-III NL. Handleiding en Verantwoording. London: The Psychological Corporation.</p> <p>Reference abbreviated IQ score: Gregoire J (2000) Comparison of three short forms of the Wechsler Intelligence Scale for Children: third edition (WISCIII). Eur Rev Appl Psychol 50:437–441</p>	
EPIcure	BSID-II	MDI (a)	Norms (USA, -)	<85 (<- ISD)			<95 (<- ISD)	K-ABC	MPC (a)	Control	<93 (<- ISD)
EPIcure-2	Bayley III	MDI and predicted MDI (a)	-	<85 (<- ISD)			K-ABC 2	MPI (a)	Control	<91 (<- ISD)	<p>Infancy: Bayley III scores were converted to a predicted mental developmental index because of difficulty in interpreting the results of Bayley III assessments as absolute values. See Moore, T., Johnson, S., Halder, S., Hennessy, E., & Marlow, N. (2012). Relationship between test scores using the second and third editions of the Bayley Scales in extremely preterm children. The Journal of pediatrics. 160(4). 553-558.</p>
EPPiPAG E 1	revised Brunet-Lezine	DQ (a)	Norms (France, -)	<85 (<- ISD)			K-ABC	MPC (a)	Norms	<85 (<- ISD)	

Supplementary Table S3 - IQ scores and missing data by cohort and by age group

Cohort	Infancy (2 to 3 years)			Early childhood (4 to 7 years)			Later childhood (8 to 15 years)		
	Missing data on IQ (%) ¹	Complete assessment (n)	mean IQ (SD)	Missing data on IQ (%) ¹	Complete assessment (n)	mean IQ (SD)	Missing data on IQ (%) ¹	Complete assessment (n)	mean IQ (SD)
ACTION	18.4	976	25.0 (4.0)	n/a	n/a	n/a	9.1	731	98.1 (19.7)
AYLS	9.4	58	93.0 (18.9)	22.6	48	91.7 (15.0)	n/a	n/a	n/a
BEST-BLS	16.1	329	88.9 (24.4)	32.5	264	84.8 (17.3)	30.4	272	87.6 (18.8)
EPIBEL	19.5	62	79.6 (19.8)	n/a	n/a	n/a	11.3	47	80.7 (18.5)
EPICure	8.4	283	81.6 (14.4)	22	241	82.1 (19.2)	28.7	219	83.7 (18.0)
EPICure-2	0	576	93.3 (15.2)	n/a	n/a	n/a	19.5	161	85.3 (18.9)
EPIPAGE 1	16.8	406	92.9 (14.7)	16.8	1535	93.5 (19.2)	n/a	n/a	n/a
EPIPAGE 2	0.3	1884 ³	223.6 (44.4)	33.2	1968	95.8 (15.2)	n/a	n/a	n/a
EPICE/SHIPS	2.8	3345	25.5 (5.2)	3.7	2799 ⁴	72.6 (19.3)	n/a	n/a	n/a
EST 02-03	n/a	n/a	n/a	19.7	49	87.1 (10.9)	n/a	n/a	n/a
EST 07	0.6	155	94.7 (15.5)	16.1	47	91.7 (18.8)	n/a	n/a	n/a
ETFOL	n/a	n/a	n/a	9	222	99.5 (15.5)	n/a	n/a	n/a
EXPRESS	19.4	398	94.3 (12.3)	26.1	359	83.9 (14.6)	n/a	n/a	n/a
PEP	n/a	n/a	n/a	15.7	258	92.8 (15.5)	n/a	n/a	n/a
PIPARI	3.3	208	101.6 (14.6)	13	181	101.1 (16.6)	11.1	176	87.8 (17.5)

Abbreviation: n/a= not available

(1) % of participants with missing data at assessment at FU

(2) only 1 region did participate at the follow up at 2-3 years

(3) exclusion of children with CP, deafness, blindness, or severe congenital brain malformations

(4) ASQ was administered to the entire sample. The WPPSI was administered to all GA<28 weeks (n=672 with complete assessment; mean: 91.5; SD 18.3)

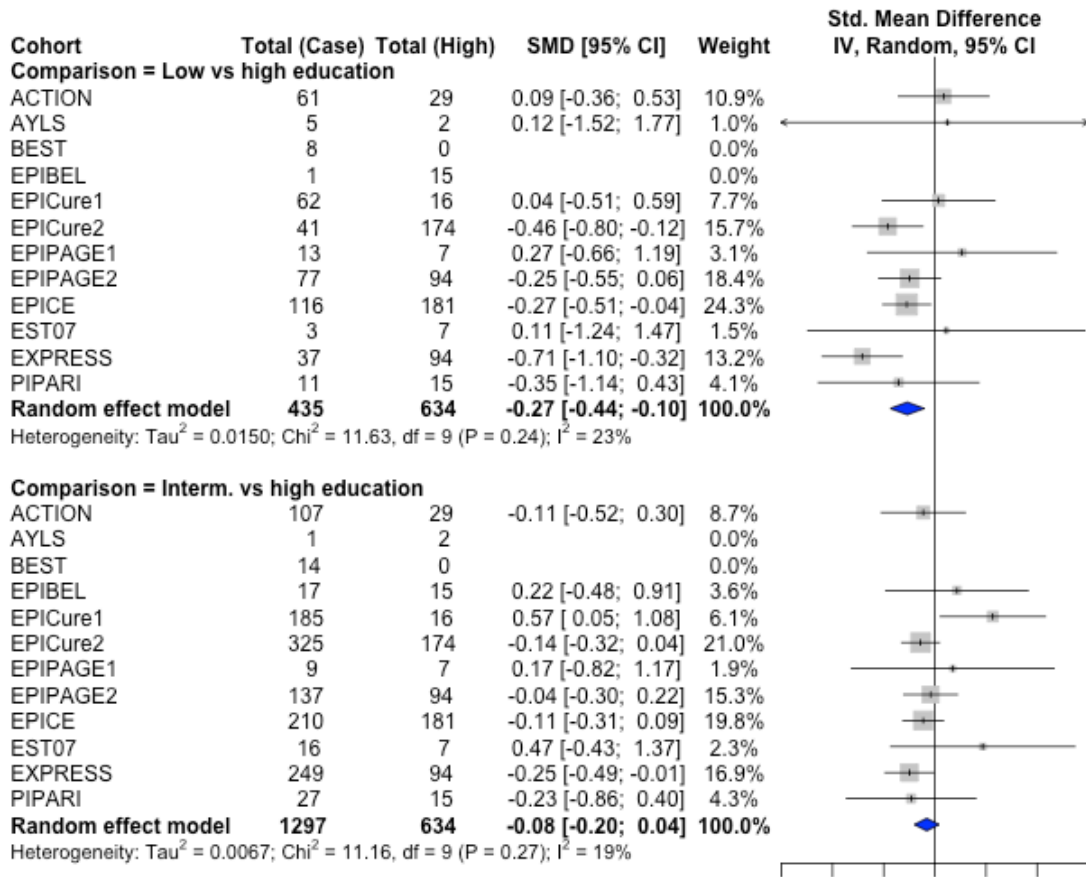
Supplementary Table S4 – Results from sensitivity analysis

Sub-groups	N cohorts	Infancy (2-3 years old)		Early childhood (4-7 years old)	
		Unadjusted SMD (low vs high) (95% CI)	p-value*	Unadjusted SMD (low vs high) (95% CI)	p-value*
Measure of maternal educational level					
At birth	6	-0.31 (-0.46; -0.15)		6	-0.59 (-0.67; -0.51)
At follow-up	5	-0.38 (-0.59; -0.16)	0.5951	6	-0.56 (-0.89; -0.24)
Type of administration					
Parent report	3	-0.20 (-0.27; -0.14)		-	-
Examiner	8	-0.49 (-0.63; -0.34)	0.0004	-	-
Type of test					
Cognitive test	7	-0.36 (-0.53; -0.18)		-	-
Multi-domains test	4	-0.31 (-0.49; -0.13)	0.6891	-	-

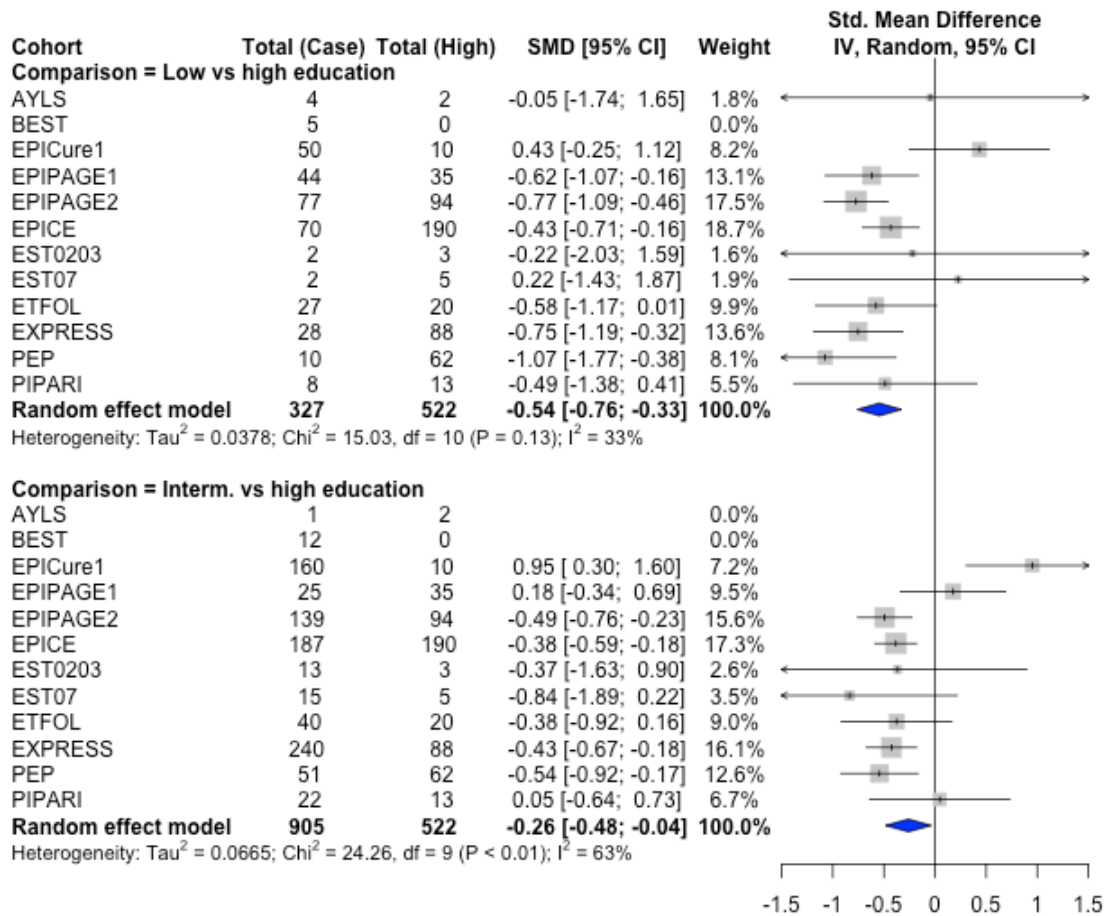
* Test for subgroup differences (random effects model)

Supplementary Figure S1 – Forest plot of standardized mean differences of unadjusted mean IQ scores (SMD and 95% CI) in children born <27 weeks of gestation

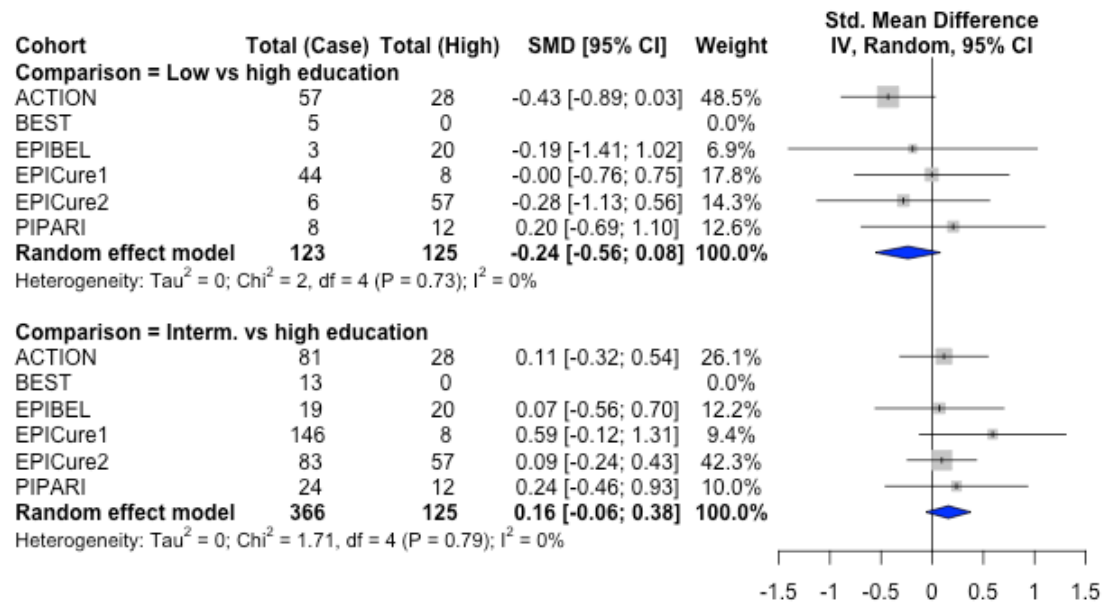
a- Infancy (2-3 years old)



b- Early childhood (4-7 years old)

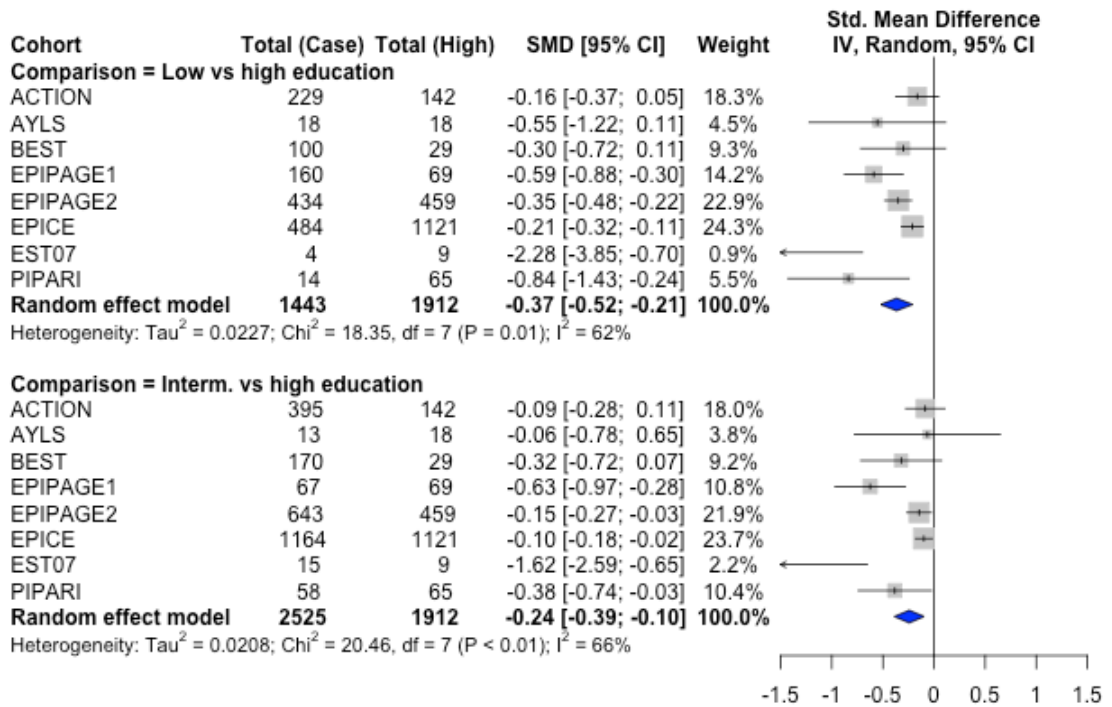


c- Later childhood (8-15 years old)

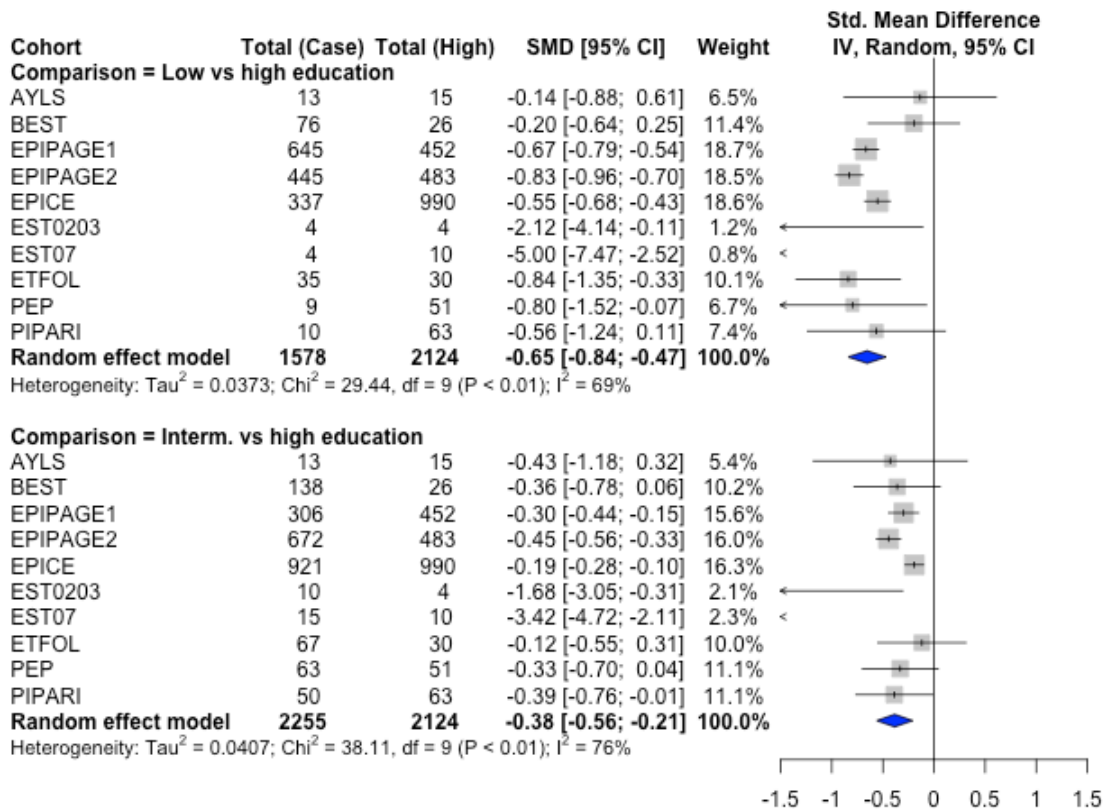


Supplementary Figure S2 – Forest plot of standardized mean differences of unadjusted mean IQ scores (SMD and 95% CI) in children born ≥ 27 weeks of gestation

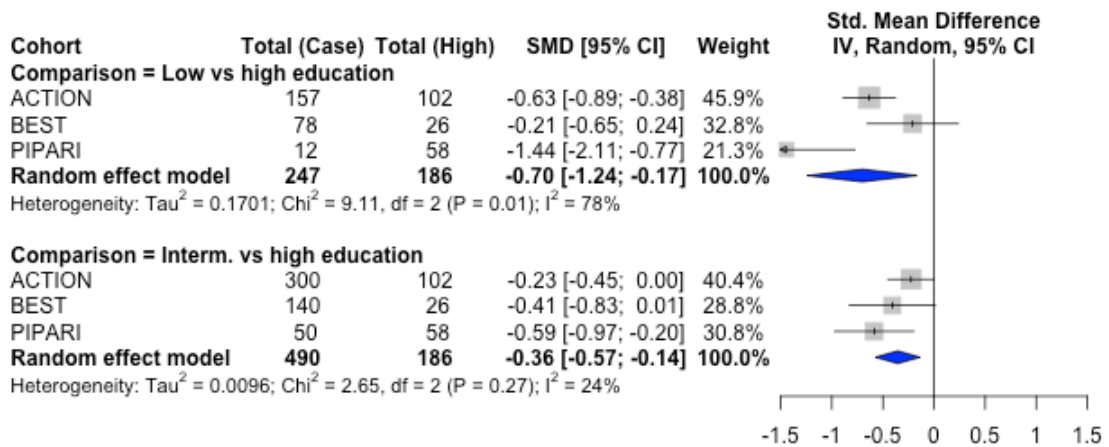
a- Infancy (2-3 years old)



b- Early childhood (4-7 years old)

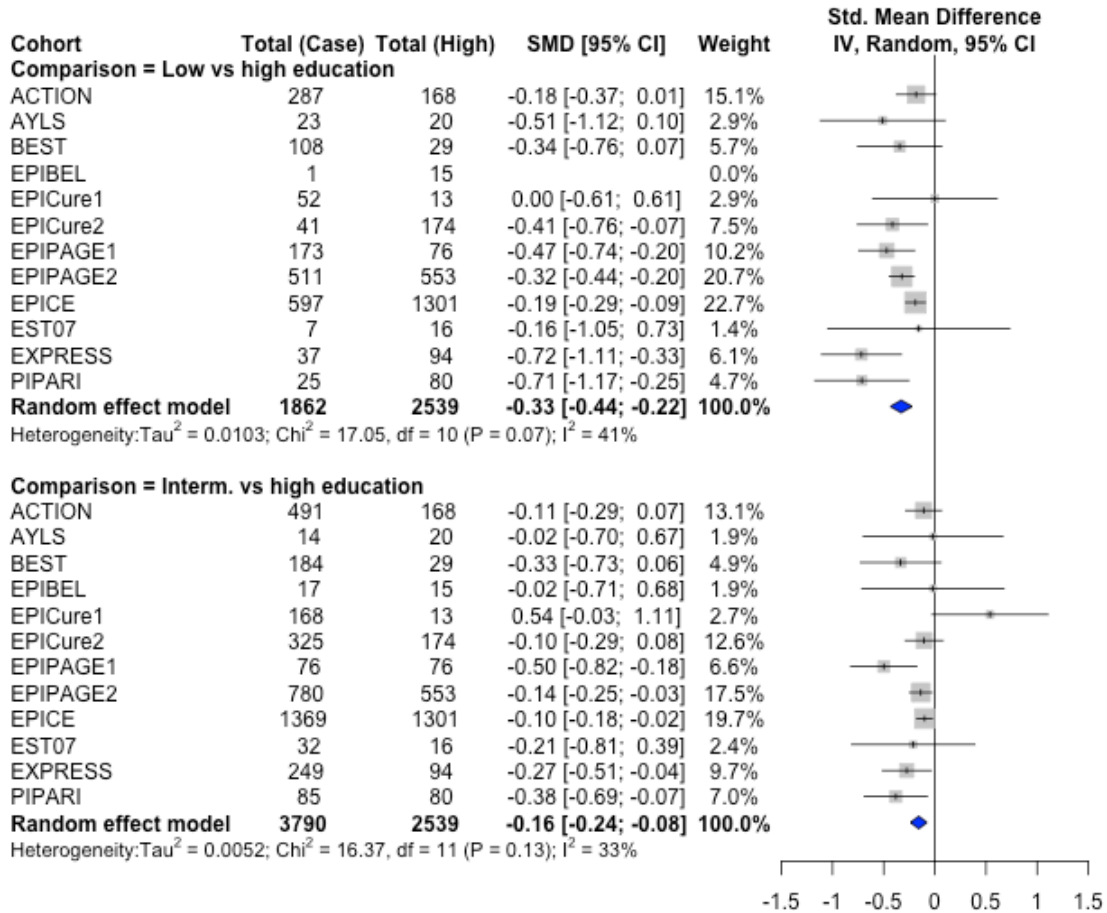


c- Later childhood (8-15 years old)

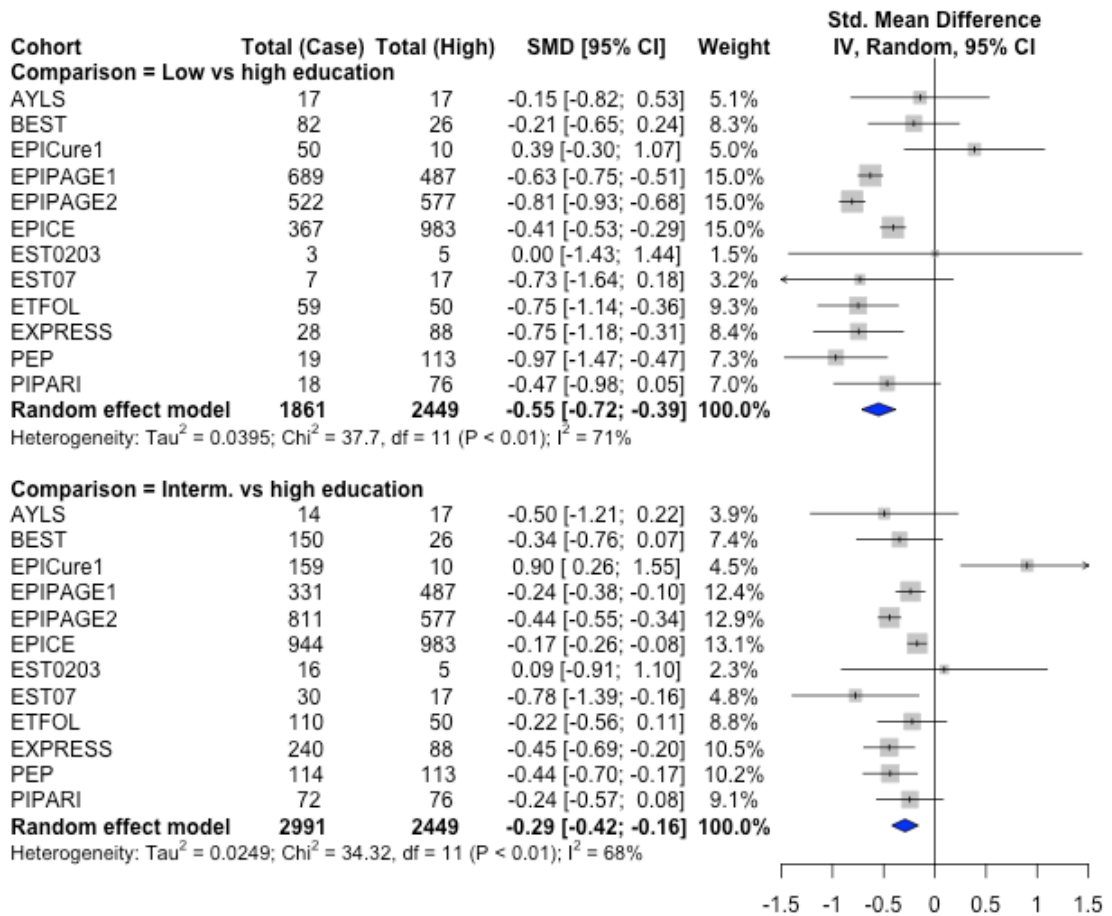


Supplementary Figure S3 – Forest plot of standardized mean differences of adjusted mean IQ scores (SMD and 95% CI) in all VPT children

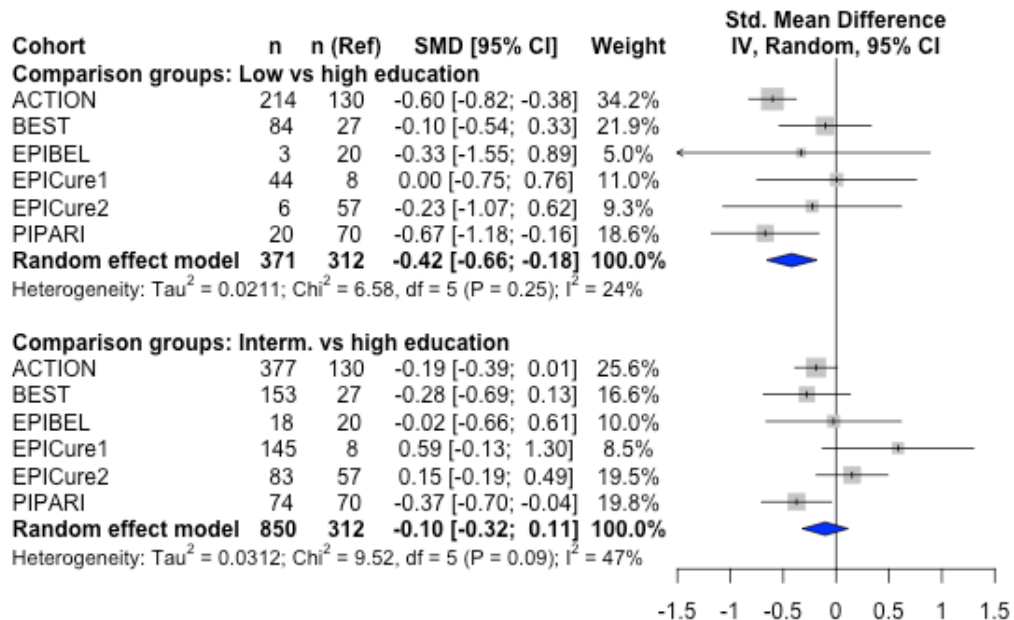
a- Infancy (2-3 years old)



b- Early childhood (4-7 years old)

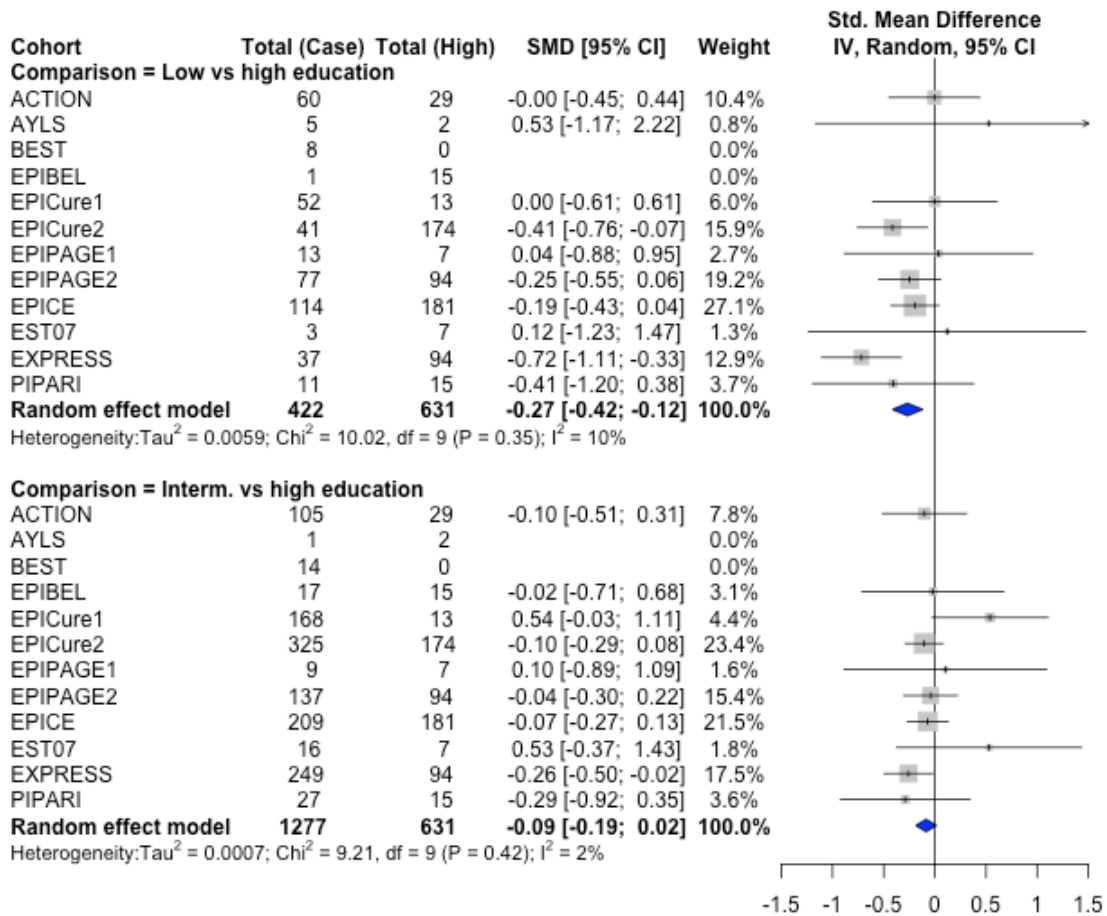


c- Later childhood (8-15 years old)

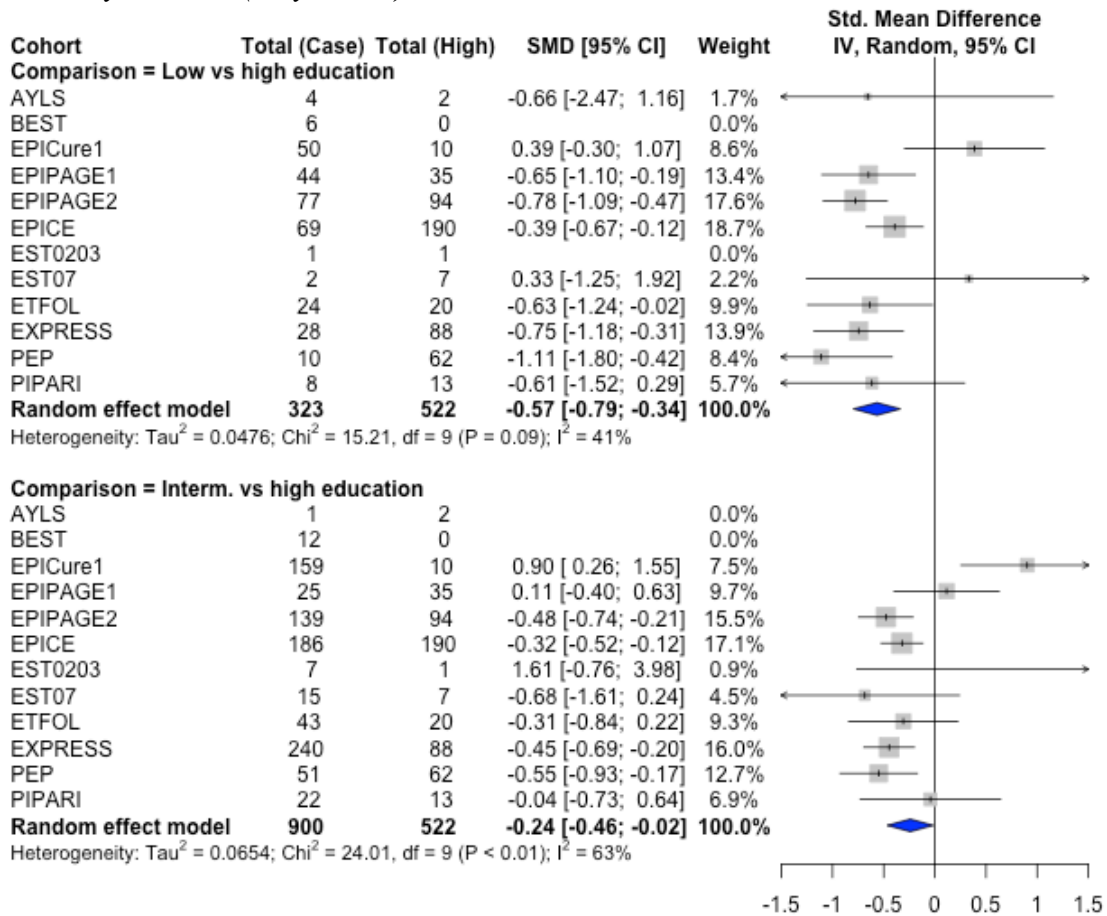


Supplementary Figure S4 – Forest plot of standardized mean differences of adjusted mean IQ scores (SMD and 95% CI) in children born <27 weeks of gestation

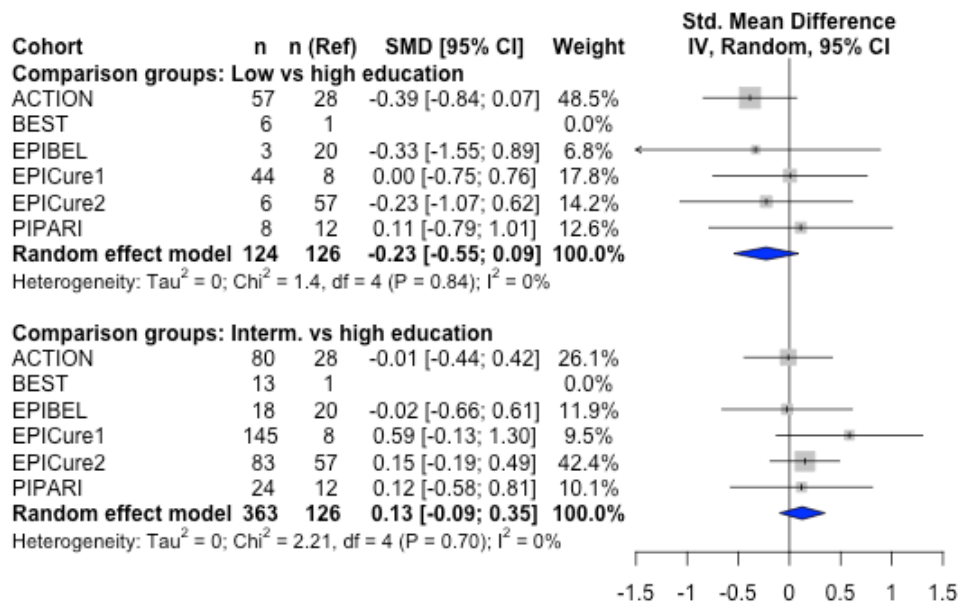
a- Infancy (2-3 years old)



b- Early childhood (4-7 years old)

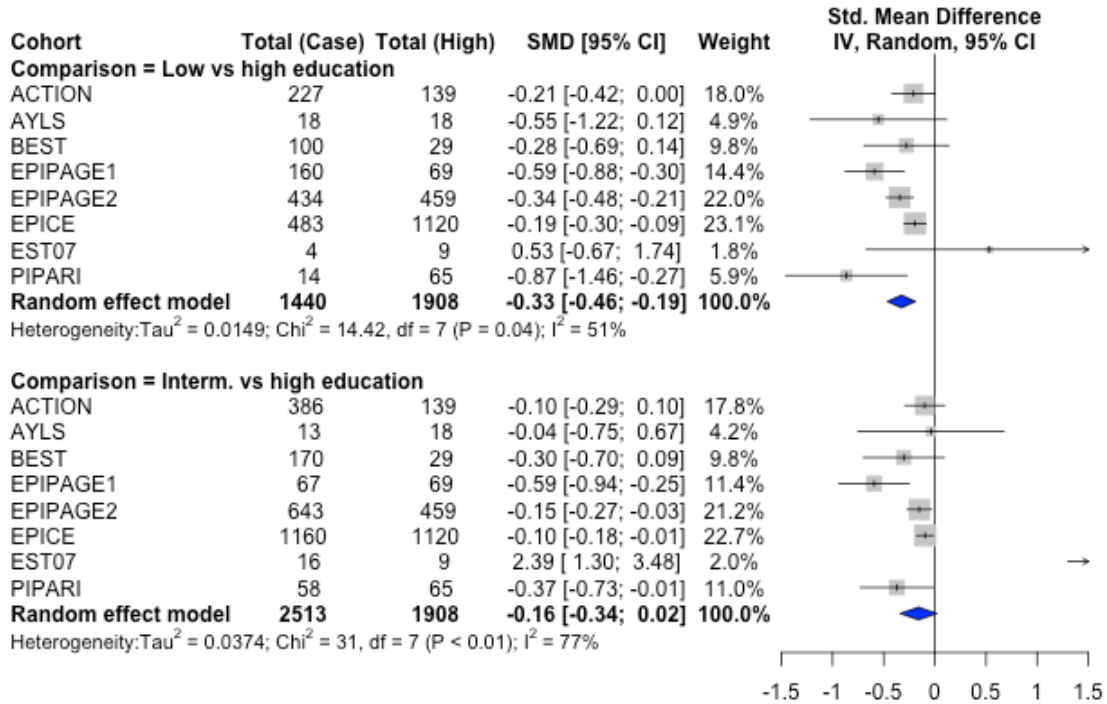


c- Later childhood (8-15 years old)

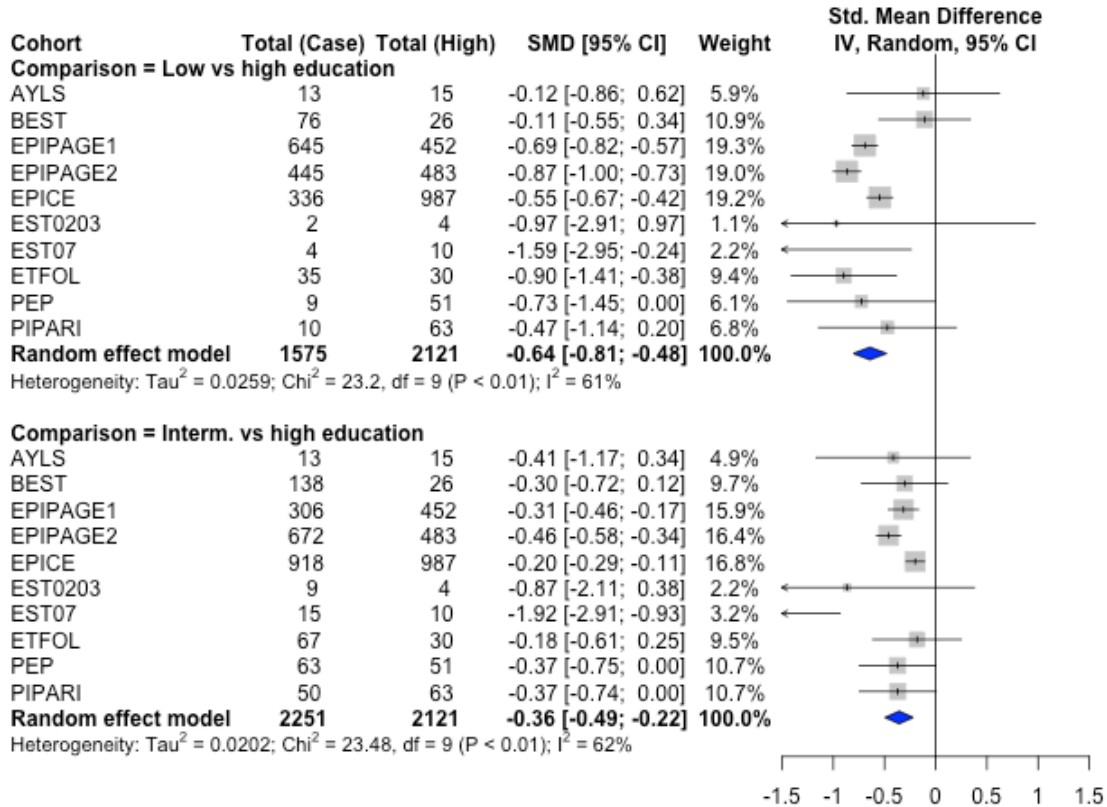


Supplementary Figure S5 – Forest plot of standardized mean differences of adjusted mean IQ scores (SMD and 95% CI) in children born ≥ 27 weeks of gestation

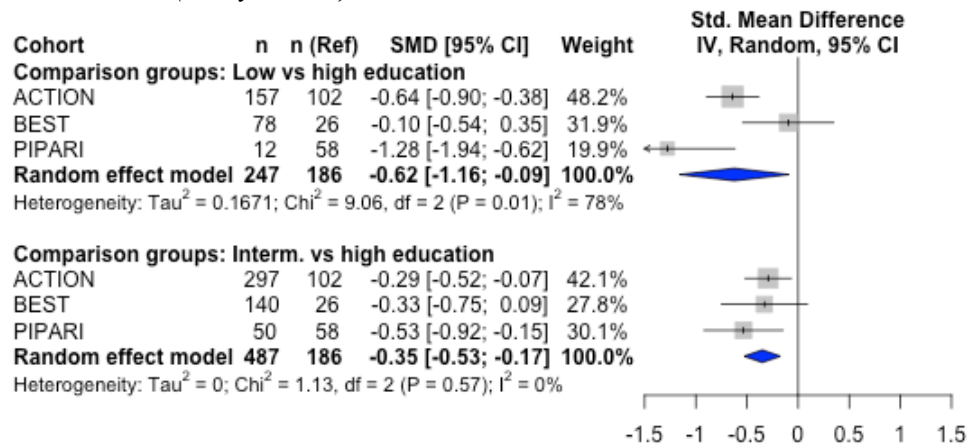
a- Infancy (2-3 years old)



b- Early childhood (4-7 years old)



c- Later childhood (8-15 years old)

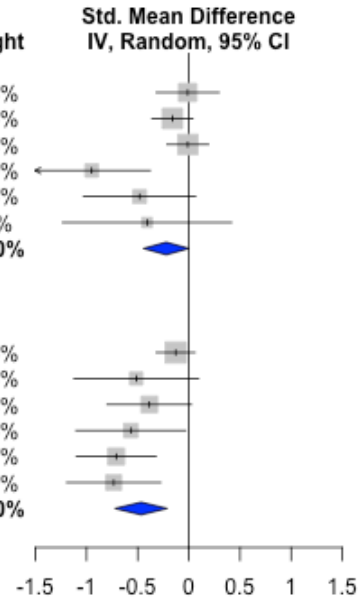


Supplementary Figure S6 – Forest plot of standardized mean differences of unadjusted mean IQ scores (SMD and 95% CI) : VPT vs term controls

a- Infancy (2-3 years old)

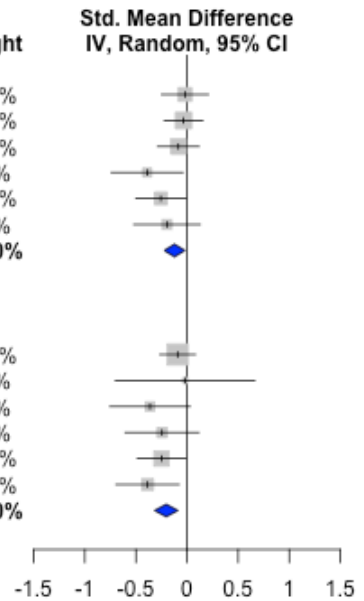
i. Low education level vs high education level

Cohort	Total (Case)	Total (High)	SMD [95% CI]	Weight
Control				
ACTION	63	115	-0.01 [-0.32; 0.30]	20.4%
AYLS	153	259	-0.16 [-0.36; 0.04]	25.5%
BEST	325	129	-0.01 [-0.21; 0.19]	25.4%
EST07	17	51	-0.95 [-1.52; -0.38]	10.9%
EXPRESS	15	95	-0.48 [-1.03; 0.07]	11.5%
PIPARI	6	97	-0.41 [-1.23; 0.42]	6.4%
Random effect model	579	746	-0.22 [-0.44; 0.00]	100.0%
Heterogeneity: Tau ² = 0.0373; Chi ² = 11.83, df = 5 (P = 0.04); I ² = 58%				
All VPT				
ACTION	290	171	-0.13 [-0.32; 0.06]	27.5%
AYLS	23	20	-0.51 [-1.12; 0.10]	10.6%
BEST	108	29	-0.39 [-0.80; 0.03]	16.8%
EST07	20	45	-0.57 [-1.10; -0.03]	12.5%
EXPRESS	37	94	-0.71 [-1.10; -0.32]	17.7%
PIPARI	25	80	-0.73 [-1.20; -0.27]	15.0%
Random effect model	503	439	-0.47 [-0.72; -0.21]	100.0%
Heterogeneity: Tau ² = 0.0549; Chi ² = 12.11, df = 5 (P = 0.03); I ² = 59%				
Test for subgroup differences: Chi ² = 2.05, df = 1 (P = 0.15)				



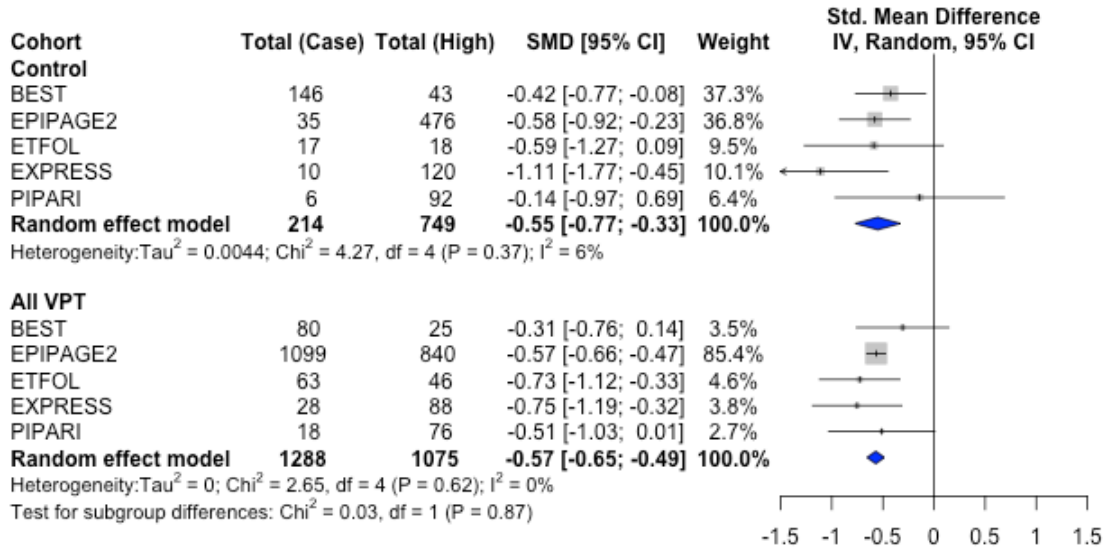
ii. Medium education level vs high education level

Cohort	Total (Case)	Total (High)	SMD [95% CI]	Weight
Control				
ACTION	202	115	-0.02 [-0.25; 0.21]	18.1%
AYLS	184	259	-0.03 [-0.22; 0.15]	26.5%
BEST	335	129	-0.09 [-0.29; 0.12]	22.9%
EST07	84	51	-0.39 [-0.74; -0.04]	7.7%
EXPRESS	202	95	-0.26 [-0.50; -0.01]	15.8%
PIPARI	59	97	-0.20 [-0.52; 0.13]	9.0%
Random effect model	1066	746	-0.12 [-0.22; -0.02]	100.0%
Heterogeneity: Tau ² = 0.0010; Chi ² = 5.32, df = 5 (P = 0.38); I ² = 6%				
All VPT				
ACTION	502	171	-0.09 [-0.27; 0.08]	42.7%
AYLS	14	20	-0.02 [-0.70; 0.66]	2.8%
BEST	184	29	-0.36 [-0.76; 0.03]	8.3%
EST07	88	45	-0.24 [-0.60; 0.12]	9.9%
EXPRESS	249	94	-0.25 [-0.49; -0.01]	22.7%
PIPARI	85	80	-0.39 [-0.69; -0.08]	13.6%
Random effect model	1122	439	-0.20 [-0.32; -0.09]	100.0%
Heterogeneity: Tau ² = 0; Chi ² = 4.04, df = 5 (P = 0.54); I ² = 0%				
Test for subgroup differences: Chi ² = 1.09, df = 1 (P = 0.30)				

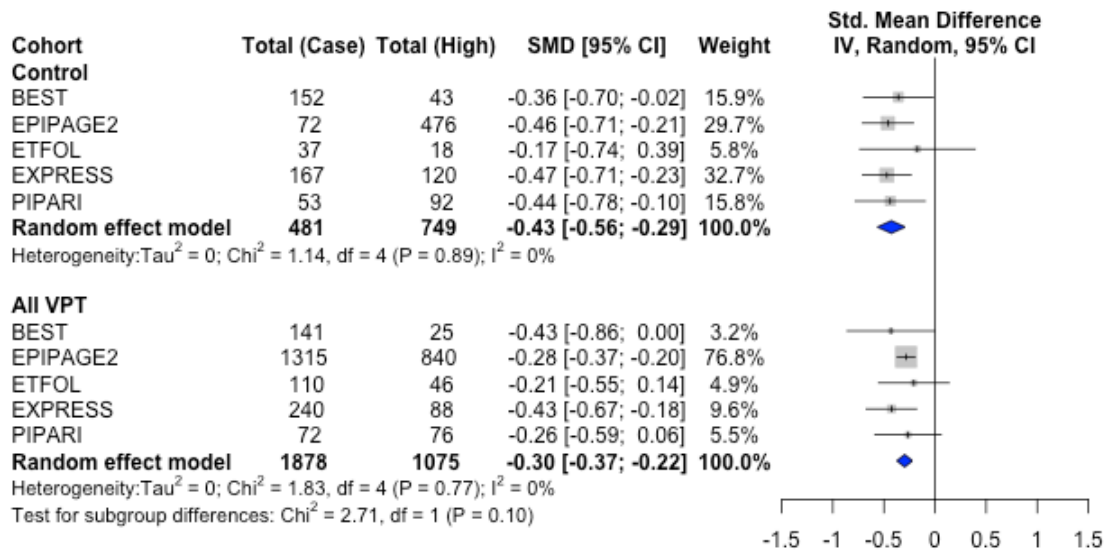


b- Early childhood (4-7 years old)

i. Low education level vs high education level

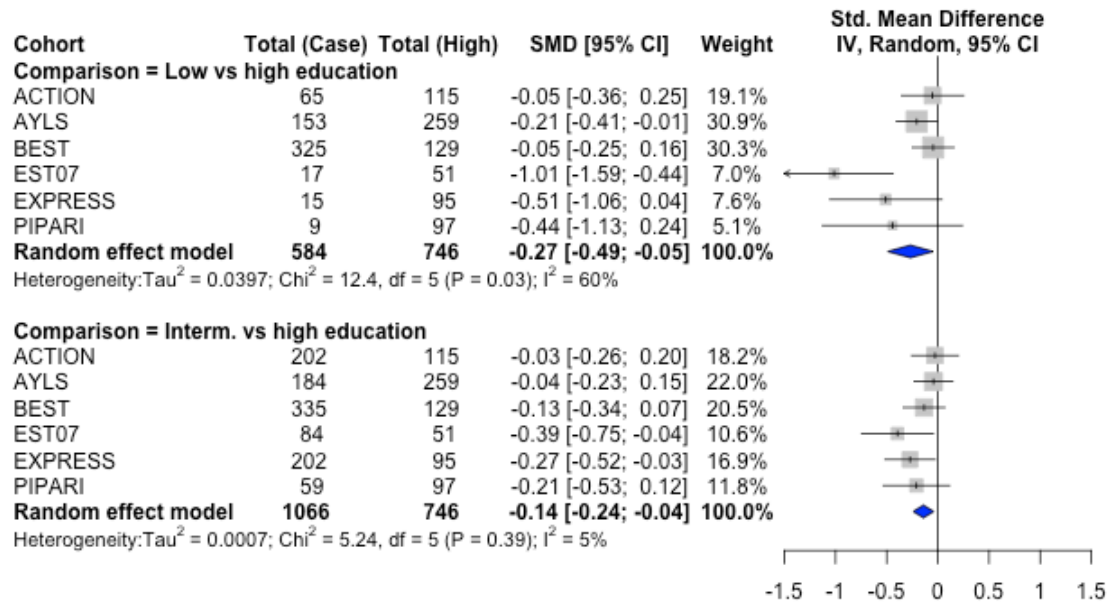


ii. Medium education level vs high education level

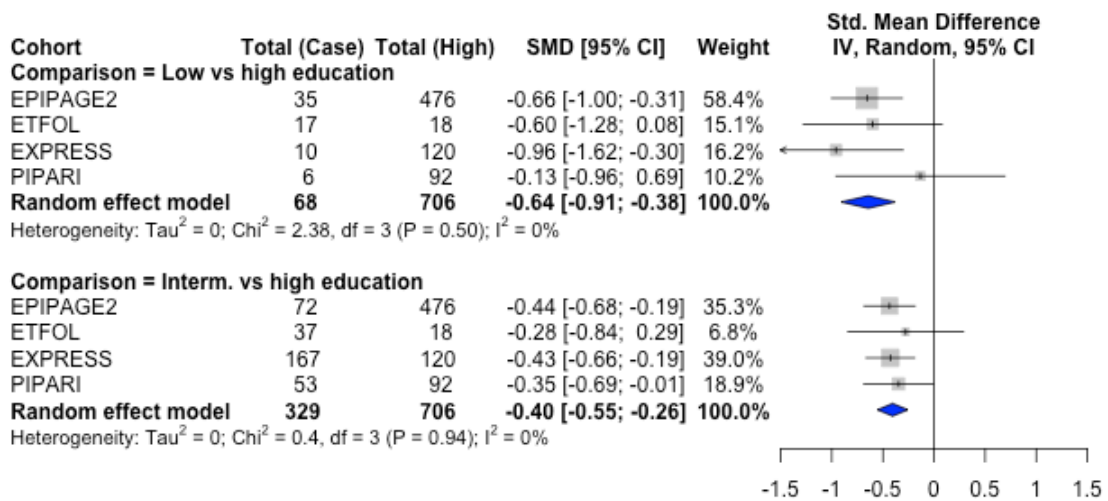


Supplementary Figure S7 – Forest plot of standardized mean differences of adjusted mean IQ scores (SMD and 95% CI) in term controls

a- Infancy (2-3 years old)



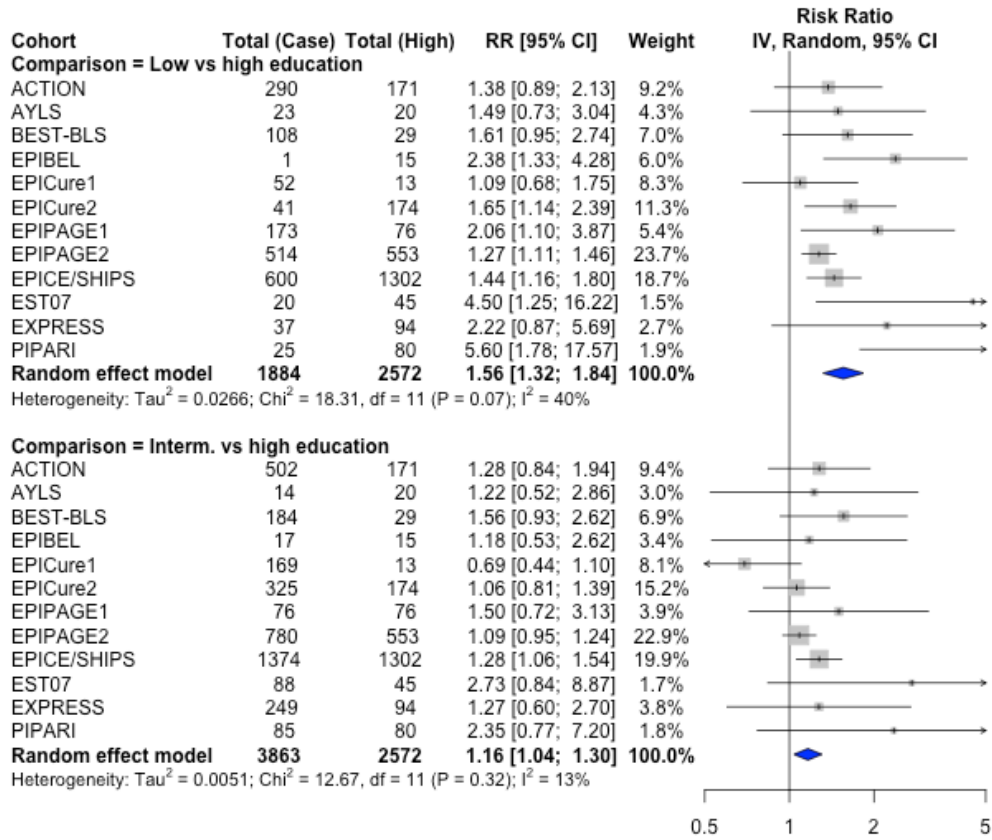
b- Early childhood (4-7 years old)



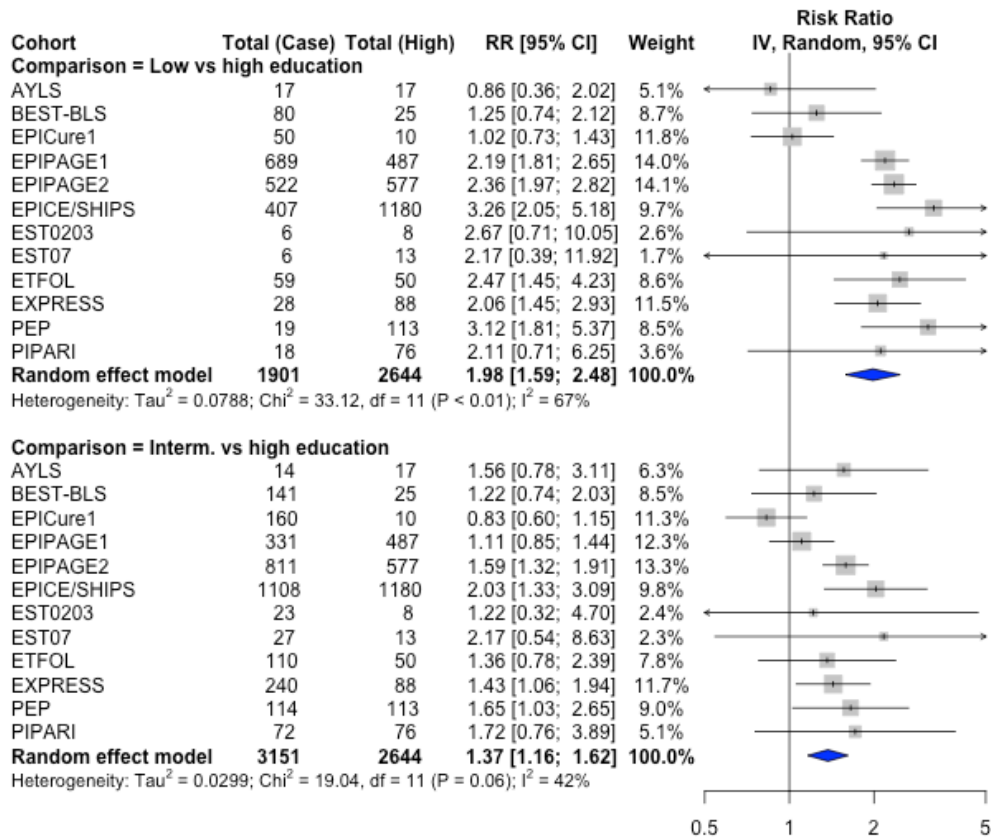
Note: estimates were unadjusted in EPIPAGE2

Supplementary Figure 8 – Forest plot of Relative Risk for cognitive deficit by maternal educational group (and 95% CI) in all VPT children

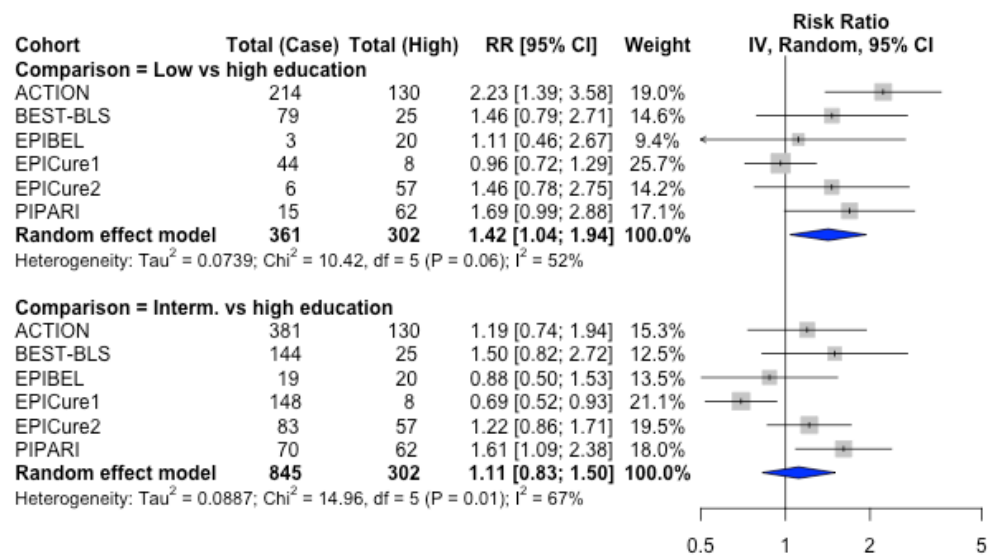
a- Infancy (2-3 years old)



b- Early childhood (4-7 years old)

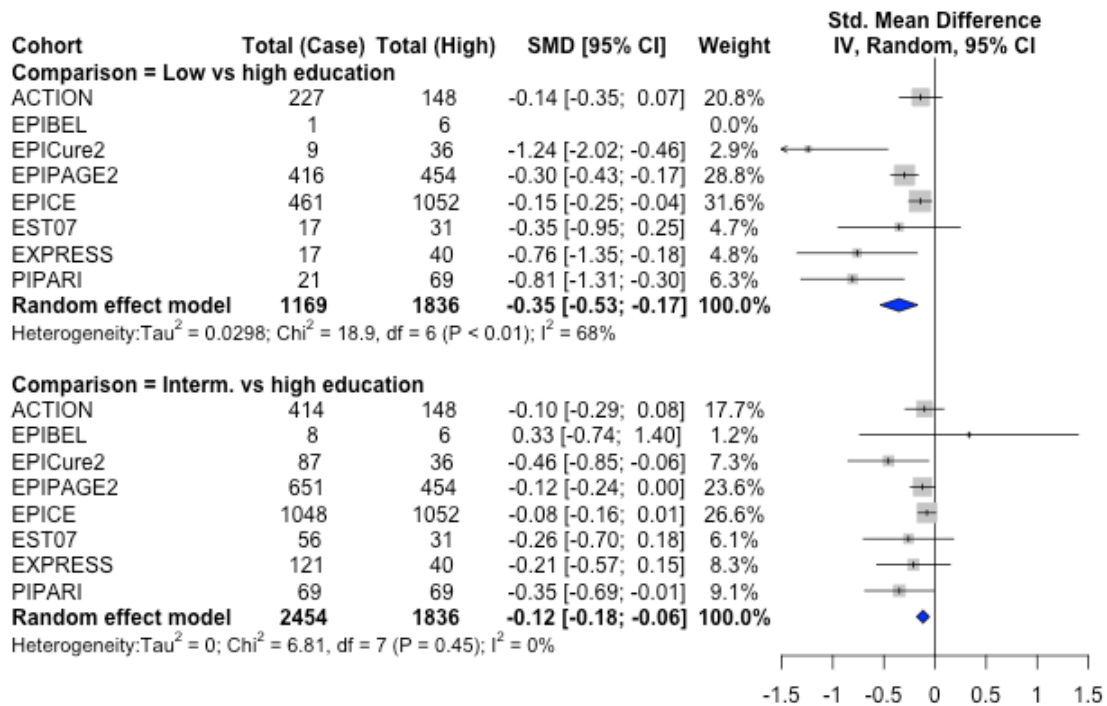


c- Later childhood (8-15 years old)

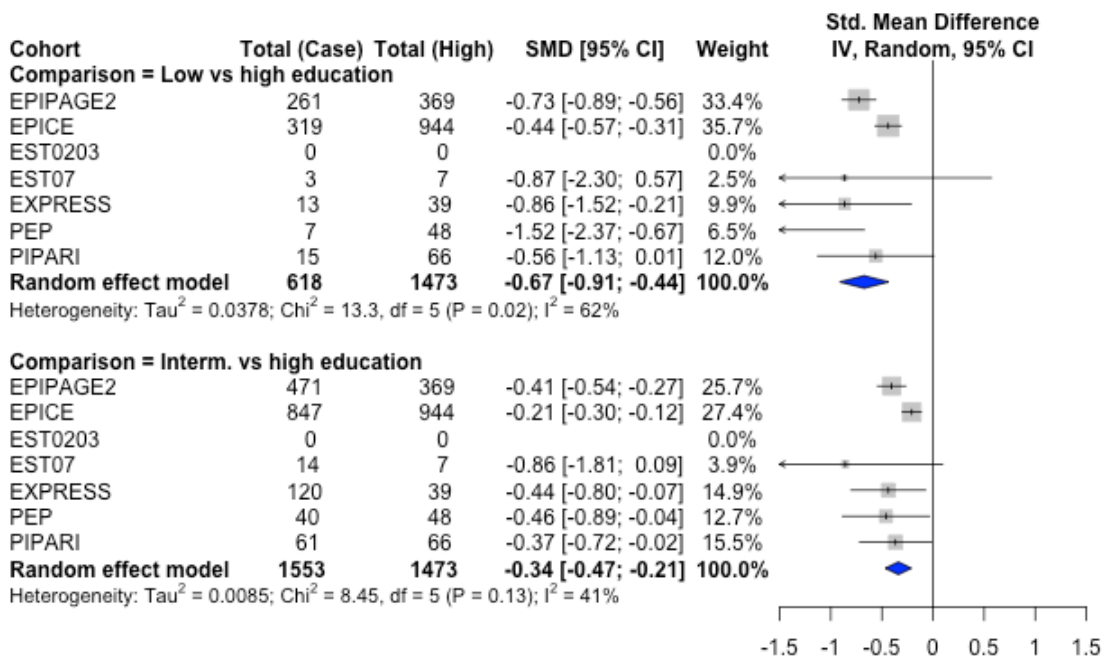


Supplementary Figure S9 – Forest plot of standardized mean differences of unadjusted mean IQ scores (SMD and 95% CI) in children without neonatal morbidities

a- Infancy (2-3 years old)

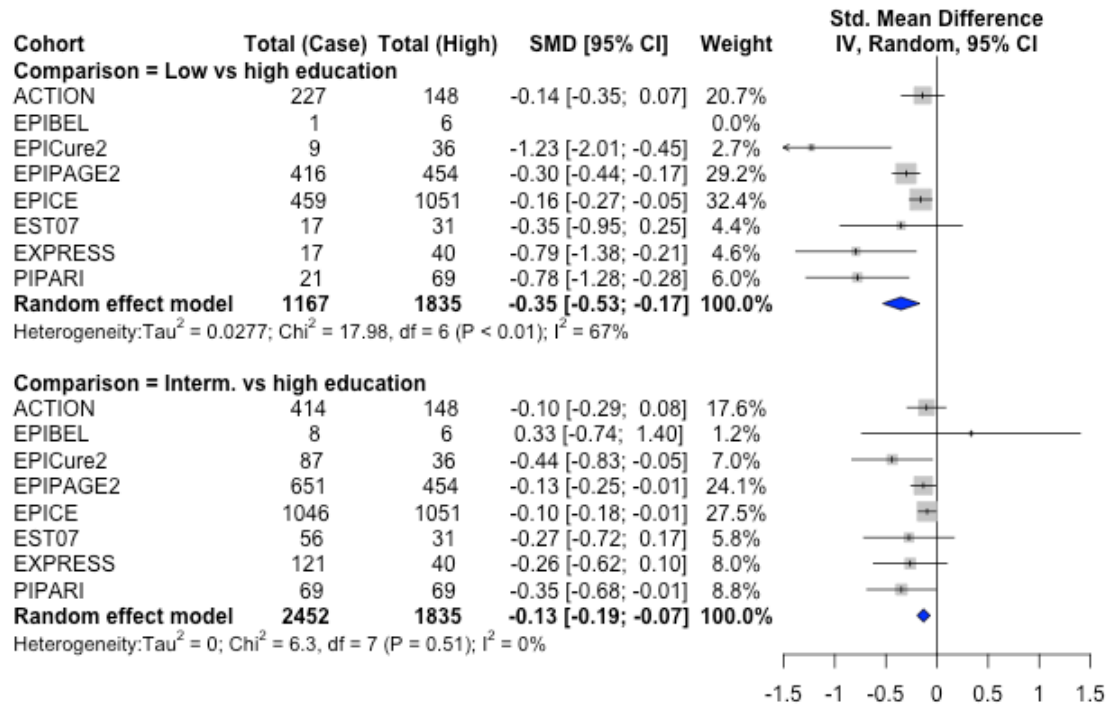


b- Early childhood (4-7 years old)

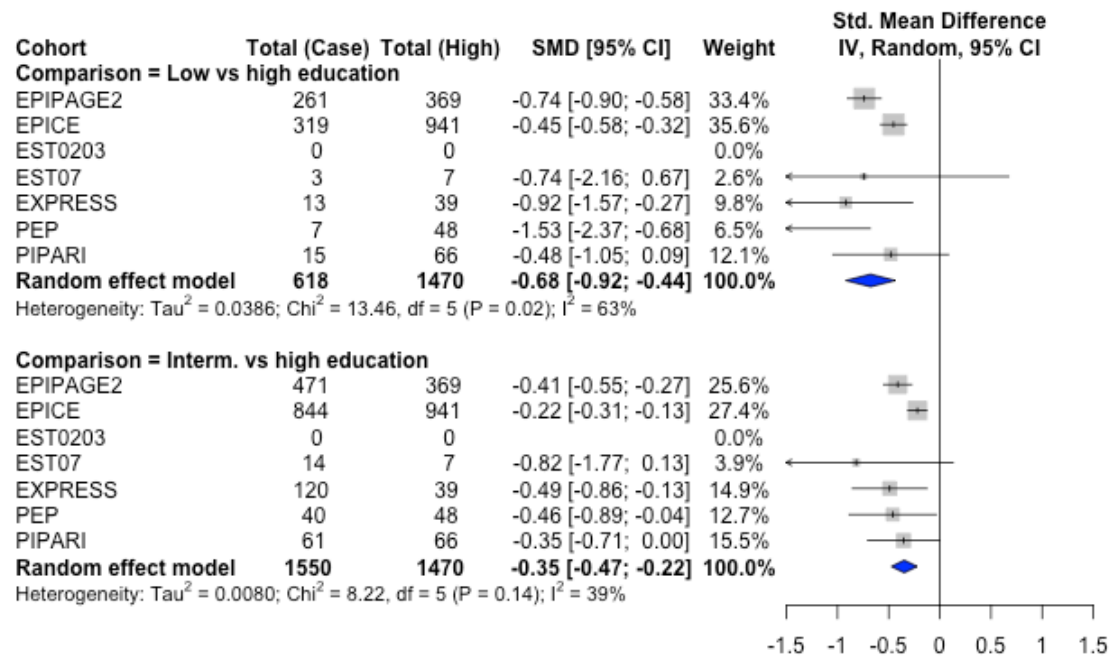


Supplementary Figure S10 – Forest plot of standardized mean differences of adjusted mean IQ scores (SMD and 95% CI) in children without neonatal morbidities

a- Infancy (2-3 years old)

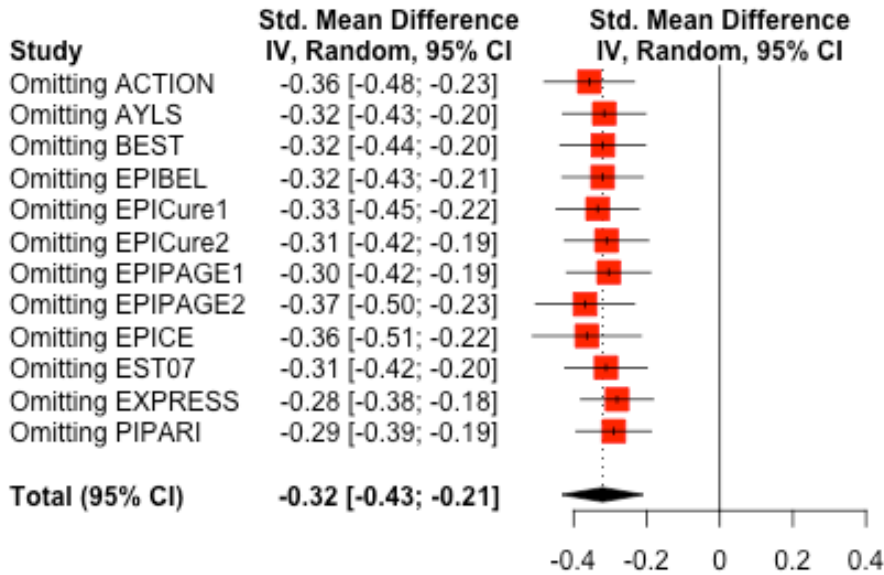


b- Early childhood (4-7 years old)



Supplementary Figure S11 – Forest plots of the results of the leave-one-out sensitivity analysis (standardized mean differences of unadjusted mean IQ scores) applied when meta-analyses with high heterogeneity ($I^2 > 50\%$)

a- Unadjusted SMDs in all VPT children in infancy (2-3 years old) ; comparison groups : low education vs high education



b- Unadjusted SMDs in all VPT children in early childhood (4-7 years old); comparison groups : medium education vs high education

