Association of Very Preterm Birth or Very Low Birth Weight With Intelligence in Adulthood: An Individual Participant Data Meta-analysis

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Importance Birth before 32 weeks' gestation (very preterm [VPT]) and birth weight below 1500 g (very low birth weight [VLBW]) have been associated with lower cognitive performance in childhood. However, there are few investigations of the association of neonatal morbidities and maternal educational levels with the adult cognitive performance of individuals born VPT or VLBW (VPT/VLBW).

Objective To assess differences in adult IQ between VPT/VLBW and term-born individuals and to examine the association of adult IQ with cohort factors, neonatal morbidities, and maternal educational level among VPT/VLBW participants.

Data Sources Systematic review of published data from PubMed and meta-analysis of individual participant data (IPD) of cohorts from 2 consortia (Research on European Children and Adults Born Preterm [RECAP] and Adults Born Preterm International Collaboration [APIC]).

Study Selection The meta-analysis included prospective longitudinal cohort studies that assessed the full-scale IQ of adults born VPT or VLBW and respective control groups comprising term-born adults.

Data Extraction And Synthesis The study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline for analyses of individual participant data and identified 8 studies that provided data from 2135 adults (1068 VPT/VLBW and 1067 term-born participants) born between 1978 and 1995. Meta-analyses of IPD were performed using a 1-stage approach, treating VPT birth or VLBW and cohort as random effects.

Main Outcomes And Measures Full-scale IQ scores were converted to z scores within each cohort using the combined SD of VPT/VLBW participants and a control group of term-born participants, with scores centered on the mean of the control group.

Results A total of 426 records were identified and screened. After exclusions, 13 studies were included in the aggregate meta-analysis. The IPD meta-analysis included 8 of the 9 RECAP and APIC cohorts with adult IQ data. The mean (SD) age among the 8 IPD cohorts was 24.6 (4.3) years, and 1163 participants (54.5%) were women. In unadjusted analyses,

VPT/VLBW participants had mean adult IQ scores that were 0.78 SD (95% CI, −0.90 to −0.66 SD) lower than term-born participants, equivalent to a difference of 12 IQ points. Among VPT/VLBW participants, lower gestational age (score difference per week of gestation, 0.11; 95% CI, 0.07-0.14), lower birth weight z scores (score difference per 1.0 SD, 0.21; 95% CI, 0.14-0.28), the presence of neonatal bronchopulmonary dysplasia (score difference, −0.16; 95% CI, −0.30 to −0.02) or any grade of intraventricular hemorrhage (score difference, −0.19; 95% CI, −0.33 to −0.05), and lower maternal educational level (score difference, 0.26; 95% CI, 0.17-0.35) were all significantly associated with lower IQ scores in adulthood.

Conclusions And Relevance In this IPD meta-analysis, lower gestational age, lower weight for gestational age, neonatal morbidities, and lower maternal educational levels were all important risk factors associated with lower IQ among young adults born VPT or VLBW.

Key Points

Question Is very preterm birth or very low birth weight vs term birth associated with intelligence in adulthood?

Findings In this meta-analysis of individual participant data from 8 cohorts comprising 2135 adults with and without very preterm birth or very low birth weight in 7 countries, IQ was significantly lower among adults who were born very preterm or with very low birth weight compared with adults who were born at term, with a mean between-group difference of approximately 12 IQ points. Lower gestational age, lower birth weight z scores, the presence of neonatal bronchopulmonary dysplasia or intraventricular hemorrhage, and lower maternal educational levels were significantly associated with lower IQ among adults born very preterm or with very low birth weight.

Meaning This individual patient data meta-analysis suggests that very preterm birth or very low birth weight may be associated with a clinically relevant difference in IQ, relative to term birth, in adulthood.

Introduction

An important life outcome after very preterm (VPT) birth (<32 weeks' gestation) or very low birth weight (VLBW; <1500 g) is intelligence, defined as "the capacity to learn from experience, using metacognitive processes to enhance learning and adapt to the surrounding environment."[1(p751)] Standardized intelligence tests in the general population provide an IQ score with a normative mean (SD) of 100 (15) points. An individual's IQ is associated with a range of life course outcomes, including physical health, premature death, educational attainment, and socioeconomic success.[2-5] Thus, adult IQ is a global factor associated with long-term outcomes among individuals born VPT or VLBW (VPT/VLBW).

While individual studies typically indicate that VPT/ VLBW individuals have lower IQ in adulthood than term-born individuals,[6-8] to our knowledge, no specific meta-analysis of adult IQ among VPT/VLBW individuals has been published. Meta-analyses of childhood IQ have reported that the scores of VPT/VLBW children are approximately 11 to 13 IQ points lower on tests than term-born children.[9-12] Sustained differences into adulthood cannot be assumed, as indicated by the smaller IQ differences in adulthood that have been reported among individuals with normal vs lowbirthweight.[13] Furthermore, considerable variation across VPT/VLBW cohorts has been found, which is potentially explained by factors such as gestational age or birth weight inclusion criteria and later selective attrition.[11] Variation in IQ may be associated with individual-level neonatal or demographic factors, such as sex, low birth weight for gestational age, neonatal morbidities, or maternal educational level.[14-17]

To investigate cohort- and individual-level factors, meta-analyses of individual participant data (IPD) have been proposed as superior to traditional meta-analyses of aggregated data.[18] Meta-analysis of IPD allows for accurate harmonization of data across cohorts and increased

statistical power for detecting individual-level risk factors.[19] Furthermore, the associations of cohort-specific factors, such as rates of attrition, can be investigated.

We performed an IPD meta-analysis of IQ in adulthood with 3 objectives. The first was to compare the difference in adult IQ among VPT/VLBW participants vs a control group of term-born participants, the second was to examine cohort-and individual-level factors associated with adult IQ among VPT/VLBW participants, and the third was to conduct a sensitivity analysis assessing whether adult IQ scores from the IPD cohorts were representative of all cohorts of VPT/VLBW individuals.

Methods

Protocol and Registration

This study was conducted as part of the Research on European Children and Adults Born Preterm (RECAP) Consortium.[20] Along with 7 adult RECAP cohorts, 6 non-European cohorts from the Adults Born Preterm International Collaboration (APIC) Consortium[21] were invited to participate. All studies had received country-specific ethical reviews, with participants providing written informed consent, and all adhered to the Declaration of Helsinki.[22] This IPD meta-analysis was registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42020162043) and followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline for analyses of individual participant data.

Eligibility Criteria and Search Strategy

Prospective longitudinal cohort studies of VPT/VLBW adult participants who had completed a standardized IQ test at a mean age of 17 years or older were eligible for inclusion. All cohort studies were required to include a control group of term-born participants to allow for

computation of harmonized and comparable IQ z scores, which minimized bias owing to different versions of tests or secular trends (ie, the Flynn effect).[23]

To assess whether the cohorts from RECAP and APIC were representative of all VPT/VLBW participants reported in the literature, we performed a PubMed search using the search string (intelligence OR IQ OR cognition OR cognitive) AND (adult OR adulthood OR late adolescence) AND (preterm OR gestation OR birthweight OR birth weight). The last search was performed on July 9, 2020.

Study Selection, Data Collection, and Data Harmonization

Eligibility for inclusion was assessed by 2 authors (R.E. and Y.N.). Any disagreements regarding eligibility were resolved by discussion. After initial data scoping, encrypted data from each cohort were transferred to the University of Warwick. Data including IQ scores, neonatal variables, maternal educational levels, the presence of neurosensory impairment (NSI) in childhood, and attrition rates were collected for all cohorts. All data were only accessible to authorized personnel from the RECAP Consortium.

To harmonize results, IQ scores were converted to z scores within each cohort using the combined SD of both groups (VPT/ VLBW and control), with scores centered on the mean of the control group. Neonatal data included gestational age at birth, sex, birth weight, presence of bronchopulmonary dysplasia (BPD), presence of intraventricular haemorrhage (IVH), and multiple birth. The definitions of BPD varied, with some studies defining BPD as oxygen dependency at 36 weeks' postmenstrual age and some defining it as oxygen dependency more than 28 days after birth. For each definition, separate sub-analyses were performed to assess each criterion's independent association with IQ. The definition of IVH was classified according to criteria provided by Papile et al[24] (ie, IVH is categorized from grades 1-4, with 1 indicating haemorrhage limited to germinal matrix, 2 indicating blood noted within the

ventricular system but not distending it, 3 indicating blood in the ventricles with distension of the ventricles, and 4 indicating intraventricular haemorrhage with parenchymal extension); however, some cohorts provided either IVH grades 3 and 4 or IVH grades 2 and 3 combined. Thus, IVH was harmonized into no IVH vs any IVH (grades 1-4), and a sub analysis was performed to compare no IVH or IVH grades 1 to 2 with IVH grades 3 to 4 among cohorts for which analysis was possible. Multiple birth was classified as a binary variable, with 0 indicating singleton birth and 1 indicating multiple birth. Birth weight z scores were determined using the Fenton inter-national growth chart for preterm infants.[25]

Maternal educational level was harmonized according to the International Standard Classification of Education (ISCED) into low (ISCED levels 0-2), medium (ISCED levels 3-5), and high (ISCED levels 6-8).[26] Evidence of childhood NSI was collated from data indicating severe visual impairment (blind in both eyes), hearing impairment (uncorrected by assistive devices), non-ambulatory cerebral palsy, or childhood cognitive impairment (IQ <70 points). If data regarding a certain NSI variable were missing for a participant, the individual was categorized as having no evidence of the presence of that impairment. Data indicating the presence of NSI were combined into a binary childhood NSI variable (any evidence of impairment vs no evidence of impairment) (eTable 1 in the Supplement). In addition, 4 cohort-level factors were assessed. For each cohort, the percentage of eligible VPT/ VLBW participants who did not have adult IQ scores was calculated (ie, the percentage of attrition among VPT/VLBW participants). To focus on selective attrition, the percentage of VPT/VLBW participants with diagnoses of childhood NSI who did not have adult IQ scores was also calculated (ie, the percentage of attrition among VPT/VLBW participants with childhood NSI). Data on year of birth and mean age at assessment among VPT/VLBW participants in each cohort were also recorded.

IPD Integrity, Risk of Bias, and Outcome Measures

Data were assessed for consistency with previous studies of the included cohorts, with any discrepancies resolved by communication with the respective study investigators. Two authors (R.E. and Y.N.) assessed cohort quality and comparability using the Newcastle-OttawaScale[27] (score range of 0-9, with higher scores indicating higher quality) (eTable 2 in the Supplement). The primary outcome of interest was the full-scale IQ z score of VPT/VLBW participants compared with term-born participants.

All participants with adult IQ scores were included. Missing neonatal data were imputed solely for VPT/VLBW participants, and missing data on maternal educational levels were imputed for both VPT/VLBW and term-born participants using multiple imputation by chained equations (mice),[28] which resulted in less than 5% of the data being imputed (Table 1).[7,8,29-34] In the first analysis, a simple comparison of IQ scores between VPT/ VLBW and term-born participants was conducted using a1-stage linear mixed model. We analysed the association of VPT birth or VLBW with IQ using a random-intercept model for each cohort and a random slope for the association of VPT birth or VLBW with IQ by cohort, which was estimated using maximum likelihood via the lme4 package, version 1.1-21, in R software, version 3.6.1 (R Foundation for Statistical Computing).[35] The association between VPT birth or VLBW and IQ was then examined after adjusting for sex and maternal educational level and after removing VPT/VLBW participants with childhood NSI or differentiating between VPT/VLBW participants with and without neonatal morbidities (ie, IVH and BPD). All analyses used a 1-stage approach with random intercepts and slopes.

Additional Analyses

To explore antecedents of IQ scores among VPT/VLBW participants, a 1-stage IPD analysis was performed. Cohort factors (age at IQ assessment, birth year, percentage of attrition

among VPT/VLBW participants, and percentage of attrition among VPT/VLBW participants with childhood NSI) were added as fixed effects. Individual-level neonatal factors and maternal educational levels were then also added as fixed effects. Beta estimates from all factors were reported for both the univariable and multivariable analyses to assess their independent and combined associations. Statistical significance was set at $P < .05$.

A sensitivity meta-analysis using aggregate data was performed by combining all cohorts used in the IPD analyses, summary data from the Hack study,6 and additional cohorts identified through the PubMed search for whom IPD were not requested. The standardized mean difference (SMD) in IQ scores between VPT/VLBW and term-born participants in each cohort were pooled using a random-effects meta-analysis via the meta package, version 4.9-7, in R software.[36] Heterogeneity across cohorts was assessed using Cochran Q and I2 statistics, and a subgroup analysis was performed to differentiate between IPD and non-IPD cohorts to test for selection bias.

Results

Study Selection and Participant Characteristics

A total of 426 records were identified and screened; of those, 413 records were identified through a PubMed search, and 13 records were known studies conducted by the RECAP and APIC consortia. Overall, 342 records were excluded based on titles and abstracts, and 84 full-text articles were assessed for eligibility (Figure 1). Of 7 potential RECAP cohort studies of adults,[7,8,29-31,37,38] 2 were excluded: the Suikkanen et al study,[37] which did not perform a full-scale IQ test, and the Weisglas-Kuperus et al study,[38] which did not include a control group. Among 6 potential APIC cohort studies,[6,32-34,39,40] 3 were excluded: the Saigal et al[39] and Doyle et al[40] studies, which did not assess adult IQ, and the Hack study,[6] for which only summary data were available. After exclusions, 13 studies (9 RECAP or APIC cohorts and 4

cohorts identified through PubMed) were included in the aggregate meta-analysis. The IPD meta-analysis included 8[7,8,29-34] of the 9 RECAP and APIC cohorts with adult IQ data, comprising a total of 2135 adults (1068 VPT/VLBW participants and 1067 term-born participants). The mean (SD) age among the 8 IPD cohorts was 24.6(4.3) years, and 1163 participants (54.5%) were women. Summary data for each cohort included in the IPD analyses are shown in Table 1.

The 8 IPD cohorts were from 7 high-income countries (Australia,[34] Finland,[29,30] Germany,[8] Ireland,[7] New Zealand,[32] Norway,[31] and the United Kingdom[7,33]); 6 of the studies were regional,[8,29-31,33,34] and 2 were national.[7,32] The mean (SD) gestational age at birth was 28.3 (2.8) weeks among VPT/VLBW participants and (mean [SD] gestational age was not available for term-born participants because some participants were recruited in childhood or adulthood), and birth years ranged from 1978 to 1995. The mean (SD) age at IQ assessment was 24.4(4.6) years among VPT/VLBW participants and 24.8 (4.3) years among term-born participants. Among VPT/VLBW participants, more recent birth year (post-1978) was associated with lower gestational age (difference per year, −0.32 weeks; 95% CI, −0.60 to −0.04 weeks) and lower birth weight (difference, −29.85 g; 95% CI, −58.78 to −0.91 g) (eTable 3 and eTable 4 in the Supplement). In total, 557 VPT/VLBW participants (52.2%) and 606 term-born participants (56.8%) were women (eTable 5 and eTable 6 in the Supplement).

Integrity and Risk of Bias

Based on the Newcastle-Ottawa Scale27 (eTable 2 in the Supplement), the mean (SD) study quality score was 7.9 (0.6), and studies were rated highly with regard to representativeness, ascertainment of exposure, and assessment of outcomes. However, studies differed in

inclusion criteria and attrition rates among VPT/VLBW participants, which were higher than 50% in 4[7,8,29,30] of 8 cohorts (Table 1).

Results of Syntheses

IPD Meta-analysis of All Participants

The analysis of all participants from IPD cohorts[7,8,29-34] indicated that mean IQ z scores among VPT/VLBW participants were 0.78 SD (95% CI, −0.90 to −0.66 SD) lower than those of term-born participants. When sex and maternal educational level were included, the estimate of the association of VPT birth or VLBW with IQ scores was minimally reduced, from a difference of −0.78 SD to a difference of −0.74 SD (95% CI, −0.85 to −0.63 SD). Excluding participants with childhood NSI reduced the IQ difference from −0.78 SD to −0.65 SD (95% CI, −0.76 to −0.55 SD). With regard to neonatal morbidities, the presence of any grade of IVH among VPT/VLBW participants was associated with a larger difference in IQ scores than no IVH (−0.99 SD [95% CI, −1.19 to −0.79 SD] vs −0.70 SD [95% CI, −0.84 to −0.57 SD], respectively). A similar difference among VPT/VLBW participants with and without neonatal BPD was also found (−0.93 SD [95% CI, −1.10 to −0.76] vs −0.67 SD [95% CI, −0.80 to −0.55], respectively).

IPD Analysis of Antecedent Risk Factors

Table 2 shows the results of the IPD meta-analysis examining the association of neonatal factors, maternal educational level, and cohort factors with IQ scores among VPT/VLBW participants. Significant associations with IQ z scores in the multi-variable analysis were gestational age (score difference per week of gestation, 0.11; 95% CI, 0.07-0.14),birthweight z score (score difference per 1.0 SD, 0.21; 95% CI, 0.14-0.28), the presence of neonatal BPD (score difference, −0.16; 95% CI, −0.30 to −0.02) or any grade of IVH (score difference, −0.19; 95% CI, −0.33 to −0.05), and maternal educational level (score difference, 0.26; 95%

CI, 0.17-0.35) (Table 2). These findings indi¬cated, for example, that among VPT/VLBW participants, each extra week of gestation was associated with an increase in IQ z score of 0.11, which was equivalent to 1.65 IQ points. In contrast, neither sex nor singleton or multiple birth significantly altered adult IQ scores among VPT/VLBW participants. In addition, none of the cohort-level factors were significant in the multivariable analysis. The association with birth year was significant in the univariable analysis (score difference, −0.02; 95% CI, −0.03 to 0), which suggested that more recent birth year was associated with lower IQ in adulthood.

Sensitivity Meta-analysis

The PubMed search of 413 records identified 4 additional non-RECAP and non-APIC cohorts[41-45] with extractable adult IQ data. Adding the summary data from the Hack study45 produced 5 non-IPD cohorts and 8 IPD cohorts (Figure 1). Characteristics of the non-IPD cohorts are shown in eTable 7 in the Supplement.

Using aggregate data, the SMD between VPT/VLBW and term-born participants was −0.61 (95% CI, −0.93 to −0.29) in non-IPD cohorts41-45 and −0.84 (95% CI, −0.97 to −0.71) in IPD cohorts7,8,29-34 (Figure 2). According to the results of the Cochran Q test, this finding suggested no significant differences between the IPD and non-IPD cohorts (Q = 1.80; P = .18). However, the heterogeneity was larger among non-IPD cohorts (I2 = 75%) compared with IPD cohorts (I2 = 41%).

Discussion

Summary of Evidence

This IPD meta-analysis examined the association between VPT birth or VLBW and adult IQ. Among 8 cohorts contributing IPD,[7,8,29-34] VPT/VLBW participants scored 0.78 SD lower in IQ score than term-born participants, which is equivalent to a be-tween-group difference of

approximately 12 IQ points. This substantial difference was marginally reduced after adjustment for sex and maternal educational level. Even when participants with childhood NSI were excluded (which also removed those with low childhood IQ), the IQ score difference between VPT/VLBW and term-born participants was 0.65 SD (equivalent to 9.8 IQ points). The addition of cohorts for which IPD were not available41-45 did not substantially alter the findings. Among VPT/VLBW participants, individual-level factors associated with lower IQ were earlier gestational age, lower birth weight z score, the presence of neonatal BPD or IVH, and lower maternal educational level.

The IQ score difference of −0.78 SD between VPT/VLBW and term-born participants is a larger standardized difference than that reported for other functional outcomes, such as mental and physical health and social functioning.46 The IQ differences between VPT/VLBW and term-born adults found in this study are also similar to those previously reported in studies of childhood IQ.[9-12] Three prospective studies found moderate to high stability in IQ scores from childhood to adulthood among VPT/VLBW individuals.[7,32,47] The adult cohorts in the present IPD analysis were followed up for decades, producing a higher risk of selective attrition over a long period. Individuals who are more socially disadvantaged or who have NSI are more frequently lost to follow-up,[48] which may be associated with the smaller difference in IQ between VPT/ VLBW and term-born participants.[49] However, the cohort differences in rates of attrition among all VPT/VLBW participants or among VPT/VLBW participants who specifically had childhood NSI were not associated with IQ, nor was the age at IQ assessment. Furthermore, the association between IQ and birth year was not significant after including individual-level factors in the multivariable analysis. This finding suggests little change in mean adult IQ scores among VPT/VLBW individuals born between 1978 and 1995 after adjustment for the lower birth weights and gestational ages among individuals born more recently. In more recent VPT/VLBW cohorts, no

improvements in childhood IQ by birth year have been reported.[12] Improvements in IQ have also not been observed in successive cohorts of children born extremely preterm from the same regions.[50,51] Thus, given the stability of IQ over time among these cohorts, changes in neonatal care and reduced mortality[52] do not appear to have translated into long-term improvements in IQ among VPT/VLBW individuals during this period.

For individual-level factors (Table 2), even when adjusting for other neonatal factors and maternal educational levels, a dose-response association was found between gestational age and IQ, replicating individual study findings.[53,54] The association of neonatal IVH and BPD with lower IQ is also consistent with previous meta-analyses of IQ in childhood and individual studies of IQ in adulthood.[12,55] After other factors were controlled for, neonatal BPD was associated with a mean reduction in IQ of 2.4 points (95% CI, −4.5 to −0.3 points; difference in z score, −0.16), and the presence of any grade of IVH was associated with a mean reduction in IQ of 2.9 points (95% CI, −5.0 to −0.8 points; difference in z score, −0.19) (Table 2). Severe IVH (grades 3-4) was only investigated in a univariable analysis that did not include all cohorts; however, severe IVH was associated with a mean decrease in IQ of 9.9 points (95% CI, −13.8 to −6.2 points; difference in z score, −0.66). However, this finding warrants cautious interpretation because other neonatal factors and maternal educational levels were not controlled for. Birth weight z scores had a significant association with IQ after other factors were controlled for. Results from the multivariable model suggest that a birth weight of −2 SD for gestational age is associated with a decrease of 6.3 IQ points (95% CI, −8.4 to −4.2 points) compared with a birth weight that is appropriate for gestational age. This finding provides additional support for the association between low birth weight for gestational age and lower IQ in adulthood among VPT/VLBW individuals.[56]

In contrast to neonatal factors, maternal educational levels and similar factors have been largely overlooked in research on VPT birth or VLBW and outcomes.[17] Compared with low

maternal educational level, VPT/VLBW participants who had mothers with medium or high educational levels had IQ scores that were generally 0.26 SD and 0.52 SD (3.9 and 7.8 IQ points) higher, respectively. These associations are equivalent in extent to those associated with serious neonatal complications (ie, BPD and IVH). The association of maternal educational level with adult IQ may reflect an amalgam of different factors. These factors may include genetic traits,[57] maternal smoking,[58] breastfeeding rates,[59] and parental behaviors.[55] Some factors could be modified postnatally and have been reported to have implications for academic achievement and development among both the general population and VPT/ VLBW groups.[60,61]

Strengths and Limitations

This study has several strengths. The harmonization and use of IPD to assess neonatal factors and maternal educational levels, the presence of childhood NSI, and adult IQ scores for 8 cohorts of VPT/VLBW participants allowed for reliable comparison across cohorts. In addition, we tested a range of specific cohort factors, which is a challenging task in an aggregate meta-analysis because these details are rarely available in published studies.

The study also has limitations. These include the differences in cohorts with regard to eligibility criteria, such as the stricter inclusion criterion of less than 26 weeks' gestational age in the Linsell et al study,[7] the use of maternal educational level rather than broader factors (such as socioeconomic status or combined parental educational level), and the different methods used for recruiting participants for the control groups. Individuals in the control groups were typically recruited in infancy; however, in some cohorts, recruitment occurred in childhood or adulthood, and neonatal data were unavailable. Thus, we could not evaluate whether factors such as birth weight z scores are similarly associated with IQ among

term-born participants. Given that the mean age at assessment was 24.6 years, the findings of the present study reflect IQ in young adulthood only.

Conclusions

Adults who were born VPT/VLBW had IQ scores that were a mean of 12 points lower than adults who were term born. This finding is similar to those reported in meta-analyses of IQ in childhood[7,9-12,47] despite the present study's greater risk of selective attrition owing to a longer follow-up period. The provision of antenatal and neonatal care that is associated with reductions in BPD and IVH[62,63] and parenting or educational interventions that help to decrease the social disparities associated with maternal educational levels[61] may improve cognitive outcomes among adults who were VPT or VLBW.

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Table 1: Summary of cohorts included in the IPD analysis

Cohort	Birth Year	Country	Mean age Assessed (SD)	IQ test	Initial Eligibility Criteria	Initial VP/ VLBW Surviving to Discharge (N)	Eligible Adult VP/ VLBW (N)	VP/ VLBW Attrition, No./total No. (%)	VP/ VLBW+ NSI Attrition No./total No. (%)	VP/ VLBW with IQ scores (N)	Control Group (N) + Information	Harmonization Issues	VPT/VLBW Neonatal / Maternal Education Data Imputed %
AYLS[37]	1985-1986	Finland	25.5 (0.6)	WAIS III (1997)	Preterm <37 Weeks (reduced to VPT/VLBW for this analysis)	108	68	40/68 (58.8)	12/15 (80.0)	28	303 - Recruited Infancy	None	0%
BLS[8]	1985-1986	Germany	26.1 (0.6)	WAIS III (1997)	VPT/VLBW (<32 weeks/ <1500 g)	510	411	208/411 (50.6)	69/91 (75.8)	203	192- Recruited Infancy	None	<1%
EPICure[7]	1995	UK & Ireland	19.3 (0.5)	WAIS II (1981)	EP (<26 weeks)	315	306	182/306 (59.5)	41/55 (74.5)	124	64- Recruited at ages 6 or 11	None	1%

HESVA[32]	1978-1985	Finland	24.6 (2.1)	WAIS III (1997)	VLBW (<1500 g)	334	254	145/254 (57.1)	11/16 (68.8)	109	98-Recruited in Adulthood	Maternal education measured in adulthood. NSI did not include IQ <70 and could not differentiate ambulatory/non-ambulatory cerebral palsy .	4%
NTNU[34]	1986-1988	Norway	26.4 (0.6)	WASI (1999)	VLBW (<1500 g)	86	82	31/82 (37.8)	6/10 (60.0)	51	75 -Recruited Infancy	Maternal education measured at 14 years	6%
NZ VLBW[33]	1986	New Zealand	28.3 (1.0)	WASI-II (2011)	VLBW (<1500 g)	338	323	98/323 (30.3)	16/25 (64.0)	225	100-Recruited in Adulthood	None	1%
UCLH[35]	1979-1984	UK	30.4 (4.0)	WAIS II (1981)	VP(<33 weeks, reduced to VPT/VLB	302[A]	220[A]	98/220 (44.5)	11/13 (84.6)	104	89- Recruited in Adulthood	BPD was not available so was fully imputed. Maternal	21%

					W for this analysis)								education reported by the participant in adulthood. NSI solely based on IQ <70 at 8 years	
VICS[36]	1991-1992	Australia	18.0 (0.8)	WAIS II (1981)	EP/ELBW (<28 weeks/ <1000 g)	299	277	53/277 (19.1)	16/43 (37.2)	224	146-Recruited Infancy	None	6%

Footnotes: Very preterm/Very Low Birthweight (VPT/VLBW), Extremely preterm/Extremely Low Birthweight (EP/ELBW), Wechsler Adult Intelligence Scale (WAIS), Intelligence Quotient (IQ), Neurosensory Impairment (NSI), bronchopulmonary dysplasia (BPD).

[A]Cohort information regarding attrition data, eligible adult sample and initial sample from UCLH is based on the criteria <33 weeks' gestation rather the VPT/VLBW (<32 weeks or <1500 g) criteria imposed subsequently. While 122 preterm individuals (<33 weeks) took part in adulthood, only 104 were VPT/VLBW and included in this analysis.

Table 2: Very Preterm/Very Low Birth Weight (VPT/VLBW) analysis: univariable and multivariable associations of individual and cohort level factors with IQ Z scores:

VPT/VLBW only analysis, N=1068

	IQ Z Scores					
	1 Stage Univariable Estimate			*1 Stage Multivariable Estimate*		
Factors	*Estimates*	*CI*	*p*	*Estimate*	*CI*	*p*
Individual Level Factors						
Gestational age (weeks)	0.04	0.02, 0.06	**<0.001**	0.11	0.07, 0.14	**<0.001**
Male	0.07	-0.05, 0.20	0.26	0.09	-0.03, 0.20	0.16
Birthweight_Z score (per 1 SD)	0.05	-0.01, 0.11	0.08	0.21	0.14, 0.28	**<0.001**
Maternal education (1=Low, 2=Medium, 3= High)	0.25	0.17, 0.34	**<0.001**	0.26	0.17, 0.35	**<0.001**
Bronchopulmonary dysplasia (Reference: No BPD)[A]	-0.37	-0.51, -0.23	**<0.001**	-0.16	-0.30, -0.02	**0.02**
-Defined as oxygen after 28 days post birth[B]	-0.34	-0.56, -0.12	**0.003**	-	-	-
-Defined as oxygen after 36 weeks' postmenstrual age[B]	-0.40	-0.56, -0.23	**<0.001**	-	-	-
Any grade of intraventricular hemorrhage (Reference: No IVH)	-0.27	-0.40, -0.13	**<0.001**	-0.19	-0.33, -0.05	**0.007**
- IVH Grade 3 or 4 (Reference: All other grades)[C]	-0.66	-0.92, -0.41	**<0.001**	-	-	-
Multiple Birth (Reference: Singleton)	0.01	-0.13, 0.15	0.86	0.00	-0.13, 0.14	0.95
Cohort Level Factors						

VPT/VLBW attrition %.	-0.00	-0.01, 0.00	0.08	-0.02	-0.06, 0.02	0.32
VPT/VLBW with NSI attrition %	-0.00	-0.01, 0.00	0.25	0.02	-0.03, 0.08	0.39
Cohort age at IQ assessment	0.00	-0.01, 0.02	0.60	-0.10	-0.26, 0.06	0.28
Year of birth	-0.02	-0.03, -0.00	**0.02**	-0.03	-0.11, 0.05	0.48

Footnotes: Very preterm/Very Low Birthweight (VPT/VLBW), Intelligence Quotient (IQ), Neurosensory Impairment (NSI), bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH).

[A] Participants from the UCLH cohort were not included in the univariable estimate but had their BPD values imputed for the multivariable estimate

[B] The AYLS, BLS, HESVA and NTNU used the criteria of 28 days post birth while EPICure, NZ VLBW and VICS used the criteria of 36 weeks' postmenstrual age.

[C] NZ VLBW participants could not have IVH harmonized into Grade 3 or 4 and thus were not included for the sub-analysis

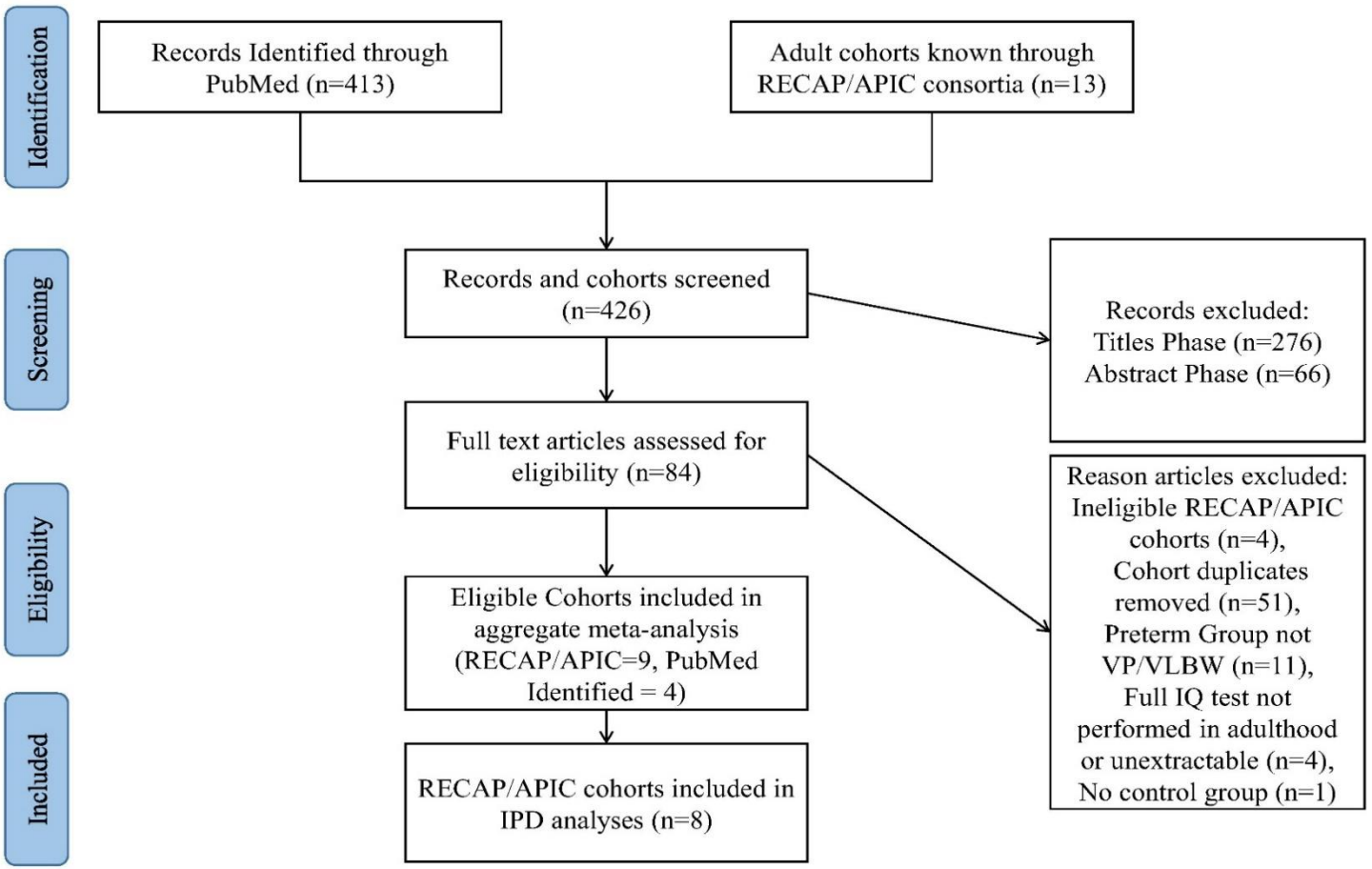

Figure 1: Flow chart of studies included in the IPD and aggregate meta-analyses.

APIC indicates Adults Born Preterm International Collaboration; RECAP, Research on European Children and Adults Born Preterm; and VPT/VLBW, very preterm or very low birth weight.

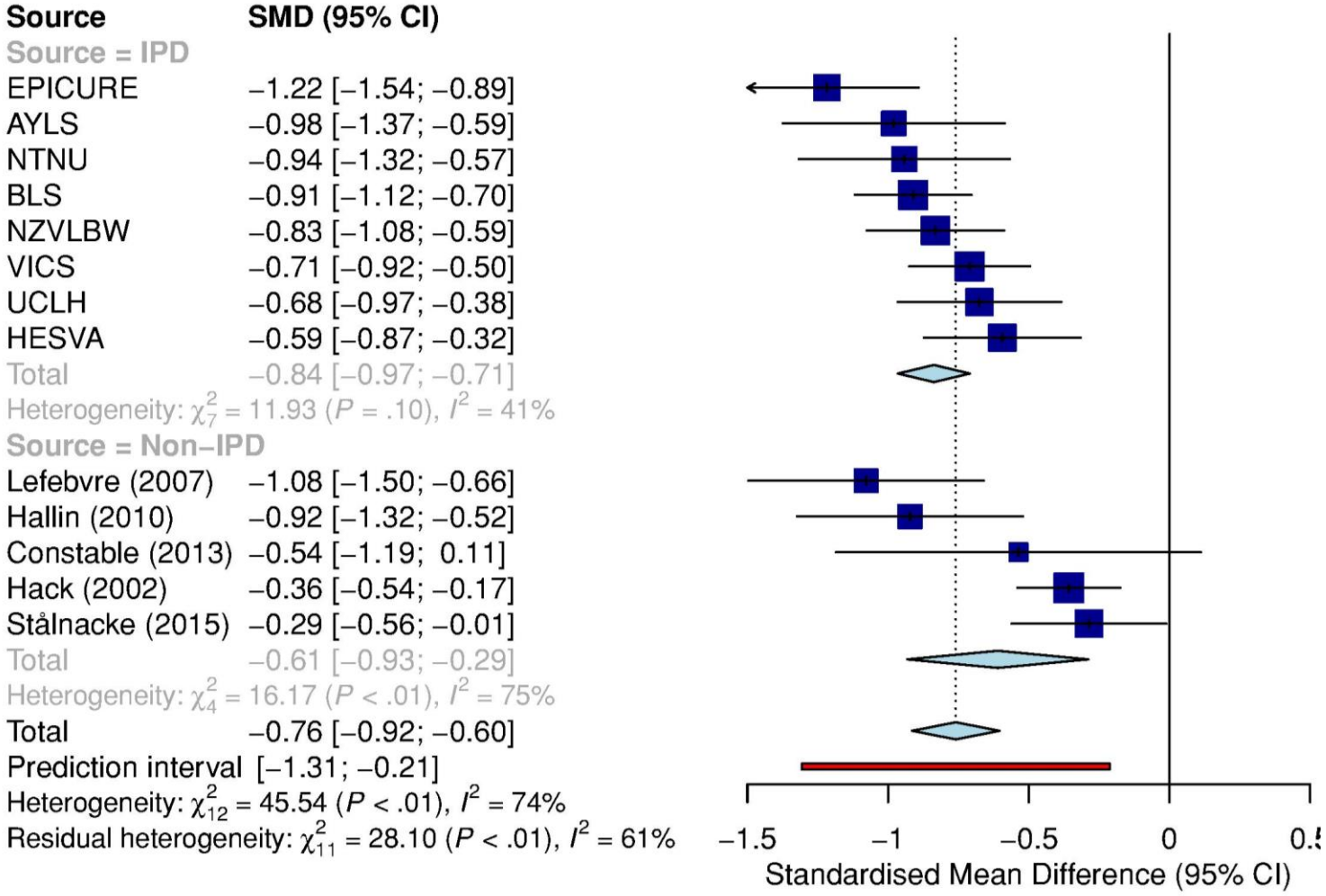

Figure 2: Aggregate meta-analysis comparing IQ performance in IPD and Non-IPD VPT/VLBW adult cohorts

Diamonds represent pooled estimates from either the IPD or non-IPD subgroup analysis or from all cohorts; diamond size indicates the 95% CI for the pooled estimate. The arrow indicates that the lower 95% CI (1.54) for the Linsell et al EPICure study7 is further than the axis limit of 1.5. Horizontal lines represent the 95% CIs of the estimates for each cohort. Box size represents the weighting given to the study. SMD indicates standardized mean difference

Supplementary Online Content

Eves R, Mendonca M, Baumann N, et al. Association of very preterm birth or very low birth weight with intelligence in adulthood: an individual participant data meta-analysis. *JAMA Pediatr*. Published online May 28, 2021. doi:10.1001/jamapediatrics.2021.1058

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Childhood Neurosensory Impairment in VPT/VLBW Participants From Each IPD Cohort

	AYLS	BLS	EPICURE	HESVA	NTNU	NZVLBW	UCLH	VICS	Overall
	VPT/ VLBW (n=28)	VPT/ VLBW (n=203)	VPT/ VLBW (n=124)	VPT/ VLBW (n=109)	VPT/ VLBW (n=51)	VPT/ VLBW (n=225)	VPT/ VLBW (n=104)	VPT/ VLBW (n=224)	VPT/ VLBW (n=1068)
Evidence of Severe NSI									
Yes	3 (10.7%)	22 (10.8%)	14 (11.3%)	5 (4.6%)	4 (7.8%)	9 (4.0%)	3 (2.9%)	27 (12.1%)	87 (8.1%)
No	25 (89.3%)	181 (89.2%)	110 (88.7%)	104 (95.4%)	47 (92.2%)	216 (96.0%)	101 (97.1%)	197 (87.9%)	981 (91.9%)
Visual Impairment									
No	26 (92.9%)	200 (98.5%)	117 (94.4%)	107 (98.2%)	37 (72.5%)	218 (96.9%)	0 (0%)	224 (100%)	929 (87.0%)
Yes	0 (0%)	2 (1.0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)	3 (0.3%)
Missing	2 (7.1%)	1 (0.5%)	7 (5.6%)	2 (1.8%)	14 (27.5%)	6 (2.7%)	104 (100%)	0 (0%)	136 (12.7%)
Hearing Impairment									
No	26 (92.9%)	201 (99.0%)	116 (93.5%)	107 (98.2%)	37 (72.5%)	217 (96.4%)	0 (0%)	223 (99.6%)	927 (86.8%)
Yes	0 (0%)	1 (0.5%)	1 (0.8%)	0 (0%)	0 (0%)	2 (0.9%)	0 (0%)	1 (0.4%)	5 (0.5%)
Missing	2 (7.1%)	1 (0.5%)	7 (5.6%)	2 (1.8%)	14 (27.5%)	6 (2.7%)	104 (100%)	0 (0%)	136 (12.7%)
Non-Ambulatory Cerebral Palsy									
No	28 (100%)	195 (96.1%)	115 (92.7%)	101 (92.7%)	49 (96.1%)	219 (97.3%)	0 (0%)	222 (99.1%)	929 (87.0%)
Yes	0 (0%)	7 (3.4%)	2 (1.6%)	5 (4.6%)	2 (3.9%)	0 (0%)	0 (0%)	2 (0.9%)	18 (1.7%)
Missing	0 (0%)	1 (0.5%)	7 (5.6%)	3 (2.8%)	0 (0%)	6 (2.7%)	104 (100%)	0 (0%)	121 (11.3%)
Child IQ <70									
No	22 (78.6%)	168 (82.8%)	108 (87.1%)	0 (0%)	39 (76.5%)	212 (94.2%)	99 (95.2%)	194 (86.6%)	842 (78.8%)

Yes	3 (10.7%)	18 (8.9%)	13 (10.5%)	0 (0%)	3 (5.9%)	7 (3.1%)	3 (2.9%)	25 (11.2%)	72 (6.7%)
Missing	3 (10.7%)	17 (8.4%)	3 (2.4%)	109 (100%)	9 (17.6%)	6 (2.7%)	2 (1.9%)	5 (2.2%)	154 (14.4%)

eTable 2. Newcastle Ottawa Criteria and Ratings for Each IPD Cohort

Criteria:

Newcastle Ottawa Rating Scale	http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp						
Selection							
1) Representativeness of the exposed cohort							
A) truly representative of the average ____**VPT/VLBW (not a sub-selection such as just those with BPD or only males)**_____ in the community ¯							
B) somewhat representative of the average ____ **VPT/VLBW** _____ in the community ¯							
C) selected group of users eg nurses, volunteers							
D) no description of the derivation of the cohort							
2) Selection of the non exposed cohort							
A) drawn from the same community as the exposed cohort ¯							
B) drawn from a different source							
C) no description of the derivation of the non exposed cohort							
3) Ascertainment of exposure							
A) secure record (eg surgical records) ¯							
B) structured interview ¯							
C) written self report							
D) no description							
4) Demonstration that outcome of interest was not present at start of study **(Was adult cognitive performance known when the participants were recruited?)**							
A) yes ¯							
B) no							

Comparability							
1) Comparability of cohorts on the basis of the design or analysis							
A) study controls for :____**maternal education**___							
B) study controls for any additional factor: **sex**							
Outcome							
1) Assessment of outcome (**Did the study use a standardised full-scale IQ assessment?)**							
A) independent blind assessment							
B) record linkage							
C) self report							
D) no description							
2) Was follow-up long enough for outcomes to occur **(Did the cohort assess adult IQ outcomes?)**							
A) yes (17 years or greater)							
B) no							
3) Adequacy of follow up of cohorts**. (Of the potential VPT/VLBW participants eligible in adulthood, were over 50% of them assessed?)**							
A) complete follow up - all subjects accounted for							
B) subjects lost to follow up unlikely to introduce bias - small number lost - > __**50**__ % follow up, or description provided of those lost)							
C) follow up rate < __**50**__% and no description of those lost							
D) no statement							

Criteria:

Cohort	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts (above or below 50%)	Overall Cohort Score
AYLS[1]	A (regional)	A	A	A	A	A	A	C	8
BLS[2,3]	A (regional)	A	A	A	A	A	A	C	8
EPICure[4,5]	A (national)	B	A	A	A	A	A	C	7
HESVA[6]	A(regional)	A	A	A	A	A	A	C	8
NTNU[7]	A (regional)	B	A	A	A	A	A	B	7
NZ_V	A (national)	B	A	A	A	A	A	B	8

LBW[8]									
UCLH[9,10]	A (regional)	B	A	A	A	A	A	B	8
VICS[11]	A (regional)	A	A	A	A	A	A	B	9

eTable 3. Linear Mixed Model Demonstrating Reducing Gestational Age by Birth Year Among VPT/VLBW Participants

VPT/VLBW only analysis			
	Gestational Age (weeks)		
Predictors	*Estimates*	*CI*	*p*
(Intercept – Estimate for 1978)	32.07	29.66 – 34.49	**<0.001**
Birth year – per year post 1978	-0.32	-0.60 – -0.04	**0.025**
Observations	1068		
Marginal R^2 / Conditional R^2	0.222 / 0.488		

eTable 4. Linear Mixed Model Demonstrating Reducing Birth Weight by Birth Year Among VPT/VLBW Participants

VPT/VLBW only analysis			
	Birthweight (g)		
Predictors	*Estimates*	*CI*	*p*
(Intercept – Estimate for 1978)	1464.87	1211.59 – 1718.14	**<0.001**
Birth year – per year post 1978	-29.85	-58.78 – -0.91	**0.043**
Observations	1068		
Marginal R^2 / Conditional R^2	0.164 / 0.411		

eTable 5. IQ and Demographic Information of All Participants From Each IPD Cohort

Cohort	**AYLS**		**BLS**		**EPICURE**		**HESVA**		**NTNU**		**NZVLBW**		**UCLH**		**VICS**	
Group	**Cons n= 303**	**VPT/ VLBW n=28**	**Cons n= 192**	**VPT/ VLBW n= 203**	**Cons n=64**	**VPT/ VLBW n=124**	**Cons n=98**	**VPT/ VLBW n= 109**	**Cons n=75**	**VPT/ VLBW n=51**	**Cons n= 100**	**VPT/ VLBW n= 225**	**Cons n= 89**	**VPT /VLBW n=104**	**Cons n= 146**	**VPT/ VLBW n= 224**
IQ Z Score																
Mean (SD)	0.00 (0.94)	-0.95 (1.21)	0.00 (0.75)	-0.83 (1.04)	0.00 (0.64)	-1.06 (0.96)	0.00 (0.84)	-0.57 (1.06)	0.00 (0.70)	-0.86 (1.15)	0.00 (0.78)	-0.78 (1.00)	0.00 (0.89)	-0.64 (1.00)	0.00 (0.84)	-0.67 (1.01)
Sex																
Male	134 (44.2 %)	16 (57.1 %)	92 (47.9 %)	108 (53.2 %)	25 (39.1 %)	56 (45.2 %)	42 (42.9 %)	47 (43.1 %)	33 (44.0 %)	25 (49.0 %)	37 (37.0 %)	100 (44.4 %)	42 (47.2 %)	63 (60.6 %)	56 (38.4 %)	96 (42.9 %)
Female	169 (55.8 %)	12 (42.9 %)	100 (52.1 %)	95 (46.8 %)	39 (60.9 %)	68 (54.8 %)	56 (57.1 %)	62 (56.9 %)	42 (56.0 %)	26 (51.0 %)	63 (63.0 %)	125 (55.6 %)	47 (52.8 %)	41 (39.4 %)	90 (61.6 %)	128 (57.1 %)
Maternal Education Level																
Low	52 (17.2 %)	7 (25.0 %)	87 (45.3 %)	61 (30.0 %)	4 (6.2 %)	23 (18.5 %)	13 (13.3 %)	17 (15.6 %)	2 (2.7 %)	2 (3.9%)	4 (4.0 %)	85 (37.8 %)	3 (3.4 %)	3 (2.9%)	9 (6.2 %)	47 (21.0 %)

Medium	101 (33.3 %)	9 (32.1 %)	72 (37.5 %)	112 (55.2 %)	48 (75.0 %)	90 (72.6 %)	56 (57.1 %)	64 (58.7 %)	31 (41.3 %)	22 (43.1 %)	33 (33.0 %)	68 (30.2 %)	23 (25.8 %)	40 (38.5 %)	34 (23.3 %)	57 (25.4 %)
High	148 (48.8 %)	12 (42.9 %)	32 (16.7 %)	27 (13.3 %)	12 (18.8 %)	4 (3.2%)	29 (29.6 %)	26 (23.9 %)	28 (37.3 %)	16 (31.4 %)	63 (63.0 %)	64 (28.4 %)	39 (43.8 %)	20 (19.2 %)	26 (17.8 %)	24 (10.7 %)
Missing	2 (0.7%)	0 (0%)	1 (0.5%)	3 (1.5%)	0 (0%)	7 (5.6%)	0 (0%)	2 (1.8%)	14 (18.7 %)	11 (21.6 %)	0 (0%)	8 (3.6%)	24 (27.0 %)	41 (39.4 %)	77 (52.7 %)	96 (42.9 %)

eTable 6. Neonatal and Demographic Data for VPT/VLBW Participants From Each IPD Cohort

	AYLS	BLS	EPICURE	HESVA	NTNU	NZVLBW	UCLH	VICS	Overall
	VPT/ VLBW (n=28)	VPT/ VLBW (n=203)	VPT/ VLBW (n=124)	VPT/ VLBW (n=109)	VPT/ VLBW (n=51)	VPT/ VLBW (n=225)	VPT/ VLBW (n=104)	VPT/ VLBW (n=224)	VPT/ VLBW (n=1068)
Gestational Age (weeks)									
Mean (SD)	29.6 (2.09)	30.4 (2.05)	24.5 (0.748)	29.3 (2.33)	29.0 (2.49)	29.3 (2.50)	28.8 (2.00)	26.6 (1.99)	28.3 (2.81)
Birthweight Z Score									
Mean (SD)	-0.00903 (1.08)	-0.603 (1.20)	0.230 (0.822)	-0.421 (1.00)	-0.182 (1.08)	-0.607 (1.07)	-0.0826 (0.930)	-0.167 (1.07)	-0.311 (1.09)
Multiple Birth									
Singleton	25 (89.3%)	149 (73.4%)	83 (66.9%)	92 (84.4%)	41 (80.4%)	169 (75.1%)	81 (77.9%)	150 (67.0%)	790 (74.0%)
Multiple	3 (10.7%)	54 (26.6%)	40 (32.3%)	17 (15.6%)	10 (19.6%)	56 (24.9%)	19 (18.3%)	74 (33.0%)	273 (25.6%)
Missing	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)	4 (3.8%)	0 (0%)	5 (0.5%)
Intraventricular Haemorrhage									
No Grade	23 (82.1%)	161 (79.3%)	44 (35.5%)	69 (63.3%)	38 (74.5%)	158 (70.2%)	48 (46.2%)	152 (67.9%)	693 (64.9%)
Any Grade	5 (17.9%)	41 (20.2%)	79 (63.7%)	14 (12.8%)	5 (9.8%)	52 (23.1%)	55 (52.9%)	72 (32.1%)	323 (30.2%)
Missing	0 (0%)	1 (0.5%)	1 (0.8%)	26 (23.9%)	8 (15.7%)	15 (6.7%)	1 (1.0%)	0 (0%)	52 (4.9%)
Bronchopulmonary Dysplasia Diagnosed									
No	27 (96.4%)	101 (49.8%)	35 (28.2%)	80 (73.4%)	39 (76.5%)	181 (80.4%)	0 (0%)	138 (61.6%)	601 (56.3%)

Yes	1 (3.6%)	102 (50.2%)	89 (71.8%)	25 (22.9%)	10 (19.6%)	44 (19.6%)	0 (0%)	86 (38.4%)	357 (33.4%)
Missing	0 (0%)	0 (0%)	0 (0%)	4 (3.7%)	2 (3.9%)	0 (0%)	104 (100%)	0 (0%)	110 (10.3%)
ISCED Maternal Education									
Low	7 (25.0%)	61 (30.0%)	23 (18.5%)	17 (15.6%)	2 (3.9%)	85 (37.8%)	3 (2.9%)	47 (21.0%)	245 (22.9%)
Medium	9 (32.1%)	112 (55.2%)	90 (72.6%)	64 (58.7%)	22 (43.1%)	68 (30.2%)	40 (38.5%)	57 (25.4%)	462 (43.3%)
High	12 (42.9%)	27 (13.3%)	4 (3.2%)	26 (23.9%)	16 (31.4%)	64 (28.4%)	20 (19.2%)	24 (10.7%)	193 (18.1%)
Missing	0 (0%)	3 (1.5%)	7 (5.6%)	2 (1.8%)	11 (21.6%)	8 (3.6%)	41 (39.4%)	96 (42.9%)	168 (15.7%)
Birth Year									
Mean (SD)	1985.3 (0.46)	1985.2 (0.41)	1995.0 (0.00)	1982.4 (2.10)	1987.2 (0.74)	1986.0 (0.00)	1982.1 (1.83)	1991.6 (0.50)	1987.4 (4.24)
Age Assessed									
Mean (SD)	25.8 (0.49)	26.2 (0.59)	19.3 (0.55)	24.5 (2.08)	26.3 (0.67)	28.4 (1.09)	30.5 (2.42)	17.9 (0.79)	24.4 (4.55)

eTable 7. Study Characteristics of VPT/VLBW Cohorts Not Included in the IPD Meta-analysis

			VPT/VLBW		Controls		
Cohort	**Birth year**	**IQ Test**	**IQ, *M (SD)***	***n***	**IQ, *M (SD)***	***n***	**Age at assessment, *M (SD)***
Constable (2013)[12]	1990	WISC TIQ	91.7 (12.4)	19	100.4 (18.7)	19	20.1 (0.9)
Hack (2002)[13]	1977	WAIS-R	86.87(14.23)[A]	236	92(14.4)	231	20
Hallin 2010)[14]	1985	WAIS-III	93 (15.4)	52	106 (12.5)	54	18.4(0.2)
Lefebvre (2005)[15]	1976	WAIS-R	94(12)	59	108(14)	44	18.1(1.8)
Stålnacke (2015)[16]	1988	WISC-III	-0.315(1.165)[B]	118	0(1)	91	18

A = Derived from weighted average of the male and female reported scores. Age at assessment SD not stated.

B = Derived from the combined Z score for verbal and non-verbal ability. Age at assessment SD not stated.

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