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Fertility of young adults born very preterm/very low birth weight: An individual participant data meta-analysis

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ABSTRACT

Objectives: To assess whether there are differences in fertility between adults born very preterm or at very low birth weight (VP/VLBW) with term-born controls, whether the association of VP/VLBW with fertility differs by sex, and which individual factors are associated with fertility among VP/VLBW adults.
Study design: Prospective longitudinal cohorts with fertility assessed in VP/VLBW and term-born adults were identified from two international consortia: Research on European Children and Adults Born Preterm (RECAP-Preterm), and Adults Born Preterm International Collaboration (APIC). Individual participant data (IPD) on neonatal, medical, sociodemographic, and fertility variables were collected and analyzed using a one-stage approach.
Results: Seven cohorts with 931 VP/VLBW and 1363 term-born young adults (mean ages at assessment ranged from 23 to 30 years) were included. VP/VLBW and term-born young adults did not significantly differ in fertility (i.e., having children) (OR 1.48, 95 % CI 0.99–2.21). No moderation effect of sex could be confirmed (OR 0.87, 95 % CI 0.53–1.42). Among VP/VLBW young adults, higher fertility was significantly associated with female sex, higher age at assessment, being married/cohabiting, the absence of childhood neurosensory impairment, and low levels of maternal and own education.
Conclusions: VP/VLBW is not associated with lower fertility in young adults. Sex does not moderate this association. In addition to childhood neurosensory impairment, mainly sociodemographic factors (partnering, maternal and own education) are associated with fertility in VP/VLBW young adults. The evidence is limited so

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far to the early reproductive window in the 20 s, further follow-up into established adulthood will be required for definite answers on fertility after VP/VLBW birth.

Introduction

Very preterm birth (VP; <32 weeks' gestation) or very low birth weight (VLBW; <1500 g) is associated with an increased risk of reduced functioning in different domains [1–5] which persist into adulthood and may reduce reproductive success. [6] Two approaches evaluating reproductive success have been suggested. One is to examine fecundity, i.e., the biologic capacity for reproduction, [7] and the results in low-birth-weight samples are inconsistent. For example, some studies reported that low birth weight is associated with either earlier or later age at menarche. [8–11] Other studies suggested a negative or no effect of low birth weight on semen quality, reproductive hormone levels, and reproductive function/health problems. [12–17]

A more direct approach is to measure fertility, i.e., the demonstrated fecundity measured by live births. [7] Population-linked registry studies [18–24] have reported a lower fertility of VP/VLBW. However, this has only been partially replicated in prospective cohort studies. [25–30] This may be partly due to the different age at assessment in different studies, where no difference in fertility was consistently reported in young adults (18–29 years). [25,27–29] A recent meta-analysis [6] suggested that VP/VLBW adults are less fertile compared with term-born controls. Yet, traditional meta-analysis does not identify which individual factors are related to fertility that may explain differences in results. Sex is of interest because sex differences in mating strategies have been consistently found across cultures, [31] and there is an age difference in mating because females tend to have children with males who are, on average, 2–3 years older. [32] According to the Sexual Strategies Theory, [33,34] VP/VLBW men may have lower fertility as they compete poorly compared with larger, healthy term-born men for women to reproduce. Conversely, women who ultimately make the choice to reproduce in intersexual selection are more assured of finding a partner to reproduce with, thus VP/VLBW and term-born women may show similar fertility. Furthermore, presence of neurosensory/cognitive disabilities which are more frequent in VP/VLBW [35] may be associated with lower fertility. [36] Alternatively, sociodemographic factors are consistently associated with fertility. [37–44] Those with lower childhood socioeconomic status tend to reproduce earlier and have more children. [37,38] Better-educated women tend to delay parenthood [39–41] and have fewer children, [42,43] while less-educated men tend to remain childless. [44] Hence, including relevant medical and sociodemographic variables in individual participant data (IPD) meta-analysis might allow to determine the factors associated with fertility in VP/VLBW.

This IPD meta-analysis aimed to assess 1) whether there are differences in fertility between VP/VLBW and term-born adults, 2) whether the association of VP/VLBW with fertility differs by sex, and 3) which individual factors are associated with fertility among VP/VLBW adults. We hypothesized that VP/VLBW adults would have lower fertility compared with term-born adults; in particular, VP/VLBW men but not women would have lower fertility compared with their same-sex term-born peers.

Methods

This IPD meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [45] and was registered with the International Prospective Register of Systematic Reviews (PROSPERO, CRD42023441985). After initial data screening, the second research question stated in the original protocol was pivoted to covariates specific to VP/VLBW individuals for the current study because most covariates (e.g., neonatal morbidities) could not be addressed in term-born controls.

Study selection

Cohorts with relevant data on fertility of VP/VLBW adults were identified from Research on European Children and Adults Born Preterm (RECAP-Preterm) (https://recap-preterm.eu/) and Adults Born Preterm International Collaboration (APIC) (https://www.apic-preterm.org) consortia. These are two large research collaborations comprising cohorts from Europe, Australia, New Zealand, and North America.

To search for possible additional cohorts, PubMed was searched for publications in English from inception to December 29, 2024. The search strategy is outlined in Appendix 1.

Eligibility criteria

Prospective longitudinal cohorts of VP/VLBW adults (mean sample age ≥18 years) were eligible for inclusion if any of the following fertility outcomes was measured: having children (any live-born biological child), number of children, or having children born preterm (PT; <37 weeks' gestation) or at low birth weight (LBW; <2500 g). All cohorts had to include a term-born (≥37 weeks' gestation) control group. Each potentially eligible study was assessed by two authors (MKYW and MM). Any disagreements regarding eligibility were resolved by discussion and consultation with the senior author (DW).

Data extraction

De-identified data from eligible cohorts were transferred to the University of Warwick under data transfer agreements. All studies had received country-specific ethical reviews, with participants providing written informed consent in adulthood. Data were checked for consistency and completeness and harmonized as necessary for data synthesis.

Fertility outcomes included having children (i.e., any live-born biological child), and if so, number of children and having children born PT/LBW (i.e., any children born PT/LBW).

Neonatal and medical variables included gestational age (completed weeks) at birth, birth weight z scores (calculated using the Fenton growth chart [46]), multiple birth (vs singleton birth), presence of bronchopulmonary dysplasia (BPD), presence of intraventricular haemorrhage (IVH), and presence of childhood neurosensory impairment (NSI). BPD was defined either as oxygen dependency at 36 weeks' postmenstrual age or at 28 days after birth. [47] IVH was classified according to Papile et al. [48] from grades 1–4 and harmonized into no IVH vs any IVH (grades 1–4). Evidence of childhood NSI was defined as having any of the following: visual impairment (blind in 1 or both eyes), hearing impairment (uncorrected), non-ambulatory cerebral palsy, or childhood cognitive impairment (IQ<70).

Sociodemographic variables included participants' mothers' (Generation 1) educational level recorded at birth or at later follow-up (an indicator of family socioeconomic status), participants' sex, age at assessment, highest level of own (Generation 2) education achieved, occupational status (being in paid work vs being in education/training vs being unemployed/in unpaid work/receiving social security), and partnership status (no partner vs being married/cohabiting) collected in adulthood. Maternal and own education was categorized according to the International Standard Classification of Education (ISCED) [49] into low (ISCED levels 0–2), medium (ISCED levels 3–5), and high (ISCED levels 6–8).

Assessment of risk of bias

Risk of bias of each cohort was assessed by two authors (MKYW and MM) using the Newcastle-Ottawa Scale [50] (Appendix 2) with disagreements resolved by discussion. Scores range from 0 to 9, with higher scores indicating higher quality.

Data synthesis

All participants with relevant fertility data were included in the analyses. Missing data on predictor variables were imputed using joint modelling approach for multiple imputation of multilevel data. [51] To examine the first two objectives, the effects of VP/VLBW, female sex, and their interaction (i.e., VP/VLBW*female sex) on fertility were analyzed using a one-stage approach in a generalized linear mixed-effects (GLME) model with maximum likelihood estimation. Odds ratios (ORs) and 95 % confidence intervals (CIs) were estimated for binary outcomes using logistic regression model. Incidence rate ratios (IRRs) and 95 % CIs were estimated for count outcome using Poisson regression model. A random-intercept model was applied to account for clustering of participants within cohorts. This procedure was repeated to estimate effect sizes after adjusting for age at assessment and maternal education, which were added as fixed effects, and excluding participants with childhood NSI. For the third objective, the effects of individual factors on fertility were analyzed with neonatal and medical factors and sociodemographic factors added as fixed effects to GLME model. Effect sizes are reported from both univariable and multivariable analyses. Sensitivity analyses just by gestation comparing VP (<32 weeks' gestation) vs term born (≥37 weeks' gestation) were conducted.

A sensitivity meta-analysis was performed to combine IPD cohorts and additional cohort studies identified via PubMed where IPD were unavailable. The results of IPD meta-analysis were compared with estimates using aggregate data extracted from non-IPD cohort studies and meta-analyzed by conducting a subgroup analysis using a two-stage IPD meta-analysis, with effect sizes pooled through a random-effects meta-analysis. Heterogeneity across cohort studies was assessed using Higgins I^2 statistic and the Cochran Q test.

All analyses were performed in R, version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study selection and individual participant data (IPD) obtained

Fig. 1 illustrates the study selection process. Nine of the 11 participating RECAP/APIC cohorts with fertility data were identified: the Arvo Ylppö Longitudinal Study (AYLS), [52] the Bavarian Longitudinal Study (BLS), [53] the EPICure study (EPICure), [54] the Preterm Birth and Early Life Programming of Adult Health and Disease Study (ESTER), [27] the Helsinki Study of Very Low Birth Weight Adults (HeSVA), [55] the Norwegian University of Science and Technology Low Birth Weight in a Lifetime Perspective Study (NTNU LBW Life), [2] the New Zealand Very Low Birth Weight Study (NZ-VLBW), [56] the University College London Hospital Study (UCLH), [57] and the Project On Preterm and Small for gestational age infants (POPS). [58] Of these, EPICure [54] was excluded because no participants have had any child at the time of assessment. POPS [58] did not include a term-born control group, thus was only included in the VP/VLBW subgroup analysis. PubMed search yielded 8 cohort studies that published aggregate data on having children: the Cleveland study, [26] two McMaster studies, [29,30] ESTER, [27] UCLH, [57] two POPS studies, [58,59] and the Victorian Infant Collaborative Study (VICS). [28] Both McMaster studies [29,30] were retained because they reported different findings on the same cohort at ages 23 and 32 years. ESTER [27] and UCLH [57] were excluded as they reported on the same data included in IPD cohorts. POPS [58,59] published aggregate data at ages 28 and 35 years; however, IPD were only available at age 28 years for analysis. VICS [28] is one of the participating APIC cohorts; it published aggregate data at age 25 years, but these IPD were unavailable at the time of final analysis. After exclusion, 7 RECAP/APIC cohorts [2,27,52,53,55–57] were included in the IPD meta-analysis, and POPS [58] was additionally included in the VP/VLBW subgroup analysis; the aggregate meta-analysis included 7 IPD cohorts [2,27,52,53,55–57] plus 4 non-IPD cohort studies [26,28–30] identified via PubMed. See Table I for a summary of the IPD cohorts and non-IPD cohort studies.

In total, the 7 IPD cohorts [2,27,52,53,55–57] contributed data to having children from 931 VP/VLBW and 1363 term-born participants, and additional 289 VP/VLBW participants from POPS [58]; 4 non-IPD cohort studies [26,28–30] provided aggregate data from 652 VP/VLBW and 581 term-born participants. After reducing the sample to participants who were parents, 5 IPD cohorts [2,27,52,53,57] contributed data to number of children, and 5 IPD cohorts [2,27,52,53,55] contributed data to having children born PT/LBW.

Study and participant characteristics

All IPD cohorts [2,27,52,53,55–58] were from high-income countries (Finland, [27,52,55] Germany, [53] Netherlands, [58] New Zealand, [56] Norway, [2] and United Kingdom [57]). The birth years of participants ranged from 1978 to 1989 and the mean ages at assessment ranged from 23 to 30 years. See Appendix 4 for participant characteristics in each cohort.

Risk of bias of included studies

The mean study quality score based on the Newcastle-Ottawa Scale [50] was 7.1 (range 6–8), indicating overall good quality (Appendix 3). Studies were rated highly on representativeness, ascertainment of exposure, and comparability.

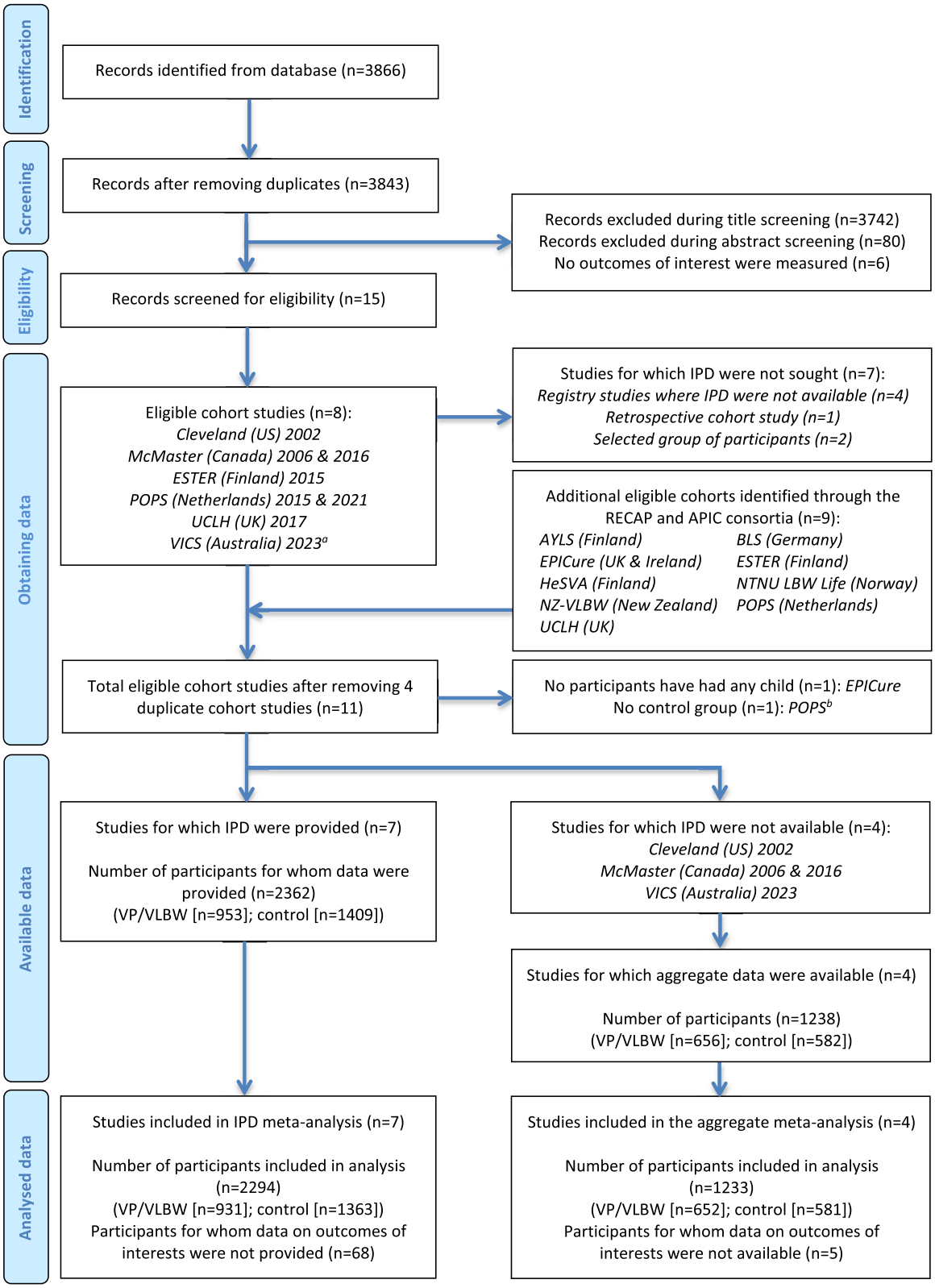
Synthesis of results

The IPD meta-analysis set out to examine the association of VP/VLBW with fertility, i.e., having children, number of children, and having children born PT/LBW. However, the multilevel models for having children born PT/LBW was underpowered and suffered from singular fit error. [60] Descriptive results are hence presented in Appendix 5. Moreover, the IPD meta-analysis examining individual factors associated with fertility among VP/VLBW adults only focused on having children due to insufficient datapoints for other fertility outcomes.

Contrary to the hypothesis, the results of the IPD meta-analysis (Table II) revealed that VP/VLBW was not significantly associated with lower fertility. Indeed, the VP/VLBW tended to be more likely to have children: unadjusted OR 1.48 (95 % CI 0.99–2.21) but not more children: unadjusted IRR 0.91 (95 % CI 0.62–1.34). These estimates remained nonsignificant after adjusting for age and maternal education or excluding participants with childhood NSI (Table II).

Sex was associated with fertility with women more likely to have children than men (unadjusted OR 1.53, 95 % CI 1.07–2.17); however, for those who were parents, no sex difference in number of children was found (unadjusted IRR 0.96, 95 % CI 0.70–1.31). Adjustment for age and maternal education or excluding participants with childhood NSI slightly increased the effect sizes (Table II). More importantly, contrary to the hypothesis, the interaction between VP/VLBW and female sex was not significant for any fertility outcomes (have children: unadjusted OR 0.87 [95 % CI 0.53–1.42]; number of children: unadjusted IRR 1.17 [95 % CI 0.72–1.91]), thus we could not confirm that the association of VP/VLBW with fertility differs by sex. Adjustment for age and maternal education or excluding participants with childhood NSI slightly reduced the effect sizes and remained nonsignificant (Table II).

Table III shows the results of the IPD meta-analysis examining the association of individual factors with fertility, i.e., having children,



[a] Adult IPD at age 25 years for VICS were not available at the time of final analysis.

[b] POPS did not include a control group, so was only included in the VP/VLBW subgroup analysis (n=289).

Fig. 1. The PRISMA-IPD flowchart for the selection process of included studies.

Table I
Summary of cohorts included in the (a) IPD meta-analysis and (b) sensitivity meta-analysis.

Cohort	Country	Birth year	Initial eligibility criteria	Mean age assessed, y (range)	Initial sample of VP/VLBW surviving to discharge, N	Assessed sample in adulthood, N	Sample with data on fertility, N	Term-born controls with data on fertility, N (age range at recruitment)	Harmonisation issues
(a) **Cohorts included in the IPD meta-analysis**									
AYLS	Finland (regional)	1985–1986	GA< 37 weeks (reduced to VP/VLBW for this analysis)	26 (24–27)	108	35	33	369 (infancy)	Partnership status not available at the time of analysis and fully imputed
BLS	Germany (regional)	1985–1986	VP/VLBW	26 (25–29)	510	260	260	229 (infancy)	None
ESTER	Finland (regional)	1985–1989	GA< 37 weeks (reduced to VP/VLBW for this analysis)	23 (20–26)	448	77	73	333 (infancy)	IVH not available and fully imputed
HeSVA	Finland (regional)	1978–1985	VLBW	25 (21–29)	334	165	161	171 (adulthood)	Maternal education measured in adulthood; NSI did not include IQ< 70
NTNU LBW Life	Norway (regional)	1986–1988	VLBW	26 (24–28)	86	62	59	87 (infancy)	Maternal education measured at 14y
NZ-VLBW	New Zealand (national)	1986	VLBW	28 (26–30)	338	250	249	99 (adulthood)	Occupational status not available at the time of analysis and fully imputed
UCLH	United Kingdom (regional)	1979–1984	VP (GA<33 weeks, reduced to VP/VLBW for this analysis)	30 (24–49)	302	102	96	75 (adulthood)	Maternal education reported by the participant in adulthood; NSI solely based on IQ< 70 at 8y; BPD not available and fully imputed
POPS	The Netherlands (national)	1983	VP/VLBW	28	1338	317	289	No controls	None
(b) **Cohorts included in the sensitivity meta-analysis**									
Cleveland	United States (regional)	1977–1979	VLBW	20	-	-	242	232 (8y)	-
McMaster	Canada (regional)	1977–1982	ELBW	2006: 23 2016: 32	-	-	2006: 149 2016: 100	2006: 133 (8y) 2016: 89 (8y)	-
VICS	Australia (regional)	1991–1992	EP/ELBW	25	-	-	161	127 (infancy)	-

Abbreviations: AYLS, Arvo Ylppö Longitudinal Study; BLS, Bavarian Longitudinal Study; BPD, bronchopulmonary dysplasia; EP/ELBW, extremely preterm (<28 weeks' gestation)/extremely low birth weight (<1000 g); ESTER, The Preterm Birth and Early Life Programming of Adult Health and Disease Study; GA, gestational age; HeSVA, Helsinki Study of Very Low Birth Weight Adults; IVH, intraventricular hemorrhage; IPD, individual participant data; NSI, neurosensory impairment; NTNU LBW Life, Norwegian University of Science and Technology Low Birth Weight in a Lifetime Perspective Study; NZ-VLBW, New Zealand Very Low Birth Weight Study; POPS, Project on Preterm and Small for Gestational Age Infants; UCLH, University College London Hospital Cohort Study; VICS, Victorian Infant Collaborative Study; VP/VLBW, very preterm/very low birth weight.

among VP/VLBW adults. The multivariable analysis found that higher fertility was associated with female sex (OR 1.80, 95 % CI 1.26–2.56), higher age at assessment (OR 1.41, 95 % CI 1.24–1.60), and being married/cohabiting (OR 5.13, 95 % CI 3.46–7.61). In contrast, lower fertility was associated with presence of childhood NSI (OR 0.40, 95 % CI 0.19–0.84), high level of maternal education (OR 0.49, 95 % CI 0.28–0.86), and high level of own education (OR 0.33, 95 % CI 0.17–0.63). Birth weight, neonatal morbidities (i.e., BPD, IVH), and multiple birth were not significantly associated with fertility in multivariable analysis. The effect of gestational age was only significant in univariable analysis (OR 1.07, 95 % CI 1.00–1.14) but not in multivariable analysis (OR 1.03, 95 % CI 0.93–1.14).

Despite smaller effect sizes, the results were unchanged in sensitivity analyses that just included VP (<32 weeks) and term-born (≥37 weeks) young adults (Appendixes 6 and 7).

Sensitivity meta-analysis comparing IPD and aggregate data did not reveal convergent results, with VP/VLBW not significantly associated with fertility in IPD cohorts (unadjusted OR 1.35, 95 % CI 0.95–1.92) but significantly associated with lower fertility in non-IPD cohort studies (unadjusted OR 0.65, 95 % CI 0.47–0.90). The overall pooled effect size indicates a nonsignificant association between VP/VLBW and fertility (unadjusted OR 1.01, 95 % CI 0.72–1.42) (Fig. 2). The results of Cochran *Q* test suggested significant difference between IPD and non-IPD cohort studies ($Q = 9.18$, df = 1, $P = 0.002$), with larger heterogeneity among IPD cohorts ($I^2 = 37$ %) vs non-IPD cohort studies ($I^2 = 0$ %).

Discussion

Main findings

This IPD meta-analysis synthesized evidence pertaining to fertility of VP/VLBW young adults from 7 prospective longitudinal cohorts. [2,27,52,53,55–57] We did not find lower fertility in VP/VLBW adults compared with term-born adults during emerging adulthood (18–29 years) [61] in high-income countries. The association of VP/VLBW with fertility remained nonsignificant even after adjusting for age and

Table II
One-stage IPD meta-analysis of the association of VP/VLBW, female sex, and their interaction with fertility.

Outcomes	N	Predictors	Effect Size (95 % CI)
Having children			
Unadjusted model	2294	VP/VLBW	OR 1.48 (0.99–2.21)
		Female	OR 1.53 (1.07–2.17)
		VP/VLBW*Female	OR 0.87 (0.53–1.42)
Adjusted for age and maternal education	2294	VP/VLBW	OR 1.33 (0.87–2.04)
		Female	OR 1.63 (1.13–2.34)
		VP/VLBW*Female	OR 0.84 (0.50–1.41)
Excluding participants with childhood NSI	2162	VP/VLBW	OR 1.50 (0.97–2.32)
		Female	OR 1.61 (1.12–2.33)
		VP/VLBW*Female	OR 0.78 (0.46–1.33)
Number of children			
Unadjusted model	183	VP/VLBW	IRR 0.91 (0.62–1.34)
		Female	IRR 0.96 (0.70–1.31)
		VP/VLBW*Female	IRR 1.17 (0.72–1.91)
Adjusted for age and maternal education	183	VP/VLBW	IRR 0.93 (0.64–1.36)
		Female	IRR 1.01 (0.73–1.40)
		VP/VLBW*Female	IRR 1.10 (0.68–1.81)
Excluding participants with childhood NSI	177	VP/VLBW	IRR 0.92 (0.63–1.36)
		Female	IRR 1.02 (0.74–1.41)
		VP/VLBW*Female	IRR 1.09 (0.66–1.81)

Abbreviations: NSI, neurosensory impairment.

Table III
One-stage IPD univariable and multivariable effects on fertility among VP/VLBW adults (N = 1220).

Individual Factors	Univariable Estimates OR (95 % CI)	Multivariable Estimates* OR (95 % CI)	Missing, % (n)
Neonatal and Medical Factors			
Gestational age, week	1.07 (1.00–1.14)	1.03 (0.93–1.14)	0.0 % (0)
Birth weight *z* score per 1 SD	0.94 (0.83–1.06)	1.07 (0.88–1.30)	0.0 % (0)
Presence of neonatal BPD (ref. = no BPD)	0.66 (0.42–1.02)	0.82 (0.50–1.34)	8.5 % (104)
Presence of neonatal IVH (ref. = no IVH)	0.90 (0.62–1.31)	1.02 (0.64–1.62)	12.2 % (149)
Multiple birth (ref. = singleton birth)	0.90 (0.62–1.30)	0.94 (0.62–1.41)	0.3 % (4)
Presence of childhood NSI (ref. = no NSI)	0.40 (0.21–0.76)	0.40 (0.19–0.84)	1.1 % (14)
Sociodemographic Factors			
Female sex (ref. = male)	1.67 (1.22–2.29)	1.80 (1.26–2.56)	0.0 % (0)
Age at assessment, year	1.44 (1.27–1.64)	1.41 (1.24–1.60)	4.3 % (52)
Maternal education (ref. = low)			10.9 % (133)
Medium	0.64 (0.43–0.93)	0.74 (0.48–1.13)	
High	0.38 (0.23–0.62)	0.49 (0.28–0.86)	
Own education (ref. = low)			2.1 % (26)
Medium	1.05 (0.68–1.62)	1.01 (0.60–1.70)	
High	0.40 (0.23–0.67)	0.33 (0.17–0.63)	
Occupational status (ref. = in paid work)			21.6 % (263)
In education/training	0.72 (0.36–1.46)	1.12 (0.55–2.27)	
Unemployed/unpaid work/social security	1.15 (0.69–1.93)	1.66 (0.92–3.00)	
Married/cohabiting (ref. = no partner)	5.81 (4.00–8.44)	5.13 (3.46–7.61)	8.7 % (106)

Abbreviations: BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; NSI, neurosensory impairment.
* Missing data were imputed in multivariable model.

maternal education, excluding participants with childhood NSI, or adding cohort studies [26,28–30] where IPD were unavailable. Moreover, our results did not show a significant interaction between VP/VLBW and female sex; thus no support of a sex difference in the association of VP/VLBW with fertility in young adults was apparent. Among VP/VLBW young adults, we found that fertility was mainly associated with childhood NSI and sociodemographic factors, especially partnering, but not neonatal factors.

Our results did not support the hypothesis that VP/VLBW adults are less fertile than term-born adults. This may be due to the young age of the IPD samples (23–30 years). They were all in the early reproductive window for high-income countries where the average age of first-time motherhood is around 29–30 years and even later for first-time fathers. [62] Indeed, the existing evidence which suggests lower fertility in VP/VLBW is mainly based on cohort studies reported at later ages [30,58,59] and reports of registry-linkage data that covered a wider age range [18–21,23,24] but not from cohort studies reported at earlier ages. [25,27–29] For example, Saigal and colleagues [29,30] reported a significant lower fertility at age 32 but not 23 years for the same cohort of extremely-low-birth-weight adults. Similarly, when stratified by chronological age, two Swedish population-based registry studies [19,21] and a meta-analysis [6] found significant lower fertility of VP/VLBW adults in late (≥25 years) but not in early age strata (<25 years). Our results echo these previous findings.

How may these different findings at different ages be explained? Life history (LH) theory, [63–66] an evolutionary theory, is concerned with maximizing reproductive success and the potential trade-offs of early or late reproduction. Reproduction requires considerable energy [67] and may have trade-offs in terms of aging. [68] According to the LH theory, early life adversity (e.g., VP/VLBW) indicates higher mortality risk and may orient individuals toward a fast LH strategy (unconsciously). Thus, VP/VLBW adults may tend to reproduce earlier to reduce the risk of not reproducing at all due to earlier aging or even death. Indeed, there is emerging evidence that those born VP/VLBW have higher risk of premature mortality [69,70] and may be aging earlier [71,72] and reproduce earlier. [22,59] A retrospective cohort study [73] also suggests that women born preterm may have a shorter childbearing period with an increased risk of early menopause. Thus, no difference in fertility in emerging adulthood of VP/VLBW may indicate a combination of a "live and reproduce fast" strategy while across the whole reproductive window, lower fertility. However, to empirically support this theory, further follow-up of the VP/VLBW cohorts into established adulthood (30–45 years) is required. A recent cohort study [74] followed 414 participants until 34–35 years of age and found that VP/VLBW is associated with lower fertility only during the late (≥30y) but not early (<30y) reproductive window. This larger sample using IPD replicates part of the result – VP/VLBW and term-born adults show no difference in fertility during the early reproductive window.

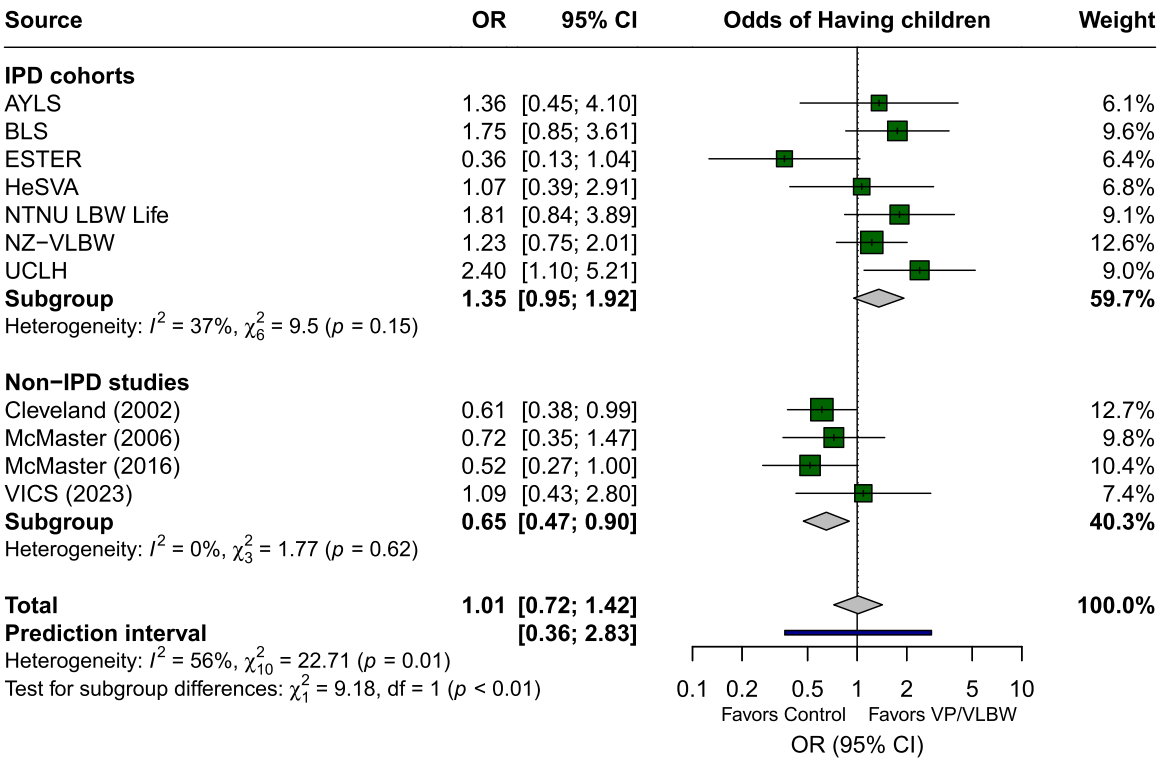


Fig. 2. Sensitivity meta-analysis comparing fertility in IPD cohorts vs non-IPD cohort studies of VP/VLBW and term-born control adults.

The association of VP/VLBW with fertility did not differ by sex in the present study, contrary to our hypothesis but consistent with previous studies [19,20,29] and a meta-analysis [6] which reported no moderation effect of sex. Conversely, two cohort studies [26,30] revealed that it is VP/VLBW women but not men being less fertile compared with their same-sex term-born peers. Thus, the Sexual Strategies Theory [33,34] may not sufficiently explain the fertility of VP/VLBW. Other individual factors may confound the potential moderation effect of sex.

Our study extends previous research by including individual-level factors. Previous studies have reported a dose-response pattern where fertility decreases with decreasing gestation or birth weight. [19,23,24] Considering all other individual factors, we found that neither gestational age nor birth weight was associated with fertility in VP/VLBW, suggesting the potential mediating effects of other medical and sociodemographic factors. One possible mediator is the presence of childhood NSI which was more frequent in VP/VLBW than term-born adults (13.1 % vs 1 %, see Appendix 4). However, given the correlation between neonatal morbidities and subsequent neurosensory impairments/disabilities, [75–77] the presence of neonatal morbidities (i.e., BPD, IVH) did not independently reduce fertility. This suggests that it is not neonatal morbidities per se but their consequences for adult functioning that are relevant for assessing mate quality, partnering, and fertility. Indeed, two meta-analyses [6,78] reported that more VP/VLBW had never experienced sexual intercourse or found no long-term partner by emerging adulthood. Long-term partnership, i.e., being married/cohabiting, as also shown in our results, emerged as the most important factor associated with fertility.

Moreover, we identified maternal and own education to be associated with fertility in VP/VLBW. Being born into a family with lower education and resources is associated with an increased risk of environmental harshness and poor body conditions, [79–81] which may trigger a fast LH strategy to engage in short-term mating, reproduce earlier, and have more children. [37,80,82] Conversely, being born into a family of highly educated parents and larger resources may favor a slow LH strategy to invest in somatic (i.e., growth, maintenance, and learning) [64] rather than reproductive effort, e.g., stay in education longer and obtain higher qualifications and delay parenthood. [83] Notably, more VP/VLBW had lower educational qualifications or ended education sooner than their term-born peers [1]; which in turn is associated with earlier adult transitions (e.g., parenthood). Thus, the association of VP/VLBW with fertility in emerging adulthood is mediated via maternal education, one marker of childhood/family socioeconomic status, and own education.

Unexpected were the incongruent results comparing IPD and aggregate data in the sensitivity meta-analysis. Among the 4 non-IPD cohort studies, [26,28–30] the Cleveland study [26] with young participants (mean sample age at 20 years) appears to be an outlier due to high teenage pregnancy rates reported for more deprived areas in the United States at the time. [84] The McMaster study [29,30] reported different findings on the same cohort at ages 23 and 32 years. The results at 23-year follow-up also indicated no difference in fertility to term-born controls. [29] The McMaster cohort [29,30] is born in the 1970's and the oldest of the studies included. It investigated participants born at extremely low birth weight (<1000 g) with a mean sample gestation of 27.1 weeks (i.e., extremely preterm) while the IPD cohorts included overall, heavier and higher gestation VP/VLBW participants. The rate of neurosensory impairments, in particular of visual impairments (retinopathy of prematurity), was high in the McMaster study [85] and may explain the lower fertility compared to the more recent VICS (2023) study [28] of extremely preterm survivors. Our IPD analysis shows that neurosensory impairment is a predictor of lower fertility.

Strengths and limitations

A strength of this meta-analysis is using IPD exclusively from prospective longitudinal cohorts, which allowed to consider individual-level factors. IPD meta-analysis has been regarded as the "gold standard" which offers considerable advantages over traditional meta-analysis. [86–89] One major benefit is improved quality and quantity of data by using consistent inclusion and exclusion criteria, [86,87] incorporating unpublished studies to avoid publication bias, [88,90] and allowing for data check and accurate data harmonization. [88,91]

Furthermore, the IPD approach can increase statistical power and lead to more precise results with the use of participant-level factors, [86,89] standardized analysis, [87] and sophisticated statistical analysis. [87,88]

Nonetheless, our findings did not capture the whole reproductive window of VP/VLBW. The age range of the IPD samples was 23–30 years and thus before most parents have children in high-income countries. [62] Despite this limitation, these IPD are the best available cohort study data from the largest dataset of prospective longitudinal studies of VP/VLBW in the world while none exist in low-to-moderate-income countries. Moreover, other relevant sociodemographic factors were not collected in most follow-up studies, e.g., the use of assisted reproductive technology (ART). However, it is estimated that infants born from ART account for only 3 % of the national births in Europe and even less < 30 years of age. [92]

Conclusion

This study examined the fertility of VP/VLBW young adults using a one-stage IPD meta-analysis. The results suggest that during emerging adulthood in high-income countries VP/VLBW is not associated with lower fertility and no sex by gestation differences were found. Among VP/VLBW young participants, sociodemographic factors have a stronger association with fertility than neonatal factors. The evidence is limited so far to the early reproductive window in the 20 s, and too few children were born to investigate whether there is cross-generational transmission of prematurity or low birth weight. Further follow-up into established adulthood will be required for definite answers on fertility after VP/VLBW birth. Taken together, this study showed that VP/VLBW adults in their 20 s and in high-income countries may not have lower fertility.

CRediT authorship contribution statement

Wolke Dieter: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Funding acquisition, Data curation, Conceptualization. **Nosarti Chiara:** Writing – review & editing, Data curation. **Indredavik Marit S.:** Writing – review & editing, Funding acquisition, Data curation. **Evensen Kari Anne I.:** Writing – review & editing, Funding acquisition, Data curation. **Räikkönen Katri:** Writing – review & editing, Funding acquisition, Data curation. **Wong Miranda Kit-Yi:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Darlow Brian A.:** Writing – review & editing, Data curation. **Horwood L. John:** Writing – review & editing, Data curation. **Harris Sarah L.:** Writing – review & editing, Data curation. **Kajantie Eero:** Writing – review & editing, Funding acquisition, Data curation. **Heinonen Kati:** Writing – review & editing, Data curation. **Mendonça Marina:** Writing – review & editing, Project administration, Methodology, Data curation. **van der Pal Sylvia:** Writing – review & editing, Funding acquisition, Data curation. **Tsalacopoulos Nicole:** Writing – review & editing, Project administration, Data curation. **Bartmann Peter:** Writing – review & editing, Data curation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.annepidem.2025.04.006.

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