Gestational age at birth and risk of intellectual disability without a common genetic cause: findings from the Stockholm Youth Cohort

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Abstract

Background: Preterm birth is linked to intellectual disability and there is evidence to suggest post-term birth may also incur risk. However, these associations have not yet been investigated in the absence of common genetic causes of intellectual disability (where risk associated with late delivery may be preventable) or with methods allowing stronger causal inference from non-experimental data. We aimed to examine risk of intellectual disability without a common genetic cause across the entire range of gestation, using a matched-sibling design to account for unmeasured confounding by shared familial factors.

Methods and Findings: We conducted a population-based retrospective study using data from the Stockholm Youth Cohort (n=499,621) and examined associations in a nested cohort of matched siblings (n=8,034). Children born at non-optimal gestational duration (before/after 40 weeks 3 days) were at greater risk of intellectual disability. Risk was greatest among those born extremely early (adjusted $OR_{24\ weeks}$=14.54 [95% CI 11.46–18.44]), lessening with advancing gestational age toward term ($aOR_{32\ weeks}$=3.59 [3.22–4.01]; $aOR_{37\ weeks}$=1.50 [1.38–1.63]); $aOR_{38\ weeks}$=1.26 [1.16-1.37]; $aOR_{39\ weeks}$=1.10 [1.04-1.17]) and increasing with advancing gestational age post-term ($aOR_{42\ weeks}$=1.16 [1.08–1.25]; $aOR_{42\ weeks}$=1.41 [1.21–1.64]; $aOR_{44\ weeks}$=1.71 [1.34–2.18]; $aOR_{45\ weeks}$=2.07 [1.47–2.92]). Associations persisted in a nested cohort of matched outcome-discordant siblings suggesting they were robust against confounding from shared genetic or environmental traits, although there may have been residual confounding by unobserved non-shared characteristics. Risk of intellectual disability was greatest among children showing evidence of fetal growth restriction, especially when birth occurred before or after term.

Conclusions: Birth at non-optimal gestational duration may be linked causally with greater risk of intellectual disability. The mechanisms underlying these associations need to be elucidated as they will be relevant to clinical practice concerning elective delivery within the term period and the mitigation of risk in children who are born post-term.

Introduction

Intellectual disability is a group of developmental disorders evident early in childhood and characterized by cognitive and functional impairments as a result of delayed or incomplete development of the mind[1]. Individuals with intellectual disability have a reduced ability to understand new or complex information and to learn and apply new skills, resulting in a reduced ability to cope independently[2]. Intellectual disability is thought to affect over 1 percent of the population[3, 4] although estimates vary with the demographic and socioeconomic composition of study populations[4, 5] and with definitions and study design[5, 6]. The cost of intellectual disability to individuals and society is substantial[7] and people living with these disabilities often face significant stigma[8] while encountering substantial health and social inequalities and early mortality[9].

Although there are many risk factors, a specific cause is identified for less than half of those with mild disabilities (IQ range 50-69) who make up the majority of cases[3, 10]. Mild intellectual disability often clusters within families[10] suggesting that genetic or other shared familial factors may influence risk. When disabilities are more severe, specific causes are identified in over 75 percent of cases, often involving genetic or chromosomal abnormalities and inborn errors of metabolism [10]. When intellectual disability is present without a specific genetic or chromosomal cause it is associated with advanced maternal age, maternal risk behaviors or medical problems during pregnancy and fetal growth restriction[11], suggesting that these may be risk factors.

While it is known that children born preterm (<37 completed weeks) are at greater risk of intellectual disability than those born at term[12], less is known about the development of risk along the gestational course, or about risk among post-term children (>41 weeks). This is important considering there is increasing evidence to suggest that post-term birth is associated with cognitive and academic deficits in childhood and adolescence[13-16], especially when the baby is growth-restricted[16].

The association between the full range of gestational duration, from very early to very late births, and intellectual disability has not yet been examined in population-based studies. Furthermore, the

evidence to date is insufficient because of incomplete control of confounding from shared familial factors and insufficient recognition that genetic causes of intellectual disability may also influence gestational duration[17, 18].

Therefore, in a large Swedish population-based cohort, we aimed to: 1) examine the associations between gestational age and intellectual disability without a common genetic cause, taking into account a range of potential confounders; 2) examine interactions between gestational duration and fetal growth in relation to risk of intellectual disability; and 3) explore the causal nature of associations between gestational duration and risk of intellectual disability in a nested cohort of matched outcome-discordant siblings.

Methods

Study cohort

The Stockholm Youth cohort is a register-based cohort of all individuals who lived in Stockholm County for at least one year between 2001 and 2011 and were aged between 0 and 17 years during that period (n=736,180)[19]. Using unique personal identification numbers, cohort members and their first degree relatives were linked with a range of national and regional registers including information on pregnancy- and birth related characteristics, socioeconomic characteristics and medical and psychiatric diagnoses.

We excluded individuals with genetic and inborn metabolic syndromes who had been diagnosed with intellectual disability (13.6 % of cases in our study population), children born outside Sweden, multiple births, adoptees, children <4 years of age by the end of follow up on the 31st of December 2011, with a missing link to biological parents, or with missing data on gestational age or other covariates (see Figure 1). We excluded individuals with implausible combinations of gestational age and birth weight following methods described elsewhere[16]. This left a cohort of 499,621 individuals to examine population-level associations between gestational age and intellectual disability. To examine

associations among matched siblings, we excluded individuals without full siblings in the cohort and families with outcome-concordant offspring (n=491,587) leaving a cohort of 8,034 matched outcome-discordant full siblings.

Exposure

We obtained information on gestational age at birth from the Medical Birth Register (MBR), constructing a categorical variable to define extremely to very preterm births (21-31 completed weeks), moderately to late preterm births (32-36 weeks), term births (37-41 weeks), post-term births (42 weeks) and very post-term births (43-45 weeks) for use in descriptive statistics and as an exposure variable in regression analyses. We also used a continuous definition of gestational age (in days) for regression analyses. A measure of weight-for-gestational age was calculated using week- and sex-specific birth weight distributions, identifying individuals in the lower and upper deciles as born small or large for gestational age respectively. To examine interactions between gestational duration and fetal growth, we constructed a categorical variable to identify those born preterm (<37 weeks) and small for gestational age, appropriate for gestational age (11th centile to 90th centile) or large for gestational age; those born at term (37-41 weeks) and small, appropriate or large for gestational age; and those born post-term (≥42) and small, appropriate or large for gestational age.

Outcome

We used a multisource ascertainment approach to identify cohort members with intellectual disability, similar to the case identification for autism described elsewhere [19]. We used the national patient register, the Stockholm county child and adolescent mental health register, the Stockholm country healthcare database (VAL) and the Stockholm adult psychiatry register to identify inpatient or outpatient diagnoses of intellectual disability recorded using ICD-10 (F70-79) and DSM-IV (317-318) codes and supplemented these diagnoses with a record of care at specialist habilitation services for individuals with intellectual disability in Stockholm County. We identified individuals with genetic

defects and inborn errors of metabolism commonly associated with intellectual disability to identify cases where a known genetic or metabolic cause was present (Table S1).

Covariates

To control for secular change in obstetric and diagnostic practice, we obtained year of birth from the Medical Birth Register (MBR). We then identified additional covariates which in the literature have been associated with pregnancy duration and risk of intellectual disability in offspring. From the MBR, we extracted data for offspring sex[5, 20], parity (1/ 2/ 3/ 4+)[11, 21], birth weight[11], maternal age (<20/ 20-24/ 25-29/ 30-34/ 35-39/ 40-44/ 45+)[11, 21], gestational diabetes[11, 22] and gestational hypertension or preeclampsia[11, 23]. We also extracted information for maternal and paternal country of birth (Sweden/ other Nordic/ other European/ Russia or Baltic States / Africa /Middle East/ Asia or Oceania/ North America/ South America)[5, 24], maternal and paternal history of psychiatric treatment[25, 26], quintiles of disposable family income adjusted for inflation and family size[27, 28], and parental educational attainment (≤9 years/ 10-12 years/ ≥13 years)[28, 29] at (or as close as possible to) birth.

Statistical analyses

Analyses were conducted in Stata/MP version 14.2. We examined the characteristics of the study cohort by gestational duration at birth. To examine population-level associations between gestational duration and risk of intellectual disability, we used generalized estimating equation (GEE) multivariable regression models with a logit link function, exchangeable correlation structure and robust variance estimators to ensure that the standard errors of our estimates were robust against clustering of intellectual disability within families[30]. We calculated restricted cubic regression splines based on five knot locations (5th, 27th, 50th, 73rd and 95th percentiles of the gestational age distribution) to allow for non-linear associations between continuously varying gestational duration and later risk of intellectual disability[31]. We statistically adjusted our estimates for covariates and calculated odds ratios by continuously varying gestational age at birth to estimate risk of intellectual disability associated with birth at specific moments along the gestational course. We investigated potential interactions

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between gestational age and fetal growth using GEE models with a categorical exposure variable to assess risk of intellectual disability among those born at varying gestational duration (preterm/ term/ post-term) and weight for gestational age (small/ appropriate/ large) with statistical adjustment for confounders.

In a nested cohort of matched outcome-discordant siblings we examined associations between continuously varying gestational age and risk of intellectual disability with conditional likelihood logistic regression models. This allowed us to explore the potential influence of unobserved familial traits, e.g. residual genetic risk/ unmeasured socioeconomic factors/ parental health behaviors, which may have confounded associations between gestational length and risk of intellectual disability. If we were to observe associations at the population level, non-association within families would suggest confounding by these shared familial traits. Conversely, replication of population-level associations within families would suggest they were robust against shared familial confounding, thereby allowing stronger causal inference from our result [32]. We statistically adjusted within-family associations for non-shared confounding characteristics including sex, parity, gestational diabetes, hypertension or preeclampsia, weight for gestational age, maternal and paternal age, disposable family income quintile, and parental educational attainment.

Sensitivity analyses

We compared characteristics for those with missing and complete data to assess whether our estimates may have been affected by selection bias (Table S2). To ensure that the association between gestational age and intellectual disability was not driven by presence of co-occurring autism spectrum disorder or attention deficit hyperactivity disorder (which are associated with intellectual disability [33-35] and for which risk may also vary by gestational age [36, 37]) we examined associations in a subset of the cohort without a record of these conditions (Figure S1 and Table S3). We examined whether the risks of intellectual disability associated with preterm or post-term birth varied with mode of delivery (Tables S4 and S5) using categorical measures to identify those born vaginally or by Caesarean section and in unassisted or forceps-/ ventouse-assisted deliveries at varying gestational duration. Finally, we

conducted post-hoc analyses to assess whether risk varied among children born in spontaneous or induced deliveries at varying gestational duration (Table S6).

Results

Prevalence of intellectual disability without a common genetic cause was estimated at 1% in our study population (Figure 1). Characteristics of the study cohort are described in Table 1. Prevalence among those born at term gestation was 0.9 percent. By contrast, 5.6 percent of children born extremely to very preterm and 1.6 percent of those born very post-term had intellectual disability.

Examining associations between gestational duration and risk of intellectual disability in a model using a continuous exposure variable with statistical adjustment for potential confounders (Figure 2), the adjusted odds ratio (aOR) for risk at extremely preterm birth (at 24 weeks) was estimated at 14.54 [95% CI 11.46 to 18.44]. This risk decreased with gestational age towards term ($aOR_{32\ weeks}$=3.59 [3.22 to 4.01]; $aOR_{37\ weeks}$=1.50 [1.38 to 1.63]; $aOR_{38\ weeks}$=1.26 [1.16 to 1.37]; $aOR_{39\ weeks}$=1.10 [1.04 to 1.17]) after which it increased with gestational age post-term ($aOR_{42\ weeks}$=1.16 [1.08 to 1.25]; $aOR_{43\ weeks}$=1.41 [1.21 to 1.64]; $aOR_{44\ weeks}$=1.71 [1.34 to 2.18]; $aOR_{45\ weeks}$=2.07 [1.47 to 2.92]).

We report associations using a categorical exposure variable in an online supplement (Table S7). Irrespective of gestational length, risk of intellectual disability was greatest among those showing evidence of fetal growth restriction (Table 2). This difference was most pronounced in the preterm group, but our results suggest risk of intellectual disability was also increased among children born post-term and growth-restricted. Associations between gestational length and risk of intellectual disability persisted when we repeated our analysis in a nested cohort of outcome-discordant siblings (Figure 3, Table S7).

In a subset of the cohort without a diagnosis of ASD or ADHD, pre- and post-term birth remained associated with increased risk of intellectual disability (Figure S1, Table S3). Among those born at 21 to 31 completed weeks of gestation, risk of intellectual disability was lesser when the baby was delivered by Caesarean section, while Caesarean birth was associated with greater risk than vaginal birth

between 37 to 41 weeks gestation (Table S4). There was no consistent variation in risk due to unassisted versus assisted delivery within gestational age categories (Table S5). Importantly, risk of intellectual disability associated with early or late birth remained when considering those born in vaginal or unassisted deliveries (Tables S4 and S5). Among those born between 37 and 41 weeks, risk of intellectual disability was greater when birth was induced (Table S6). This effect existed independently of the influence of fetal growth restriction or other potential confounders. Finally, children born in induced post-term deliveries were at greater risk of intellectual disability than children born spontaneously at term, while the increase in risk associated with spontaneous post-term birth was lesser (Table S6).

Discussion

In this large population-based study, we found a greater risk of intellectual disability without a common genetic cause among preterm and post-term births compared with term births. These associations were evident in analyses using the full sample, as well as in a nested cohort of matched outcome-discordant siblings. Risk of intellectual disability was greatest among those showing evidence of fetal growth restriction, especially when born before or after term. To our knowledge, this is the first total-population study to estimate risk of intellectual disability without a common genetic cause over the entire range of gestation using high-quality prospectively measured data. In addition to a range of measured confounders, this study explored the influence of unmeasured familial effects using a matched sibling design. This allowed us to take into account unmeasured familial confounding of the association between intellectual disability and gestational length, as these traits are heritable within families[10, 38, 39].

There were several limitations. First, 5 percent of the study cohort had missing data on gestational age at birth or other covariates. Although we cannot know with certainty how these exclusions may have affected our result, sensitivity analyses suggest that our estimates may have been conservative as they may have excluded preterm children with higher prevalence of intellectual disability (Table S2).

Second, we did not have information on whether gestational length was calculated by the mother's report of her last menstrual period or based on ultrasound measurement in specific pregnancies. As our sample includes births from 1984 onwards, it is likely that there is greater measurement error in earlier cohort years, where gestational length would have been estimated on the basis of last menstrual period for a larger proportion of pregnancies. This may have resulted in overestimation of rates of post-term birth[40-42] and underestimation of population-level[43] and within-family associations[44] between gestational length and later risk of intellectual disability. Third, while the matched-sibling design provides a powerful method to examine the influence of shared confounding, it is more sensitive than traditional methods to confounders not perfectly shared by the siblings. Selection based on exposure-discordance could also prompt discordance in terms of non-shared confounding characteristics, which may bias the within-family effect[44] . The size and direction of such bias depends on the similarity or dissimilarity of matched siblings in terms of exposure and confounding characteristics[44]. Given that measurement error in the gestational age variable would have downwardly biased our estimate of the within-family effect, additional bias due to sibling non-shared confounding would have either offset this downward bias or further enhanced it. Fourth, there may be bias due to omitted non-shared confounding characteristics in our matched sibling analyses. For example, it is possible that prenatal infection[45], maternal obesity[46, 47], or use of drugs or alcohol[48] may have influenced gestational length and resulted in greater risk of offspring intellectual disability in as far as these factors were present in one pregnancy but not the other.

The mechanisms underlying our findings are likely to differ depending on whether birth occurred before or after the due date. With regards to preterm birth, perturbations in development of the fetal brain because of shortened gestation can increase risk for longer-term neurodevelopmental problems [49], [50]. Our findings for preterm small-for-gestational age children would suggest that these effects might become particularly apparent if the fetus is already growth-restricted. After birth, further injury to the brain could result from respiratory support for preterm infants with immature pulmonary function [51]. Mechanisms linking post-term birth with later risk of intellectual disability might involve

placental deterioration or insufficiency causing fetal hypoxia or nutritional deficiencies [52], which in turn could result in injury to the fetal brain. Meconium aspiration, which is more common in post-term birth[52], may result in neonatal asphyxia thereby incurring risk for brain injury and later neurodevelopmental problems[53].

Our finding of associations among those born in unassisted or vaginal deliveries suggested that adverse obstetric circumstances did not explain the higher risk of intellectual disability associated with birth at <37 or >42 weeks. Furthermore, our findings suggest that risk of intellectual disability increases with induction of labor at further post-term gestation, although these estimates are likely to be biased by the higher risk nature of induced pregnancies as a whole (Table S6). Risk of intellectual disability may have also increased with advancing post-term gestational age when delivery started spontaneously, although our data may have been underpowered to detect these more subtle effects (Table S6). Importantly, given that the decision to induce labor will be informed by other factors than gestational length alone, we cannot infer from our data whether the risks associated with post-term delivery could be curtailed by induction of labor around term. This question may therefore be better answered by future research studies designed specifically to address this issue. Finally, in terms of the generalizability of our findings, the risks identified in our study may vary with regional differences in practice regarding the management of pre- or post-term pregnancy and in the quality of obstetric and neonatal care.

Our findings are consistent with other studies examining risk of cognitive deficit in relation to birth before or after term gestational duration [12-16, 54-60]. These studies suggest there may be increased risk of intellectual disability[12, 54], special educational needs[14, 58, 59], poorer performance in school[12, 15, 16, 55, 59] and lower IQ in childhood[13, 60] or adulthood[56, 57]. The independent risk of intellectual disability associated with being born small for gestational age is consistent with earlier studies examining other outcomes for fetal growth-restriction in infants born at preterm or post-term gestational duration[13, 15, 61, 62].

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In conclusion, our findings suggest that delivery at non-optimal gestational age is associated with greater risk of intellectual disability in offspring in the absence of common genetic causes. This association existed independently of a range of measured potential confounders as well as unmeasured confounding from shared familial factors. While this study cannot provide conclusive evidence for causality, our use of a matched sibling design offered a stronger approach to dealing with confounding due to unmeasured shared familial factors, therefore providing a better estimate of the causal effect than studies using traditional methods for dealing with confounding. As birth at non-optimal gestational duration may be linked causally with greater risk of intellectual disability, it is important that the mechanisms underlying these associations are elucidated because of their relevance to clinical practice concerning elective delivery within the term period and the mitigation of risk in children who are born post-term.

Conflict of interest statement: The authors declare having no conflicting interests.

Fig 1: Selection of the study cohort

Born alive between January 1st 1984 and December 31st 2011 (n=736,180) [1]

Remain (n=735,126)

Those with genetic or inborn metabolic errors who also had intellectual disability (n=1,054 [13.6% of ID cases])

Remain (n=662,663)

Child with missing data on gestational age due to being born outside Sweden (n=72,463)

Remain (n=531,948)

Multiple births, adoptees and children aged <4 years on December 31st 2011 (n=130,715)

Remain (n=524,777)

Missing link to biological parents (n=7,171)

Remain (n=502,998)

Missing on gestational age (n=21,779)

Remain (n=499,881)

Missing data on covariates (n=3,117)

Population-level analysis n=499,621 (n$_{ID}$=5,069)

Implausible birth weight for gestational age (n=260)

Matched outcome-discordant sibling comparison of n=8,034 children born to n=3,199 mothers

Individuals without full siblings in the cohort and families with outcome-concordant offspring (n=491,587)
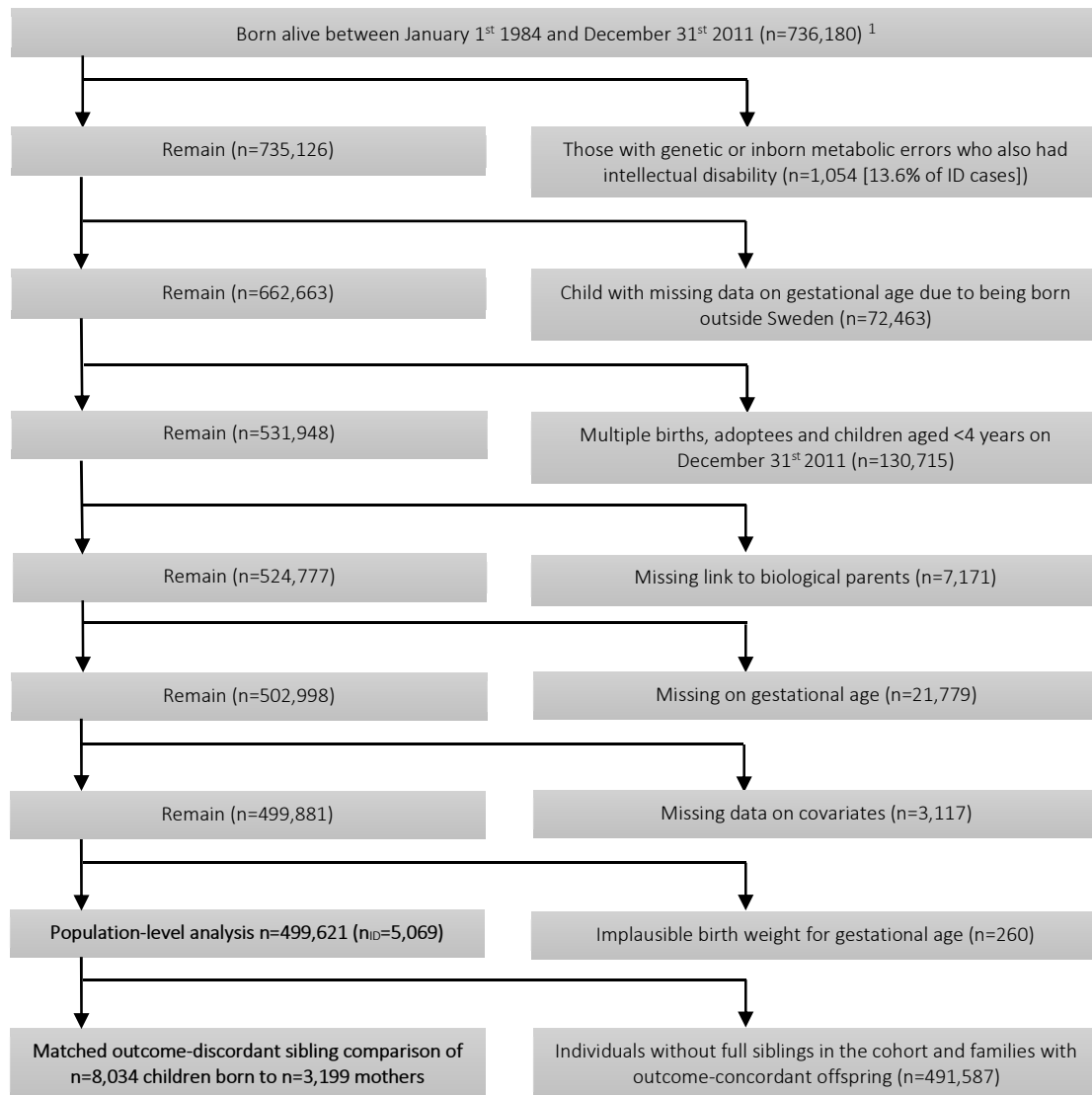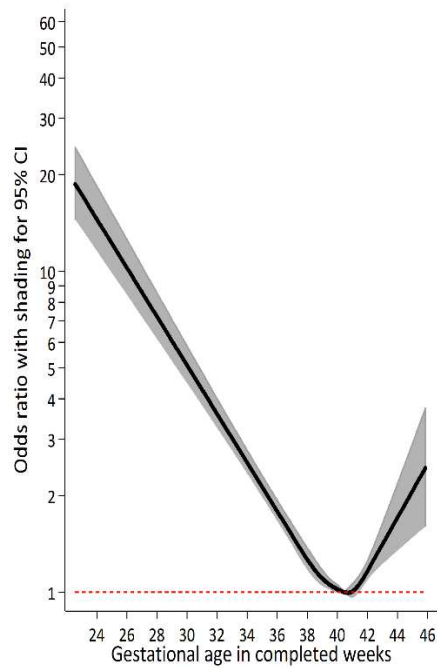
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Table 1: Characteristics of the sample by exposure status

		Extremely to very preterm	Moderate to late preterm	Term	Post-term	Very Post-term
Gestational weeks		21 - 31	32 - 36	37 - 41	42	43 - 45
Number of observations		2,601	20,271	438,215	34,828	3,706
Percentage of the cohort		0.5	4.1	87.7	7.0	0.7
		%	%	%	%	%
Female child		45.2	46.3	49.3	44.1	43.9
Mother's number of prior pregnancies	0	53.4	53.4	44.2	53.8	61.5
	1	27.1	28.4	37.0	30.1	23.5
	2	12.5	11.8	13.6	11.6	10.0
	3+	7.0	6.4	5.3	4.5	5.0
Birth weight in grams	<2500	99.7	37.6	1.1	0.1	0.1
	2500 – 4500	0.4	62.5	98.6	98.5	98.0
	>4500	0.0	0.0	0.3	1.4	1.9
Gestational hypertension or preeclampsia		23.6	12.9	3.2	1.9	1.5
Gestational diabetes		1.5	1.7	0.8	0.4	0.4
Delivery by Caesarean Section		58.9	32.4	13.3	16.5	22.5
Delivery assisted with ventouse or forceps		1.4	4.7	8.0	14.1	14.9
Maternal psychiatric history		38.6	37.0	32.7	31.5	33.0
Paternal psychiatric history		23.7	22.6	20.9	20.4	21.2
Mother's country of birth	Sweden	72.2	75.2	76.0	78.5	78.5
	Other	27.8	24.8	24.0	21.5	21.5
Father's country of birth	Sweden	70.7	74.7	74.7	77.3	77.6
	Other	29.3	25.3	25.3	22.7	22.4
Family disposable income quintile at birth	Lowest	14.3	15.1	14.7	13.3	15.4
	Second	21.7	20.4	20.8	19.4	19.1
	Third	19.9	20.4	21.6	21.1	19.3
	Fourth	22.3	22.3	21.6	22.6	22.1
	Highest	21.8	21.8	21.4	23.6	24.2
Parental educational attainment at birth	≤9 years	9.0	8.0	6.5	5.8	7.0
	10 - 11 years	42.0	43.3	40.5	39.9	40.7
	≥13 years	49.0	48.7	53.0	54.2	52.3
Maternal age	≤20	1.8	2.6	1.8	1.6	1.9
	20-24	13.0	15.7	14.7	13.4	16.3
	25-29	26.6	30.3	31.0	31.3	32.0
	30-34	32.1	31.1	33.8	34.9	31.8
	35-39	21.4	16.4	15.7	16.0	15.1
	40+	5.2	4.0	3.2	2.8	2.9
Paternal age	≤20	0.7	0.8	0.5	0.5	0.4
	20-24	7.2	8.9	7.2	7.0	8.2
	25-29	20.8	24.2	23.5	23.5	25.0
	30-34	30.8	31.5	33.5	33.7	32.5
	35-39	22.8	20.4	22.0	22.0	21.4
	40+	17.7	14.2	13.3	13.3	12.6

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Table 1: continued

		Extremely to very preterm	Moderate to late preterm	Term	Post-term	Very Post-term
	Gestational weeks	21 - 31	32 - 36	37 - 41	42	43 - 45
	Number of observations	2,601	20,271	438,215	34,828	3,706
	Percentage of the cohort	0.5	4.1	87.7	7.0	0.7
		%	%	%	%	%
Maternal country of birth	Sweden	72.2	75.2	76.0	78.5	78.5
	Other Nordic	5.1	4.6	4.2	4.2	4.6
	Other European	4.3	3.6	3.6	3.5	3.3
	Baltic States /Russia	0.6	0.5	0.5	0.7	0.5
	Africa	5.3	3.1	3.4	4.9	5.5
	Middle East	7.3	6.7	7.0	4.8	4.5
	Asia /Oceania	3.2	3.7	2.8	1.7	1.7
	North America	0.5	0.6	0.6	0.6	0.4
	South America	1.5	2.0	1.9	1.3	1.1
Paternal country of birth	Sweden	70.7	74.7	74.7	77.3	77.6
	Other Nordic	4.3	3.5	3.2	3.0	3.4
	Other European	4.6	4.5	4.7	4.6	4.5
	Baltic States /Russia	0.2	0.2	0.2	0.2	0.2
	Africa	6.2	4.1	4.1	5.7	5.8
	Middle East	8.6	7.6	8.3	5.8	5.5
	Asia /Oceania	2.4	2.3	1.9	1.2	1.1
	North America	0.8	0.7	0.8	0.7	0.70
	South America	2.3	2.3	2.2	1.5	1.21
Intellectual disability		5.6	1.8	0.9	1.0	1.6

Fig 2: Population-level association between gestational duration and risk of intellectual disability.


Notes: N=499,621. The population-level association between gestational duration and risk of intellectual disability was estimated using a generalized estimating equations model with a logit link, and adjusted statistically for year of birth, child sex, parity, gestational hypertension or preeclampsia, gestational diabetes, birth weight for gestational age, maternal and paternal age, maternal and paternal psychiatric history, maternal and paternal country of birth, family disposable income quintile at birth, and parental educational attainment at birth. Those born at 40 weeks and 3 gestational days are the referent.

Table 2: Interaction between gestational duration and fetal growth in relation to risk of intellectual disability

Gestational duration [a] / weight-for-gestational age category [b]	Odds ratio [c]	95% CI (lower	upper)	p	n (%) [d]	N [e]	Percentage of the cohort
Preterm / small	3.77	(2.97	4.84)	<0.001	73 (3.8)	1,935	0.4 %
Preterm / appropriate	2.24	(2.01	2.51)	<0.001	380 (2.1)	18,256	3.7 %
Preterm / large	2.36	(1.81	3.07)	<0.001	61 (2.3)	2,681	0.5 %
Term / small	1.88	(1.73	2.05)	<0.001	731 (1.8)	41,579	8.3 %
Term / appropriate	1.00				3,008 (0.9)	352,016	70.5 %
Term / large	1.06	(0.95	1.18)	0.27	402 (0.9)	44,620	8.9 %
Post-term / small	2.29	(1.83	2.85)	<0.001	85 (2.2)	3,822	0.8 %
Post-term / appropriate	1.11	(0.98	1.25)	0.10	292 (1.0)	30,840	6.2 %
Post-term / large	1.22	(0.87	1.69)	0.24	37 (1.0)	3,872	0.8 %

Notes: (a) Preterm was defined as birth < 37 completed weeks of gestation. Term birth was defined as birth between 37-41 completed weeks of gestation. Post-term birth was defined as birth at ≥42 completed weeks of gestation. (b) Fetal growth categories were defined as small-for-gestational age [in the lowest decile of the gestational age-specific birthweight distribution], appropriate-for-gestational age [in the 11th to 90th decile of the gestational age-specific birthweight distribution] and large-for-gestational age [in the upper decile of the gestational age-specific birthweight distribution]. (c) Population-level associations were estimated using a generalized estimating equations model with a logit link, and adjusted statistically for year of birth, child sex, parity, gestational hypertension or preeclampsia, gestational diabetes, maternal and paternal age, maternal and paternal psychiatric history, maternal and paternal country of birth, family disposable income quintile at birth, and parental educational attainment at birth. (d) Number and percentage of ID cases within gestational duration / fetal growth category; (e) Number of observations within gestational duration / fetal growth category. (e) N=499,621.

Fig 3: Within-family association between gestational duration and risk of intellectual disability
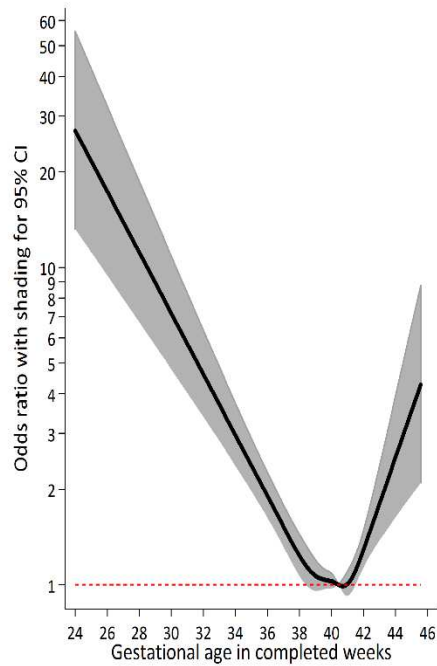
Notes: N=8,034. The within-family association was estimated using a conditional likelihood logistic regression model, and adjusted statistically for year of birth, child sex, parity, gestational hypertension or preeclampsia, gestational diabetes, birth weight for gestational age, maternal and paternal age, family disposable income quintile at birth, and parental educational attainment at birth. Those born at 40 weeks and 3 gestational days are the referent. The upper 95% confidence interval was truncated at OR=30 to ensure identical scaling with or population-level result.

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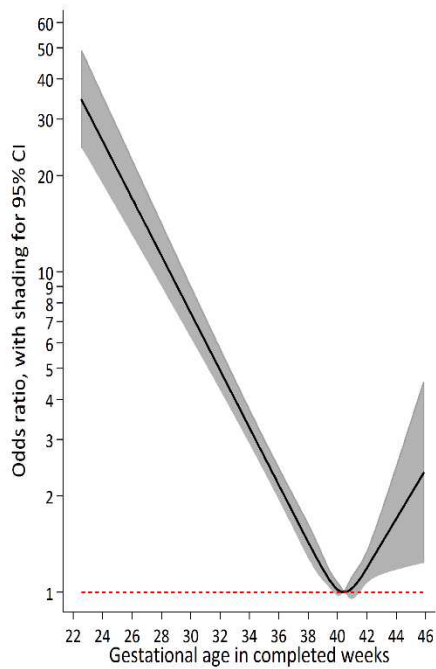## Table S1. Excluded genetic and inborn metabolic syndromes

	ICD-10 diagnostic code and description		ICD-9 diagnostic code and description		ICD-8 diagnostic code and description	
Genetic defects	Q85.0	Neurofibromatosis (non-malignant)	237.7	Neurofibromatosis (uncertain behavior)	743.4	Neurofibromatosis
	Q85.1	Tuberous sclerosis	759.5	Tuberous sclerosis	759.6	Tuberous sclerosis
	All Q90-Q99	Chromosomal abnormalities, not elsewhere specified	758	Chromosomal anomalies	759.3	Down's syndrome
					759.4	Other syndromes due to autosomal abnormality
					759.5	Syndromes due to sex chromosome abnormality
					759.8	Other specified syndromes
					759.9	Multiple congenital anomalies, unspecified
Inborn errors of metabolism	All of E70-E72	Metabolic disorders	All of 270	Disorders of amino-acid transport and metabolism	All of 270	Congenital disorders of amino-acid metabolism

Table S2: Characteristics of individuals with complete and missing data

		Complete data [a]	Missing data	Association between characteristic and risk of missing data
Number of observations		499,881	24,896	
Percentage of the cohort		95.26	4.74	
		%	%	OR (95% CI) [b]
Female		48.8	48.1	0.97 (0.95 – 1.00)
Gestational hypertension or preeclampsia	No	96.4	92.4	
	Yes	3.6	4.1	1.19 (1.12 – 1.27)
	Missing	0.0	3.5	
Gestational diabetes	No	99.2	95.7	
	Yes	0.8	0.7	0.92 (0.79 – 1.06)
	Missing	0.0	3.5	
Maternal psychiatric history	No	67.1	68.0	
	Yes	32.9	32.1	0.96 (0.94 – 0.99)
Paternal psychiatric history	No	79.1	79.9	
	Yes	20.9	20.1	0.95 (0.92 – 0.98)
Mother's country of birth	Sweden	76.1	66.7	
	Other	23.9	33.2	1.59 (1.55 – 1.63)
	Missing	0.0	0.1	
Father's country of birth	Sweden	74.9	65.2	
	Other	25.1	34.5	1.58 (1.54 – 1.62)
	Missing	0.0	0.3	
Family disposable income quintile around birth	Lowest	14.6	27.1	2.07 (1.99 – 2.15)
	Second	20.6	17.1	0.93 (0.89 – 0.96)
	Third	21.5	16.3	0.85 (0.81 – 0.88)
	Fourth	21.7	16.5	0.85 (0.81 – 0.88)
	Highest	21.6	19.3	
	Missing	0.0	3.7	
Highest parental educational attainment around birth	≤9 years	6.6	6.6	0.94 (0.89 – 0.99)
	10 - 11 years	40.6	31.4	0.72 (0.70 – 0.74)
	≥13 years	52.8	56.8	
	Missing	0.0	5.2	
Maternal age	<20	1.8	1.9	1.18 (1.07 – 1.30)
	20-24	14.6	13.1	
	25-29	31.0	28.6	1.08 (1.02 – 1.14)
	30-34	33.7	35.4	1.22 (1.15 – 1.29)
	35-39	15.7	17.3	1.32 (1.24 – 1.40)
	40+	3.2	3.6	1.44 (1.36 – 1.53)
Paternal age	<20	0.5	0.5	1.19 (0.99 – 1.44)
	20-24	7.3	6.0	
	25-29	23.5	20.7	1.08 (1.02 – 1.14)
	30-34	33.4	33.3	1.22 (1.15 – 1.29)
	35-39	21.9	23.6	1.32 (1.24 – 1.40)
	40+	13.4	15.8	1.44 (1.36 – 1.53)
	Missing	0.0	0.2	
Intellectual disability		1.0	1.6	1.57 (1.42 – 1.74)

Notes: (a) Individuals has complete data on gestational age and covariate measures. (b) Odds ratio with 95% confidence interval. (c) Assuming the associations reported in Table 1 in the main text, higher prevalence of parental foreign-birth and advanced parental age suggests prevalence of preterm birth may have been higher among those who were excluded due to having missing data.

Figure S1. Population-level associations between risk of intellectual disability and gestational duration among those without ASD or ADHD.

Notes: N=476,957. The population-level association between gestational duration and risk of intellectual disability was estimated using a generalized estimating equations model with a logit link, and adjusted statistically for year of birth, child sex, parity, gestational hypertension or preeclampsia, gestational diabetes, birth weight for gestational age, maternal and paternal age, maternal and paternal psychiatric history, maternal and paternal country of birth, family disposable income quintile at birth, and parental educational attainment at birth. Those born at 40 weeks and 3 gestational days are the referent.

Table S3. Population-level associations between risk of intellectual disability and gestational duration among those without ASD or ADHD.

Number of completed weeks	Odds ratio	95% CI (lower	upper)	p	n [3]	N [4]
21 - 31	8.25	(6.49	10.48)	<0.001	79	2,323
32 - 36	2.22	(1.90	2.60)	<0.001	185	19,073
37 - 41	1.00				1,694	418,827
42	1.07	(0.90	1.27)	0.44	139	33,227
43 - 45	1.68	(1.13	2.49)	0.011	25	3,507

Notes: N=476,957. The population-level association between gestational duration and risk of intellectual disability was estimated using a generalized estimating equations model with a logit link, and adjusted statistically for year of birth, child sex, parity, gestational hypertension or preeclampsia, gestational diabetes, birth weight for gestational age, maternal and paternal age, maternal and paternal psychiatric history, maternal and paternal country of birth, family disposable income quintile at birth, and parental educational attainment at birth. Those born between 37 and 41 completed weeks are the referent.

Table S4. Risk of intellectual disability among those born at varying gestational duration in vaginal or Caesarean deliveries

		Odds ratio	95% CI (lower	upper)	p	n [3]	N [4]
21 - 31 weeks	Vaginal	8.02	(6.29	10.23)	<0.001	77	1,070
	Caesarean	4.65	(3.63	5.96)	<0.001	69	1,530
32 - 36 weeks	Vaginal	1.68	(1.46	1.93)	<0.001	221	13,699
	Caesarean	2.17	(1.82	2.58)	<0.001	147	6,572
37 - 41 weeks	Vaginal	1.00				3,520	380,114
	Caesarean	1.23	(1.12	1.35)	<0.001	621	58,101
42 weeks	Vaginal	1.09	(0.96	1.22)	0.18	294	29,077
	Caesarean	1.36	(1.06	1.76)	0.017	62	5,751
43 - 45 weeks	Vaginal	1.52	(1.13	2.06)	0.006	44	2,873
	Caesarean	1.93	(1.13	3.31)	0.017	14	834

Notes: N=499,621. The population-level association between gestational duration and risk of intellectual disability was estimated using a generalized estimating equations model with a logit link, and adjusted statistically for year of birth, child sex, parity, gestational hypertension or preeclampsia, gestational diabetes, birth weight for gestational age, maternal and paternal age, maternal and paternal psychiatric history, maternal and paternal country of birth, family disposable income quintile at birth, and parental educational attainment at birth. Those born vaginally between 37 and 41 completed weeks are the referent.

Table S5. Risk of intellectual disability among those born at varying gestational duration in unassisted or assisted deliveries

		Odds ratio	95% CI (lower	upper)	p	n [3]	N [4]
21 - 31 weeks	Unassisted	5.81	(4.86	6.93)	<0.001	144	2,564
	Forceps or ventouse	6.89	(1.66	28.51)	0.008	2	36
32 - 36 weeks	Unassisted	1.80	(1.61	2.02)	<0.001	354	19,321
	Forceps or ventouse	1.80	(1.04	3.10)	0.036	14	950
37 - 41 weeks	Unassisted	1.00				3,814	403,120
	Forceps or ventouse	1.12	(0.99	1.25)	0.065	327	35,095
42 weeks	Unassisted	1.13	(1.00	1.26)	0.045	316	29,928
	Forceps or ventouse	0.96	(0.70	1.33)	0.82	40	4,900
43 - 45 weeks	Unassisted	1.51	(1.13	2.01)	0.006	48	3,154
	Forceps or ventouse	2.03	(1.08	3.81)	0.027	10	553

Notes: N=499,621. The population-level association between gestational duration and risk of intellectual disability was estimated using a generalized estimating equations model with a logit link, and adjusted statistically for year of birth, child sex, parity, gestational hypertension or preeclampsia, gestational diabetes, birth weight for gestational age, maternal and paternal age, maternal and paternal psychiatric history, maternal and paternal country of birth, family disposable income quintile at birth, and parental educational attainment at birth. Those born between 37 and 41 completed weeks in unassisted deliveries are the referent.

Table S6. Risk of intellectual disability among those born at varying gestational duration in spontaneous or induced deliveries

		Odds ratio	95% CI (lower	upper)	p	n [3]	N [4]
21 - 31 weeks	Spontaneous	5.73	(4.65	7.07)	<0.001	103	1,990
	Induced	5.07	(0.77	33.43)	0.092	1	21
32 - 36 weeks	Spontaneous	1.83	(1.59	2.11)	<0.001	225	13,108
	Induced	1.94	(1.30	2.91)	0.001	26	1,456
37 - 41 weeks	Spontaneous	1.00				2,671	303,315
	Induced	1.26	(1.10	1.45)	<0.001	259	23,845
42 weeks	Spontaneous	1.04	(0.88	1.21)	0.67	163	17,032
	Induced	1.36	(1.10	1.68)	0.005	90	8,593
43 - 45 weeks	Spontaneous	1.25	(0.76	2.06)	0.38	16	1,204
	Induced	1.74	(1.10	2.75)	0.018	19	1,241

Notes: N=371,805. The population-level association between gestational duration and risk of intellectual disability was estimated using a generalized estimating equations model with a logit link, and adjusted statistically for year of birth, child sex, parity, gestational hypertension or preeclampsia, gestational diabetes, birth weight for gestational age, maternal and paternal age, maternal and paternal psychiatric history, maternal and paternal country of birth, family disposable income quintile at birth, and parental educational attainment at birth. Those born between 37 and 41 completed weeks in spontaneous deliveries are the referent.

Table S7. Population-level and within-family associations between gestational duration and risk of intellectual disability

Number of completed weeks	Population-level association [a]						Within-family association [b]					
	Odds ratio	95% CI (lower	upper)	p	n [c]	N [d]	Odds ratio	95% CI (lower	upper)	p	n [c]	N [d]
21 - 31	5.72	(4.80	6.82)	<0.001	146	2,601	7.84	(4.55	13.50)	<0.001	85	112
32 - 36	1.78	(1.60	2.00)	<0.001	368	20,271	1.79	(1.42	2.24)	<0.001	213	430
37 - 41	1.00				4,141	438,215	1.00				2,706	6,836
42	1.08	(0.97	1.21)	0.15	356	34,828	1.21	(0.99	1.48)	0.056	252	579
43 - 45	1.54	(1.19	2.01)	0.001	58	3,706	2.07	(1.28	3.36)	0.003	40	77

Notes: (a) Population-level associations were estimated using a generalized estimating equations model with a logit link, and adjusted statistically for year of birth, child sex, parity, gestational hypertension or preeclampsia, gestational diabetes, birth weight for gestational age, maternal and paternal age, maternal and paternal psychiatric history, maternal and paternal country of birth, family disposable income quintile at birth, and parental educational attainment at birth. (b) The within-family association was estimated using a conditional likelihood logistic regression model, and adjusted statistically for year of birth, child sex, parity, gestational hypertension or preeclampsia, gestational diabetes, birth weight for gestational age, maternal and paternal age, family disposable income quintile at birth, and parental educational attainment at birth. (c) Number of ID cases within gestational age category; (d) Number of observations within gestational age category.