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ORIGINAL RESEARCH ARTICLE

Preterm birth and subsequent intelligence and academic performance in youth: A cohort study

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Abstract

Introduction: Worldwide, more children than before survive preterm birth. Preterm birth can affect long-term cognitive outcomes. The aim of our study was to investigate the association between preterm birth and academic performance and intelligence in youth.

Material and methods: This cohort study included all liveborn children in Denmark from 1978 to 2000. We used uni- and multivariable logistic and linear regressions to analyze associations between gestational age and school graduation, grade point average (GPA), attending conscription, and male intelligence scores at conscription. We adjusted for a priori defined potential confounders.

Results: The study included 1 450 681 children and found an association between preterm birth and lower academic performance, with children born extremely preterm having the lowest odds of graduating from lower- and upper secondary education (LSE and USE) and appearing before the conscription board (odds ratios of 0.45 [0.38–0.54], 0.52 [0.46–0.59], and 0.47 [0.39–0.56] for LSE, USE, and conscription, respectively, compared to the term group). Statistically significant differences were observed in LSE for total GPA and core subject GPA with higher GPAs in the term group, which were considered clinically relevant for mathematics with a 0.71 higher grade point for the term compared to the extremely preterm. Conversely, USE differences were less evident, and in linear regression models we found that preterm birth was associated with higher GPAs in the adjusted analyses; however, this was not statistically significant. We demonstrated statistically significant differences in intelligence scores at conscription with lower scores in the three preterm groups (−5.13, −2.73, and − 0.76, respectively) compared to the term group.

Conclusions: Low gestational age at birth was associated with not graduating from LSE and USE, achieving lower GPAs in LSE, not attending conscription, and lower

Abbreviations: BPP, Børge Priens Prøve test; GA, gestational age; GPA, grade point average; LSE, lower secondary education; MBR, The Danish Medical Birth Registry; NPR, The Danish National Patient Registry; USE, upper secondary education.

Emilie Pi Fogtmann Sejer and Agnes Kielgast Ladelund share first authorship.

intelligence scores in young adulthood. The findings remained significant after adjusting for potential confounders.

KEYWORDS
academic performance, conscription, gestational age, intelligence, preterm birth, school graduation

1 | INTRODUCTION

Preterm birth is defined as a live birth before 37 weeks of gestation. The global occurrence of preterm birth is 11%,[1,2] while in Denmark the rate is approximately 6%.[3,4] With improved treatment options, the proportion of surviving prematurely born children is increasing,[5] highlighting the need for studies investigating long-term consequences of preterm birth. The brain is vulnerable to preterm birth, and multiple studies have shown an association between preterm birth and cognitive impairment, impaired motor development (eg cerebral palsy), attention- and behavioral problems, as well as low intelligence, low academic performance,[6–17] and increased need for special education.[18–20] However, most previous studies have been limited by small sample sizes[7–9,20] and inadequate control for confounders such as parental education[17–19] and maternal intelligence,[8,14,20] which in a Danish study were established as significant predictors of child intelligence explaining 24% of the variance when also including study design variables and child's sex in the model.[21]

We conducted a study investigating the association between gestational age (GA) and intelligence and academic performance in youth. Using Danish national registers, we were able to retrieve large amounts of data and adjust for important confounders such as maternal and paternal educational level, ethnicity, maternal chronic disease, and medical complications during delivery, which makes our study unique.

Cognitive performance can be measured in various ways and at different time points in life. Focusing on long-term consequences of preterm birth, we chose to explore school grades in lower- and upper secondary education (LSE and USE) and intelligence scores from military conscription tests in youth, as these outcomes are meaningful and diverse measures of cognitive performance and available in the Danish registers. Previous studies from Norway and Sweden[22,23] found a significant association between low GA and low intelligence test scores at conscription. A recent Danish study[10] showed an association between preterm birth and lower grades in LSE and lower intelligence test scores at conscription; however, this study did not investigate academic performance in USE, which in Denmark is crucial to qualify for higher education and to our knowledge not yet examined. Also, their study design was different compared to ours with adjustment for other possible confounders.

We believe that determining the association of GA with intelligence and academic performance in youth, together with existing knowledge, can help clinicians make informed decisions about preterm delivery in collaboration with the parents to be, and improve follow-up care for individuals at risk of long-term cognitive impairment.

The aims of this study in a Danish cohort were to investigate the association between preterm birth and academic performance in LSE and USE and the association between preterm birth and intelligence scores at conscription in young men.

Key message

More infants survive preterm birth. In a large Danish cohort, adjusting for confounders we found associations of preterm birth with a lower chance of graduating from secondary education, lower final grades, and lower intelligence scores at conscription.

2 | MATERIAL AND METHODS

2.1 | Study population

This was a register-based cohort study. In Denmark, every person receives a unique social security number and a civil registration number (CPR-number). The CPR-number is used by nearly all public authorities and will identify a person throughout his or her entire life and across different public authorities and registers.

We defined the cohort as all registered liveborn children in The Danish Medical Birth Registry (MBR) in the period 1978–2000. MBR was established in 1968 and computerized in 1973. The registry contains data on the pregnancies, parents, and births of all liveborn children in Denmark. Since its establishment, the register has continued to evolve both in terms of the variables registered and the registration details, causing some of the variables to change over time.[24,25]

Some of the data needed for this study was either inadequately registered or not registered at all in MBR. Therefore, we also accessed The Danish National Patient Registry (NPR) for further information on the children and their mothers where inadequately registered or not registered at all in MBR. NPR was established in 1977 and includes information on all somatic inpatients. Since 1995, the register also contains data on all outpatients and patients from emergency rooms and psychiatric wards. NPR has been used as a source-register for MBR since 1995.[26,27] NPR contains the date of the contact, the associated diagnosis codes (ICD8 and ICD10), and if relevant, the codes from the classification of surgical procedures called OPR codes (1977–1995) and SKS codes (1996 up until now).

2.2 | Gestational age

GA was measured in completed weeks. Before 2005, the GA was based on information on the last menstrual period. We categorized GA into four groups according to WHO:[28] Extremely preterm: 22–27 completed weeks, very preterm: 28–31 completed weeks, moderate to late preterm: 32–36 completed weeks, and term: 37–45 completed weeks. All registered GAs less than 22 and higher than 45 completed weeks were considered wrongfully registered and were set as missing.

2.3 | School grades

In Denmark, primary and lower secondary education consist of 10 years of education at approximately age 6–16 years. At graduation from LSE, the students receive grades from the final exams and final annual grades reflecting their daily performance in class. In 2007, the current Danish grading system was introduced. It consists of a seven-point grading scale with numeric and corresponding letter grades according to the EU ECTS grading scale. The grading scale is as follows: −3 (F), 00 (Fx), 02 (E), 4 (D), 7 (C), 10 (B), and 12 (A), where −3 is the lowest possible score and 12 is the highest possible score. The minimum grade to pass an examination or subject is 02,[29] and 7 is the expected medium ranking.[30] All grades given previous to the current scale have been converted to the seven-point grading scale according to The Ministry of Higher Education and Science.[29]

The Danish general USE programs qualify for access to higher education. The duration of the programs is usually 2–3 years, and most often the USE is initiated directly after LSE or after an 11th year of voluntary LSE making most of the students between 16 and 17 years when initiating USE and 18–21 years when graduating. As for LSE, the results at graduation from USE are most often a combination of final examinations and final annual grades. In the study period, there have been numerous changes in the mandatory school subjects, and in addition, each student must choose to specialize in different subjects at different levels, making the possible combinations of subjects numerous.

We performed analyses on the total grade point average (GPA) including all examinations and annual grades of the year and the GPA for the core subjects Danish, mathematics, and English which were mandatory at the final examinations during all the years.

We excluded children with no address in Denmark at age 14 and 17 from the LSE and USE analyses, respectively ($N = 36\,617$ and $N = 33\,903$).

Since we did not have access to data on school grades after 2017, we only included children born before 1998 with an address in Denmark at age 17 in USE analyses.

2.4 | Intelligence

Data on male children's intelligence in young adulthood were obtained from the Danish Conscription Registry. The Danish Conscription Registry was established in 1987 and contains information on all men and women having appeared before a Danish Conscription Board for assessment prior to military or civil service. All men are invited when they become 18 years old. The Danish constitution demands all Danish male citizens to appear before the board unless one of the board's doctors declares the person unfit for service prior to the examination due to severe and well documented somatic or psychiatric disorders.[31] The examinations at conscription include an intelligence test, the Børge Priens Prøve (BPP) test, and a physical examination.[32]

Since 1956, the BPP has included the exact same 78 items. The test consists of four individually timed subtests of 17–24 items comprising spatial, numeric, logical, and verbal tasks. The final test score is the sum of correct answers, thus making 78 the highest possible score.[31,33] Teasdale et al. found that the correlation between the BPP score and educational level has remained stable through the 1990s and 2000s, that the BPP has a satisfactory test–retest reliability, and that the test scores are not positively associated with expressed attitude to being called upon to serve conscription, supporting the reliability and validity of the BPP in relation to cognitive ability.[33] Furthermore, Mortensen et al. found that the BPP correlates 0.82 with the full-scale Wechsler Adult Intelligence Scale and is therefore suited to epidemiological studies of intelligence.[34]

We retrieved the total BPP scores and dates of registration from the Danish Conscription Registry up until 2017, and therefore we included male children born before 1997 with an address in Denmark at age 18 in the analyses.

Figure 1 shows an overview of the cohort. The outcomes are analyzed at different ages due to the nature and availability of the data with young people graduating LSE and USE and attending conscription at different ages. However, most people graduate LSE at 16–17 years, USE at 18–21 years, and attend conscription in the early years after turning 18 years old.

2.5 | Covariates

A priori, we identified possible confounders and mediators based on directed acyclic graphs (Figure S1).[35] The following variables were considered potential confounders: Congenital malformations, breech presentation, delivery complications, cesarean section, multiple pregnancy, parity, maternal chronic disease, mother's age at the time of delivery, civil status of the mother (parents living together or not), maternal educational level, paternal educational level, and ethnicity of the child. We also adjusted for the sex of the child to minimize the variance.

If possible, data on covariates were retrieved from MBR. Some variables were inadequately registered for some or the entire study period, and others were not included in MBR at all. We retrieved

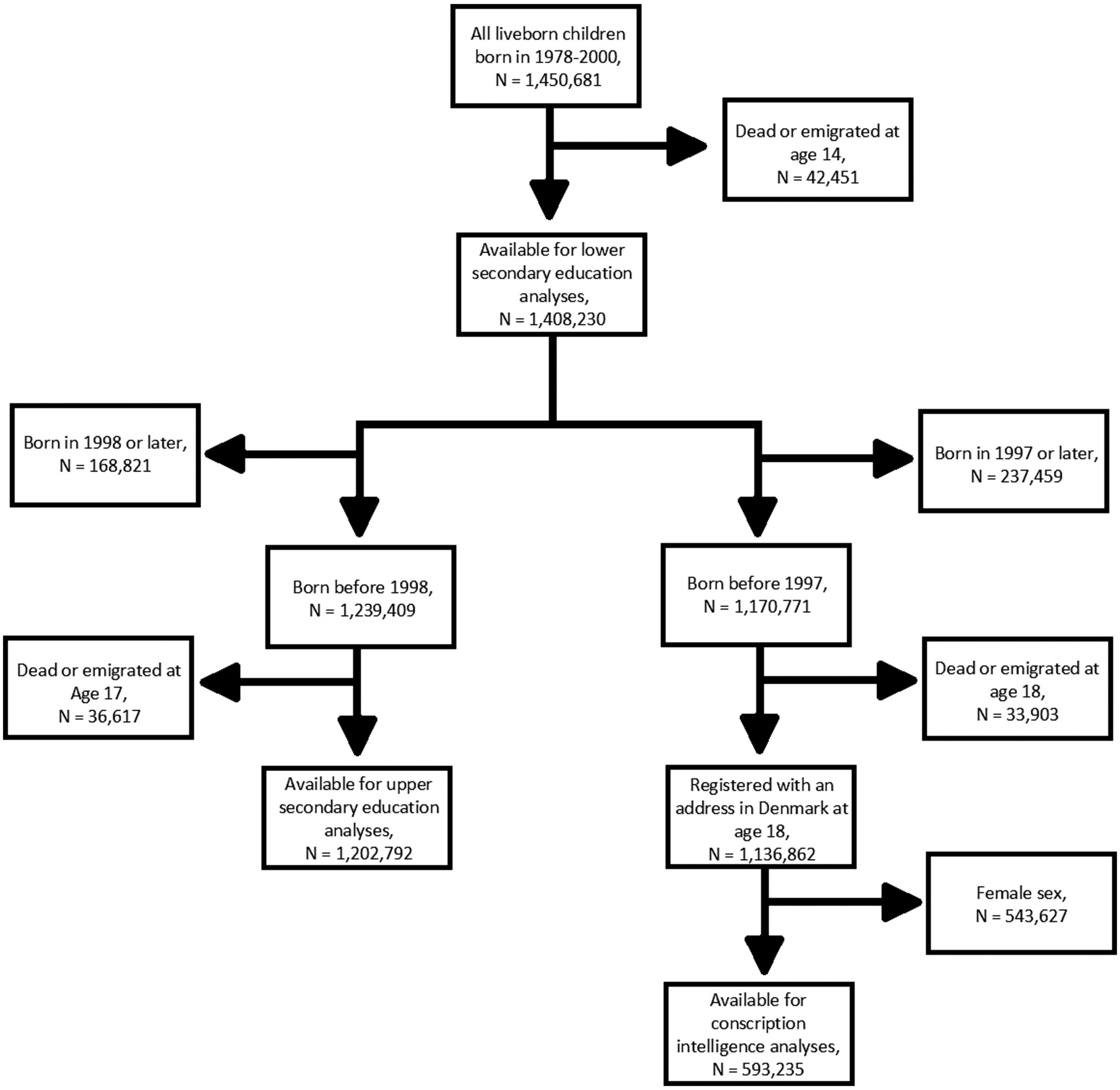

FIGURE 1 Flow chart of the study cohort.

these variables from NPR instead, and if a variable in NPR was not adequate for all the years, the gaps were completed with data from MBR when possible.

Data on sex of the child, breech presentation, multiple pregnancy, and mother's age were obtained from MBR and were available for the entire study period.

Data on cesarean section were retrieved from both MBR and NPR: If the mother was registered in NPR with an OPR, SKS, or ICD code indicating cesarean section between 2 weeks before to 20 weeks after the date of birth, the child was registered as born by cesarean section.

The OPR, SKS, ICD8, and ICD10 codes are listed in Table S1.

Data on delivery complications were obtained from NPR and included the diagnoses placenta previa, placental insufficiency, pre-eclampsia, placental abruption, uterine rupture, and umbilical complications. Only the umbilical complications variable was supplemented with data from MBR in the period 1978–1986. The diagnoses were included if they were registered in the period of 1 week before to 1 week after the date of birth (2 weeks for pre-eclampsia) to avoid diagnoses from earlier or later pregnancies. The ICD8 and ICD10 diagnosis codes included are listed in Table S2.

Data on congenital malformations, irrespective of age at diagnosis, were obtained from NPR in the period 1978–1996 and from MBR in the period 1997–2000. The data from MBR were reported by the maternity wards no later than 1 week after birth. Congenital malformations were defined as all ICD8 codes 74xxx and 75xxx and all ICD10 codes DQxxx exclusive all minor malformations according to Eurocat's guideline from 2005.[36]

For maternal chronic disease, the diagnoses and corresponding ICD8 and ICD10 codes were defined according to the comorbidity index reported by Joelving et al.[37] and included diabetes mellitus, thyroid- and parathyroid diseases, Cushing syndrome, polycystic ovary syndrome, polyglandular dysfunction, polyarthritis nodosa, rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, epilepsy, multiple sclerosis, hypertension, ischemic- and chronic heart diseases, cardiovascular diseases, atherosclerosis, coagulation disorders, chronic lung diseases, human immunodeficiency virus, mood disorders, schizophrenia and other paranoid psychoses, anxiety, and personality disorders. The diagnosis codes were retrieved from NPR, and we included all registered diagnoses before the date of delivery irrespective of time span before the index delivery.

The parity of the mother was available in MBR for children born between 1996 and 2000. For children born between 1982 and 1996, we investigated the cohort for one or more previous deliveries of the mother. For children born between 1978 and 1981, the parity of the mother was decided by multiple imputation (see below).

Statistics Denmark delivered data on parental educational level at birth. Statistics Denmark successfully identified all the mothers, while 10 834 (0.8%) of the fathers were unidentified. The educational level at the time of the child's birth was available from Statistics Denmark for 96% of the identified fathers and 98% of the identified mothers.

In the period 1978–1986, the marital status of the mother was available as married/unmarried. For 1986–2000, data on whether the children were living with two adults one year after birth were provided by Statistics Denmark thus enabling the variable "parents living together."

The ethnicity of the children was also provided by Statistics Denmark. Since immigrated children not born in Denmark were not included in the cohort, all children were categorized as either Danish or descendants of an immigrant.

Table S3 provides an overview of the data origin.

2.6 | Statistical analyses

Statistical analyses were performed using RStudio and SAS 9.4 TS Level 1M3.

We performed uni- and multivariable logistic regression analyses on the association between GA and graduating/attending LSE, USE, and conscription. In the multivariable analyses, we adjusted for the above-mentioned covariates. The results are presented as odds ratios with 95% confidence intervals.

We performed uni- and multivariable linear regression analyses on the association between GA and GPAs obtained in LSE and USE, and intelligence scores at conscription. We adjusted for the above-mentioned covariates. The results are presented as regression coefficients with 95% confidence intervals.

We performed secondary analyses investigating (1) differences in baseline characteristics and educational and intelligence outcomes between children with known and missing GA, (2) excluding the post-term births after GA 41+6 from the reference group, (3) removing the variables delivery complications, breech presentation, and cesarean section from the adjusted analyses, and (4) relating mothers' educational level to children passing USE.

Missing values appeared in the variables GA, ethnicity of the child, marital status of the mother, maternal and paternal educational level, and parity. To avoid discarding data, we performed multiple imputations with 10 imputations of five iterations each in RStudio using the package MICE.

3 | RESULTS

The study cohort consisted of 1 450 681 children with 3086 born extremely preterm, 8842 very preterm, 65 162 moderately to late preterm, 1 301 330 at term, and 72 261 with missing GA at birth.

Table 1 shows the characteristics of the children and their parents. In the term group, the mothers were more likely to be young, multiparous, and living together with a partner, and a tendency towards longer parental education was seen. In the preterm groups, maternal chronic disease, multiple pregnancy, delivery complications, and breech presentation of the baby were more frequent. Term-born children were more likely to be female, of Danish origin, and less likely to have died or emigrated at age 18. Generally, the distribution of all baseline characteristics differed <3 percentage points between women and their children with known and missing GA except civil status of the mother (85% living together with a partner for known GA vs. 74% for missing GA). This is shown in Table S4.

Table 2 shows a statistically significant association between preterm birth and lower academic performance, with children born extremely preterm having the lowest likelihood of graduating from LSE (ranging from 90.1% if born extremely preterm to 95.9% if born at term), USE (40.6%–55.4%), and appearing before the conscription board (52.6%–75.0%). Statistically significant differences were also observed in LSE for total GPA and core subject GPA with higher grades in the term group. The largest disparities between the groups were seen in mathematics (0.71 grade points higher for term vs. extremely preterm). Although the extremely preterm group had the highest grades in English (foreign language), this difference was not considered clinically relevant (0.03 grade point). In USE, no statistically significant difference in the total GPA was seen between the groups, and differences in core subject GPA were considered clinically insignificant. The BPP intelligence score at conscription showed a statistically significant difference between the groups with higher scores in the term group (42.8 points vs. 36.9 points in the extremely preterm group).

Table 3 shows the odds ratios of graduating from LSE and USE and conscription appearance, indicating that preterm birth is associated with lower odds of graduating from LSE and USE and appearing before the conscription board. These associations persisted after adjusting for potential confounders, with children born extremely preterm having the lowest odds of graduating from LSE, USE, and appearing before the conscription board.

Table 4 presents the linear model results, which demonstrate that preterm birth is associated with lower total GPA and core subject GPA in LSE, though, only a difference up to 0.27 grade points were seen between the groups. Conversely, in USE, preterm birth was associated with higher GPAs in the adjusted analyses (except for core subject GPA in the extremely preterm group); however,

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TABLE 1 Characteristics of pregnant women and their children born in Denmark in 1978–2000.[a]

Characteristics	Extremely preterm (<28 weeks)	Very preterm (28 to 31 + 6 weeks)	Moderate to late preterm (32 to 36 + 6 weeks)	Term (≥37 weeks)	Missing, *n* (%)
Number (%) (*n* = 1 450 681)	3086 (0.21)	8842 (0.61)	65 162 (4.49)	1 301 330 (89.70)	72 261 (4.98)
Sex, *n* (%)					
Male	1710 (55.41)	4975 (56.27)	36 112 (55.42)	676 365 (51.97)	0 (0)
Female	1376 (44.59)	3867 (43.73)	29 050 (44.58)	624 965 (48.03)	
Ethnicity, *n* (%)					
Danish	1402 (45.43)	7260 (82.11)	59 531 (91.36)	1 218 755 (93.65)	13 891 (0.96)
Second generation immigrant	110 (3.56)	443 (5.01)	3947 (6.06)	74 273 (5.71)	
Mother's civil status, *n* (%)					
Together	1473 (47.73)	6603 (74.68)	53 046 (81.41)	1 101 791 (84.67)	10 359 (0.71)
Apart	407 (13.19)	1553 (17.56)	11 000 (16.88)	193 108 (14.84)	
Paternal education, *n* (%)					
Very short	2236 (72.46)	6765 (76.51)	50 113 (76.91)	971 547 (74.66)	57 928 (3.99)
Short	79 (2.56)	293 (3.31)	2301 (3.53)	45 019 (3.46)	
Medium	222 (7.19)	838 (9.48)	5912 (9.07)	141 686 (10.89)	
Long	185 (5.99)	443 (4.90)	3700 (5.68)	92 790 (7.13)	
Maternal education, *n* (%)					
Very short	2400 (77.77)	6902 (78.06)	50 344 (77.26)	953 962 (73.31)	33 630 (2.32)
Short	65 (2.11)	246 (2.78)	1937 (2.97)	41 595 (3.20)	
Medium	421 (13.64)	1213 (13.72)	9242 (14.18)	227 511 (17.48)	
Long	114 (3.69)	247 (2.79)	1995 (3.06)	49 375 (3.79)	
Mother's age, years (SD)[b]	28.66 (5.43)	28.16 (5.26)	28.03 (5.18)	27.91 (4.82)	0 (0)
Maternal chronic disease, *n* (%)					
Yes	291 (9.43)	764 (8.64)	5545 (8.51)	59 471 (4.57)	0 (0)
No	2795 (90.57)	8078 (91.36)	59 617 (91.49)	1 241 859 (95.43)	
Maternal parity, *n* (%)					
Primipara	1630 (52.82)	4642 (52.50)	32 143 (49.33)	539 204 (41.43)	237 531 (16.37)
Multipara	1167 (37.82)	3224 (36.46)	25 226 (38.71)	587 963 (45.18)	
Delivery complications, *n* (%)					
Yes	282 (9.14)	1157 (13.09)	5415 (8.37)	40 663 (3.12)	0 (0)
No	2804 (90.86)	7685 (86,91)	59 711 (91.63)	1 260 667 (96.88)	
Breech presentation, *n* (%)					
Yes	962 (31.17)	2099 (23.74)	8848 (13.58)	48 451 (3.72)	0 (0)
No	2124 (68.83)	6743 (76.25)	56 314 (86.42)	1 252 879 (96.28)	
Multiple pregnancy, *n* (%)					
Yes	761 (24,66)	2093 (23.67)	12 465 (19.13)	23 595 (1.81)	0 (0)
No	2325 (75,34)	6749 (76.33)	52 697 (80.87)	1 277 735 (98.19)	
Dead or emigrated, *n* (%)					
At age 14	1636 (53.53)	1323 (14.96)	2971 (4.56)	34 056 (2.62)	0 (0)
At age 17	1636 (53.53)	1337 (15.12)	3031 (4.65)	35 305 (2.71)	0 (0)
At age 18	1634 (53.47)	1339 (15.14)	2988 (4.59)	34 584 (2.66)	0 (0)

[a]Observed data.

[b]Standard deviation.

these differences did not reach statistical significance. The mothers' educational level could not explain these findings. Statistically significant differences in intelligence were observed with BPP scores −5.13 (95% confidence interval −6.21 to −4.05) in the extremely preterm group, −2.73 (−3.15 to −2.30) in the very preterm group, and −0.76 (−0.91 to −0.62) in the moderate to late preterm

TABLE 2 Educational and intelligence outcomes of children born in Denmark in 1978–2000.[a]

Characteristics	Extremely preterm (<28 weeks)	Very preterm (28 to 31 + 6 weeks)	Moderate to late preterm (32 to 36 + 6 weeks)	Term (≥37 weeks)	*p*-value	Participants with no grades, *n* (%)
Lower secondary education, *n* (%) (N = 1 408 230)	1450 (0.10)	7519 (0.53)	62 191 (4.42)	1 267 274 (89.99)	–	Missing: 69 796 (4.96)
Graduated lower secondary education, *n* (%)						
Yes	1307 (90.14)	6945 (92.37)	58 582 (94.20)	1 215 177 (95.89)	<0.001	NA[b]
No	143 (9.86)	574 (7.63)	3609 (5.80)	52 097 (4.11)		
Registered with at least four grades, *n* (%)						
Yes	965 (66.55)	4824 (64.16)	40 717 (65.47)	819 667 (64.68)	<0.001	NA
No	485 (33.45)	2695 (35.84)	21 474 (34.53)	447 607 (35.32)		
Total grade average, mean (SD[c])	6.26 (2.31)	6.24 (2.30)	6.30 (2.31)	6.44 (2.26)	<0.001	527 540 (37.46)
English grade average, mean (SD)	6.70 (3.09)	6.53 (3.09)	6.53 (3.08)	6.67 (3.03)	<0.001	527 531 (37.46)
Danish grade average, mean (SD)	6.35 (2.39)	6.32 (2.33)	6.32 (2.32)	6.50 (2.26)	<0.001	527 531 (37.46)
Mathematics grade average, mean (SD)	5.84 (2,80)	6.06 (2,83)	6.37 (2.84)	6.55 (2.76)	<0.001	527 531 (37.46)
Core subjects grade average, mean (SD)	6.30 (2.45)	6.30 (2.46)	6.41 (2.45)	6.57 (2.40)	<0.001	527 531 (37.46)
Upper secondary education, *n* (%) (N = 1 202 792)	1086 (0.090)	5997 (0.50)	51 107 (4.25)	1 079 119 (89.72)	–	Missing: 65 483 (5.44)
Graduated upper secondary education, *n* (%)						
Yes	441 (40.61)	2607 (43.47)	25 287 (49.48)	597 871 (55.40)	<0.001	NA
No	654 (59.39)	3390 (56.23)	25 820 (50.52)	481 248 (44.60)		
Registered with at least four grades, *n* (%)						
Yes	454 (41.80)	2602 (43.39)	24 815 (48.55)	578 187 (53.58)	<0.001	NA
No	632 (58.20)	3395 (56.61)	26 292 (51.45)	500 932 (46.42)		
Total grade average, mean (SD)	6.62 (2.18)	6.60 (2.14)	6.55 (2.15)	6.58 (2.12)	0.13	570 790 (47.46)
English grade average, mean (SD)	6.54 (2.72)	6.50 (2.78)	6.38 (2.74)	6.41 (2.71)	0.094	571 116 (47.48)
Danish grade average, mean (SD)	6.50 (2.53)	6.48 (2.50)	6.39 (2.47)	6.45 (2.44)	0.0037	571 090 (47.48)
Mathematics grade average, mean (SD)	5.49 (3.42)	5.76 (3.29)	5.78 (3.34)	5.86 (3.329	<0.001	629 931 (52.37)
Core subjects grade average, mean (SD)	6.21 (2.31)	6.26 (2.39)	6.19 (2.39)	6.24 (2.37)	0.0039	630 319 (52.40)
Conscription, *n* (%) (N = 593 235)	533 (0.090)	3115 (0.53)	26 778 (4.51)	531 762 (89.64)	–	Missing: 31 047 (5.23)
Appearance before conscription board, *n* (%)						
Yes	291 (52.62)	1936 (62.15)	19 006 (70.98)	399 041 (75.04)	<0.001	NA
No	242 (43.67)	1179 (37.85)	7772 (29.02)	132 721 (24.96)		
BPP[d] score, mean (SD)	36.87 (10.31)	39.59 (10.43)	41.64 (10.20)	42.75 (9.97)	<0.001	149 951 (25.28)

[a]Observed data.
[b]None applicable.
[c]Standard deviation.
[d]Børge Priens Prøve test.

TABLE 3 Logistic model of the association between gestational age and graduating from lower- and upper secondary education and appearing before a conscription board.

	Extremely preterm (<28 weeks)	Very preterm (28 to 31+6 weeks)	Moderate to late preterm (32 to 36+6 weeks)	Term (≥37 weeks)
Graduating lower secondary education	n[a] = 1518	n[a] = 7789	n[a] = 65 146	n[a] = 1 333 777
Unadjusted OR (95% CI)	0.40 (0.33–0.47)	0.52 (0.48–0.57)	0.70 (0.67–0.72)	Reference
Adjusted[b] OR (95% CI)	0.45 (0.38–0.54)	0.61 (0.55–0.66)	0.78 (0.75–0.81)	Reference
Graduating upper secondary education	n[a] =1141	n[a] = 6230	n[a] = 53 812	n[a] = 1 141 610
Unadjusted OR (95% CI)	0.56 (0.49–0.63)	0.62 (0.59–0.65)	0.79 (0.78–0.80)	Reference
Adjusted[b] OR (95% CI)	0.52 (0.46–0.59)	0.65 (0.61–0.68)	0.84 (0.82–0.86)	Reference
Appearance before a conscription board	n[a] = 556	n[a] = 3210	n[a] = 27 909	n[a] = 561 560
Unadjusted OR (95% CI)	0.41 (0.34–0.55)	0.55 (0.52–0.60)	0.82 (0.79–0.84)	Reference
Adjusted[b] OR (95% CI)	0.47 (0.39–0.56)	0.61 (0.56–0.65)	0.85 (0.83–0.87)	Reference

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Mean of the 10 imputations.

[b]Adjusted for: Sex, delivery complications, breech presentation, cesarean section, congenital malformations, multiple pregnancy, maternal parity, mother's age, maternal chronic disease, maternal educational level, paternal educational level, civil status of the mother, and ethnicity of the child.

group compared to the term group after adjusting for potential confounders.

Differences in educational and intelligence outcomes between children with known and missing GA (5% of the population) are shown in Table S5. For graduation from LSE and USE, the differences were <4 percentage points between children with known and missing GA. Looking at grade averages across LSE and USE, all differences were <0.2 grade points except for English in LSE. Appearance before the conscription board differed by seven percentage points in favor of children with known GA; however, the BPP score differed only by 1.63 points in favor of the children with missing GA.

We included post-term births in our reference group in the main analyses but performed post hoc analyses excluding the post-term births after GA 41+6 from the reference (term) group and found that no considerable differences were seen. These analyses are shown in Tables S6 and S7.

Finally, we also performed post hoc analyses removing the variables delivery complications, breech presentation, and cesarean section from the adjusted analyses, which changed the results very little.

4 | DISCUSSION

In this study, we found that GA was associated with LSE and USE graduation with almost 10% of the extremely prematurely born infants not being able to achieve a mandatory educational degree (LSE), while this was only the case for 4% of the children born at term. When looking at total and core subject GPAs, the prematurely born children achieved statistically significantly lower grades in LSE, especially for mathematics; however, for the other subjects, the differences were rather small and clinically insignificant. We found a tendency towards higher GPAs among the prematurely born children in USE, which was the only association in favor of the prematurely born; however, this was not statistically significant. We hypothesized that this could be due to it being a selected group of prematurely born infants with extra good resources (having mothers with longer educations) who graduate USE; however, post hoc analyses showed that this was not the case (Table S8). None of the other covariates could explain the finding either. We believe that the main reason is probably selection bias, as USE is a voluntary educational degree to qualify for higher education, in contrast to LSE and conscription, which are mandatory. Therefore, the young people who enter and are capable of finishing USE represent a selected group.

With regard to conscription and BPP scores, we found statistically significantly lower odds of attending conscription and lower BPP scores in the preterm groups compared to the children born at term, which were considered clinically relevant. A part of the non-attending young men must have been deemed unfit for conscription prior to the conscription date. It is likely that some of those who did not attend conscription would be reported as unfit for the BPP and would have performed worse compared to the attendees, if they had appeared, and therefore, our findings may be an underestimation of the true differences in BPP scores between the groups.

Generally, our findings are in line with previous studies. A similar study to ours[10] with a sibling design also found lower grades at LSE graduation, especially for mathematics, and lower intelligence test scores at conscription for children born before 34 weeks of gestation. A systematic review and meta-analysis[15] of 7323 participants aged 5–18 years of whom 4006 were born preterm concluded that premature infants are at greater risk of academic underperformance in aggregate measures of reading and mathematics. Another meta-analysis[16] involving 74 studies and 64 061 children from 2 years of age found lower scores for preterm children in motor skills, behavior, reading, mathematics, and spelling that persisted to secondary school, except for mathematics. GA accounted for 38%–48% of the observed intelligence quotient variance. A study from Sweden[17] with more than 2 million

TABLE 4 Linear model of the association between gestational age and lower- and upper secondary education grades and conscription intelligence test scores.

	Extremely preterm (<28 weeks)	Very preterm (28 to 31 + 6 weeks)	Moderate to late preterm (32 to 36 + 6 weeks)	Term (≥37 weeks)
Lower secondary education	n[a] = 1518	n[a] = 7789	n[a] = 65 146	n[a] = 1 333 777
Unadjusted total mean grade average (95% CI)	−0.18 (−0.32 to 0.037)	−0.21 (−0.27 to 0.14)	−0.14 (−0.17 to 0.12)	Reference
Unadjusted core subject mean grade average (95% CI)	−0.26 (−0.41 to 0.11)	−0.27 (−0.34 to 0.20)	−0.17 (−0.19 to 0-14)	Reference
Adjusted[b] total mean grade average (95% CI)	−0.21 (−0.33 to 0.080)	−0.16 (−0.22 to 0.10)	−0.081 (−0.10 to 0.060)	Reference
Adjusted[b] core subject mean grade average (95% CI)	−0.27 (0.41 to 0.14)	−0.21 (−0.27 to 0.14)	−0.094 (−0.12 to 0.071)	Reference
Upper secondary education	n[a] = 1141	n[a] = 6230	n[a] = 53 812	n[a] = 1141,610
Unadjusted total mean grade average (95% CI)	0.027 (−0.17 to 0.21)	0.020 (−0.060 to 0.10)	−0.033 (−0.060 to 0.0066)	Reference
Unadjusted core subject mean grade average (95% CI)	−0.053 (−0.28 to 0.17)	0.010 (−0.084 to 0.10)	−0.060 (−0.091 to 0.029)	Reference
Adjusted[b] total mean grade average (95% CI)	0.033 (−0.15 to 0.22)	0.071 (−0.0059 to 0.15)	0.024 (−0.0021 to 0.051)	Reference
Adjusted[b] core subject mean grade average (95% CI)	−0.038 (−0.25 to 0.10)	0.084 (−0.0062 to 0.17)	0.016 (−0.015 to 0.047)	Reference
Børge Priens Prøve (BPP) test	n[a] = 556	n[a] = 3210	n[a] = 27 909	n[a] = 561 560
Unadjusted score (95% CI)	−5.79 (−6.91 to 4.67)	−3.21 (−3.65 to 2.77)	−1.16 (−1.30 to 1.01)	Reference
Adjusted[b] score (95% CI)	−5.13 (−6.21 to 4.05)	−2.73 (−3.15 to 2.30)	−0.76 (−0.91 to 0.62)	Reference

Abbreviation: CI, confidence interval.

[a]Mean of the 10 imputations.

[b]Adjusted for: Sex, delivery complications, breech presentation, cesarean section, congenital malformations, multiple pregnancy, maternal parity, mother's age, maternal chronic disease, maternal educational level, paternal educational level, civil status of the mother, and ethnicity of the child.

children showed a negative effect of preterm birth on the grades achieved when leaving lower secondary education, but the effect became smaller from 1973 to 1994. However, the effect persisted, although attenuated, when comparing siblings.

In contrast, a recent study[38] that investigated the relationship between moderate to late preterm birth and long-term educational outcomes after adjusting for socioeconomic status showed that the negative effects of preterm birth (GA > 32 weeks) washed out after eighth grade. This is not quite in line with our findings; however, the study showed a relationship in the lower grades with the largest adverse effects among the most preterm. Also, they found a higher risk of suspension among the prematurely born children in grades 9–12 suggesting associations between preterm birth and later behavioral outcomes. A Swedish[39] and Danish study[10] suggested that the negative association of school performance with preterm birth is attributable to other factors than preterm birth itself, as the association vanished after GA 31 and 34 weeks, respectively, when comparing siblings. In our study, we did not compare siblings but adjusted for a wide range of socioeconomic confounders which did not alter our results.

Norwegian and Swedish conscription studies observed the same association between GA and intelligence at conscription,[22,23] which was also expected as the populations are comparable. Moreover, in Norway, Eide et al. found statistically significant lower intelligence scores for the highest categories of GA after week 41. This negative effect of post-term birth was also seen on school performance in the previously mentioned study by Abel et al.[17] We included post-term births in the reference group in our main, preplanned analyses but performed post hoc analyses excluding the post-term births after GA 41 + 6 from the reference (term) group and found that no considerable differences were seen.

The estimated adverse effects of preterm birth on educational achievement and cognitive performance, as demonstrated in several studies, are to some extent likely to be due to the incomplete maturation of the brain at birth and the current lack of treatment options to fully compensate for such effects. Social circumstances and nurturing also play an important role.[14,40] A better understanding of these links requires future studies on mediation, and clinical studies on prevention of especially cognitive impairment.

One of the strengths of this study is the nationwide cohort of almost 1.5 million individuals, which minimizes the risk of selection bias and provides strong statistical power. Due to the Danish registers with relatively few missing data, we have been able to obtain high quality information on a wide range of covariates, eliminate recall bias, and construct directed acyclic graphs to identify and adjust for relevant confounders. Nevertheless, residual confounding may still be present, especially since social and environmental factors were not accounted for. Ideally, the analyses should be adjusted for maternal intelligence, maternal obesity, drinking and smoking during pregnancy, but unfortunately, we were not able to obtain these variables. Also, measurement errors for GA were not accounted for. We performed secondary analyses investigating differences in characteristics and outcomes between children with known and missing GA which showed no consistent pattern of differences (parents living together and conscription appearance were more likely with known GA, while higher English grades in LSE and higher BPP scores were more likely for those with missing GA).

The cohort spans two decades, and both the school system and medical practice may have changed in that period. A meta-analysis on the subject concluded that the association between GA and intelligence has been stable over time,[6] therefore, we found it reasonable to have a cohort spanning our study period.

Many studies focus on outcomes in early childhood which provide some information, but outcomes at school-age are more informative indicators of life-long functioning. By using measurements of intelligence quotient, obtained education, and academic performance, we have sought to analyze the widest possible palette of factors related to young adults' prospects, in a world heavily relying on education.

5 | CONCLUSION

In a large Danish cohort, low GA is associated with not graduating from LSE and USE, achieving lower GPAs in LSE, especially for mathematics, having lower odds of attending conscription, and obtaining lower results in the BPP intelligence test at conscription. These findings remained significant after adjusting for a wide range of important confounders. Interestingly, in USE, the effect of low GA on GPA was not evident, probably due to selection bias. We believe that this study contributes essential knowledge about possible long-term consequences of preterm birth that can be useful to clinicians working in this field and the implicated parents. Our findings underline the importance of addressing preterm birth prevention and optimizing care for preterm infants to improve their long-term outcomes.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Data collection and analyses were performed by FJB and AKL. The first draft of the manuscript was written by EPFS and AKL and all authors interpreted the data and commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

All authors have no relevant financial or nonfinancial interests to disclose.

ETHICS STATEMENT

This study was approved by the Danish Data Protection Agency (file no. 2012-58-0004, local file no. HGH-2017-0015). This study is solely based on register information, hence no patient consent or consent from the ethics committee system was necessary according to Danish law.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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