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Impact of gestational age on child intelligence, attention, and executive function at age five: a cohort study

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Abstract

Objectives: Preterm birth can affect cognition, but other factors including parental education and intelligence may also play a role, but few studies have adjusted for these potential confounders. We aimed to assess the impact of gestational age (GA), late preterm birth (34-<37 weeks GA), and very to moderately preterm birth (<34 weeks GA) on intelligence, attention, and executive function in a population of 5-year-old Danish children.

Design: Follow-up study.

Setting: Denmark 2003-2008.

Participants: A cohort of 1776 children sampled from the Danish National Birth Cohort with information on GA, family and background factors, and completed neuropsychological assessment at age five.

Primary outcome measures: Wechsler Preschool and Primary Scale of Intelligence-Revised, Test of Everyday Attention for Children at Five, and Behaviour Rating Inventory of Executive Function scores.

Results: For preterm birth <34 weeks GA (*n*=8), the mean difference in full-scale intelligence quotient was -10.6 points [95% confidence interval; -19.4 to -1.8] when compared to the term group (≥37 weeks GA), and adjusted for potential confounders. For the teacher-assessed Global Executive Composite, the mean difference was 5.3 points [2.4 to 8.3] in the adjusted analysis, indicating more executive function difficulties in the preterm group <34 weeks GA compared to the term group. Only part of the effect was mediated through low birthweight. Maternal intelligence and parental education proved to be weak confounders.

No associations between late preterm birth 34-<37 weeks GA (*n*=40) and poor cognition were shown.

Conclusions: This study showed significantly lower intelligence and poorer executive function in children born <34 weeks GA compared to children born at term. GA has a crucial role in determining cognitive abilities independent of birthweight, maternal intelligence, and parental education. Studies with larger sample sizes are needed to confirm these findings.

Article summary

Strengths and limitations of this study

- In this study population, thorough information on family and background factors that may influence the cognitive outcome of a child was obtained.
- Directed acyclic graphs were composed to identify potential confounders prior to data analysis, and it was possible to adjust for an exhaustive set of confounders.
- The study population was sampled based on average alcohol consumption and binge drinking during pregnancy and may not be representative for the entire population, however, sample weights were applied in analyses to accommodate this.
- Robust standard errors were used to account for the sample design and shortcomings in the data.
- The proportion of children born preterm in this study population was small.

Keywords

Attention, child development, executive function, gestational age, intelligence, preterm birth.

Abbreviations

GA: gestational age

LDPS: Lifestyle During Pregnancy Study

DNBC: Danish National Birth Cohort

MBR: Danish Medical Birth Registry

IQ: intelligence quotient

WPPSI-R: Wechsler Preschool and Primary Scales of Intelligence-Revised

VIQ: verbal intelligence quotient

PIQ: performance intelligence quotient

FIQ: full-scale intelligence quotient

TEACh-5: Test of Everyday Attention for Children at Five

SD: standard deviation

BRIEF: Behaviour Rating Inventory of Executive Function

GEC: Global Executive Composite

BRI: Behavioural Regulation Index

MI: Metacognition Index

DAG: directed acyclic graph

CI: confidence interval

INTRODUCTION

In the past decades there has been an increase in the number of children being born preterm.[1] Advances in treatment have led to lower mortality rates, but morbidity rates have not been reduced to the same degree.[2] Many organs are vulnerable to preterm birth, and the preterm brain in particular can suffer long-term neurological impairments.[3] A dose-response relationship has been proposed, suggesting that the lower the gestational age (GA), the higher the risk of cognitive impairment.[4]

A study showed that at age five 10% of preterm infants received care in centres specialised for children with disabilities.[5] Hence, it is important to determine the association between preterm birth and cognitive outcomes in order to advise women at risk of preterm delivery and to give informed predictions about the future. Also, the knowledge can be of value to the obstetrician and pediatrician when making decisions about time and mode of delivery and on whether or not resuscitation should be offered at a GA as low as 22-24 weeks.

Previous studies have shown associations between preterm birth and low intelligence, attention deficits, and impaired executive function.[4 6] These negative outcomes may in part be a consequence of low GA, but other biological and social factors including parental education and intelligence may also affect the cognitive outcome of a child. In our dataset, parental education and maternal intelligence quotient (IQ) have proven to be strong predictors of child IQ,[7] and a recent study has shown that maternal IQ predicts IQ in very preterm children at age five.[8] Thus, it is important to adjust for these potential confounders when investigating an association between preterm birth and cognitive outcomes. Previous studies have adjusted for parental education,[9 10] but to our knowledge, only one study[11] has adjusted for maternal intelligence. In that study children born before 34 weeks GA were excluded, and the sample size was small (*n*=336).

The aim of our study was to investigate the influence of GA, late preterm birth (34-<37 weeks GA), and very to moderately preterm birth (<34 weeks GA) on intelligence, attention, and executive function in a population of 5-year-old Danish children adjusted for relevant socioeconomic confounders including parental educational level and maternal intelligence.

MATERIAL AND METHODS

Study sample

We used data from the Lifestyle During Pregnancy Study (LDPS),[12] which is a sample from the Danish National Birth Cohort (DNBC). The DNBC contains information on 101 042 Danish women and their children recruited from 1997 to 2003. Of the invited women, 60% chose to participate, and 30% of all pregnant women at that time were included.

A total of 3478 women with singleton pregnancies were sampled from the DNBC and invited to participate in the LDPS from 2003 to 2008, with oversampling of women reporting a relatively high alcohol intake or binge drinking episodes during pregnancy.[12 13] Out of these, 1776 had neuropsychological tests performed and had information on GA available, and thus were included in our analyses. There were no considerable differences between the participants and non-participants.[13] Exclusion criteria were multiple pregnancies, congenital diseases with a large risk of mental retardation (the diagnostic term used at the time of data collection), inability to speak Danish, and impaired vision or hearing abilities preventing the child from completing the tests.[12]

Data collection

Exposure variables

Information on GA was obtained from the Danish Medical Birth Registry (MBR). We used GA as a continuous and categorical variable, comparing *late preterm* birth (34 -<37 completed weeks of gestation) and *very to moderately preterm* birth (GA<34 weeks) with birth at *term* (GA ≥37 weeks), respectively.

Outcome measures

At child age five (age span: 60-64 months chronological age), a neuropsychological test battery was administered by specially trained psychologists.

Intelligence

The child's IQ was assessed using the Wechsler Preschool and Primary Scales of Intelligence-Revised (WPPSI-R).[14] WPPSI-R includes five verbal and five performance subtests that are used to calculate an overall verbal IQ (VIQ), overall performance IQ (PIQ), and full-scale IQ (FIQ). In this test battery, only three of the verbal (arithmetic, information, and vocabulary) and three of the performance (block design, geometric design, and object assembly) subtests were carried out to ensure the child's cooperation throughout the testing. Standard procedures were used to prorate scores from the shortened test. Swedish norms were applied to derive the IQ scores, since no Danish norms exist. This should not affect any comparisons made internally within the sample with respect to GA differences.

Attention

Attention measures were assessed with the Test of Everyday Attention for Children at Five (TEACh-5).[15] For this study, two subtests assessing selective attention ('Great Balloon Hunt' and 'Hide and Seek II') and two subtests assessing sustained attention ('Barking' and 'Draw a line') were used. Each subtest score was standardised to a mean of 0 and a standard deviation (SD) of 1.

To calculate composite scores for overall, selective, and sustained attention, the means of the respective standardised subtest scores for each individual were calculated and re-standardised to a mean of 0 and SD of 1.

Executive function

Executive function was assessed using the Behaviour Rating Inventory of Executive Function (BRIEF) questionnaire.[16] The questionnaire consists of two versions, one for parents and one for teachers. Each questionnaire evaluates eight domains of executive functioning and form the Global Executive Composite (GEC). Three of the eight domains form the Behavioural Regulation Index (BRI), and five of the domains form the Metacognition Index (MI). Since the eight domains do not follow a normal distribution, we performed a normalising t-score transformation to standardise each domain to a mean of 50 and SD of 10. To compute the GEC, BRI, and MI, the means of the respective domains for each individual were calculated and re-standardised to a mean of 50 and SD of 10. For all BRIEF scores, a higher score indicates more executive function difficulties.

Covariates

To identify relevant covariates, we constructed directed acyclic graphs (DAGs)[17] using the graphical tool DAGitty.

Important covariates were obtained from prenatal and postnatal telephone interviews, a parent-administered questionnaire at follow-up, the Danish social security number, and the MBR. In addition, the mother's intelligence was assessed at follow-up with Raven's Standard Progressive Matrices[18] and two subtests (vocabulary and information) of the Wechsler Adult Intelligence Scale.[19] The three test results were weighted equally and combined to derive an IQ score.

Prior to analysis, we evaluated the five lowest and five highest observations for all outcomes and covariates to detect unrealistic values (+/- 4 SD for the normally distributed data). This resulted in removal of three birthweight observations that exceeded our threshold when evaluated according to Danish standards.[20] Moreover, we removed one unrealistic body mass index of 13.9 kg/m^2 and one observation of average alcohol intake of 36 drinks/week during pregnancy.

Statistical analyses

We performed multiple linear regression analyses using SAS, Version 9.4 (© SAS Institute Inc., Cary, NC, USA).

We assessed term vs. late preterm birth and term vs. very or moderately preterm birth.

We adjusted for a set of a priori defined variables based on a DAG (see supplementary figure 1). This included maternal age (continuous), maternal IQ (continuous), average alcohol consumption in pregnancy (0, 1-4, 5+ drinks per week), smoking in pregnancy (yes/no), parity (0, 1, 2+), maternal marital status (single/cohabitating), parental educational level (continuous), and child sex (male/female). Moreover, we adjusted for the psychologist administering the tests (8 categories) and age at testing (continuous).

In the study sample, maternal IQ and parental educational level (total duration in years averaged for both parents, if information on the father was missing, maternal only) are important predictors of child intelligence,[7] and in order to evaluate the importance of adjusting for these factors, sensitivity analyses were conducted removing these two factors separately and simultaneously from the regression models. Moreover, to investigate how much of the effect that could be attributed to birthweight, we inserted this potential intermediate factor in a regression model.

Since the women in our population were sampled based on alcohol intake during pregnancy,[21] we used sample weights in our analyses to account for the oversampling of women with relatively high alcohol intake or binge drinking episodes.[12 13] To account for the complex stratified sampling design and possible deviations from normality and variance homogeneity, we applied robust standard errors. All statistical tests were two-sided and with a significance level at 0.05.

We performed complete case analyses, as multiple imputation strategies to handle missing data in this cohort have produced essentially the same results when compared to complete case analyses.[21]

Complete information on child IQ scores was available for 99.3% of the sample, for attention scores 84.7%, and for executive function, 99.8% of the parents and 86.6% of the teachers had completed the questionnaire. All covariates were available for 98.6% of the sample. No significant differences between the term and the two preterm groups were evident with regard to the proportion of missing outcome and covariate data.

Ethical approval

The data collection for the LDPS was approved by the DNBC Board of Directors, the DNBC Steering committee, the regional Ethics Committee, the Danish Data Protection Agency, and the Institutional Review Board at the Centers for Disease Control and Prevention. Signed informed consent was obtained for the LDPS. The current study was further approved by the Danish Data Protection Agency (file number 2012-58-0004).

RESULTS

The characteristics of the 1776 mother and child pairs are presented in table 1. There were no significant group differences with respect to health, lifestyle, and socioeconomic characteristics.

Although not statistically significant, the mothers of the children born very or moderately preterm were more likely to be younger, first-time mothers, without a partner, having smoked during pregnancy, but they also had slightly higher IQ and longer education. The mothers of the late preterm children were less likely to have consumed alcohol in pregnancy, but more likely to have male births and lower IQ when compared to the other groups.

With children born at term as the reference, the mean difference in FIQ, VIQ, and PIQ for the very or moderately preterm group was -10.6 points [95% CI; -19.4 to -1.8], -7.4 points [-13.4 to -1.5], and -11.7 points [-21.9 to -1.5], respectively, when adjusting for potential confounders. Among the late preterm children, a tendency towards lower IQs was evident, but this trend diminished when adjusting for potential confounders.

For the attention measures, the mean differences were small, and none of the adjusted analyses reached statistical significance.

With regard to executive function, no significant findings were evident in the parents' assessment. However, analyses of the teachers' assessment showed a mean difference in GEC, BRI, and MI in the very or moderately preterm group of 5.3 points [95% CI; 2.4 to 8.3], 4.2 points [-0.6 to 9.0], and 5.5 points [2.0 to 9.0], respectively, when compared to the term group and adjusting for potential confounders. For the late preterm group, the results were similar but did not reach statistical significance (see table 2).

Analyses with GA as a continuous variable did not alter the conclusions above (see table 3).

When maternal IQ and parental education were removed from the regression analyses separately or simultaneously (data not shown), the estimates of association did not change notably. However, when these variables were removed simultaneously from the regression, most estimates became insignificant due to wider CIs.

When introducing birthweight in the regression analyses (data not shown), the association between

GA and all IQ outcomes became considerably weaker and were no longer significant. However, a trend towards lower IQ in the very or moderately preterm group was still evident, as the mean differences in FIQ, VIQ, and PIQ were reduced to -7.0 points [95% CI; -15.7 to 1.6], -5.9 points [-12.2 to 0.3], and -6.8 points [-16.6 to 3.0], respectively, when compared to the term group. When birthweight was introduced in the analyses of attention and executive function outcomes, the results did not change substantially.

DISCUSSION

Main findings

We found a statistically significant effect of very or moderately preterm birth on IQ and teacher-assessed executive function, even when adjusting for potential confounders. Although maternal IQ and parental education accounted for much of the variance in child IQ in this dataset,[7] these two factors should only be considered weak confounders with no significant association with GA. The inclusion of birthweight in the regression analyses for IQ outcomes attenuated the associations for the very or moderately preterm group, suggesting that the association between low GA and low IQ in this group is, in part, mediated through low birthweight. For the late preterm group, the associations completely vanished when including birthweight in the regression, suggesting that the effect of low GA in this group is predominantly explained by low birthweight. This underlines the importance of looking at GA relatively to birthweight when investigating effects of preterm birth, though our results for the very to moderately preterm children indicate that there may be cognitive effects of GA which are independent of birthweight, perhaps reflecting effects of very low GA on brain development.

Strengths and limitations

One of the strengths of this study is the relatively large sample size with thorough information on family and background factors that may influence the cognitive outcome of a child. Specially trained psychologists, unaware of the gestational age, conducted neuropsychological tests with a high interrater reliability of 97-97.5 %.[12] To minimise bias in our analyses, we composed DAGs to identify potential confounders prior to data analysis. Due to our large sample size, we were able to adjust for an exhaustive set of confounders. Other strengths of our study were a predefined protocoled methodology, and use of robust standard errors to account for the sample design and shortcomings in the data.

Our study has some limitations. The study population was sampled based on average alcohol consumption and binge drinking during pregnancy,[12 13] and therefore, the sample is not representative of the entire DNBC population. We applied sample weights in the analyses to accommodate this. However, the use of weights may be problematic for small subgroups, and together with the use of robust standard errors, this approach may have reduced the power to obtain statistically significant results and widened the CIs.

Another weakness of this study is the relatively small proportion of children born preterm, especially children born very preterm (<32 weeks GA). According to MBR records from 2000 (our recruitment period was from 1997 to 2003), we would expect 6.3% of all new-borns to be born preterm.[22] In our population it was only 2.7%, which is equal to an underrepresentation of 57%. Only 0.2% of our sample was born very preterm, although we would expect 1.0%.[22] This can be a result of various factors that prevent parents with children born preterm from participating in a clinical study, in particular if the children are born very preterm and need special care.

However, studies have shown that the influence of selection bias on several exposure-outcome associations in the DNBC is limited.[23] We adjusted for a large number of covariates associated with selection, still we cannot rule out that the low prevalence of preterm births in our cohort may have limited our power to detect any true differences as significant. Moreover, the low prevalence of preterm births prevented us from performing analyses investigating the impact of very or extremely preterm birth.

Interpretation

For the IQ outcomes, the findings in our study are generally in line with previous findings with an IQ reduction of approximately 10 points in children born preterm.[4 24] However, in our study, this clinically very relevant difference was only seen among the very or moderately preterm children, and not in the late preterm group. A meta-analysis by Chan et al.[25] showed a statistically significant impact of late preterm birth on general cognitive ability and non-verbal intelligence. Our study in part contradicts these findings, as no associations between late preterm birth and IQ (full-scale, verbal, and non-verbal) were found. In our unadjusted analyses, we saw a trend towards lower IQ among late preterm children, but the trend disappeared when adjusting for confounders. This discrepancy may reflect insufficient adjustments in other studies but also the limited power of our study.

When assessing attention measures, we only found one borderline statistically significant result. This is not in line with previous findings suggesting that preterm infants are at increased risk of developing eg Attention Deficit Hyperactivity Disorder with a relative risk of 2.64 [95% CI 1.85, 3.78].[24] However, TEACh-5 has not been validated as a diagnostic test, and given the unambiguous findings in the present study, it is possible that GA does not have an impact on test of basic attention function.

In the field of executive function, it has been suggested that extremely preterm infants (<28 weeks GA) are at increased risk of developing executive function difficulties.[26] Studies investigating the association between very, moderately, or late preterm birth and poor BRIEF scores have not detected any convincing deficits when evaluating the parents' questionnaire,[27 28] and to our knowledge, the teachers' questionnaire has not previously been used for this purpose. Hodel et al. detected deficits in a population of moderately to late preterm infants at the age of 9 months and at 4 years,[29] but in these studies, other executive function measures than BRIEF were applied.

In extremely low birthweight children, teachers have proven to report significantly more difficulties on the BRI subscale compared to the parents.[30] In our study, we found that teachers reported more difficulties in all areas (GEC, BRI, and MI) when compared to the parents. This can be due to teachers having a more objective viewpoint and being more experienced in working with children with and without difficulties.

CONCLUSION

This study showed significantly lower IQ and poorer executive function in children born very or moderately preterm (<34 weeks GA) compared to children born at term (≥37 weeks GA), but only the differences in IQ were considered clinically relevant. Part of the effect was mediated through low birthweight. No associations between late preterm birth (34-<37 weeks GA) and poor cognitive outcomes were shown.

Maternal IQ and parental education are strong predictors of child IQ in our dataset but were only weak confounders of the association between GA and cognitive outcomes. Therefore, GA has a crucial role in determining cognitive abilities independent of birthweight, maternal IQ, and parental educational level. Further studies with larger sample sizes to confirm these findings are needed.

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Contributors

Dr. Fogtmann contributed to the conception and design of the study, performed data management and statistical analyses, analysed and interpreted the data, drafted the initial manuscript, and wrote the final manuscript with contributions from the co-authors.

Miss Slavensky and Mr. Jager Bruun contributed to the conception and design of the study, assisted with statistical analyses and interpretation of the data, and critically reviewed and revised the manuscript.

Mr. Mortensen and Dr. Kesmodel conceptualised and designed the study, analysed and interpreted the data, and critically reviewed and revised the manuscript.

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

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Competing interests

None declared.

Data sharing statement

No additional data are available for this study.

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Tables

Table 1. Family characteristics among singletons born at term or preterm. Denmark 2003-2008 (*n*=1776)

Characteristics	Born at term (≥37 weeks)	Late preterm birth (34-<37 weeks)	Moderately or very preterm birth (<34 weeks)[a]
Number of infants (n)	1728	40	8
Maternal age (years, mean [SD])	30.8 (4.4)	30.4 (4.5)	28.8 (3.4)
Maternal pre-pregnancy BMI (kg/m^2, median [10/90 percentile])[b]	22.6 (19.6/28.7)	22.7 (18.4/33.0)	22.8 (16.5/28.2)
Maternal smoking in pregnancy (%)	31.7	30.0	37.5
Maternal alcohol consumption in pregnancy (%)[c]			
0 drinks/week	47.6	55.0	50.0
1-4 drinks/week	41.3	37.5	37.5
5+ drinks/week[d]	11.1	7.5	12.5
Maternal marital status (%)[e]			
Single[f]	12.4	10.3	25.0
Cohabitating	87.6	89.7	75.0
Maternal IQ (mean [SD])[g]	100.0 (14.9)	97.7 (16.9)	104.3 (17.9)
Parental educational level (years, mean [SD])[h]	13.2 (1.9)	13.0 (1.6)	14.2 (1.8)
Parity (%)			
0	50.7	60.0	87.5
1	32.1	30.0	12.5
2+	17.2	10.0	0.0
Child gender (%)			
Male	51.7	60.0	50.0
Females	48.3	40.0	50.0
Gestational age (days, median [10/90 percentile])	282.0 (269.0/293.0)	251.5 (241.0/257.5)	227.5 (206.0/236.0)
Birthweight (grams, mean [SD])[i]	3627.3 (483.4)	2740.8 (482.6)	2040.9 (458.4)
Child age at testing (years, median [10/90 percentile])	5.23 (5.12/5.30)	5.26 (5.13/5.31)	5.23 (5.10/5.29)

N, number; SD, standard deviation; BMI, body mass index; IQ, intelligence quotient. [a] Lowest observation 29 weeks. [b] Information missing for 35 term and 1 late preterm birth. [c] Information missing for 1 term birth. [d] Range 5-14 drinks/week. [e] Information missing for 13 term and 1 late preterm birth. [f] If reported being single either during pregnancy or at follow-up at 60-64 months postpartum. [g] Information missing for 9 term births. [h] Information missing for 5 term and 1 late preterm birth. [i] Information missing for 12 term and 2 late preterm births.

Table 2. Mean differences in intelligence, attention, and executive function between 5-year-old children born at term (reference group) and children born preterm. Denmark 2003-2008 (*n*=1776)[a]

	Born at term ≥37 weeks (*n*=1728)	Late preterm birth 34-<37 weeks (*n*=40)		Moderately or very preterm birth <34 weeks (*n*=8)	
	Mean (SD)	**Mean difference**	**95% CI**	**Mean difference**	**95% CI**
Intelligence (WPPSI-R)					
Full scale IQ					
Unadjusted	105.64 (12.86)	-2.09	-6.91, 2.74	-9.22	-20.25, 1.81
Adjusted[b]		-0.05	-4.62, 4.53	-10.56	-19.37, -1.75
Verbal IQ					
Unadjusted	104.81 (10.80)	-1.73	-5.23, 1.76	-7.11	-15.64, 1.41
Adjusted		-0.40	-4.84, 4.05	-7.41	-13.37, -1.45
Performance IQ					
Unadjusted	105.14 (16.22)	-2.00	-9.02, 5.03	-9.51	-20.46, 1.45
Adjusted		0.38	-5.39, 6.15	-11.71	-21.89, -1.52
Attention (TEACh-5)					
Overall attention					
Unadjusted	0.01 (1.00)	-0.21	-0.70, 0.28	-0.10	-0.72, 0.52
Adjusted		-0.16	-0.59, 0.26	-0.25	-1.00, 0.50
Sustained attention					
Unadjusted	0.01 (1.00)	-0.39	-0.76, -0.01	-0.09	-0.62, 0.44
Adjusted		-0.23	-0.64, 0.19	-0.16	-0.83, 0.52
Selective attention					
Unadjusted	0.00 (1.00)	0.09	-0.46, 0.63	0.02	-0.41, 0.45
Adjusted		0.06	-0.42, 0.53	-0.19	-0.65, 0.27
Executive function (BRIEF)[c]					
- Parent version					
Global Executive Composite					
Unadjusted	49.97 (9.98)	1.44	-4.03, 6.90	-0.39	-16.52, 15.74
Adjusted		2.26	-2.01, 6.53	-0.20	-14.27, 13.87
Behavioural Regulation Index					
Unadjusted	50.01 (9.98)	-0.35	-5.50, 4.79	-1.18	-16.17, 13.81
Adjusted		0.40	-3.97, 4.76	-1.95	-14.87, 10.97
Metacognition Index					
Unadjusted	49.95 (9.98)	2.41	-3.10, 7.92	0.13	-15.24, 15.51
Adjusted		3.19	-1.11, 7.49	0.90	-12.60, 14.41
- Teacher version					
Global Executive Composite					
Unadjusted	49.94 (10.03)	4.47	-0.77, 9.70	5.47	2.57, 8.36
Adjusted		3.99	-0.82, 8.81	5.33	2.39, 8.27
Behavioural Regulation Index					
Unadjusted	49.95 (10.01)	4.42	-0.38, 9.21	5.29	2.08, 8.50
Adjusted		3.79	-0.89, 8.48	4.24	-0.56, 9.03
Metacognition Index					
Unadjusted	49.95 (10.03)	4.09	-1.55, 9.73	5.07	0.61, 9.54
Adjusted		3.77	-1.32, 8.85	5.46	1.97, 8.95

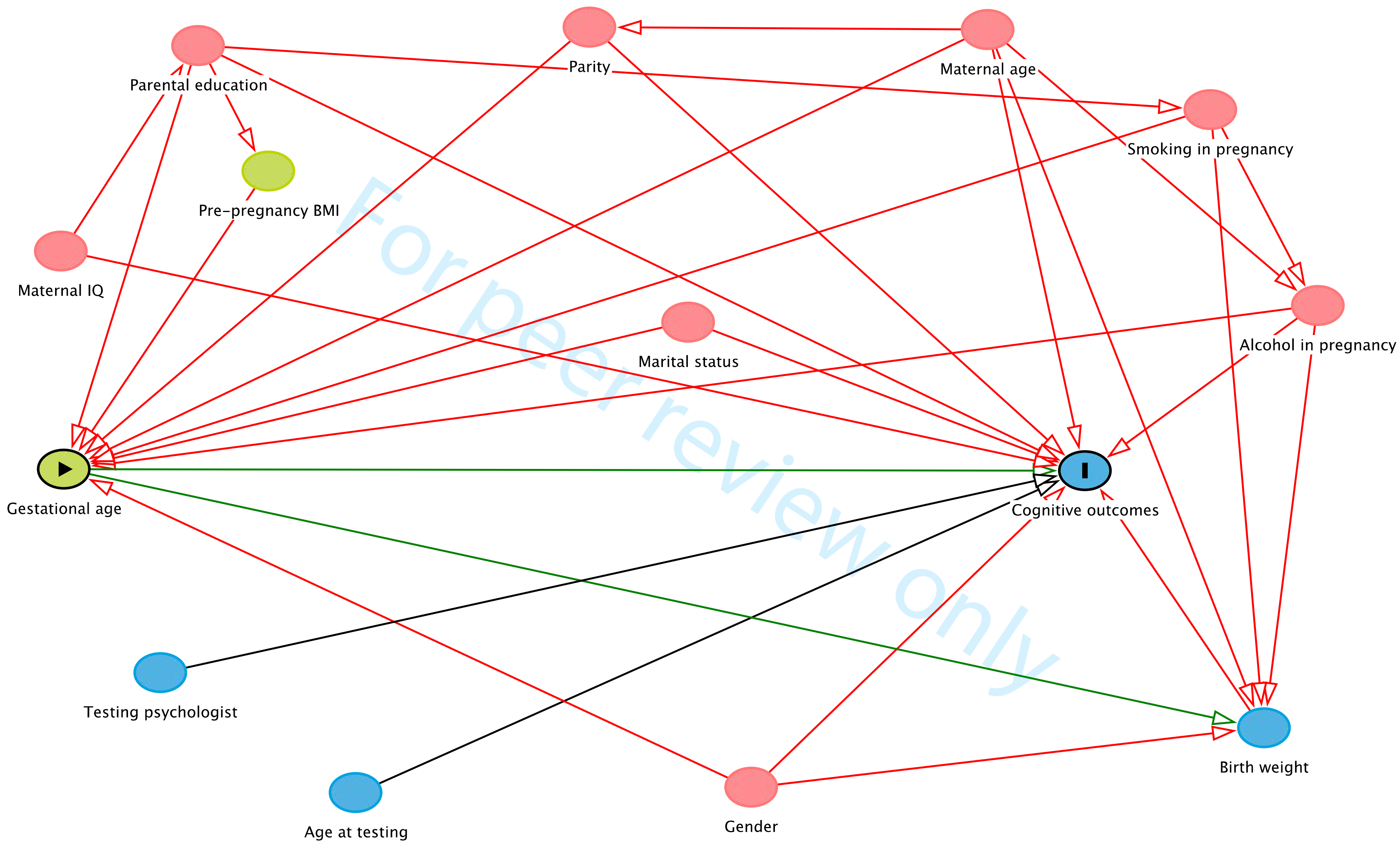
N, number; SD, standard deviation; CI, confidence interval; WPPSI-R, Wechsler Preschool and Primary Scales of Intelligence-Revised; IQ, intelligence quotient; TEACh-5, Test of Everyday Attention for Children at Five; BRIEF, Behaviour Rating Inventory of Executive Function. [a] Overall number of participants. Due to complete case analyses, for the adjusted analyses, the actual number of participants for each outcome was: Full-scale IQ (*n*=1748), verbal IQ (*n*=1749), performance IQ (*n*=1749), overall attention (*n*=1493), sustained attention (*n*=1586), selective attention (*n*=1612), Global Executive Composite (parents, *n*=1748; teachers, *n*=1525), Behavioural Regulation Index (parents, *n*=1748; teachers, *n*=1530), Metacognition Index (parents, *n*=1748; teachers, *n*=1525). [b] All adjusted analyses adjusted for maternal age, maternal IQ, average alcohol consumption in pregnancy, smoking in pregnancy, parity, maternal marital status, parental educational level, child sex, testing psychologist, and age at testing. [c] A higher BRIEF score indicates more executive function difficulties (opposite than the other outcome measures).

Table 3. Regression coefficients for the association between gestational age (in days) and intelligence, attention, and executive function in 5-year-old children. Denmark 2003-2008 (*n*=1776)[a]

Intelligence (WPPSI-R)	Beta (95% CI)	Attention (TEACh-5)	Beta (95% CI)	Executive function (BRIEF)[c] *- Parent version*	Beta (95% CI)	Executive function (BRIEF) *- Teacher version*	Beta (95% CI)
Full scale IQ		***Overall attention***		***Global Executive Composite***		***Global Executive Composite***	
Unadjusted	0.10 (0.02, 0.19)	Unadjusted	0.00 (0.00, 0.01)	Unadjusted	-0.03 (-0.10, 0.05)	Unadjusted	-0.07 (-0.14, -0.01)
Adjusted[b]	0.08 (0.01, 0.15)	Adjusted	0.00 (0.00, 0.01)	Adjusted	-0.02 (-0.08, 0.05)	Adjusted	-0.06 (-0.12, 0.01)
Verbal IQ		***Sustained attention***		***Behavioural Regulation Index***		***Behavioural Regulation Index***	
Unadjusted	0.07 (0.00, 0.14)	Unadjusted	0.00 (-0.01, 0.01)	Unadjusted	-0.02 (-0.09, 0.05)	Unadjusted	-0.06 (-0.13, 0.01)
Adjusted	0.06 (0.00, 0.13)	Adjusted	0.00 (-0.01, 0.01)	Adjusted	-0.01 (-0.08, 0.05)	Adjusted	-0.04 (-0.11, 0.02)
Performance IQ		***Selective attention***		***Metacognition Index***		***Metacognition Index***	
Unadjusted	0.12 (0.01, 0.22)	Unadjusted	0.00 (0.00, 0.01)	Unadjusted	-0.03 (-0.10, 0.05)	Unadjusted	-0.07 (-0.14, -0.01)
Adjusted	0.08 (-0.01, 0.18)	Adjusted	0.00 (0.00, 0.01)	Adjusted	-0.02 (-0.08, 0.04)	Adjusted	-0.06 (-0.12, 0.00)

N, number; CI, confidence interval; WPPSI-R, Wechsler Preschool and Primary Scales of Intelligence-Revised; IQ, intelligence quotient; TEACh-5, Test of Everyday Attention for Children at Five; BRIEF, Behaviour Rating Inventory of Executive Function. [a] Overall number of participants. Due to complete case analyses, for the adjusted analyses, the actual number of participants for each outcome was: Full-scale IQ (*n*=1748), verbal IQ (*n*=1749), performance IQ (*n*=1749), overall attention (*n*=1493), sustained attention (*n*=1586), selective attention (*n*=1612), Global Executive Composite (parents, *n*=1748; teachers, *n*=1525), Behavioural Regulation Index (parents, *n*=1748; teachers, *n*=1530), Metacognition Index (parents, *n*=1748; teachers, *n*=1525). [b] All adjusted analyses adjusted for maternal age, maternal IQ, average alcohol consumption in pregnancy, smoking in pregnancy, parity, maternal marital status, parental educational level, child sex, testing psychologist, and age at testing. [c] A higher BRIEF score reflects more executive function difficulties (opposite than the other outcome measures).

Supplementary Figure 1. Directed acyclic graph



IQ, intelligence quotient; BMI, body mass index. Green circle with triangle: exposure. Blue circle with vertical rectangle: outcome. Green circle: ancestor of exposure. Blue circle: ancestor of outcome. Red circle: ancestor of exposure *and* outcome. Green connection: causal path. Red connection: biasing path. From dagitty.net.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7-9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-9
Bias	9	Describe any efforts to address potential sources of bias	9-11
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10-11
		(*b*) Describe any methods used to examine subgroups and interactions	-
		(*c*) Explain how missing data were addressed	11
		(*d*) If applicable, explain how loss to follow-up was addressed	-
		(*e*) Describe any sensitivity analyses	10
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11-12 + table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12 + tables 2+3
		(*b*) Report category boundaries when continuous variables were categorized	10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12-13
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	14-15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17-18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Impact of gestational age on child intelligence, attention, and executive function at age five: a cohort study

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Impact of gestational age on child intelligence, attention, and executive function at age five: a cohort study

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Abstract

Objectives: Preterm birth can affect cognition, but other factors including parental education and intelligence may also play a role, but few studies have adjusted for these potential confounders. We aimed to assess the impact of gestational age (GA), late preterm birth (34 to <37 weeks GA), and very to moderately preterm birth (<34 weeks GA) on intelligence, attention, and executive function in a population of 5-year-old Danish children.

Design: Population-based prospective cohort study.

Setting: Denmark 2003-2008.

Participants: A cohort of 1776 children and their mothers sampled from the Danish National Birth Cohort with information on GA, family and background factors, and completed neuropsychological assessment at age five.

Primary outcome measures: Wechsler Preschool and Primary Scale of Intelligence-Revised, Test of Everyday Attention for Children at Five, and Behaviour Rating Inventory of Executive Function scores.

Results: For preterm birth <34 weeks GA (*n*=8), the mean difference in full-scale intelligence quotient was -10.6 points [95% confidence interval; -19.4 to -1.8] when compared to the term group ≥37 weeks GA (*n*=1728), and adjusted for potential confounders. For the teacher-assessed Global Executive Composite, the mean difference was 5.3 points [2.4 to 8.3] in the adjusted analysis, indicating more executive function difficulties in the preterm group <34 weeks GA compared to the term group. Maternal intelligence and parental education were weak confounders.

No associations between late preterm birth 34 to <37 weeks GA (*n*=40) and poor cognition were shown.

Conclusions: This study showed substantially lower intelligence and poorer executive function in children born <34 weeks GA compared to children born at term. GA has an essential role in determining cognitive abilities independent of maternal intelligence and parental education. Studies with larger sample sizes are needed to confirm these findings, as the proportion of children born preterm in this study population was small.

Article summary

Strengths and limitations of this study

- In this study population, thorough information on family and background factors that may influence the cognitive outcome of a child was obtained.
- Directed acyclic graphs were composed to identify potential confounders prior to data analysis, and it was possible to adjust for an extensive set of confounders.
- The study population was sampled based on average alcohol consumption and binge drinking during pregnancy and may not be representative for the entire population, however, sample weights were applied in analyses to accommodate this.
- Robust standard errors were used to account for the sample design, possible deviations from normality and variance homogeneity.
- The proportion of children born preterm in this study population was small (48 out of 1776), which limited our power to detect any true differences as significant.

Keywords

Attention, child development, executive function, gestational age, intelligence, preterm birth.

Abbreviations

GA: gestational age

LDPS: Lifestyle During Pregnancy Study

DNBC: Danish National Birth Cohort

IQ: intelligence quotient

WPPSI-R: Wechsler Preschool and Primary Scales of Intelligence-Revised

VIQ: verbal intelligence quotient

PIQ: performance intelligence quotient

FIQ: full-scale intelligence quotient

TEACh-5: Test of Everyday Attention for Children at Five

SD: standard deviation

BRIEF: Behaviour Rating Inventory of Executive Function

GEC: Global Executive Composite

BRI: Behavioural Regulation Index

MI: Metacognition Index

DAG: directed acyclic graph

CI: confidence interval

INTRODUCTION

In the past decades there has been an increase in the number of children being born preterm.[1] Advances in treatment have led to lower mortality rates, but morbidity rates have not been reduced to the same degree.[2] Many organs are vulnerable to preterm birth, and the preterm brain in particular can suffer long-term neurological impairments.[3] A dose-response relationship has been proposed, suggesting that the lower the gestational age (GA), the higher the risk of cognitive impairment.[4]

A study showed that at age five 10% of children born preterm still received care in centres specialised for children with disabilities compared to 2% of children born at term (odds ratio 7.9 [95% CI; 3.5 to 18.0]).[5] Hence, it is important to determine the association between preterm birth and cognitive outcomes in order to advise women at risk of preterm delivery and to give informed predictions about the future. Also, the knowledge can be of value to the obstetrician and pediatrician when making decisions about time and mode of delivery and on whether or not resuscitation should be offered at a GA as low as 22-24 weeks.

Previous studies have shown associations between preterm birth and low intelligence, attention deficits, and impaired executive function.[4 6] These negative outcomes may in part be a consequence of low GA, but other biological and social factors including parental education and intelligence may also affect the cognitive outcome of a child. In our dataset, parental education and maternal intelligence quotient (IQ) have proven to be strong predictors of child IQ,[7] and a recent study has shown that maternal IQ predicts IQ in very preterm children at age five.[8] Thus, it is important to adjust for these potential confounders when investigating an association between preterm birth and cognitive outcomes. Previous studies have adjusted for parental education,[9 10] but to our knowledge, only one study[11] has adjusted for maternal intelligence. In that study children born before 34 weeks GA were excluded, and the sample size was small (*n*=336).

The aim of our study was to investigate the influence of GA, late preterm birth (34 to <37 weeks GA), and very to moderately preterm birth (<34 weeks GA) on intelligence, attention, and executive function in a population of 5-year-old Danish children adjusted for relevant confounders including parental educational level and maternal intelligence.

MATERIAL AND METHODS

Study sample

We used data from the Lifestyle During Pregnancy Study (LDPS),[12] which is a sample from the Danish National Birth Cohort (DNBC). The DNBC contains information on 101 042 Danish women and their children recruited from 1997 to 2003. Of the invited women, 60% chose to participate, and 30% of all pregnant women at that time were included.

A total of 3478 women with singleton pregnancies were sampled from the DNBC and invited to participate in the LDPS from 2003 to 2008. Participants were sampled in strata defined by the prenatal maternal average alcohol intake with oversampling of women reporting a relatively high alcohol intake or binge drinking episodes during pregnancy.[12 13] Out of the sampled mother and child pairs, 1776 children had neuropsychological tests performed at age five and had information on GA available, and thus were included in our analyses. There were no considerable differences between the participants and non-participants with regard to maternal age, body mass index, parity, marital status, prenatal smoking and alcohol consumption, child sex, birthweight, and gestational age at birth.[13] Exclusion criteria were multiple pregnancies and congenital diseases with a large risk of mental retardation (the diagnostic term used at the time of data collection), as they represent a fundamentally different group of individuals that may not be representative of the norm. Other exclusion criteria were inability to speak Danish, and impaired vision or hearing abilities preventing the child from completing the tests.[12]

Data collection

Exposure variables

Information on GA was obtained from the Danish Medical Birth Register and determined by ultrasound, while date of last menses was only used to determine GA in very few cases where an ultrasound estimate was not available. We used GA as 1) a continuous variable (days) and 2) a categorical variable, comparing *late preterm* birth (34 to <37 completed weeks of gestation) and *very to moderately preterm* birth (GA<34 weeks) with birth at *term* (GA ≥37 weeks), respectively.

Outcome measures

At child age five (age span: 60-64 months chronological age), a neuropsychological test battery was administered by specially trained psychologists.

Intelligence

The child's IQ was assessed using the Wechsler Preschool and Primary Scales of Intelligence-Revised (WPPSI-R).[14] WPPSI-R includes five verbal and five performance subtests that are used to calculate an overall verbal IQ (VIQ), overall performance IQ (PIQ), and full-scale IQ (FIQ). In this test battery, only three of the verbal (arithmetic, information, and vocabulary) and three of the performance (block design, geometric design, and object assembly) subtests were carried out to ensure the child's cooperation throughout the testing. Standard procedures were used to prorate scores from the shortened test. Swedish norms were applied to derive the IQ scores, since no

Danish norms exist. This should not affect any comparisons made internally within the sample with respect to GA differences.

Attention

Attention measures were assessed with the Test of Everyday Attention for Children at Five (TEACh-5).[15] For this study, two subtests assessing selective attention ('Great Balloon Hunt' and 'Hide and Seek II') and two subtests assessing sustained attention ('Barking' and 'Draw a line') were used. Each subtest score was standardised to a mean of 0 and a standard deviation (SD) of 1. To calculate composite scores for overall, selective, and sustained attention, the means of the respective standardised subtest scores for each individual were calculated and re-standardised to a mean of 0 and SD of 1.

Executive function

Executive function was assessed using the Behaviour Rating Inventory of Executive Function (BRIEF) questionnaire.[16] The questionnaire consists of two versions, one for parents and one for teachers. Each questionnaire evaluates eight domains of executive functioning and form the Global Executive Composite (GEC). Three of the eight domains form the Behavioural Regulation Index (BRI), and five of the domains form the Metacognition Index (MI). Since the eight domains do not follow a normal distribution, we performed a normalising t-score transformation to standardise each domain to a mean of 50 and SD of 10. To compute the GEC, BRI, and MI, the means of the respective domains for each individual were calculated and re-standardised to a mean of 50 and SD of 10. For all BRIEF scores, a higher score indicates more executive function difficulties.

Covariates

To identify relevant covariates, we constructed directed acyclic graphs (DAGs)[17] using the graphical tool DAGitty.[18]

Important covariates were obtained from prenatal and postnatal telephone interviews, a parent-administered questionnaire at follow-up, the Danish social security number, and the MBR. In addition, the mother's intelligence was assessed at follow-up with Raven's Standard Progressive Matrices[19] and two subtests (vocabulary and information) of the Wechsler Adult Intelligence Scale.[20] The three test results were weighted equally and combined to derive an IQ score.

Prior to analysis, we evaluated the five lowest and five highest observations for all outcomes and covariates to detect unrealistic values (+/- 4 SD for the normally distributed data). This resulted in removal of three birthweight observations (one from the term group and two from the late preterm group) that exceeded our threshold when evaluated according to Danish standards.[21] Moreover, we removed one unrealistic body mass index of 13.9 kg/m^2 and one observation of average alcohol intake of 36 drinks/week during pregnancy (from the term group).

Statistical analyses

We performed multivariable linear regression using SAS, Version 9.4 (© SAS Institute Inc., Cary, NC, USA).

We assessed term vs. late preterm birth and term vs. very or moderately preterm birth. We adjusted for a set of a priori defined variables. This included maternal age at birth (continuous), maternal IQ (continuous), average alcohol consumption in pregnancy (0, 1-4, 5+ drinks per week), smoking in pregnancy (yes/no), parity (0, 1, 2+), maternal marital status (single/cohabitating), parental educational level (total duration in years averaged for both parents, if information on the father was missing, maternal only [continuous]), and child sex (male/female). Moreover, we adjusted for the psychologist administering the tests (8 categories) and age at testing (continuous). We created dummy variables from the categorical variables before inserting them in the regression models.

In the study sample, maternal IQ and parental educational level are important predictors of child intelligence,[7] and in order to evaluate the importance of adjusting for these factors, sensitivity analyses were conducted removing these two factors separately and simultaneously from the regression models. Moreover, to investigate how much of the effect that could be attributed to birthweight, we inserted this variable in the regression models.

Since the women in our population were sampled based on alcohol intake during pregnancy,[22] we used sample weights in our analyses to account for the oversampling of women with relatively high alcohol intake or binge drinking episodes.[12 13] To account for the complex stratified sampling design and possible deviations from normality and variance homogeneity, we applied robust standard errors.[23] All statistical tests were two-sided and with a significance level at 0.05. We performed complete case analyses, as multiple imputation strategies to handle missing data in this cohort have produced essentially the same results when compared to complete case analyses.[22] We investigated the possibility for collinearity between covariates and found no evidence of this, as the variance inflation factor never exceeded a value of 2 for any of the covariates in the regression models.

Complete information on child IQ scores was available for 99.3% of the sample, for attention scores 84.7%, and for executive function, 99.8% of the parents and 86.6% of the teachers had completed the questionnaire. All covariates were available for 98.6% of the sample. No statistically significant differences between the term and the two preterm groups were evident with regard to the proportion of missing outcome and covariate data.

Ethical approval

The data collection for the LDPS was approved by the DNBC Board of Directors, the DNBC Steering committee, the regional Ethics Committee, the Danish Data Protection Agency, and the Institutional Review Board at the Centers for Disease Control and Prevention. Signed informed consent was obtained for the LDPS. The current study was further approved by the Danish Data Protection Agency (file number 2012-58-0004).

Patient and public involvement

For this study, there was no direct patient or public involvement. However, all study results within the DNBC population are available to the study participants, and a participants' panel is ensuring that as many participants as possible wish to continue being part of the cohort.

RESULTS

The characteristics of the 1776 mother and child pairs are presented in table 1. There were no statistically significant group differences with respect to health, lifestyle, and socioeconomic characteristics. Although not statistically significant, the mothers of the children born very or moderately preterm were more likely to be younger, first-time mothers, without a partner, having smoked during pregnancy, but they also had slightly higher IQ and longer education. The mothers of the late preterm children were less likely to have consumed alcohol in pregnancy, but more likely to have male births and lower IQ when compared to the other groups.

With children born at term as the reference, the mean difference in FIQ, VIQ, and PIQ for the very or moderately preterm group was -10.6 points [95% CI; -19.4 to -1.8], -7.4 points [-13.4 to -1.5], and -11.7 points [-21.9 to -1.5], respectively, when adjusting for potential confounders. Among the late preterm children, a tendency towards lower IQs was evident in the unadjusted analyses, but we found no statistically significant differences after adjusting for potential confounders.

For the attention measures, the mean differences were small, and we did not find evidence of statistically significant associations.

With regard to executive function, no statistically significant findings were evident in the parents' assessment. However, analyses of the teachers' assessment showed a mean difference in GEC, BRI, and MI in the very or moderately preterm group of 5.3 points [95% CI; 2.4 to 8.3], 4.2 points [-0.6 to 9.0], and 5.5 points [2.0 to 9.0], respectively, when compared to the term group and adjusting for potential confounders. For the late preterm group, the results were similar but did not reach statistical significance (see table 2).

Analyses with GA as a continuous variable did not alter the conclusions substantially (see table 3). We found a statistically significant increase in FIQ of 0.08 points [95% CI; 0.01, 0.15] per increase in GA (in days) in the adjusted analysis. Similar estimates were seen in the analyses of VIQ and PIQ, however we found no statistically significant associations in the adjusted analyses. For teacher-assessed executive function, we found a statistically significant decrease in GEC and MI of -0.07 points [95% CI; -0.14, -0-01] per increase in GA (in days) indicating better executive function with increasing GA, however these estimates also became insignificant when adjusting for potential confounders.

When maternal IQ and parental education were removed from the regression analyses separately or simultaneously (see supplementary table 1), the estimates of association did not change notably. However, when these variables were removed simultaneously from the regression, most estimates became insignificant due to wider CIs.

When introducing birthweight in the regression analyses (see supplementary table 1), the association between GA and all IQ outcomes became considerably weaker and were no longer statistically significant. However, a trend towards lower IQ in the very or moderately preterm group was still evident, as the mean differences in FIQ, VIQ, and PIQ were reduced to -7.0 points [95% CI; -15.7 to 1.6], -5.9 points [-12.2 to 0.3], and -6.8 points [-16.6 to 3.0], respectively, when compared to the term group. When birthweight was introduced in the analyses of attention and executive function outcomes, the results did not change substantially.

In a post hoc analysis, we excluded the early term births (GA 37-38) and made a direct comparison between the very or moderately preterm group and the term group with GA ≥ 39 weeks (*n*=1443), and the late preterm group and the term group (GA ≥ 39 weeks), respectively (see supplementary table 2). In these analyses, the results did not change notably for any of the outcomes.

DISCUSSION

Main findings

We found a statistically significant effect of very or moderately preterm birth on IQ and teacher-assessed executive function when adjusting for potential confounders. Although maternal IQ and parental education accounted for much of the variance in child IQ in this dataset,[7] these two factors should only be considered weak confounders with no significant association with GA, as removing these variables from our analyses did not alter the associations notably. However, removal of the variables produced wider CIs confirming that they explain substantial parts of the variance.
The inclusion of birthweight in the regression analyses for IQ outcomes attenuated the associations for the very or moderately preterm group, and the results were no longer statistically significant. For the late preterm group, the associations completely vanished. This could be suggestive of mediation and underlines the importance of looking at GA relatively to birthweight when investigating effects of preterm birth, though our results for the very to moderately preterm children indicate that there

may be cognitive effects of GA which are independent of birthweight, perhaps reflecting effects of very low GA on brain development.

Strengths and limitations

One of the strengths of this study is the relatively large sample size with thorough information on family and background factors that may influence the cognitive outcome of a child. Specially trained psychologists, unaware of the gestational age, conducted neuropsychological tests with a high interrater reliability of 97-97.5 %.[12] To minimise bias in our analyses, we composed DAGs to identify potential confounders prior to data analysis. Due to our large sample size, we were able to adjust for an exhaustive set of confounders. Other strengths of our study were a predefined protocoled methodology, and use of robust standard errors to account for the sample design and shortcomings in the data.

Our study has some limitations. The study population was sampled based on average alcohol consumption and binge drinking during pregnancy,[12 13] and therefore, the sample is not representative of the entire DNBC population. We applied sample weights in the analyses to accommodate this. However, the use of weights may be problematic for small subgroups, and together with the use of robust standard errors, this approach may have reduced the power to obtain statistically significant results and widened the CIs.

Another weakness of this study is the relatively small proportion of children born preterm, especially children born very preterm (<32 weeks GA). According to MBR records from 2000 (our recruitment period was from 1997 to 2003), we would expect 6.3% of all new-borns to be born preterm.[24] In our population it was only 2.7%, which is equal to an underrepresentation of 57%. Only 0.2% of our sample was born very preterm, although we would expect 1.0%.[24] This can be a result of various factors that prevent parents with children born preterm from participating in a clinical study, in particular if the children are born very preterm and need special care. However, studies have shown that the influence of selection bias on several exposure-outcome associations in the DNBC is limited.[25] We adjusted for a large number of covariates associated with selection, still we cannot rule out that the low prevalence of preterm births in our cohort may have limited our power to detect any true differences as statistically significant. A post hoc power analysis showed that analyses comparing very or moderately preterm birth (*n*=8) with birth at term (*n*=1728) had a power of 0.48, 0.28, and 0.59 for FIQ, VIQ, and PIQ outcomes, respectively. The low prevalence of preterm births also prevented us from performing analyses investigating the impact of very or extremely preterm birth.

Despite the limitations, especially the low number of preterm births, we believe that this study contributes with important knowledge that together with existing evidence in the literature may improve the clinicians' ability to advise women at risk of preterm delivery and give informed predictions about the future.

Interpretation

For the IQ outcomes, the findings in our study are generally in line with previous findings with an IQ reduction of approximately 10 points in children born preterm.[4 26] However, in our study, this clinically very relevant difference was only seen among the very or moderately preterm children, and not in the late preterm group. A meta-analysis by Chan et al.[27] showed a statistically significant impact of late preterm birth on general cognitive ability and non-verbal intelligence. Our study in part contradicts these findings, as no associations between late preterm birth and IQ (full-scale, verbal, and non-verbal) were found. In our unadjusted analyses, we saw a trend towards lower IQ among late preterm children, but the trend disappeared when adjusting for confounders. This discrepancy may reflect insufficient adjustments in other studies but also the limited power of our study.

When assessing attention measures, we only found one statistically significant result, which might be because of chance alone. This is not in line with previous findings suggesting that preterm infants are at increased risk of developing eg Attention Deficit Hyperactivity Disorder with a relative risk of 2.64 [95% CI 1.85, 3.78].[26] However, TEACh-5 has not been validated as a diagnostic test, and given the unambiguous findings in the present study, it is possible that GA does not have an impact on test of basic attention function.

In the field of executive function, it has been suggested that extremely preterm infants (<28 weeks GA) are at increased risk of developing executive function difficulties.[28] Studies investigating the association between very, moderately, or late preterm birth and poor BRIEF scores have not detected any convincing deficits when evaluating the parents' questionnaire,[29 30] and to our knowledge, the teachers' questionnaire has not previously been used for this purpose. Hodel et al. detected deficits in a population of moderately to late preterm infants at the age of 9 months and at 4 years,[31] but in these studies, other executive function measures than BRIEF were applied.
In extremely low birthweight children, teachers have proven to report significantly more difficulties on the BRI subscale compared to the parents.[32] In our study, we found that teachers reported more difficulties in all areas (GEC, BRI, and MI) when compared to the parents. This can be due to teachers having a more objective viewpoint and being more experienced in working with children with and without difficulties.

CONCLUSION

This study showed significantly lower IQ and poorer executive function in children born very or moderately preterm (<34 weeks GA) compared to children born at term (≥37 weeks GA), but only the differences in IQ were considered clinically relevant. No associations between late preterm birth

(34 to <37 weeks GA) and poor cognitive outcomes were shown.

Maternal IQ and parental education are strong predictors of child IQ in our dataset but were only weak confounders of the association between GA and cognitive outcomes. Therefore, GA has an essential role in determining cognitive abilities independent of maternal IQ and parental educational level. Further studies with larger sample sizes to confirm these findings are needed.

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Contributors

Dr. Sejer contributed to the conception and design of the study, performed data management and statistical analyses, analysed and interpreted the data, drafted the initial manuscript, and wrote the final manuscript with contributions from the co-authors.

Miss Slavensky and Mr. Bruun contributed to the conception and design of the study, assisted with statistical analyses and interpretation of the data, and critically reviewed and revised the manuscript.

Mr. Mortensen and Dr. Kesmodel conceptualised and designed the study, analysed and interpreted the data, and critically reviewed and revised the manuscript.

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

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Competing interests

None declared.

Data sharing statement

No additional data are available for this study.

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Tables

Table 1. Family characteristics among singletons born at term or preterm. Denmark 2003-2008 (*n*=1776)

Characteristics	Born at term (≥37 weeks)	Late preterm birth (34 to <37 weeks)	Moderately or very preterm birth (<34 weeks)[a]
Number of infants (n)	1728	40	8
Maternal age (years, mean [SD])	30.8 (4.4)	30.4 (4.5)	28.8 (3.4)
Maternal pre-pregnancy BMI (kg/m^2, median [10/90 percentile])[b]	22.6 (19.6/28.7)	22.7 (18.4/33.0)	22.8 (16.5/28.2)
Maternal smoking in pregnancy (%)	31.7	30.0	37.5
Maternal alcohol consumption in pregnancy (%)[c]			
0 drinks/week	47.6	55.0	50.0
1-4 drinks/week	41.3	37.5	37.5
5+ drinks/week[d]	11.1	7.5	12.5
Maternal marital status (%)[e]			
Single[f]	12.4	10.3	25.0
Cohabitating	87.6	89.7	75.0
Maternal IQ (mean [SD])[g]	100.0 (14.9)	97.7 (16.9)	104.3 (17.9)
Parental educational level (years, mean [SD])[h]	13.2 (1.9)	13.0 (1.6)	14.2 (1.8)
Parity (%)			
0	50.7	60.0	87.5
1	32.1	30.0	12.5
2+	17.2	10.0	0.0
Child sex (%)			
Male	51.7	60.0	50.0
Females	48.3	40.0	50.0
Gestational age (days, median [10/90 percentile])	282.0 (269.0/293.0)	251.5 (241.0/257.5)	227.5 (206.0/236.0)
Birthweight (grams, mean [SD])[i]	3627.3 (483.4)	2740.8 (482.6)	2040.9 (458.4)
Child age at testing (years, median [10/90 percentile])	5.23 (5.12/5.30)	5.26 (5.13/5.31)	5.23 (5.10/5.29)

N, number; SD, standard deviation; BMI, body mass index; IQ, intelligence quotient. [a] Lowest observation 29 weeks. [b] Information missing for 35 term and 1 late preterm birth. [c] Information missing for 1 term birth. [d] Range 5-14 drinks/week. [e] Information missing for 13 term and 1 late preterm birth. [f] If reported being single either during pregnancy or at follow-up at 60-64 months postpartum. [g] Information missing for 9 term births. [h] Information missing for 5 term and 1 late preterm birth. [i] Information missing for 12 term and 2 late preterm births.

Table 2. Mean differences in intelligence, attention, and executive function between 5-year-old children born at term (reference group) and children born preterm. Denmark 2003-2008 (*n*=1776)[a]

	Born at term ≥37 weeks (*n*=1728)	Late preterm birth 34 to <37 weeks (*n*=40)		Moderately or very preterm birth <34 weeks (*n*=8)	
	Mean (SD)	**Mean difference**	**95% CI**	**Mean difference**	**95% CI**
Intelligence (WPPSI-R)					
Full scale IQ					
Unadjusted	105.64 (12.86)	-2.09	-6.91, 2.74	-9.22	-20.25, 1.81
Adjusted[b]		-0.05	-4.62, 4.53	-10.56	-19.37, -1.75
Verbal IQ					
Unadjusted	104.81 (10.80)	-1.73	-5.23, 1.76	-7.11	-15.64, 1.41
Adjusted		-0.40	-4.84, 4.05	-7.41	-13.37, -1.45
Performance IQ					
Unadjusted	105.14 (16.22)	-2.00	-9.02, 5.03	-9.51	-20.46, 1.45
Adjusted		0.38	-5.39, 6.15	-11.71	-21.89, -1.52
Attention (TEACh-5)					
Overall attention					
Unadjusted	0.01 (1.00)	-0.21	-0.70, 0.28	-0.10	-0.72, 0.52
Adjusted		-0.16	-0.59, 0.26	-0.25	-1.00, 0.50
Sustained attention					
Unadjusted	0.01 (1.00)	-0.39	-0.76, -0.01	-0.09	-0.62, 0.44
Adjusted		-0.23	-0.64, 0.19	-0.16	-0.83, 0.52
Selective attention					
Unadjusted	0.00 (1.00)	0.09	-0.46, 0.63	0.02	-0.41, 0.45
Adjusted		0.06	-0.42, 0.53	-0.19	-0.65, 0.27
Executive function (BRIEF)[c]					
- Parent version					
Global Executive Composite					
Unadjusted	49.97 (9.98)	1.44	-4.03, 6.90	-0.39	-16.52, 15.74
Adjusted		2.26	-2.01, 6.53	-0.20	-14.27, 13.87
Behavioural Regulation Index					
Unadjusted	50.01 (9.98)	-0.35	-5.50, 4.79	-1.18	-16.17, 13.81
Adjusted		0.40	-3.97, 4.76	-1.95	-14.87, 10.97
Metacognition Index					
Unadjusted	49.95 (9.98)	2.41	-3.10, 7.92	0.13	-15.24, 15.51
Adjusted		3.19	-1.11, 7.49	0.90	-12.60, 14.41
- Teacher version					
Global Executive Composite					
Unadjusted	49.94 (10.03)	4.47	-0.77, 9.70	5.47	2.57, 8.36
Adjusted		3.99	-0.82, 8.81	5.33	2.39, 8.27
Behavioural Regulation Index					
Unadjusted	49.95 (10.01)	4.42	-0.38, 9.21	5.29	2.08, 8.50
Adjusted		3.79	-0.89, 8.48	4.24	-0.56, 9.03
Metacognition Index					
Unadjusted	49.95 (10.03)	4.09	-1.55, 9.73	5.07	0.61, 9.54
Adjusted		3.77	-1.32, 8.85	5.46	1.97, 8.95

N, number; SD, standard deviation; CI, confidence interval; WPPSI-R, Wechsler Preschool and Primary Scales of Intelligence-Revised; IQ, intelligence quotient; TEACh-5, Test of Everyday Attention for Children at Five; BRIEF, Behaviour Rating Inventory of Executive Function. [a] Overall number of participants. Due to complete case analyses, for the adjusted analyses, the actual number of participants for each outcome was: Full-scale IQ (*n*=1748 [missing data for 1 late preterm birth]), verbal IQ (*n*=1749 [missing data for 1 late preterm birth]), performance IQ (*n*=1749 [missing data for 1 late preterm birth]), overall attention (*n*=1493 [missing data for 7 late preterm births]), sustained attention (*n*=1586 [missing data for 4 late preterm births]), selective attention (*n*=1612 [missing data for 4 late preterm births]), Global Executive Composite (parents, *n*=1748 [missing data for 1 late preterm birth]; teachers, *n*=1525 [missing data for 7 late preterm births and 1 very to moderate preterm birth]), Behavioural Regulation Index (parents, *n*=1748 [missing data for 1 late preterm birth]; teachers, *n*=1530 [missing data for 7 late preterm births and 1 very to moderate preterm birth]), Metacognition Index (parents, *n*=1748 [missing data for 1 late preterm birth]; teachers, *n*=1525 [missing data for 7 late preterm births and 1 very to moderate preterm birth]). [b] All adjusted analyses adjusted for maternal age, maternal IQ, average alcohol consumption in pregnancy, smoking in pregnancy, parity, maternal marital status, parental educational level, child sex, testing psychologist, and age at testing. [c] A higher BRIEF score indicates more executive function difficulties (opposite than the other outcome measures).

Table 3. Regression coefficients for the association between gestational age (in days) and intelligence, attention, and executive function in 5-year-old children. Denmark 2003-2008 (*n*=1776)[a]

Intelligence (WPPSI-R)	Beta (95% CI)	Attention (TEACh-5)	Beta (95% CI)	Executive function (BRIEF)[c] - *Parent version*	Beta (95% CI)	Executive function (BRIEF) - *Teacher version*	Beta (95% CI)
Full scale IQ		***Overall attention***		***Global Executive Composite***		***Global Executive Composite***	
Unadjusted	0.10 (0.02, 0.19)	Unadjusted	0.00 (0.00, 0.01)	Unadjusted	-0.03 (-0.10, 0.05)	Unadjusted	-0.07 (-0.14, -0.01)
Adjusted[b]	0.08 (0.01, 0.15)	Adjusted	0.00 (0.00, 0.01)	Adjusted	-0.02 (-0.08, 0.05)	Adjusted	-0.06 (-0.12, 0.01)
Verbal IQ		***Sustained attention***		***Behavioural Regulation Index***		***Behavioural Regulation Index***	
Unadjusted	0.07 (0.00, 0.14)	Unadjusted	0.00 (-0.01, 0.01)	Unadjusted	-0.02 (-0.09, 0.05)	Unadjusted	-0.06 (-0.13, 0.01)
Adjusted	0.06 (0.00, 0.13)	Adjusted	0.00 (-0.01, 0.01)	Adjusted	-0.01 (-0.08, 0.05)	Adjusted	-0.04 (-0.11, 0.02)
Performance IQ		***Selective attention***		***Metacognition Index***		***Metacognition Index***	
Unadjusted	0.12 (0.01, 0.22)	Unadjusted	0.00 (0.00, 0.01)	Unadjusted	-0.03 (-0.10, 0.05)	Unadjusted	-0.07 (-0.14, -0.01)
Adjusted	0.08 (-0.01, 0.18)	Adjusted	0.00 (0.00, 0.01)	Adjusted	-0.02 (-0.08, 0.04)	Adjusted	-0.06 (-0.12, 0.00)

N, number; CI, confidence interval; WPPSI-R, Wechsler Preschool and Primary Scales of Intelligence-Revised; IQ, intelligence quotient; TEACh-5, Test of Everyday Attention for Children at Five; BRIEF, Behaviour Rating Inventory of Executive Function. [a] Overall number of participants. Due to complete case analyses, for the adjusted analyses, the actual number of participants for each outcome was: Full-scale IQ (*n*=1748 [missing data for 1 late preterm birth]), verbal IQ (*n*=1749 [missing data for 1 late preterm birth]), performance IQ (*n*=1749 [missing data for 1 late preterm birth]), overall attention (*n*=1493 [missing data for 7 late preterm births]), sustained attention (*n*=1586 [missing data for 4 late preterm births]), selective attention (*n*=1612 [missing data for 4 late preterm births]), Global Executive Composite (parents, *n*=1748 [missing data for 1 late preterm birth]; teachers, *n*=1525 [missing data for 7 late preterm births and 1 very to moderate preterm birth]), Behavioural Regulation Index (parents, *n*=1748 [missing data for 1 late preterm birth]; teachers, *n*=1530 [missing data for 7 late preterm births and 1 very to moderate preterm birth]), Metacognition Index (parents, *n*=1748 [missing data for 1 late preterm birth]; teachers, *n*=1525 [missing data for 7 late preterm births and 1 very to moderate preterm birth]). [b] All adjusted analyses adjusted for maternal age, maternal IQ, average alcohol consumption in pregnancy, smoking in pregnancy, parity, maternal marital status, parental educational level, child sex, testing psychologist, and age at testing. [c] A higher BRIEF score reflects more executive function difficulties (opposite than the other outcome measures).

Supplementary table 1. Mean differences in intelligence, attention, and executive functions between 5-year-old children born at term (reference group) and children born preterm. Denmark 2003-2008 (*n*=1776)

	Born at term ≥37 weeks (*n*=1728)	Late preterm birth 34 to <37 weeks (*n*=40)		Moderately or very preterm birth <34 weeks (*n*=8)	
	Mean (SD)	**Mean difference**	**95% CI**	**Mean difference**	**95% CI**
Intelligence (WPPSI-R)					
Full scale IQ					
Unadjusted	105.64 (12.86)	-2.09	-6.91, 2.74	-9.22	-20.25, 1.81
Adjusted[a]		-0.05	-4.62, 4.53	-10.56	-19.37, -1.75
Excluding maternal IQ[b]		-0.00	-4.91, 4.91	-11.23	-21.00, -1.45
Excluding parental education		-0.64	-5.16, 3.87	-10.04	-19.60, -0.48
Excluding IQ + parental education		-1.42	-6.47, 3.63	-10.34	-22.19, 1.51
With all including birthweight[c]		2.21	-2.82, 7.25	-7.04	-15.67, 1.59
Verbal IQ					
Unadjusted	104.81 (10.80)	-1.73	-5.23, 1.76	-7.11	-15.64, 1.41
Adjusted		-0.40	-4.84, 4.05	-7.41	-13.37, -1.45
Excluding maternal IQ		-0.33	-4.48, 3.83	-7.86	-14.89, -0.83
Excluding parental education		-0.98	-5.40, 3.44	-6.89	-13.14, -0.64
Excluding IQ + parental education		-1.53	-5.55, 2.49	-7.10	-15.24, 1.05
With all including birthweight		0.59	-4.22, 5.40	-5.93	-12.19, 0.33
Performance IQ					
Unadjusted	105.14 (16.22)	-2.00	-9.02, 5.03	-9.51	-20.46, 1.45
Adjusted		0.38	-5.39, 6.15	-11.71	-21.89, -1.52
Excluding maternal IQ		0.42	-6.23, 7.07	-12.46	-23.38, -1.54
Excluding parental education		-0.12	-5.82, 5.59	-11.28	-22.20, -0.36
Excluding IQ + parental education		-0.93	-7.85, 5.99	-11.63	-24.73, 1.47
With all including birthweight		3.49	-2.78, 9.76	-6.80	-16.60, 3.00
Attention (Teach-5)					
Overall attention					
Unadjusted	0.01 (1.00)	-0.21	-0.70, 0.28	-0.10	-0.72, 0.52
Adjusted		-0.16	-0.59, 0.26	-0.25	-1.00, 0.50
Excluding maternal IQ		-0.15	-0.59, 0.30	-0.28	-1.05, 0.49
Excluding parental education		-0.21	-0.63, 0.22	-0.22	-0.88, 0.44
Excluding IQ + parental education		-0.21	-0.67, 0.25	-0.25	-0.90, 0.40
With all including birthweight		-0.11	-0.56, 0.34	-0.20	-0.98, 0.59
Sustained attention					
Unadjusted	0.01 (1.00)	-0.39	-0.76, -0.01	-0.09	-0.62, 0.44
Adjusted		-0.23	-0.64, 0.19	-0.16	-0.83, 0.52
Excluding maternal IQ		-0.23	-0.64, 0.18	-0.17	-0.86, 0.52
Excluding parental education		-0.25	-0.66, 0.16	-0.13	-0.75, 0.48
Excluding IQ + parental education		-0.27	-0.68, 0.13	-0.15	-0.75, 0.46
With all including birthweight		-0.10	-0.55, 0.35	0.01	-0.72, 0.73
Selective attention					
Unadjusted	0.00 (1.00)	0.09	-0.46, 0.63	0.02	-0.41, 0.45
Adjusted		0.06	-0.42, 0.53	-0.19	-0.65, 0.27
Excluding maternal IQ		0.07	-0.41, 0.56	-0.20	-0.69, 0.29
Excluding parental education		0.03	-0.45, 0.51	-0.16	-0.56, 0.24
Excluding IQ + parental education		0.03	-0.47, 0.53	-0.17	-0.57, 0.23
With all including birthweight		0.00	-0.50, 0.50	-0.31	-0.80, 0.18

Executive functions (BRIEF)[d]					
- Parent version					
Global Executive Composite					
Unadjusted	49.97 (9.98)	1.44	-4.03, 6.90	-0.39	-16.52, 15.74
Adjusted		2.26	-2.01, 6.53	-0.20	-14.27, 13.87
Excluding maternal IQ		2.23	-2.15, 6.62	-0.13	-14.00, 13.73
Excluding parental education		2.67	-1.65, 7.00	-0.58	-15.69, 14.54
Excluding IQ + parental education		2.85	-1.77, 7.47	-0.54	-15.79, 14.71
With all including birthweight		1.62	-2.96, 6.20	-1.13	-15.16, 12.90
Behavioural Regulation Index					
Unadjusted	50.01 (9.98)	-0.35	-5.50, 4.79	-1.18	-16.17, 13.81
Adjusted		0.40	-3.97, 4.76	-1.95	-14.87, 10.97
Excluding maternal IQ		0.37	-4.06, 4.80	-1.84	-14.55, 10.87
Excluding parental education		0.75	-3.68, 5.18	-2.27	-16.08, 11.54
Excluding IQ + parental education		0.93	-3.67, 5.54	-2.21	-16.17, 11.75
With all including birthweight		-0.27	-4.92, 4.38	-3.03	-15.90, 9.85
Metacognition Index					
Unadjusted	49.95 (9.98)	2.41	-3.10, 7.92	0.13	-15.24, 15.51
Adjusted		3.19	-1.11, 7.49	0.90	-12.60, 14.41
Excluding maternal IQ		3.17	-1.24, 7.58	0.94	-12.40, 14.27
Excluding parental education		3.61	-0.73, 7.95	0.52	-14.03, 15.07
Excluding IQ + parental education		3.77	-0.87, 8.40	0.54	-14.11, 15.20
With all including birthweight		2.63	-2.01, 7.27	0.15	-13.37, 13.66
- Teacher version					
Global Executive Composite					
Unadjusted	49.94 (10.03)	4.47	-0.77, 9.70	5.47	2.57, 8.36
Adjusted		3.99	-0.82, 8.81	5.33	2.39, 8.27
Excluding maternal IQ		4.08	-0.85, 9.02	5.56	2.55, 8.56
Excluding parental education		4.06	-0.74, 8.87	5.23	2.23, 8.23
Excluding IQ + parental education		4.30	-0.67, 9.27	5.40	2.17, 8.62
With all including birthweight		4.20	-1.02, 9.42	5.39	1.67, 9.12
Behavioural Regulation Index					
Unadjusted	49.95 (10.01)	4.42	-0.38, 9.21	5.29	2.08, 8.50
Adjusted		3.79	-0.89, 8.48	4.24	-0.56, 9.03
Excluding maternal IQ		3.89	-0.91, 8.70	4.49	-0.26, 9.24
Excluding parental education		3.81	-0.87, 8.49	4.21	-0.62, 9.05
Excluding IQ + parental education		4.04	-0.78, 8.85	4.38	-0.71, 9.47
With all including birthweight		4.44	-0.63, 9.52	4.81	-0.72, 10.34
Metacognition Index					
Unadjusted	49.95 (10.03)	4.09	-1.55, 9.73	5.07	0.61, 9.54
Adjusted		3.77	-1.32, 8.85	5.46	1.97, 8.95
Excluding maternal IQ		3.84	-1.33, 9.01	5.64	2.05, 9.23
Excluding parental education		3.86	-1.21, 8.93	5.32	1.96, 8.69
Excluding IQ + parental education		4.07	-1.14, 9.29	5.47	2.03, 8.91
With all including birthweight		3.66	-1.84, 9.17	5.17	1.08, 9.25

N, number; SD, standard deviation; CI, confidence interval; WPPSI-R, Wechsler Preschool and Primary Scales of Intelligence-Revised; IQ, intelligence quotient; TEACh-5, Test of Everyday Attention for Children at Five; BRIEF, Behaviour Rating Inventory of Executive Function. [a] All adjusted analyses adjusted for maternal age, maternal IQ, average alcohol consumption in pregnancy, smoking in pregnancy, parity, maternal marital status, parental educational level, child sex, testing psychologist, and age at testing. [b] Adjusted for all the above-mentioned covariates except maternal IQ. [c] Adjusted for all the above-mentioned covariates and birthweight. [d] A higher BRIEF score indicates more executive function difficulties (opposite than the other outcome measures).

Supplementary table 2. Mean differences in intelligence, attention, and executive function between 5-year-old children born at term (≥39, reference group) and children born preterm. Denmark 2003-2008 (*n*=1491)

	Born at term ≥39 weeks (*n*=1443)	Late preterm birth 34 to <37 weeks (*n*=40)		Moderately or very preterm birth <34 weeks (*n*=8)	
	Mean (SD)	**Mean difference**	**95% CI**	**Mean difference**	**95% CI**
Intelligence (WPPSI-R)					
Full scale IQ					
Unadjusted	105.92 (12.91)	-2.49	-7.34, 2.35	-9.63	-20.67, 1.41
Adjusted[a]		-0.22	-4.84, 4.41	-10.27	-19.27, -1.26
Verbal IQ					
Unadjusted	104.93 (10.71)	-1.95	-5.46, 1.56	-7.33	-15.87, 1.20
Adjusted		-0.35	-4.88, 4.17	-7.22	-13.31, -1.14
Performance IQ					
Unadjusted	105.53 (16.27)	-2.51	-9.56, 4.53	-10.02	-20.99, 0.95
Adjusted		0.03	-5.73, 5.79	-11.38	-21.60, -1.17
Attention (TEACh-5)					
Overall attention					
Unadjusted	0.01 (1.00)	-0.22	-0.71, 0.27	-0.10	-0.73, 0.52
Adjusted		-0.15	-0.58, 0.28	-0.22	-0.98, 0.54
Sustained attention					
Unadjusted	0.01 (1.01)	-0.39	-0.77, -0.02	-0.10	-0.63, 0.44
Adjusted		-0.22	-0.63, 0.20	-0.15	-0.86, 0.55
Selective attention					
Unadjusted	0.00 (1.01)	0.07	-0.48, 0.61	0.00	-0.43, 0.43
Adjusted		0.04	-0.44, 0.53	-0.15	-0.59, 0.29
Executive function (BRIEF)[b]					
- Parent version					
Global Executive Composite					
Unadjusted	49.75 (9.93)	1.60	-3.87, 7.08	-0.23	-16.36, 15.90
Adjusted		2.48	-1.80, 6.75	-0.16	-14.49, 14.17
Behavioural Regulation Index					
Unadjusted	49.76 (9.91)	-0.09	-5.24, 5,07	-0.91	-15.91, 14.08
Adjusted		0.73	-3.69, 5.15	-1.72	-14.67, 11.22
Metacognition Index					
Unadjusted	49.77 (9.94)	2.49	-3.03, 8.02	0.22	-15.16, 15.60
Adjusted		3.32	-0.94, 7.59	0.82	-13.07, 14.72
- Teacher version					
Global Executive Composite					
Unadjusted	49.83 (10.15)	4.68	-0.56, 9.93	5.69	2.76, 8.61
Adjusted		4.12	-0.78, 9.02	5.30	2.30, 8.30
Behavioural Regulation Index					
Unadjusted	49.88 (10.06)	4.57	-0.24, 9.39	5.45	2.21, 8.68
Adjusted		3.95	-0.72, 8.63	4.21	-0.83, 9.24
Metacognition Index					
Unadjusted	49.82 (10.14)	4.33	-1.33, 9.98	5.31	0.83, 9.80
Adjusted		3.86	-1.36, 9.09	5.42	2.20, 8.63

N, number; SD, standard deviation; CI, confidence interval; WPPSI-R, Wechsler Preschool and Primary Scales of

Intelligence-Revised; IQ, intelligence quotient; TEACh-5, Test of Everyday Attention for Children at Five; BRIEF, Behaviour Rating Inventory of Executive Function. [a] All adjusted analyses adjusted for maternal age, maternal IQ, average alcohol consumption in pregnancy, smoking in pregnancy, parity, maternal marital status, parental educational level, child sex, testing psychologist, and age at testing. [b] A higher BRIEF score indicates more executive function difficulties (opposite than the other outcome measures).

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7-9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-9
Bias	9	Describe any efforts to address potential sources of bias	9-11
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10-11
		(*b*) Describe any methods used to examine subgroups and interactions	-
		(*c*) Explain how missing data were addressed	11
		(*d*) If applicable, explain how loss to follow-up was addressed	-
		(*e*) Describe any sensitivity analyses	11
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7-8
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12 + table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-14 + tables 2-3
		(*b*) Report category boundaries when continuous variables were categorized	10-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13-14
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Impact of gestational age on child intelligence, attention, and executive function at age five: a cohort study

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Abstract

Objectives: Preterm birth can affect cognition, but other factors including parental education and intelligence may also play a role, but few studies have adjusted for these potential confounders. We aimed to assess the impact of gestational age (GA), late preterm birth (34 to <37 weeks GA), and very to moderately preterm birth (<34 weeks GA) on intelligence, attention, and executive function in a population of 5-year-old Danish children.

Design: Population-based prospective cohort study.

Setting: Denmark 2003-2008.

Participants: A cohort of 1776 children and their mothers sampled from the Danish National Birth Cohort with information on GA, family and background factors, and completed neuropsychological assessment at age five.

Primary outcome measures: Wechsler Preschool and Primary Scale of Intelligence-Revised, Test of Everyday Attention for Children at Five, and Behaviour Rating Inventory of Executive Function scores.

Results: For preterm birth <34 weeks GA (*n*=8), the mean difference in full-scale intelligence quotient was -10.6 points [95% confidence interval; -19.4 to -1.8] when compared to the term group ≥37 weeks GA (*n*=1728), and adjusted for potential confounders. For the teacher-assessed Global Executive Composite, the mean difference was 5.3 points [2.4 to 8.3] in the adjusted analysis, indicating more executive function difficulties in the preterm group <34 weeks GA compared to the term group. Maternal intelligence and parental education were weak confounders.

No associations between late preterm birth 34 to <37 weeks GA (*n*=40) and poor cognition were shown.

Conclusions: This study showed substantially lower intelligence and poorer executive function in children born <34 weeks GA compared to children born at term. GA may play an important role in determining cognitive abilities independent of maternal intelligence and parental education. Studies with larger sample sizes are needed to confirm these findings, as the proportion of children born preterm in this study population was small.

Article summary

Strengths and limitations of this study

- In this study population, thorough information on family and background factors that may influence the cognitive outcome of a child was obtained.
- Directed acyclic graphs were composed to identify potential confounders prior to data analysis, and it was possible to adjust for an extensive set of confounders.
- The study population was sampled based on average alcohol consumption and binge drinking during pregnancy and may not be representative for the entire population, however, sample weights were applied in analyses to accommodate this.
- Robust standard errors were used to account for the sample design, possible deviations from normality and variance homogeneity.
- The proportion of children born preterm in this study population was small (48 out of 1776), which limited our power to detect any true differences.

Keywords

Attention, child development, executive function, gestational age, intelligence, preterm birth.

Abbreviations

GA: gestational age

LDPS: Lifestyle During Pregnancy Study

DNBC: Danish National Birth Cohort

IQ: intelligence quotient

WPPSI-R: Wechsler Preschool and Primary Scales of Intelligence-Revised

VIQ: verbal intelligence quotient

PIQ: performance intelligence quotient

FIQ: full-scale intelligence quotient

TEACh-5: Test of Everyday Attention for Children at Five

SD: standard deviation

BRIEF: Behaviour Rating Inventory of Executive Function

GEC: Global Executive Composite

BRI: Behavioural Regulation Index

MI: Metacognition Index

DAG: directed acyclic graph

CI: confidence interval

INTRODUCTION

In the past decades there has been an increase in the number of children being born preterm.[1] Advances in treatment have led to lower mortality rates, but morbidity rates have not been reduced to the same degree.[2] Many organs are vulnerable to preterm birth, and the preterm brain in particular can suffer long-term neurological impairments.[3] A dose-response relationship has been proposed, suggesting that the lower the gestational age (GA), the higher the risk of cognitive impairment.[4]

A study showed that at age five 10% of children born preterm still received care in centres specialised for children with disabilities compared to 2% of children born at term (odds ratio 7.9 [95% CI; 3.5 to 18.0]).[5] Hence, it is important to determine the association between preterm birth and cognitive outcomes in order to advise women at risk of preterm delivery and to give informed predictions about the future. Also, the knowledge can be of value to the obstetrician and pediatrician when making decisions about time and mode of delivery and on whether or not resuscitation should be offered at a GA as low as 22-24 weeks.

Previous studies have shown associations between preterm birth and low intelligence, attention deficits, and impaired executive function.[4 6] These negative outcomes may in part be a consequence of low GA, but other biological and social factors including parental education and intelligence may also affect the cognitive outcome of a child. In our dataset, parental education and maternal intelligence quotient (IQ) have proven to be strong predictors of child IQ,[7] and a recent study has shown that maternal IQ predicts IQ in very preterm children at age five.[8] Thus, it is important to adjust for these potential confounders when investigating an association between preterm birth and cognitive outcomes. Previous studies have adjusted for parental education,[9 10] but to our knowledge, only one study[11] has adjusted for maternal intelligence. In that study children born before 34 weeks GA were excluded, and the sample size was small (*n*=336).

The aim of our study was to investigate the influence of GA, late preterm birth (34 to <37 weeks GA), and very to moderately preterm birth (<34 weeks GA) on intelligence, attention, and executive function in a population of 5-year-old Danish children adjusted for relevant confounders including parental educational level and maternal intelligence.

MATERIAL AND METHODS

Study sample

We used data from the Lifestyle During Pregnancy Study (LDPS),[12] which is a sample from the Danish National Birth Cohort (DNBC). The DNBC contains information on 101 042 Danish women and their children recruited from 1997 to 2003. Of the invited women, 60% chose to participate, and 30% of all pregnant women at that time were included.

A total of 3478 women with singleton pregnancies were sampled from the DNBC and invited to participate in the LDPS from 2003 to 2008. Participants were sampled in strata defined by the prenatal maternal average alcohol intake with oversampling of women reporting a relatively high alcohol intake or binge drinking episodes during pregnancy.[12 13] Out of the sampled mother and child pairs, 1776 children had neuropsychological tests performed at age five and had information on GA available, and thus were included in our analyses. There were no considerable differences between the participants and non-participants with regard to maternal age, body mass index, parity, marital status, prenatal smoking and alcohol consumption, child sex, birthweight, and gestational age at birth.[13] Exclusion criteria were multiple pregnancies and congenital diseases with a large risk of mental retardation (the diagnostic term used at the time of data collection), as they represent a fundamentally different group of individuals that may not be representative of the norm. Other exclusion criteria were inability to speak Danish, and impaired vision or hearing abilities preventing the child from completing the tests.[12]

Data collection

Exposure variables

Information on GA was obtained from the Danish Medical Birth Register and determined by ultrasound, while date of last menses was only used to determine GA in very few cases where an ultrasound estimate was not available. We used GA as 1) a continuous variable (days) and 2) a categorical variable, comparing *late preterm* birth (34 to <37 completed weeks of gestation) and *very to moderately preterm* birth (GA<34 weeks) with birth at *term* (GA ≥37 weeks), respectively.

Outcome measures

At child age five (age span: 60-64 months chronological age), a neuropsychological test battery was administered by specially trained psychologists.

Intelligence

The child's IQ was assessed using the Wechsler Preschool and Primary Scales of Intelligence-Revised (WPPSI-R).[14] WPPSI-R includes five verbal and five performance subtests that are used to calculate an overall verbal IQ (VIQ), overall performance IQ (PIQ), and full-scale IQ (FIQ). In this test battery, only three of the verbal (arithmetic, information, and vocabulary) and three of the performance (block design, geometric design, and object assembly) subtests were carried out to ensure the child's cooperation throughout the testing. Standard procedures were used to prorate scores from the shortened test. Swedish norms were applied to derive the IQ scores, since no

Danish norms exist. This should not affect any comparisons made internally within the sample with respect to GA differences.

Attention

Attention measures were assessed with the Test of Everyday Attention for Children at Five (TEACh-5).[15] For this study, two subtests assessing selective attention ('Great Balloon Hunt' and 'Hide and Seek II') and two subtests assessing sustained attention ('Barking' and 'Draw a line') were used. Each subtest score was standardised to a mean of 0 and a standard deviation (SD) of 1. To calculate composite scores for overall, selective, and sustained attention, the means of the respective standardised subtest scores for each individual were calculated and re-standardised to a mean of 0 and SD of 1.

Executive function

Executive function was assessed using the Behaviour Rating Inventory of Executive Function (BRIEF) questionnaire.[16] The questionnaire consists of two versions, one for parents and one for teachers. Each questionnaire evaluates eight domains of executive functioning and form the Global Executive Composite (GEC). Three of the eight domains form the Behavioural Regulation Index (BRI), and five of the domains form the Metacognition Index (MI). Since the eight domains do not follow a normal distribution, we performed a normalising t-score transformation to standardise each domain to a mean of 50 and SD of 10. To compute the GEC, BRI, and MI, the means of the respective domains for each individual were calculated and re-standardised to a mean of 50 and SD of 10. For all BRIEF scores, a higher score indicates more executive function difficulties.

Covariates

To identify relevant covariates, we constructed directed acyclic graphs (DAGs)[17] using the graphical tool DAGitty.[18]

Important covariates were obtained from prenatal and postnatal telephone interviews, a parent-administered questionnaire at follow-up, the Danish social security number, and the MBR. In addition, the mother's intelligence was assessed at follow-up with Raven's Standard Progressive Matrices[19] and two subtests (vocabulary and information) of the Wechsler Adult Intelligence Scale.[20] The three test results were weighted equally and combined to derive an IQ score.

Prior to analysis, we evaluated the five lowest and five highest observations for all outcomes and covariates to detect unrealistic values (+/- 4 SD for the normally distributed data). This resulted in removal of three birthweight observations (one from the term group and two from the late preterm group) that exceeded our threshold when evaluated according to Danish standards.[21] Moreover, we removed one unrealistic body mass index of 13.9 kg/m^2 and one observation of average alcohol intake of 36 drinks/week during pregnancy (from the term group).

Statistical analyses

We performed multivariable linear regression using SAS, Version 9.4 (© SAS Institute Inc., Cary, NC, USA).

We assessed term vs. late preterm birth and term vs. very or moderately preterm birth. We adjusted for a set of a priori defined variables. This included maternal age at birth (continuous), maternal IQ (continuous), average alcohol consumption in pregnancy (0, 1-4, 5+ drinks per week), smoking in pregnancy (yes/no), parity (0, 1, 2+), maternal marital status (single/cohabitating), parental educational level (total duration in years averaged for both parents, if information on the father was missing, maternal only [continuous]), and child sex (male/female). Moreover, we adjusted for the psychologist administering the tests (8 categories) and age at testing (continuous). We created dummy variables from the categorical variables before inserting them in the regression models.

In the study sample, maternal IQ and parental educational level are important predictors of child intelligence,[7] and in order to evaluate the importance of adjusting for these factors, sensitivity analyses were conducted removing these two factors separately and simultaneously from the regression models. Moreover, to investigate how much of the effect that could be attributed to birthweight, we inserted this variable in the regression models.

Since the women in our population were sampled based on alcohol intake during pregnancy,[22] we used sample weights in our analyses to account for the oversampling of women with relatively high alcohol intake or binge drinking episodes.[12 13] To account for the complex stratified sampling design and possible deviations from normality and variance homogeneity, we applied robust standard errors.[23] All statistical tests were two-sided and with a significance level at 0.05. We performed complete case analyses, as multiple imputation strategies to handle missing data in this cohort have produced essentially the same results when compared to complete case analyses.[22] We investigated the possibility for collinearity between covariates and found no evidence of this, as the variance inflation factor never exceeded a value of 2 for any of the covariates in the regression models.

Complete information on child IQ scores was available for 99.3% of the sample, for attention scores 84.7%, and for executive function, 99.8% of the parents and 86.6% of the teachers had completed the questionnaire. All covariates were available for 98.6% of the sample. No statistically significant differences between the term and the two preterm groups were evident with regard to the proportion of missing outcome and covariate data.

Ethical approval

The data collection for the LDPS was approved by the DNBC Board of Directors, the DNBC Steering committee, the regional Ethics Committee, the Danish Data Protection Agency, and the Institutional Review Board at the Centers for Disease Control and Prevention. Signed informed consent was obtained for the LDPS. The current study was further approved by the Danish Data Protection Agency (file number 2012-58-0004).

Patient and public involvement

For this study, there was no direct patient or public involvement. However, all study results within the DNBC population are available to the study participants, and a participants' panel is ensuring that as many participants as possible wish to continue being part of the cohort.

RESULTS

The characteristics of the 1776 mother and child pairs are presented in table 1. There were no statistically significant group differences with respect to health, lifestyle, and socioeconomic characteristics. Although not statistically significant, the mothers of the children born very or moderately preterm were more likely to be younger, first-time mothers, without a partner, having smoked during pregnancy, but they also had slightly higher IQ and longer education. The mothers of the late preterm children were less likely to have consumed alcohol in pregnancy, but more likely to have male births and lower IQ when compared to the other groups.

With children born at term as the reference, the mean difference in FIQ, VIQ, and PIQ for the very or moderately preterm group was -10.6 points [95% CI; -19.4 to -1.8], -7.4 points [-13.4 to -1.5], and -11.7 points [-21.9 to -1.5], respectively, when adjusting for potential confounders. Among the late preterm children, a tendency towards lower IQs was evident in the unadjusted analyses, but we found no statistically significant differences after adjusting for potential confounders.

For the attention measures, the mean differences were small, and we did not find evidence of statistically significant associations.

With regard to executive function, no statistically significant findings were evident in the parents' assessment. However, analyses of the teachers' assessment showed a mean difference in GEC, BRI, and MI in the very or moderately preterm group of 5.3 points [95% CI; 2.4 to 8.3], 4.2 points [-0.6 to 9.0], and 5.5 points [2.0 to 9.0], respectively, when compared to the term group and adjusting for potential confounders. For the late preterm group, the results were similar but did not reach statistical significance (see table 2).

In analyses with GA as a continuous variable (see table 3), we found a statistically significant increase in FIQ of 0.08 points [95% CI; 0.01, 0.15] per increase in GA (in days) in the adjusted analysis. Similar estimates were seen in the analyses of VIQ and PIQ. However, we found no statistically significant associations in the adjusted analyses. For teacher-assessed executive function, we found a statistically significant decrease in GEC and MI of -0.07 points [95% CI; -0.14, -0-01] per increase in GA (in days) indicating better executive function with increasing GA, however these estimates also became statistically non-significant when adjusting for potential confounders.

When maternal IQ and parental education were removed from the regression analyses separately or simultaneously (see supplementary table 1), the estimates of association did not change notably. However, when these variables were removed simultaneously from the regression, most estimates became statistically non-significant due to wider CIs.

When introducing birthweight in the regression analyses (see supplementary table 1), the association between GA and all IQ outcomes became considerably weaker and were no longer statistically significant. However, a trend towards lower IQ in the very or moderately preterm group was still evident, as the mean differences in FIQ, VIQ, and PIQ were reduced to -7.0 points [95% CI; -15.7 to 1.6], -5.9 points [-12.2 to 0.3], and -6.8 points [-16.6 to 3.0], respectively, when compared to the term group. When birthweight was introduced in the analyses of attention and executive function outcomes, the results did not change substantially.

In a post hoc analysis, we excluded the early term births (GA 37-38) and made a direct comparison between the very or moderately preterm group and the term group with GA ≥ 39 weeks (*n*=1443), and the late preterm group and the term group (GA ≥ 39 weeks), respectively (see supplementary table 2). In these analyses, the results did not change notably for any of the outcomes.

DISCUSSION

Main findings

We found a statistically significant effect of very or moderately preterm birth on IQ and teacher-assessed executive function when adjusting for potential confounders. Although maternal IQ and parental education accounted for much of the variance in child IQ in this dataset,[7] these two factors should only be considered weak confounders with no significant association with GA, as removing these variables from our analyses did not alter the associations notably. However, removal of the variables produced wider CIs confirming that they explain substantial parts of the variance.

The inclusion of birthweight in the regression analyses for IQ outcomes attenuated the associations for the very or moderately preterm group, and the results were no longer statistically significant. For the late preterm group, the associations completely vanished. This could be suggestive of mediation and underlines the importance of looking at GA relatively to birthweight when investigating effects of preterm birth, though our results for the very to moderately preterm children indicate that there may be cognitive effects of GA which are independent of birthweight, perhaps reflecting effects of very low GA on brain development.

Strengths and limitations

One of the strengths of this study is the relatively large sample size with thorough information on family and background factors that may influence the cognitive outcome of a child. Specially trained psychologists, unaware of the gestational age, conducted neuropsychological tests with a high interrater reliability of 97-97.5 %.[12] To minimise bias in our analyses, we composed DAGs to identify potential confounders prior to data analysis. Due to our large sample size, we were able to adjust for an exhaustive set of confounders. Other strengths of our study were a predefined protocoled methodology, and use of robust standard errors to account for the sample design and shortcomings in the data.

Our study has some limitations. The study population was sampled based on average alcohol consumption and binge drinking during pregnancy,[12 13] and therefore, the sample is not representative of the entire DNBC population. We applied sample weights in the analyses to accommodate this. However, the use of weights may be problematic for small subgroups, and together with the use of robust standard errors, this approach may have reduced the power to obtain statistically significant results and widened the CIs. Generally, the effect estimates are subject to some uncertainty illustrated by the wide CIs.[24]

Another weakness of this study is the relatively small proportion of children born preterm, especially children born very preterm (<32 weeks GA). According to MBR records from 2000 (our recruitment period was from 1997 to 2003), we would expect 6.3% of all new-borns to be born preterm.[25] In our population it was only 2.7%, which is equal to an underrepresentation of 57%. Only 0.2% of our sample was born very preterm, although we would expect 1.0%.[25] This can be a result of various factors that prevent parents with children born preterm from participating in a clinical study, in particular if the children are born very preterm and need special care. However, studies have shown that the influence of selection bias on several exposure-outcome associations in the DNBC is limited.[26] We adjusted for a large number of covariates associated with selection, still we cannot rule out that the low prevalence of preterm births in our cohort may have limited our power to detect any true differences as statistically significant. A post hoc power analysis showed that analyses comparing very or moderately preterm birth (n=8) with birth at term (n=1728) had a power of 0.48, 0.28, and 0.59 for FIQ, VIQ, and PIQ outcomes, respectively. The low prevalence of preterm births also prevented us from performing analyses investigating the impact of very or extremely preterm birth.

Despite the limitations, especially the low number of preterm births, we believe that this study contributes with important knowledge that together with existing evidence in the literature may improve the clinicians' ability to advise women at risk of preterm delivery and give informed predictions about the future.

Interpretation

For the IQ outcomes, the findings in our study are generally in line with previous findings with an IQ reduction of approximately 10 points in children born preterm.[4 27] However, in our study, this clinically very relevant difference was only seen among the very or moderately preterm children, and not in the late preterm group. A meta-analysis by Chan et al.[28] showed a statistically significant impact of late preterm birth on general cognitive ability and non-verbal intelligence. Our study in part contradicts these findings, as no associations between late preterm birth and IQ (full-scale, verbal, and non-verbal) were found. In our unadjusted analyses, we saw a trend towards lower IQ among late preterm children, but the trend disappeared when adjusting for confounders. This discrepancy may reflect insufficient adjustments in other studies but also the limited power of our study.

When assessing attention measures, we only found one statistically significant result, which might be because of chance alone. This is not in line with previous findings suggesting that preterm infants are at increased risk of developing eg Attention Deficit Hyperactivity Disorder with a relative risk of 2.64 [95% CI 1.85, 3.78].[27] However, TEACh-5 has not been validated as a diagnostic test, and given the unambiguous findings in the present study, it is possible that GA does not have an impact on test of basic attention function.

In the field of executive function, it has been suggested that extremely preterm infants (<28 weeks GA) are at increased risk of developing executive function difficulties.[29] Studies investigating the association between very, moderately, or late preterm birth and poor BRIEF scores have not detected any convincing deficits when evaluating the parents' questionnaire,[30 31] and to our knowledge, the teachers' questionnaire has not previously been used for this purpose. Hodel et al. detected deficits in a population of moderately to late preterm infants at the age of 9 months and at 4 years,[32] but in these studies, other executive function measures than BRIEF were applied. In extremely low birthweight children, teachers have proven to report significantly more difficulties on the BRI subscale compared to the parents.[33] In our study, we found that teachers reported more difficulties in all areas (GEC, BRI, and MI) when compared to the parents. This can be due to teachers having a more objective viewpoint and being more experienced in working with children with and without difficulties.

CONCLUSION

This study showed significantly lower IQ and poorer executive function in children born very or moderately preterm (<34 weeks GA) compared to children born at term (≥37 weeks GA), but only the differences in IQ were considered clinically relevant. No associations between late preterm birth (34 to <37 weeks GA) and poor cognitive outcomes were shown.

Maternal IQ and parental education are strong predictors of child IQ in our dataset but were only weak confounders of the association between GA and cognitive outcomes. Therefore, GA may play an important role in determining cognitive abilities independent of maternal IQ and parental educational level. Further studies with larger sample sizes to confirm these findings are needed.

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Contributors

Dr. Sejer contributed to the conception and design of the study, performed data management and statistical analyses, analysed and interpreted the data, drafted the initial manuscript, and wrote the final manuscript with contributions from the co-authors.

Miss Slavensky and Mr. Bruun contributed to the conception and design of the study, assisted with statistical analyses and interpretation of the data, and critically reviewed and revised the manuscript.

Mr. Mortensen and Dr. Kesmodel conceptualised and designed the study, analysed and interpreted the data, and critically reviewed and revised the manuscript.

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

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Competing interests

None declared.

Data sharing statement

No additional data are available for this study.

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Tables

Table 1. Family characteristics among singletons born at term or preterm. Denmark 2003-2008 (*n*=1776)

Characteristics	Born at term (≥37 weeks)	Late preterm birth (34 to <37 weeks)	Moderately or very preterm birth (<34 weeks)[a]
Number of infants (n)	1728	40	8
Maternal age (years, mean [SD])	30.8 (4.4)	30.4 (4.5)	28.8 (3.4)
Maternal pre-pregnancy BMI (kg/m^2, median [10/90 percentile])[b]	22.6 (19.6/28.7)	22.7 (18.4/33.0)	22.8 (16.5/28.2)
Maternal smoking in pregnancy (%)	31.7	30.0	37.5
Maternal alcohol consumption in pregnancy (%)[c]			
0 drinks/week	47.6	55.0	50.0
1-4 drinks/week	41.3	37.5	37.5
5+ drinks/week[d]	11.1	7.5	12.5
Maternal marital status (%)[e]			
Single[f]	12.4	10.3	25.0
Cohabitating	87.6	89.7	75.0
Maternal IQ (mean [SD])[g]	100.0 (14.9)	97.7 (16.9)	104.3 (17.9)
Parental educational level (years, mean [SD])[h]	13.2 (1.9)	13.0 (1.6)	14.2 (1.8)
Parity (%)			
0	50.7	60.0	87.5
1	32.1	30.0	12.5
2+	17.2	10.0	0.0
Child sex (%)			
Male	51.7	60.0	50.0
Females	48.3	40.0	50.0
Gestational age (days, median [10/90 percentile])	282.0 (269.0/293.0)	251.5 (241.0/257.5)	227.5 (206.0/236.0)
Birthweight (grams, mean [SD])[i]	3627.3 (483.4)	2740.8 (482.6)	2040.9 (458.4)
Child age at testing (years, median [10/90 percentile])	5.23 (5.12/5.30)	5.26 (5.13/5.31)	5.23 (5.10/5.29)

N, number; SD, standard deviation; BMI, body mass index; IQ, intelligence quotient. [a] Lowest observation 29 weeks. [b] Information missing for 35 term and 1 late preterm birth. [c] Information missing for 1 term birth. [d] Range 5-14 drinks/week. [e] Information missing for 13 term and 1 late preterm birth. [f] If reported being single either during pregnancy or at follow-up at 60-64 months postpartum. [g] Information missing for 9 term births. [h] Information missing for 5 term and 1 late preterm birth. [i] Information missing for 12 term and 2 late preterm births.

Table 2. Mean differences in intelligence, attention, and executive function between 5-year-old children born at term (reference group) and children born preterm. Denmark 2003-2008 (*n*=1776)[a]

	Born at term ≥37 weeks (*n*=1728)	Late preterm birth 34 to <37 weeks (*n*=40)		Moderately or very preterm birth <34 weeks (*n*=8)	
	Mean (SD)	**Mean difference**	**95% CI**	**Mean difference**	**95% CI**
Intelligence (WPPSI-R)					
Full scale IQ					
Unadjusted	105.64 (12.86)	-2.09	-6.91, 2.74	-9.22	-20.25, 1.81
Adjusted[b]		-0.05	-4.62, 4.53	-10.56	-19.37, -1.75
Verbal IQ					
Unadjusted	104.81 (10.80)	-1.73	-5.23, 1.76	-7.11	-15.64, 1.41
Adjusted		-0.40	-4.84, 4.05	-7.41	-13.37, -1.45
Performance IQ					
Unadjusted	105.14 (16.22)	-2.00	-9.02, 5.03	-9.51	-20.46, 1.45
Adjusted		0.38	-5.39, 6.15	-11.71	-21.89, -1.52
Attention (TEACh-5)					
Overall attention					
Unadjusted	0.01 (1.00)	-0.21	-0.70, 0.28	-0.10	-0.72, 0.52
Adjusted		-0.16	-0.59, 0.26	-0.25	-1.00, 0.50
Sustained attention					
Unadjusted	0.01 (1.00)	-0.39	-0.76, -0.01	-0.09	-0.62, 0.44
Adjusted		-0.23	-0.64, 0.19	-0.16	-0.83, 0.52
Selective attention					
Unadjusted	0.00 (1.00)	0.09	-0.46, 0.63	0.02	-0.41, 0.45
Adjusted		0.06	-0.42, 0.53	-0.19	-0.65, 0.27
Executive function (BRIEF)[c]					
- Parent version					
Global Executive Composite					
Unadjusted	49.97 (9.98)	1.44	-4.03, 6.90	-0.39	-16.52, 15.74
Adjusted		2.26	-2.01, 6.53	-0.20	-14.27, 13.87
Behavioural Regulation Index					
Unadjusted	50.01 (9.98)	-0.35	-5.50, 4.79	-1.18	-16.17, 13.81
Adjusted		0.40	-3.97, 4.76	-1.95	-14.87, 10.97
Metacognition Index					
Unadjusted	49.95 (9.98)	2.41	-3.10, 7.92	0.13	-15.24, 15.51
Adjusted		3.19	-1.11, 7.49	0.90	-12.60, 14.41
- Teacher version					
Global Executive Composite					
Unadjusted	49.94 (10.03)	4.47	-0.77, 9.70	5.47	2.57, 8.36
Adjusted		3.99	-0.82, 8.81	5.33	2.39, 8.27
Behavioural Regulation Index					
Unadjusted	49.95 (10.01)	4.42	-0.38, 9.21	5.29	2.08, 8.50
Adjusted		3.79	-0.89, 8.48	4.24	-0.56, 9.03
Metacognition Index					
Unadjusted	49.95 (10.03)	4.09	-1.55, 9.73	5.07	0.61, 9.54
Adjusted		3.77	-1.32, 8.85	5.46	1.97, 8.95

N, number; SD, standard deviation; CI, confidence interval; WPPSI-R, Wechsler Preschool and Primary Scales of Intelligence-Revised; IQ, intelligence quotient; TEACh-5, Test of Everyday Attention for Children at Five; BRIEF, Behaviour Rating Inventory of Executive Function. [a] Overall number of participants. Due to complete case analyses, for the adjusted analyses, the actual number of participants for each outcome was: Full-scale IQ (*n*=1748 [missing data for 1 late preterm birth]), verbal IQ (*n*=1749 [missing data for 1 late preterm birth]), performance IQ (*n*=1749 [missing data for 1 late preterm birth]), overall attention (*n*=1493 [missing data for 7 late preterm births]), sustained attention (*n*=1586 [missing data for 4 late preterm births]), selective attention (*n*=1612 [missing data for 4 late preterm births]), Global Executive Composite (parents, *n*=1748 [missing data for 1 late preterm birth]; teachers, *n*=1525 [missing data for 7 late preterm births and 1 very to moderate preterm birth]), Behavioural Regulation Index (parents, *n*=1748 [missing data for 1 late preterm birth]; teachers, *n*=1530 [missing data for 7 late preterm births and 1 very to moderate preterm birth]), Metacognition Index (parents, *n*=1748 [missing data for 1 late preterm birth]; teachers, *n*=1525 [missing data for 7 late preterm births and 1 very to moderate preterm birth]). [b] All adjusted analyses adjusted for maternal age, maternal IQ, average alcohol consumption in pregnancy, smoking in pregnancy, parity, maternal marital status, parental educational level, child sex, testing psychologist, and age at testing. [c] A higher BRIEF score indicates more executive function difficulties (opposite than the other outcome measures).

Table 3. Regression coefficients for the association between gestational age (in days) and intelligence, attention, and executive function in 5-year-old children. Denmark 2003-2008 (*n*=1776)[a]

Intelligence (WPPSI-R)	Beta (95% CI)	Attention (TEACh-5)	Beta (95% CI)	Executive function (BRIEF)[c] *- Parent version*	Beta (95% CI)	Executive function (BRIEF) *- Teacher version*	Beta (95% CI)
Full scale IQ		***Overall attention***		***Global Executive Composite***		***Global Executive Composite***	
Unadjusted	0.10 (0.02, 0.19)	Unadjusted	0.00 (0.00, 0.01)	Unadjusted	-0.03 (-0.10, 0.05)	Unadjusted	-0.07 (-0.14, -0.01)
Adjusted[b]	0.08 (0.01, 0.15)	Adjusted	0.00 (0.00, 0.01)	Adjusted	-0.02 (-0.08, 0.05)	Adjusted	-0.06 (-0.12, 0.01)
Verbal IQ		***Sustained attention***		***Behavioural Regulation Index***		***Behavioural Regulation Index***	
Unadjusted	0.07 (0.00, 0.14)	Unadjusted	0.00 (-0.01, 0.01)	Unadjusted	-0.02 (-0.09, 0.05)	Unadjusted	-0.06 (-0.13, 0.01)
Adjusted	0.06 (0.00, 0.13)	Adjusted	0.00 (-0.01, 0.01)	Adjusted	-0.01 (-0.08, 0.05)	Adjusted	-0.04 (-0.11, 0.02)
Performance IQ		***Selective attention***		***Metacognition Index***		***Metacognition Index***	
Unadjusted	0.12 (0.01, 0.22)	Unadjusted	0.00 (0.00, 0.01)	Unadjusted	-0.03 (-0.10, 0.05)	Unadjusted	-0.07 (-0.14, -0.01)
Adjusted	0.08 (-0.01, 0.18)	Adjusted	0.00 (0.00, 0.01)	Adjusted	-0.02 (-0.08, 0.04)	Adjusted	-0.06 (-0.12, 0.00)

N, number; CI, confidence interval; WPPSI-R, Wechsler Preschool and Primary Scales of Intelligence-Revised; IQ, intelligence quotient; TEACh-5, Test of Everyday Attention for Children at Five; BRIEF, Behaviour Rating Inventory of Executive Function. [a] Overall number of participants. Due to complete case analyses, for the adjusted analyses, the actual number of participants for each outcome was: Full-scale IQ (*n*=1748 [missing data for 1 late preterm birth]), verbal IQ (*n*=1749 [missing data for 1 late preterm birth]), performance IQ (*n*=1749 [missing data for 1 late preterm birth]), overall attention (*n*=1493 [missing data for 7 late preterm births]), sustained attention (*n*=1586 [missing data for 4 late preterm births]), selective attention (*n*=1612 [missing data for 4 late preterm births]), Global Executive Composite (parents, *n*=1748 [missing data for 1 late preterm birth]; teachers, *n*=1525 [missing data for 7 late preterm births and 1 very to moderate preterm birth]), Behavioural Regulation Index (parents, *n*=1748 [missing data for 1 late preterm birth]; teachers, *n*=1530 [missing data for 7 late preterm births and 1 very to moderate preterm birth]), Metacognition Index (parents, *n*=1748 [missing data for 1 late preterm birth]; teachers, *n*=1525 [missing data for 7 late preterm births and 1 very to moderate preterm birth]). [b] All adjusted analyses adjusted for maternal age, maternal IQ, average alcohol consumption in pregnancy, smoking in pregnancy, parity, maternal marital status, parental educational level, child sex, testing psychologist, and age at testing. [c] A higher BRIEF score reflects more executive function difficulties (opposite than the other outcome measures).

Supplementary table 1. Mean differences in intelligence, attention, and executive functions between 5-year-old children born at term (reference group) and children born preterm. Denmark 2003-2008 (*n*=1776)

	Born at term ≥37 weeks (*n*=1728)	Late preterm birth 34 to <37 weeks (*n*=40)		Moderately or very preterm birth <34 weeks (*n*=8)	
	Mean (SD)	**Mean difference**	**95% CI**	**Mean difference**	**95% CI**
Intelligence (WPPSI-R)					
Full scale IQ					
Unadjusted	105.64 (12.86)	-2.09	-6.91, 2.74	-9.22	-20.25, 1.81
Adjusted[a]		-0.05	-4.62, 4.53	-10.56	-19.37, -1.75
Excluding maternal IQ[b]		-0.00	-4.91, 4.91	-11.23	-21.00, -1.45
Excluding parental education		-0.64	-5.16, 3.87	-10.04	-19.60, -0.48
Excluding IQ + parental education		-1.42	-6.47, 3.63	-10.34	-22.19, 1.51
With all including birthweight[c]		2.21	-2.82, 7.25	-7.04	-15.67, 1.59
Verbal IQ					
Unadjusted	104.81 (10.80)	-1.73	-5.23, 1.76	-7.11	-15.64, 1.41
Adjusted		-0.40	-4.84, 4.05	-7.41	-13.37, -1.45
Excluding maternal IQ		-0.33	-4.48, 3.83	-7.86	-14.89, -0.83
Excluding parental education		-0.98	-5.40, 3.44	-6.89	-13.14, -0.64
Excluding IQ + parental education		-1.53	-5.55, 2.49	-7.10	-15.24, 1.05
With all including birthweight		0.59	-4.22, 5.40	-5.93	-12.19, 0.33
Performance IQ					
Unadjusted	105.14 (16.22)	-2.00	-9.02, 5.03	-9.51	-20.46, 1.45
Adjusted		0.38	-5.39, 6.15	-11.71	-21.89, -1.52
Excluding maternal IQ		0.42	-6.23, 7.07	-12.46	-23.38, -1.54
Excluding parental education		-0.12	-5.82, 5.59	-11.28	-22.20, -0.36
Excluding IQ + parental education		-0.93	-7.85, 5.99	-11.63	-24.73, 1.47
With all including birthweight		3.49	-2.78, 9.76	-6.80	-16.60, 3.00
Attention (Teach-5)					
Overall attention					
Unadjusted	0.01 (1.00)	-0.21	-0.70, 0.28	-0.10	-0.72, 0.52
Adjusted		-0.16	-0.59, 0.26	-0.25	-1.00, 0.50
Excluding maternal IQ		-0.15	-0.59, 0.30	-0.28	-1.05, 0.49
Excluding parental education		-0.21	-0.63, 0.22	-0.22	-0.88, 0.44
Excluding IQ + parental education		-0.21	-0.67, 0.25	-0.25	-0.90, 0.40
With all including birthweight		-0.11	-0.56, 0.34	-0.20	-0.98, 0.59
Sustained attention					
Unadjusted	0.01 (1.00)	-0.39	-0.76, -0.01	-0.09	-0.62, 0.44
Adjusted		-0.23	-0.64, 0.19	-0.16	-0.83, 0.52
Excluding maternal IQ		-0.23	-0.64, 0.18	-0.17	-0.86, 0.52
Excluding parental education		-0.25	-0.66, 0.16	-0.13	-0.75, 0.48
Excluding IQ + parental education		-0.27	-0.68, 0.13	-0.15	-0.75, 0.46
With all including birthweight		-0.10	-0.55, 0.35	0.01	-0.72, 0.73
Selective attention					
Unadjusted	0.00 (1.00)	0.09	-0.46, 0.63	0.02	-0.41, 0.45
Adjusted		0.06	-0.42, 0.53	-0.19	-0.65, 0.27
Excluding maternal IQ		0.07	-0.41, 0.56	-0.20	-0.69, 0.29
Excluding parental education		0.03	-0.45, 0.51	-0.16	-0.56, 0.24
Excluding IQ + parental education		0.03	-0.47, 0.53	-0.17	-0.57, 0.23
With all including birthweight		0.00	-0.50, 0.50	-0.31	-0.80, 0.18

Executive functions (BRIEF)[d]					
- Parent version					
Global Executive Composite					
Unadjusted	49.97 (9.98)	1.44	-4.03, 6.90	-0.39	-16.52, 15.74
Adjusted		2.26	-2.01, 6.53	-0.20	-14.27, 13.87
Excluding maternal IQ		2.23	-2.15, 6.62	-0.13	-14.00, 13.73
Excluding parental education		2.67	-1.65, 7.00	-0.58	-15.69, 14.54
Excluding IQ + parental education		2.85	-1.77, 7.47	-0.54	-15.79, 14.71
With all including birthweight		1.62	-2.96, 6.20	-1.13	-15.16, 12.90
Behavioural Regulation Index					
Unadjusted	50.01 (9.98)	-0.35	-5.50, 4.79	-1.18	-16.17, 13.81
Adjusted		0.40	-3.97, 4.76	-1.95	-14.87, 10.97
Excluding maternal IQ		0.37	-4.06, 4.80	-1.84	-14.55, 10.87
Excluding parental education		0.75	-3.68, 5.18	-2.27	-16.08, 11.54
Excluding IQ + parental education		0.93	-3.67, 5.54	-2.21	-16.17, 11.75
With all including birthweight		-0.27	-4.92, 4.38	-3.03	-15.90, 9.85
Metacognition Index					
Unadjusted	49.95 (9.98)	2.41	-3.10, 7.92	0.13	-15.24, 15.51
Adjusted		3.19	-1.11, 7.49	0.90	-12.60, 14.41
Excluding maternal IQ		3.17	-1.24, 7.58	0.94	-12.40, 14.27
Excluding parental education		3.61	-0.73, 7.95	0.52	-14.03, 15.07
Excluding IQ + parental education		3.77	-0.87, 8.40	0.54	-14.11, 15.20
With all including birthweight		2.63	-2.01, 7.27	0.15	-13.37, 13.66
- Teacher version					
Global Executive Composite					
Unadjusted	49.94 (10.03)	4.47	-0.77, 9.70	5.47	2.57, 8.36
Adjusted		3.99	-0.82, 8.81	5.33	2.39, 8.27
Excluding maternal IQ		4.08	-0.85, 9.02	5.56	2.55, 8.56
Excluding parental education		4.06	-0.74, 8.87	5.23	2.23, 8.23
Excluding IQ + parental education		4.30	-0.67, 9.27	5.40	2.17, 8.62
With all including birthweight		4.20	-1.02, 9.42	5.39	1.67, 9.12
Behavioural Regulation Index					
Unadjusted	49.95 (10.01)	4.42	-0.38, 9.21	5.29	2.08, 8.50
Adjusted		3.79	-0.89, 8.48	4.24	-0.56, 9.03
Excluding maternal IQ		3.89	-0.91, 8.70	4.49	-0.26, 9.24
Excluding parental education		3.81	-0.87, 8.49	4.21	-0.62, 9.05
Excluding IQ + parental education		4.04	-0.78, 8.85	4.38	-0.71, 9.47
With all including birthweight		4.44	-0.63, 9.52	4.81	-0.72, 10.34
Metacognition Index					
Unadjusted	49.95 (10.03)	4.09	-1.55, 9.73	5.07	0.61, 9.54
Adjusted		3.77	-1.32, 8.85	5.46	1.97, 8.95
Excluding maternal IQ		3.84	-1.33, 9.01	5.64	2.05, 9.23
Excluding parental education		3.86	-1.21, 8.93	5.32	1.96, 8.69
Excluding IQ + parental education		4.07	-1.14, 9.29	5.47	2.03, 8.91
With all including birthweight		3.66	-1.84, 9.17	5.17	1.08, 9.25

N, number; SD, standard deviation; CI, confidence interval; WPPSI-R, Wechsler Preschool and Primary Scales of Intelligence-Revised; IQ, intelligence quotient; TEACh-5, Test of Everyday Attention for Children at Five; BRIEF, Behaviour Rating Inventory of Executive Function. [a] All adjusted analyses adjusted for maternal age, maternal IQ, average alcohol consumption in pregnancy, smoking in pregnancy, parity, maternal marital status, parental educational level, child sex, testing psychologist, and age at testing. [b] Adjusted for all the above-mentioned covariates except maternal IQ. [c] Adjusted for all the above-mentioned covariates and birthweight. [d] A higher BRIEF score indicates more executive function difficulties (opposite than the other outcome measures).

Supplementary table 2. Mean differences in intelligence, attention, and executive function between 5-year-old children born at term (≥39, reference group) and children born preterm. Denmark 2003-2008 (*n*=1491)

	Born at term ≥39 weeks (*n*=1443)	Late preterm birth 34 to <37 weeks (*n*=40)		Moderately or very preterm birth <34 weeks (*n*=8)	
	Mean (SD)	**Mean difference**	**95% CI**	**Mean difference**	**95% CI**
Intelligence (WPPSI-R)					
Full scale IQ					
Unadjusted	105.92 (12.91)	-2.49	-7.34, 2.35	-9.63	-20.67, 1.41
Adjusted[a]		-0.22	-4.84, 4.41	-10.27	-19.27, -1.26
Verbal IQ					
Unadjusted	104.93 (10.71)	-1.95	-5.46, 1.56	-7.33	-15.87, 1.20
Adjusted		-0.35	-4.88, 4.17	-7.22	-13.31, -1.14
Performance IQ					
Unadjusted	105.53 (16.27)	-2.51	-9.56, 4.53	-10.02	-20.99, 0.95
Adjusted		0.03	-5.73, 5.79	-11.38	-21.60, -1.17
Attention (TEACh-5)					
Overall attention					
Unadjusted	0.01 (1.00)	-0.22	-0.71, 0.27	-0.10	-0.73, 0.52
Adjusted		-0.15	-0.58, 0.28	-0.22	-0.98, 0.54
Sustained attention					
Unadjusted	0.01 (1.01)	-0.39	-0.77, -0.02	-0.10	-0.63, 0.44
Adjusted		-0.22	-0.63, 0.20	-0.15	-0.86, 0.55
Selective attention					
Unadjusted	0.00 (1.01)	0.07	-0.48, 0.61	0.00	-0.43, 0.43
Adjusted		0.04	-0.44, 0.53	-0.15	-0.59, 0.29
Executive function (BRIEF)[b]					
- Parent version					
Global Executive Composite					
Unadjusted	49.75 (9.93)	1.60	-3.87, 7.08	-0.23	-16.36, 15.90
Adjusted		2.48	-1.80, 6.75	-0.16	-14.49, 14.17
Behavioural Regulation Index					
Unadjusted	49.76 (9.91)	-0.09	-5.24, 5,07	-0.91	-15.91, 14.08
Adjusted		0.73	-3.69, 5.15	-1.72	-14.67, 11.22
Metacognition Index					
Unadjusted	49.77 (9.94)	2.49	-3.03, 8.02	0.22	-15.16, 15.60
Adjusted		3.32	-0.94, 7.59	0.82	-13.07, 14.72
- Teacher version					
Global Executive Composite					
Unadjusted	49.83 (10.15)	4.68	-0.56, 9.93	5.69	2.76, 8.61
Adjusted		4.12	-0.78, 9.02	5.30	2.30, 8.30
Behavioural Regulation Index					
Unadjusted	49.88 (10.06)	4.57	-0.24, 9.39	5.45	2.21, 8.68
Adjusted		3.95	-0.72, 8.63	4.21	-0.83, 9.24
Metacognition Index					
Unadjusted	49.82 (10.14)	4.33	-1.33, 9.98	5.31	0.83, 9.80
Adjusted		3.86	-1.36, 9.09	5.42	2.20, 8.63

N, number; SD, standard deviation; CI, confidence interval; WPPSI-R, Wechsler Preschool and Primary Scales of

Intelligence-Revised; IQ, intelligence quotient; TEACh-5, Test of Everyday Attention for Children at Five; BRIEF, Behaviour Rating Inventory of Executive Function. [a] All adjusted analyses adjusted for maternal age, maternal IQ, average alcohol consumption in pregnancy, smoking in pregnancy, parity, maternal marital status, parental educational level, child sex, testing psychologist, and age at testing. [b] A higher BRIEF score indicates more executive function difficulties (opposite than the other outcome measures).

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7-9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-9
Bias	9	Describe any efforts to address potential sources of bias	9-11
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10-11
		(*b*) Describe any methods used to examine subgroups and interactions	-
		(*c*) Explain how missing data were addressed	11
		(*d*) If applicable, explain how loss to follow-up was addressed	-
		(*e*) Describe any sensitivity analyses	11
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7-8
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12 + table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-14 + tables 2-3
		(*b*) Report category boundaries when continuous variables were categorized	10-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13-14
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.