Gestational age at birth and cognitive outcomes in adolescence: population based full sibling cohort study

Anders Husby,[1,2] Jan Wohlfahrt,[2] Mads Melbye[3,4,5,6]

[1]Department of Epidemiology and Biostatistics, School of Public Health, Faculty of Medicine, Imperial College London, London, UK

[2]Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark

[3]Center for Fertility and Health, Norwegian Institute of Public Health, Norway

[4]K.G. Jebsen Center for Genetic Epidemiology, Norwegian University for Science and Technology, Norway

[5]Department of Genetics, Stanford University School of Medicine, CA, USA

[6]Danish Cancer Society Research Center, Copenhagen, Denmark

Correspondence to: A Husby Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark andh@ssi.dk (ORCID 0000-0002-7634-8455)

Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2023;380:e072779
http://dx.doi.org/10.1136/bmj-2022-072779

Accepted: 21 December 2022

ABSTRACT

OBJECTIVE
To investigate the association between gestational age at birth and cognitive outcomes in adolescence.

DESIGN
Nationwide population based full sibling cohort study.

SETTING
Denmark.

PARTICIPANTS
1.2 million children born between 1 January 1986 and 31 December 2003, of whom 792 724 had one or more full siblings born in the same period.

MAIN OUTCOME MEASURES
Scores in written language (Danish) and mathematics examinations as graded by masked assessors at the end of compulsory schooling (ninth grade, ages 15-16 years), in addition to intelligence test score at military conscription (predominantly at age 18 years) for a nested sub-cohort of male adolescents. School grades were standardised as z scores according to year of examination, and intelligence test scores were standardised as z scores according to year of birth.

RESULTS
Among 792 724 full siblings in the cohort, 44 322 (5.6%) were born before 37+0 weeks of gestation. After adjusting for multiple confounders (sex, birth weight, malformations, parental age at birth, parental educational level, and number of older siblings) and shared family factors between siblings, only children born at <34 gestational weeks showed reduced mean grades in written language (z score difference −0.10 (95% confidence interval −0.20 to −0.01) for ≤27 gestational weeks) and mathematics (−0.05 (−0.08 to −0.01) for 32-33 gestational weeks, −0.13 (−0.17 to −0.09) for 28-31 gestational weeks, and −0.23 (−0.32 to −0.15) for ≤27 gestational weeks), compared with children born at 40 gestational weeks. In a nested sub-cohort of full brothers with intelligence test scores, those born at 32-33, 28-31, and ≤27 gestational weeks showed a reduction in IQ points of 2.4 (95% confidence interval 1.1 to 3.6), 3.8 (2.3 to 5.3), and 4.2 (0.8 to 7.5), respectively, whereas children born at 34-39 gestational weeks showed a reduction in intelligence of <1 IQ point, compared with children born at 40 gestational weeks.

CONCLUSIONS
Cognitive outcomes in adolescence did not differ between those born at 34-39 gestational weeks and those born at 40 gestational weeks, whereas those with a gestational age of <34 weeks showed substantial deficits in multiple cognitive domains.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Studies have found reduced long term cognitive outcomes in children born at <40 weeks of gestation, suggesting harm to those born preterm and early term

Previous studies did not, however, account for potential biases from unmeasured confounding and non-participation in school examinations

WHAT THIS STUDY ADDS

Our findings suggest cognitive impairment in children with a gestational age of <34 weeks, specifically for results in mathematics and intelligence tests

Deficits associated with later births, however, are explained primarily by shared family factors, unrelated to gestational age

Introduction

The fetal brain undergoes substantial development during the third trimester of pregnancy, with a fivefold increase in myelinated white matter volume in the last five weeks of gestation.[1] Preterm and early term birth have been suggested to have a negative impact on later brain function, with most observational cohort studies finding worse long term cognitive outcomes in infants born before term, even for those born only two or three weeks before 40 weeks of gestation.[2-15] These findings are supported by a brain magnetic resonance imaging study of 3079 children aged 10 years that found a reduction in brain volume associated with decreasing gestational age at birth.[16] Previous cohort studies, however, have been primarily limited to one cognitive outcome, such as an average of all school grades or the results of intelligence tests at military conscription, or they were relatively small with low power among children born preterm. In addition, previous studies only moderately adjusted for potentially strong confounders (eg, maternal intelligence)[3 8 10 11 13 14 17] or did not account for the reduced frequency of examination attendance for children born before term, which might have biased the findings.[9 10 12-15]

To determine more accurately the impact of gestational age at birth on long term cognitive outcomes, we used nationwide registry information on 1.2 million Danish children with linkage to family members. Utilising these data, we created a nested full sibling cohort including 792 724 children with examination grades in written language (Danish) and mathematics during the final year of compulsory schooling in Denmark. Furthermore, we created a nested sub-cohort of male adolescents with test scores for the intelligence test taken at mandatory military conscription.

Methods

Since 1968 the Danish Civil Registration System has provided Danish residents with a mandatory unique identifier number,[18] and this provides deterministic linkage between parents and children and enables linkage between siblings.

Information on gestational age at birth (in weeks) of nearly all children born in Denmark have been registered in the Medical Birth Registry since 1978, in addition to other childbirth characteristics, such as birth weight.[19] Information on malformations is registered in the Danish National Patient Registry, which has been found to have high predictive value and completeness.[20]

The educational registers at Statistics Denmark[21] contain near complete information on schooling level, in addition to information on all school grades given in written and oral examinations at the end of compulsory schooling (ninth grade, ages 15-16 years) in Denmark starting from the 2001/2002 school year.

Intelligence test results from military conscription in Denmark are registered with the Danish Ministry of Defence and were fully digitised from 2006. The conscription intelligence test is mandatory for all men with Danish citizenship at age 18 years, and people are only exempt for specific medical reasons.[22]

Full sibling cohort

Using information from the Danish registries, we created a nationwide population cohort of all people born in Denmark from 1 January 1986 to 31 December 2003. We restricted the cohort to all children who were alive and had not emigrated by their 16th birthday. In addition, to account for shared family factors we restricted our cohort to children with one or more full siblings (same mother and father), comprising our full sibling study cohort (see table 1 and supplementary table S1 for characteristics of the cohort). In a nested male sub-cohort, we restricted the final full sibling cohort to only males with one or more full brothers in the cohort and who were alive and had not emigrated by their 18th birthday.

Gestational age at birth

Gestational age was categorised as very early preterm (<28+0 gestational weeks), early preterm (28+0 to 31+6), moderate preterm (32+0 to 33+6), late preterm (34+0 to 36+6), and born in gestational week 37, 38, 39, 40, 41, or 42 or later. Children with a registered gestational age of ≤23 weeks were censored from the cohort because of a low chance of survival and a high risk of misclassification. We classified children with an unrealistically high gestational age (≥46 weeks) as having a missing gestational age.

Covariates

For the main analysis we used several covariates: sex, relative birth weight (calculated as the centile of birth weight within the given gestational week), malformations, maternal age at childbirth, maternal educational level, paternal age at childbirth, paternal educational level, and number of older siblings. We used mode imputation for the few mothers with missing information on educational level. Table 1 and supplementary table S1 describe the categorisation of the covariates. In supplemental analysis we used information on diagnostic codes for prematurity associated morbidity (defined in supplementary table S2), and, from 1991, maternal smoking during pregnancy. Supplementary table S3 describes the educational categories.

Outcomes

The main outcomes were grades (standardised as z score relative to year of examination) in written Danish (the primary school language) and mathematics at the end of compulsory schooling (ninth grade, ages 15-16 years). Both outcomes were taken from national yearly examinations that were graded by masked assessors. The outcomes covered the school years from 2001/2002 to 2018/2019. Additionally, for a male subset of the cohort we used intelligence test scores (standardised as z score relative to year of birth) at mandatory military conscription (predominantly at age 18 years) as an additional outcome, with 10 December 2020 as the latest test date. The conscription intelligence test is highly correlated with the standard Wechsler adult intelligence scale test,[23] hence we could use the intelligence test results to estimate the differences in IQ. We estimated IQ from the intelligence test scores as described previously,[24] but we did not include a secular trend as the z scores of the intelligence test had been calculated relative to birth year. Supplementary table S4 presents estimates for children with missing gestational age compared with children born at 40 gestational weeks, in written language, mathematics, and conscription intelligence test.

Statistical analyses

We used multivariable linear regression models to estimate adjusted mean differences in z scores for each of three cognitive outcomes according to gestational age. In addition to gestational age, the models included as adjustment covariates: sex (except for analyses of the male sub-cohort), relative birth weight, malformations, parental age at childbirth, parental educational level, and number of older siblings. Children with missing gestational age were included in the analyses as a separate category group (see supplementary table S5 for estimates in this group). Finally, shared family factors, as well as unmeasured factors (eg, parental genetic or unmeasured social factors), were taken into account by conditioning on sibling membership using a unique sibling identifier for each full sibling group (ie, all children with the same mother and father) in the ABSORB statement in the PROC GLM procedure in SAS version 9.4.[25] For the analysis of intelligence, we restricted the cohort to full brothers (ie, same mother and father). In supplementary analysis, we also investigated effects of gestational age when differentiating post-term births into separate categories.

In sensitivity analyses, to evaluate confounding, bias from non-participation, and factors mediating the effects of gestational age, we investigated effects of different degrees of adjustment: inclusion of children who did not take examinations by imputing the 1% centile lowest grade, and adjustment for potential

Table 1 | Characteristics of 792 724 children in the sibling cohort

Characteristics	Sibling cohort* (%)	% of children† Born <37 weeks	Language: z score <0	Math: z score <0
Gestational age at birth (weeks)				
≤27	930 (0.1)	100	60.9	67.1
28-31	4686 (0.6)	100	54.5	59.6
32-33	6234 (0.8)	100	53.2	53.8
34-36	32 472 (4.1)	100	50.6	51.1
37	36 932 (4.7)	0	49.6	51.1
38	87 494 (11.0)	0	48.7	50.2
39	162 285 (20.5)	0	47.0	48.3
40	240 045 (30.3)	0	45.7	47.2
41	142 808 (18.0)	0	45.0	46.5
≥42	65 891 (8.3)	0	46.6	47.4
Missing	12 947 (1.6)	-	47.3	50.2
Sex				
Female	384 787 (48.5)	5.2	35.4	49.1
Male	407 937 (51.5)	5.9	57.5	47.3
Relative birth weight by gestational week (centile)				
0-4	34 649 (4.4)	5.6	51.8	58.7
5-9	34 583 (4.4)	5.8	48.9	55.6
10-24	108 607 (13.7)	5.6	47.4	52.1
25-49	190 904 (24.1)	5.4	46.2	48.9
50-74	197 164 (24.9)	5.2	45.4	46.0
75-89	123 601 (15.6)	5.3	46.0	44.3
90-95	42 833 (5.4)	4.7	47.2	43.4
95-100	43 238 (5.5)	4.8	48.1	43.7
Missing	17 145 (2.2)	19.2	51.0	54.4
Malformations				
Present	91 504 (11.5)	8.6	51.0	52.9
Not present	701 220 (88.5)	5.2	46.2	47.5
Maternal age at childbirth (years)				
<20	12 388 (1.6)	6.7	71.3	76.2
20-24	134 507 (17.0)	5.6	57.9	60.4
25-29	321 076 (40.5)	5.2	46.1	47.0
30-34	241 714 (30.5)	5.6	41.9	43.1
35-39	74 407 (9.4)	6.8	41.6	43.1
≥40	8632 (1.1)	8.0	43.7	45.3
Maternal educational level‡				
Primary education	200 368 (25.3)	6.5	64.0	69.0
Upper secondary education	80 948 (10.2)	4.9	38.9	39.9
Vocational education and training	276 575 (34.9)	5.7	48.2	49.4
Short term higher education	29 223 (3.7)	5.3	39.1	35.7
Vocational bachelor education	147 410 (18.6)	4.8	32.6	32.2
Academic bachelor's degree	8287 (1.0)	5.0	28.2	26.1
Academic master's degree	40 577 (5.1)	4.6	24.5	20.1
PhD or other doctoral degree	1284 (0.2)	4.8	22.5	15.3
No maternal education stated	8052 (1.0)	6.7	71.9	75.8
No of older full siblings				
0	331 978 (41.9)	7.2	43.5	44.3
1	336 071 (42.4)	4.4	47.8	49.5
2	96 471 (12.2)	4.3	50.3	52.3
3	20 639 (2.6)	5.2	57.4	60.5
≥4	7565 (1.0)	5.9	67.0	71.3
Diagnosis of prematurity morbidity§ (among children born <37 weeks)				
Yes	1762 (4.0)	100	62.5	67.7
No	42 560 (96.0)	100	51.1	52.1

See supplementary table S1 for additional characteristics of the cohort.
*Created from a population cohort of 1 161 406 children, of whom 9286 died before age 16 years. Among those who died, 35.1% were born before 37+0 gestational weeks.
†Among those with a registered gestational age and grades for written language and mathematics examinations, respectively.
‡Highest educational level attained at time of childbirth. See supplementary table S3 for description and examples of specific educational categories.
§Diagnosis of neurological birth trauma, retinopathy of prematurity, respiratory impairment owing to prematurity, cardiovascular impairment owing to prematurity, neonatal non-traumatic haemorrhage or haemolytic disease, gastrointestinal impairment owing to prematurity, or other registered neonatal cerebral damage (see supplementary table S2 for diagnostic codes).

mediators (prematurity associated morbidity and number of hospital admissions during childhood). In addition, we performed stratified analyses by morbidity status to evaluate the impact of morbidity on cognitive outcome. Furthermore, in supplemental analyses we investigated effects within groups based on sex, birth cohort, cohort type (population cohort versus sibling cohort), and relative birth weight, and we explored potential effects of adjusting for intrauterine growth restriction, pregnancy related maternal comorbidities, and twin status. These analyses were performed to investigate both the association in different settings and the potential effects of the intrauterine environment. Lastly, to evaluate the robustness of our approach, we examined different types and methods of imputation for children with missing outcomes and different types of covariate adjustment, in addition to including in the analyses children who died in childhood (age <16 years).

Patient and public involvement

No patients or members of the public were involved in the design, analysis, or writing up of the study, as the research project was undertaken by a small research group without funds or staff for patient and public involvement measures. The results of the study will, nevertheless, be disseminated to the public and health professionals by press releases written using layman's terms, social media postings, and presentations at scientific conferences.

Results

Of 1 161 406 children born between 1 January 1986 and 31 December 2003, a total of 792 724 with one or more full siblings born in the same period were included in the main study cohort (table 1). Overall, 44 322 children (5.6%) were born before 37+0 weeks of gestation, 384 787 (48.5%) were female participants, 321 076 (40.5%) were born to mothers aged 25-29 years, and 276 575 (34.9%) were born to mothers with an educational attainment of vocational education and training, the most common educational level among the mothers at the time of birth. At the time of birth, 336 071 (42.4%) of the children had one older full sibling, but only 7565 (1.0%) had four or more older full siblings. Among children born before 37+0 gestational weeks, 1762 (4.0%) had a registered hospital diagnosis code for prematurity associated morbidity (see supplementary table S2 for definitions). Supplementary table S1 provides information on paternal age at childbirth, paternal educational level, and number of children by birth cohort.

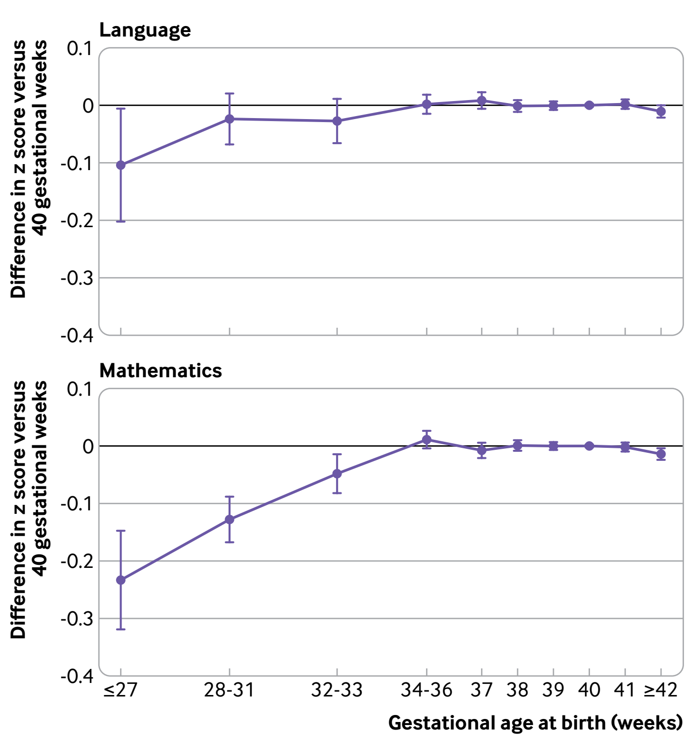

Fig 1 | Difference in standardised grade (z score) for written language and mathematics by gestational age at birth compared with 40 gestational weeks, among children in full sibling cohort (born in Denmark 1986-2003). Analyses are adjusted for sex, relative birth weight, malformations, parental age, parental educational level, number of older siblings, and shared family factors

Gestational age at birth and examination grades in adolescence

When we estimated the difference in z score by written language grade for specific gestational ages at birth compared with gestational age 40 weeks, only children born at <27 gestational weeks showed a significantly lower mean grade in written language (z score difference −0.10 (95% confidence interval −0.20 to −0.01) when accounting for shared family factors (fig 1). For mathematics, we found that only children born at <34 gestational weeks or >41 gestational weeks had significantly lower z scores compared with children born at 40 gestational weeks (fig 1). For children with <34 weeks gestational age, the grades progressively decreased with increasing prematurity: z score difference −0.05 (−0.08 to −0.01) for 32-33 gestational weeks, −0.13 (−0.17 to −0.09) for 28-31 gestational weeks, and −0.23 (−0.32 to −0.15) for ≤27 gestational weeks. We found no consistent effects of post-term birth on school grades for written language and mathematics, although statistical power was limited (see supplementary figure S1).

School performance by specific factors

Adjustment

When not accounting for shared family factors but adjusting for all covariates, we found a significant decrease in written language grade for children born in all gestational weeks before 40 weeks of gestation (fig 2), ranging from a z score difference of −0.11 (−0.18 to −0.05) for ≤27 gestational weeks to −0.01 (−0.01 to −0.00) for 39 gestational weeks, compared with 40 gestational weeks. Similarly, in mathematics (fig 2) we found significantly decreased grades for children born in all gestational weeks before 40 weeks of gestation, ranging from a z score difference of −0.31 (−0.38 to −0.25) for ≤27 gestational weeks to −0.01 (−0.02 to −0.00) for 39 gestational weeks. In general, estimates adjusted for all covariates but not accounting for shared family factors were more similar to crude, non-adjusted estimates than estimates that were adjusted for both covariates and shared family factors.

Non-participation in final examinations

A small proportion of children did not take the final examinations at the end of compulsory schooling,

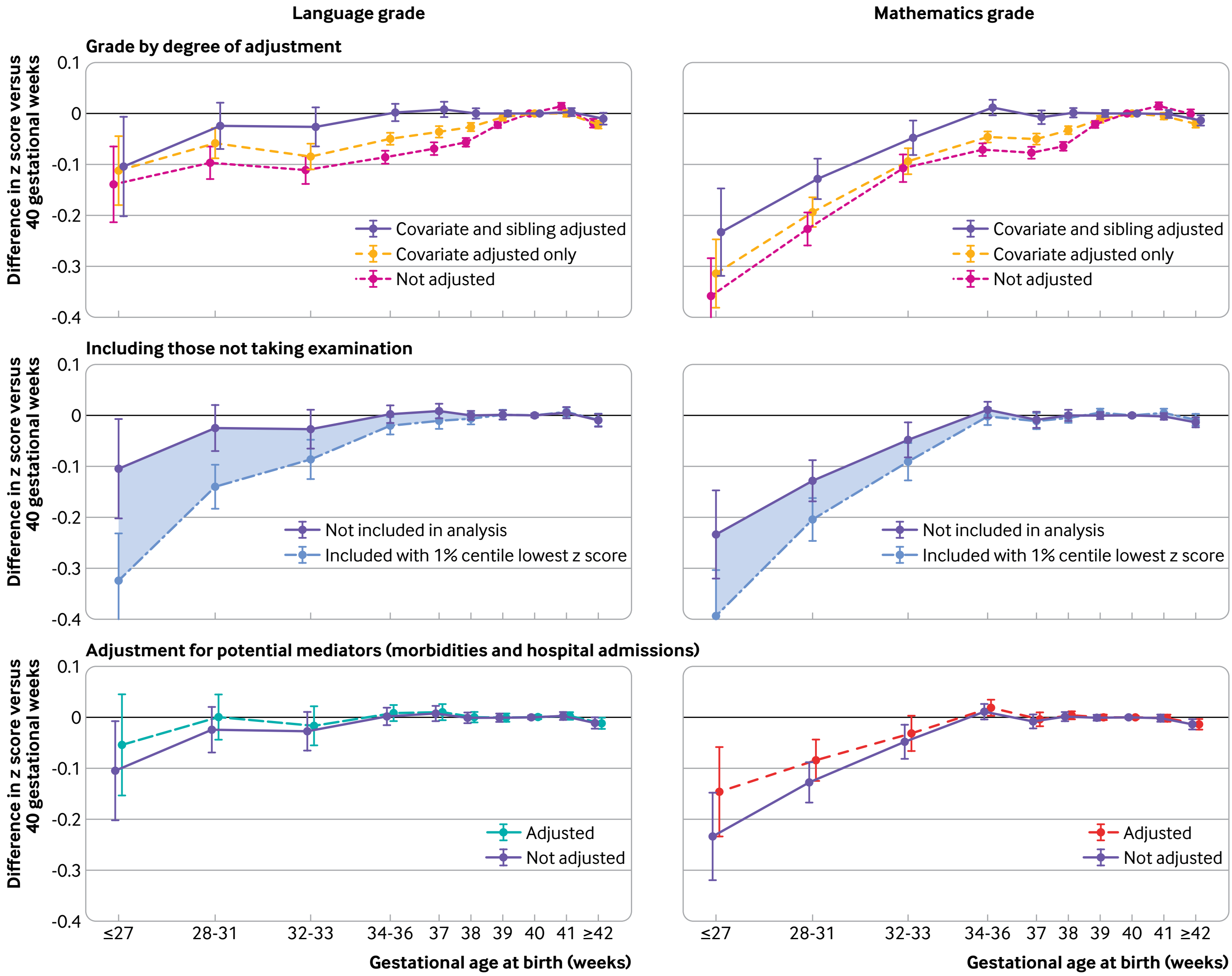

Fig 2 | Difference in standardised grade (z score) in written language and mathematics among children in the full sibling cohort (born in Denmark 1986-2003) by gestational age at birth compared with 40 gestational weeks, by adjustment, inclusion of those not taking examinations, and adjustment for potential mediators. For children not taking examinations, the 1% lowest centile standardised grade was imputed according to birth year. Potential mediators are prematurity associated morbidity and number of hospital admissions for children aged <16 years. Covariate adjusted only=adjustment for sex, relative birth weight, malformations, parental age, parental educational level, and number of older siblings. Covariate and sibling adjusted additionally includes adjustment for shared family factors. Analyses including children not taking examinations and those adjusted for potential mediators were adjusted for covariates and shared family factors

in some because of cognitive impairment, and the proportion increased markedly with decreasing gestational age (see supplementary table S4). As this phenomenon is a potential result of morbidity associated with preterm birth, we conducted an analysis including children without final examination grades by imputing the 1% lowest centile standardised grade according to birth year (fig 2). We found pronounced differences in z scores for children born at <34 gestational weeks, with z scores significantly reduced for both written language and mathematics. The z score for written language in children born at ≤27 gestational weeks was reduced from −0.10 (95% confidence interval −0.20 to −0.01) to −0.32 (−0.42 to −0.23), and the z score for mathematics was reduced from −0.23 (−0.32 to −0.15) to −0.39 (−0.48 to −0.31).

Potential mediators

In additional sensitivity analyses, we adjusted our main analysis for prematurity associated morbidity and number of hospital admissions during childhood, which could act as potential mediators between a low gestational age and later cognitive outcomes (fig 2). The reduction in standardised grades in written language and mathematics showed some attenuation, but the standardised grade in mathematics remained significantly reduced for children born early preterm and very early preterm compared with children born at term (z score of −0.15 (95% confidence interval −0.23 to −0.06) for children born at ≤27 gestational weeks, and −0.08 (−0.12 to −0.04) for children born at 28-31 gestational weeks). In supplementary analyses, we stratified our results by whether or not

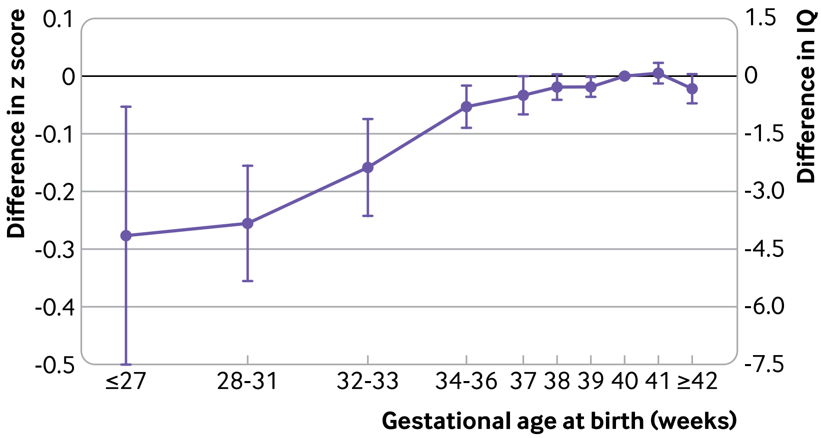

Fig 3 | Difference in standardised test score (z score) and difference in IQ in conscription intelligence test by gestational age at birth compared with 40 gestational weeks among full brothers (same mother and father). Analysis is adjusted for relative birth weight, malformations, parental age, parental educational level, number of older siblings, and shared family factors

children had a diagnosis of a prematurity associated morbidity (see supplementary figure S2) and not only found considerable negative effects of such a diagnosis but also persistent negative effects of gestational age on mathematics grade among those born at <34 gestational weeks but without a diagnosis of prematurity associated morbidity.

Sensitivity analyses

Sensitivity analyses conducted separately by sex, relative birth weight, maximal age difference between siblings, and birth cohort revealed only minor modifying effects of these factors (see supplementary figures S3-S6). When we adjusted for potential intrauterine growth restriction using ultrasound determined intrauterine growth curves, a slight attenuation of the negative impact of low gestational age on cognitive outcomes was found, but the overall pattern of association remained unchanged (see supplementary figure S7). Additional adjustment for maternal smoking during pregnancy for children born from 1991, maternal pregnancy related comorbidities, or twin status did not indicate any substantial effects of these adjustments in our study design (see supplementary figures S8-S10). Furthermore, when we compared our full sibling cohort with the complete population cohort (which included singletons and individuals with only half siblings), findings were similar when adjusted for covariates only, suggesting no major independent modifying effects of sibship status on the relationship between gestational age and later cognitive outcomes (see supplementary figure S11). To evaluate imputation, we also tried different methods of imputation for children with missing outcomes, including quantile regression (see supplementary figure S12). Moreover, when we used clustering of measured covariates at the family level we found no substantial bias reduction compared with using a sibling design (see supplementary figure S13). Lastly, when we included children in the cohort who died before age 16 years and also assigned those the 1% centile lowest examination grades, a pattern of progressively decreasing outcomes by lower gestational age intensified (see supplementary figure S14).

Gestational age at birth and intelligence in adolescence

In a male subset of the cohort, consisting of 227 403 brothers aged 18 years or older with the same mother and father, we additionally had information on attendance and test scores for the mandatory conscription intelligence test (fig 3). Overall results in this sub-cohort were similar to the main cohort, with markedly lower test scores in children born at <34 gestational weeks. The estimated difference in intelligence for children born at ≥34 gestational weeks compared with 40 gestational weeks was <1 IQ point, whereas estimated reductions in IQ points were 2.4 (95% confidence interval 1.1 to 3.6) for 32-33 gestational weeks, 3.8 (2.3 to 5.3) for 28-31 gestational weeks, and 4.2 (0.8 to 7.5) for ≤27 gestational weeks. We found lower estimates for children born early preterm and very early preterm if including children not attending the military conscription (see supplementary figure S15). In this analysis, the estimated reductions in IQ points were 2.4 (1.4 to 3.4) for children born at 32-33 gestational weeks, 4.4 (3.2 to 5.5) for children born at 28-31 gestational weeks, and 6.4 (3.9 to 8.8) for children born at ≤27 gestational weeks. We found no significant reduction in IQ for children born post term, although statistical power was limited (see supplementary figure S16).

Discussion

In a nationwide cohort of 792 724 full siblings, cognitive outcomes in adolescence did not differ between children born at 34 gestational weeks or later compared with 40 gestational weeks. In contrast, a gestational age of 34 weeks was associated with a markedly reduced cognitive outcome, which was even more pronounced when all Danish children not participating in school written language and mathematics examinations were included in the analysis with the 1% lowest centile score imputed.

Comparison with previous studies

Most previous observational studies on gestational age and cognitive outcomes found reductions in cognitive outcomes even for children born just two or three weeks before the term date, but most did not use a sibling design.[3 7 8 10 11 13 14] Of the previous sibling studies, only two studies included children born at <37 gestational weeks.[12 15] Furthermore, both of these studies combined all school grades into a single outcome and did not compare effects on intelligence. Finally, none of the previous sibling studies quantified the effect of children without a registered outcome (eg, non-participation in school examinations). As in our cohort, a higher percentage of children with low gestational age do not have a registered outcome. When we included these children in the analysis

doi: 10.1136/bmj-2022-072779 | BMJ 2023;380:e072779 | thebmj

with imputed lowest 1% centile scores, we found that it enhanced negative effects of gestational age on written language and mathematics grades, but predominantly among children born at <34 gestational weeks. This finding was consistent across different types of imputation and suggests considerable bias for estimating cognitive outcomes of children born at <34 gestational weeks when not accounting for non-participation in the examinations. Thus, adverse effects in children born at <34 gestational weeks might be even more pronounced than previously reported.

Origins of cognitive deficits associated with low gestational age

Underlying factors that explain particular negative effects of being born at <34 gestational weeks are not clear and in our study were not fully explained by sequelae that are well known to be related to prematurity (eg, neonatal haemorrhage, retinopathy, or more hospital admissions during childhood). Nevertheless, we estimated that intrauterine growth restriction explains a small part of the cognitive deficits related to low gestational age, which is in line with the findings of a recent systematic review[26]—although taking this factor into account did not change the pattern of association. Poor detection or registration of adverse neonatal outcomes could potentially explain the remaining deficits, but our findings might also reflect that a substantial amount of cognitive impairment associated with a low gestational age is subclinical and not apparent at routine neonatal assessment.

Policy implications

We estimated a significant reduction of 2.4 to 4.6 IQ points associated with being born from 32-33 to ≤27 gestational weeks, relative to birth at term. Furthermore, sensitivity analysis suggested that the reduction could be as low as 6.4 IQ points for children born at ≤27 gestational weeks, if the disproportionately high proportion of children born preterm who did not take the intelligence test was considered—although the uncertainty is large for this group. A previous highly detailed study of IQ in children born at ≤27 gestational weeks suggested even larger reductions in IQ compared with children born at term,[27] but this study was limited to follow-up at 6.5 years and did not take confounding by shared family factors into account. Nevertheless, these findings underline a considerable negative impact on long term cognitive abilities in children born at <34 gestational weeks. Given that low cognitive ability in itself is linked to decreased lifelong quality of life[28] and early death,[29] our findings stress the need for more research into how these adverse outcomes can be prevented. Cognitive outcomes are not, however, predetermined at birth but are heavily influenced by social circumstances[30] and nurturing,[31] and this is why early intervention is warranted for children born early preterm.

Evaluation of post-term births

In supplementary analyses with differentiation of post-term births, we did not find any consistent reduction in cognitive outcomes from being born post term. For both mathematics and intelligence, however, we found a pattern suggestive of lower scores by higher post-term gestational age. Nevertheless, an even larger sample of post-term births is needed to investigate this association.

Strengths and limitations of this study

Our cohort study had the advantage of comprising a large sample size from a complete population, with deterministic linkage between parents and siblings. In addition, we avoided recall bias as all information on gestational age at birth, covariates, and outcomes were registered prospectively. Furthermore, the outcomes of the study were graded by examiners masked to the given gestational age of the individual. The outcomes, moreover, covered diverse mental tasks and in two different settings and thus cognitive functioning was investigated broadly and not just related to one specific situation. Although smoking during pregnancy was not registered before 1991, the sibling design most likely accounted for maternal smoking; as also supported by our sensitivity analysis of children born from 1991. Finally, using a sibling design allowed us to examine and control for effects of unmeasured shared family factors on top of typical individual confounders, such as sex and relative birth weight.

Nevertheless, a requirement for bias reduction in a sibling design is that the total set of confounders needs to be more strongly shared than the exposure.[32] This scenario seems likely because gestational age has little heritability (maternal effects are estimated to account for only 15.2% of the variation in gestational age[33]) and primarily is a result of individual environmental effects. Another potential drawback of the sibling design is that misclassification can intensify attenuation of findings. We would, however, suspect misclassification to be most probable among early and very early preterm births, among which we still find considerable adverse effects, and why this seems not to be a major concern. Lastly, the outcomes included in our study are cognitive performance on testing and thus might differ from real life outcomes such as educational attainment or lifetime income, which future studies of this cohort will be able to address in detail.

Conclusions

In this study, children born at ≥34 gestational weeks had comparable written language, mathematics, and intelligence results to those born at 40 gestational weeks, whereas those with a gestational age <34 weeks showed deficits in all three cognitive outcomes.

Contributors: AH and MM conceived the study. AH and JW planned the statistical analysis plan and had full access to all of the data used in the study. AH processed the data and carried out the data analysis. All authors participated in the discussion and interpretation of the results. AH wrote the initial draft. All authors critically revised the manuscript for intellectual content, approved the final version, and meet the ICMJE criteria for authorship. AH is the guarantor of the study. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding: This study was funded by a grant from the Lundbeck Foundation to AH (grant No R322-2019-2800). The funder had no

role in the design or conduct of the study or the decision to submit the manuscript for publication. All researchers acted independently from the study sponsor in all aspects of the study.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: no support from any organisation for the submitted work, besides a research grant from the Lundbeck Foundation to AH; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: This study was conducted using deidentified information from Danish national registers, and study participants were not contacted. According to Danish law, ethical approval is not required for such research. The study's use of register data was covered by an approval from the Danish Data Protection Agency for register based studies conducted by Statens Serum Institut (approval No 2015-57-0102).

Data sharing: Data can be obtained by submitting a research protocol to the Danish Data Protection Agency and by applying to the Ministry of Health's Research Service, Statistics Denmark, and the Danish Ministry of Defence, respectively. The data do not belong to the authors, and they are not permitted to share data, except in aggregate form.

The guarantor (AH) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: The results of the study will be disseminated through social media postings, press releases, and interviews explaining the result to news media and the general public.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Supplementary information: additional tables S1-S5 and figures S1-S16