Birth Weight and Intelligence in Young Adulthood and Midlife

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abstract

OBJECTIVES: We examined the associations between birth weight and intelligence at 3 different adult ages.

METHODS: The Copenhagen Perinatal Cohort is comprised of children born in Copenhagen from 1959 to 1961. Information on birth weight and ≥1 tests of intelligence was available for 4696 members of the cohort. Intelligence was assessed at a mean age of 19 years with the Børge Priens Prøve test, at age 28 years with the Wechsler Adult Intelligence Scale, and at age 50 years with the Intelligenz-Struktur-Test 2000 R.

RESULTS: Birth weight was significantly associated with intelligence at all 3 follow-up assessments, with intelligence scores increasing across 4 birth weight categories and declining for the highest birth weight category. The adjusted differences between those in the <2.5kg birth weight group and those in the 3.5 to 4.00kg group were >5 IQ points at all 3 follow-up assessments, corresponding to one-third of a SD. The association was stable from young adulthood into midlife,and not weaker at age 50 years. Adjustment for potential confounding factors, including infant socioeconomic status and gestational age, did not dilute the associations, and associations with intelligence were evident across the normal birth weight range and so were not accounted for by low birth weight only.

CONCLUSIONS: The association between birth weight and intelligence is stable from young adulthood into midlife. These long-term cognitive consequences may imply that even small shifts in the distribution of birth size, in normal-sized infants as well, may have a large impact at the population level.

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Dr Flensborg-Madsen conceptualized and designed the study, performed statistical analysis, analyzed and interpreted the data, drafted the initial manuscript, and wrote the final manuscript with contribution from the coauthor; Mr Mortensen conceptualized and designed the study, analyzed and interpreted the data, reviewed and revised the initial manuscripts, and approved the final manuscript as submitted; and both authors had full access to all of the data and take responsibility for the integrity of the data and the accuracy of the data analysis.

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WHAT'S KNOWN ON THIS SUBJECT: Lower birth weight has been associated with lower intelligence in childhood and young adulthood. Few studies have examined this association across the full birth weight range, and from young adult through midlife.

WHAT THIS STUDY ADDS: Birth weight was significantly associated with intelligence at 3 follow-up assessments between the ages of 19 and 50 years. These associations were observed in the full range of birth weights and within the normal birth weight range.

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There is considerable evidence that small size at birth is associated with poorer cognitive development.[1] Most studies, however, focus on clinically low birth weight groups, although evidence of the association across the full birth weight range in the general population is of particular interest, because this would imply potential benefits of birth weight interventions targeting women with normal pregnancies.

Population-based studies have suggested that there is a positive association, although probably of small magnitude, between birth weight and intelligence in childhood[1,2] and young adulthood,[3,4] even in the normal range of birth weights. However, the associations in the normal birth weight range have been found to be less conclusive, and several studies have not found such relationships.[5,6] In addition, only a few population-based studies have examined the association between birth weight and intelligence in midlife or later,[4,7,8] and only 2 studies found that the association was significant; 1 was retrospective[9] whereas the other was based on a male sample.[10]

The scarce findings of associations between birth weight and intelligence in midlife raises the issue of whether any cognitive developmental effects of birth weight are temporary and will eventually disappear as the individual is exposed to numerous factors influencing cognition through the life span, or whether the associations with birth weight are permanent and imply that individuals with lower birth weight will not catch up and achieve the same level of intellectual functioning as individuals with a higher birth weight.

Birth weight may be considered a crude marker of the developmental quality of the prenatal environment, and the developmental origins of health and disease hypothesis[11] suggests that fetal growth has long-term consequences on health and morbidity. The potential association between birth weight and intelligence may reflect long-term consequences of fetal growth on brain development, and studies investigating this issue will therefore help illuminate whether midlife individual differences in cognitive ability originate early in life and will perhaps help to identify some of the prenatal factors that influence the development of intelligence.

Consequently, we examined the relationship between birth weight and intelligence at 3 different ages in the Copenhagen Perinatal Cohort based on data from different but overlapping follow-up assessments. A particular advantage of this cohort is the use of repeated intelligence assessments (although with different intelligence tests) beginning at age 19 years and extending to age 50 years, allowing evaluation of the intelligence-birth weight association across 3 decades of the adult life span.

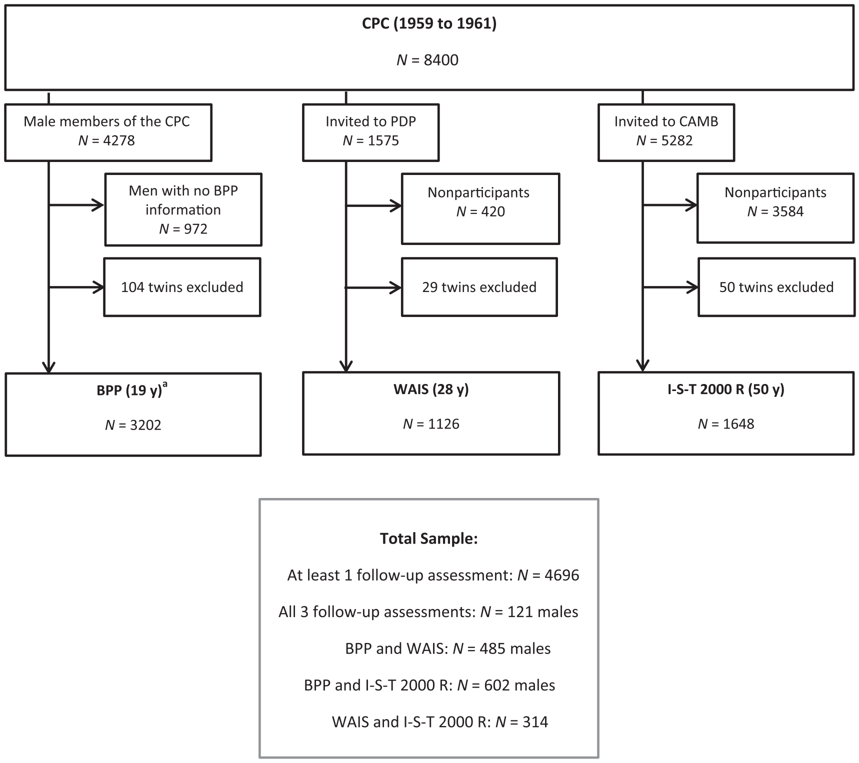

FIGURE 1
Overview of the study population. [a] Males only.

METHODS

The Copenhagen Perinatal Cohort

Data on 8949 mothers and their 9125 consecutive deliveries at the National University Hospital in Copenhagen, Denmark between October 1959 and December 1961[12] constitutes the Copenhagen Perinatal Cohort (CPC). A total of 8400 infants survived the first month after birth. Demographic, socioeconomic, prenatal, and postnatal data were recorded prospectively during pregnancy and delivery.[12] Intelligence was assessed at 3 different ages with the intelligence tests described below. At each follow-up assessment, test administrators were completely blind to the birth weight of the participants and other perinatal information. An overview of the study population is illustrated in Fig 1 showing the number of participants and exclusions at each follow-up.

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Børge Priens Prøve Test Sample

The earliest measure of intelligence is the Danish draft board's intelligence test. All Danish men are required to appear before the draft board (unless they suffer from conditions such as epilepsy, diabetes, intellectual disability, or volunteer for military service at an earlier age).[13] To obtain information on intelligence, the unique person identification number was used to link the CPC to the Danish military draft board register. In the current study, the mean age of appearing before the board was 19.2 years (range: 17.0–26.2 years). The Danish military draft board administers a 45-minute intelligence test, the Børge Priens Prøve (BPP), with 4 subtests (letter matrices, verbal analogies, number series, and geometric figures) and a total score ranging from 0 to 78. The total score correlates 0.82 with the IQ of the widely used Wechsler Adult Intelligence Scale (WAIS), indicating that the BPP is a high-quality measure of general intelligence.[14] BPP scores and information on birth weight were available for 3306 men. Of these, 104 twins were excluded because the relationship between birth weight and adult intelligence may differ between twins and singletons and because data for twin pairs are not statistically independent. The final sample included 3202 singletons with information on BPP score and information on birth weight.

Wechsler Adult Intelligence Scale Sample

A subsample from the CPC participated in the Prenatal Development Project follow-up study[15] conducted from 1982 to 1994 with the full WAIS included in the cognitive assessment. Based on perinatal records, a subsample of 1575 potential participants were invited to the Prenatal Development Project, and 1155 (73%) completed the Danish version of the original WAIS.[16] Of these, 29 twins were excluded, and information on birth weight was available for 1126 singletons, of whom 568 were men and 558 were women. The mean age at assessment was 27.7 years (range: 20.4–34.5 years). Among the male participants, 485 (85.4%) were also included in the BPP sample. The WAIS[16] generates 3 IQ scores: verbal (6 subtests), performance (5 subtests), and full-scale IQs (sum of 11 subtests). The WAIS was individually administered by 3 psychologists. IQ scores were derived from Danish test norms.[15]

Intelligenz-Struktur-Test 2000 R Sample

Between 2009 and 2011, a subsample from the CPC participated in the Copenhagen Aging and Midlife Biobank (CAMB) follow-up study.[17] A total of 5282 members of the CPC were invited to participate in the CAMB, and 1698 (32.1%) completed the Danish version of the Intelligenz-Struktur-Test 2000 R (I-S-T 2000 R)[18] (translated into Danish by Hogrefe Publishers). Of these, 50 twins were excluded, and information on birth weight was available for 1648 singletons, of whom 722 were men and 926 were women. The mean age at assessment was 50.1 years (range: 48.5–51.4 years). A total of 602 (83.4%) of the men were also included in the BPP sample, whereas 314 (19.1%) men and women of the CAMB sample were also included in the WAIS sample. Assessment of intelligence in this study was based on 3 subtests from the I-S-T 2000 R[18]: sentence completion, verbal analogies, and number series, providing a total score ranging from 0 to 59. A correlation of 0.70 was found with an interval of almost 40 years between BPP and I-S-T 2000 R.[19] Additional details on the tests are described by Mortensen et al.[20]

Covariates

The following variables were considered potential confounders and included as covariates in the analyses of adjusted mean differences: (1) sex; (2) infant socioeconomic status (SES), assessed on a 1–8-point scale at the 1-year examination based on the social grouping of the Centre International de l'Enfance[21] (with 8 being the highest SES)[22]; (3) mother's age at birth (years); (4) birth order (number); (5) mother's smoking in the last trimester; and (6) gestational age (weeks). All variables were included as linear continuous variables except for smoking (included as a binary yes/no variable). Unadjusted associations of covariates with intelligence at all 3 follow-up assessments are shown in Table 1.

Statistical Analyses

For each follow-up assessment, all intelligence scores for participants with a valid score were standardized to a mean of 100 and a SD of 15. Birth weight was split into 5 categories (≤2.5 kg, >2.5–3.0 kg, >3.0–3.5 kg, >3.5–4.0 kg, and >4.0 kg). The unadjusted associations between birth weight and intelligence are presented in Table 2, whereas the adjusted regression models are presented in Table 3. In the adjusted regression models, between 62% and 80% in the 3 follow-up samples had complete information on all covariates, including gestational age. To test the independent effects of birth weight on intelligence conditioned on previous intelligence, we additionally adjusted for the score at the previous age. Finally, tests of linear trend using birth weight as a continuous variable were conducted (Table 4).

Because no significant interaction was found between birth weight and sex in any of the models (unadjusted and adjusted), results are not stratified by sex. To check that any statistically significant effects were not driven by the lowest or highest birth weight groups, all tests of

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TABLE 1 Unadjusted Associations of Early Life Characteristics With Intelligence at 3 Follow-up Assessments

	BPP (*N* = 3202)			PDP (*N* = 1126)			CAMB (*N* = 1648)		
	N	Mean (SD)	*P*[a]	*N*	Mean (SD)	*P*[a]	*N*	Mean (SD)	*P*[a]
Birth characteristics									
Birth weight (kg)									
≤2.50	323	96.0	<.001	94	96.3	<.001	148	96.1	<.001
2.51–3.00	629	99.0		256	99.0		380	99.8	
3.01–3.50	1153	100.2		457	99.7		657	99.6	
3.51–4.00	819	101.6		252	102.4		345	102.0	
>4.00	278	101.5		67	102.0		118	101.7	
Missing	0	—		0	—		0	—	
Birth length (cm)									
<50	610	96.7 (15.0)	<.001	226	97.1 (14.8)	<.001	352	97.6 (14.5)	<.001
50–53	2300	100.4 (14.9)		837	100.5 (15.2)		1178	100.5 (15.1)	
≥54	291	103.5 (14.6)		61	103.5 (11.5)		117	102.4 (14.5)	
Missing	1	—		2	—		1	—	
Head circumference at birth (cm)									
<33	332	95.7 (15.1)	<.001	122	94.7 (14.0)	<.001	212	96.0 (14.4)	<.001
33–35	1947	99.8 (14.8)		748	100.2 (15.1)		1064	100.7 (15.1)	
≥36	656	102.7 (15.3)		157	102.1 (14.5)		245	102.3 (14.6)	
Missing	267	—		99	—		127	—	
Gestational age (wk)									
<38	475	99.6 (14.8)	<.43	136	98.5 (14.6)	.91	218	99.8 (15.6)	.03
38–40	1794	101.0 (15.0)		808	100.5 (15.3)		1005	101.1 (14.8)	
≥41	304	97.7 (15.2)		70	97.6 (13.1)		142	94.6 (14.0)	
Missing	629	—		112	—		283	—	
Pregnancy characteristics									
Birth order (No.)									
1	1644	100.7 (14.6)	<.001	528	99.8 (15.1)	.02	796	99.8 (14.6)	.32
2	793	100.8 (15.1)		300	101.9 (14.4)		444	100.1 (14.8)	
3	438	99.0 (15.3)		187	97.5 (15.5)		251	101.4 (16.0)	
≥4	322	95.5 (15.5)		110	100.0 (14.7)		156	98.7 (15.0)	
Missing	5	—		1	—		1	—	
Mother smoking in last trimester									
No	1568	102.0 (14.8)	<.001	622	100.8 (14.9)	.07	856	101.1 (15.1)	.004
Yes	1581	98.1 (15.0)		492	99.2 (14.9)		766	98.9 (14.7)	
Missing	53	—		12	—		26	—	
Parental characteristics									
Infant SES (category)									
1–2 (lowest)	582	92.4 (14.0)	<.001	118	93.9 (14.5)	<.001	246	93.2 (13.7)	<.001
3	603	96.3 (13.9)		201	93.2 (14.8)		309	95.2 (13.7)	
4	496	100.8 (13.8)		195	97.2 (14.9)		243	99.8 (14.0)	
5–6	566	105.2 (13.5)		266	103.1 (13.9)		351	103.6 (14.4)	
7–8 (highest)	332	112.0 (13.1)		223	108.2 (12.8)		236	108.7 (14.0)	
Missing	623	—		123	—		263	—	
Maternal age at birth (y)									
14–19	688	95.9 (13.8)	<.001	120	95.8 (15.2)	<.001	313	95.4 (14.0)	<.001
20–24	978	99.1 (14.3)		289	97.7 (14.4)		467	98.8 (14.3)	
25–29	710	102.9 (14.7)		265	101.3 (14.7)		377	103.1 (15.2)	
30–34	462	102.1 (15.8)		236	102.1 (15.7)		255	100.8 (14.8)	
≥35	364	101.6 (16.5)		216	101.5 (14.5)		236	102.6 (15.7)	
Missing	0	—		0	—		0	—	

BPP, Børge Priens Prøve; CAMB, Copenhagen Aging and Midlife Biobank; PDP, Prenatal Development Project; —, not applicable.
[a] Tests of trend across groups.

associations between birth weight and intelligence were repeated on a subsample with normal birth weight (ie, 2.5–4.0 kg).

RESULTS

A total of 4696 singletons from the CPC were administered a test of intelligence at ≥1 of the 3 follow-up assessments and had information on birth weight. The mean birth weight of these individuals was 3.3 kg (SD:

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TABLE 2 Mean Differences (95% Confidence Intervals) in Standardized Intelligence Score by Birth Weight Group Compared With the Middle Birth Weight Group (3.0–3.5) for Tests at Ages 19, 28, and 50 Years

Average Test Age	Birth Weight (kg)					P^a (P for Normal Birth Weight: 2.5–4.0 kg)
	Low (≤2.5)	>2.5–3.0	>3.0–3.5	>3.5–4.0	>4.0	
19 y[b] (n = 3302)	−4.15 (−5.99 to −2.31)	−1.21 (−2.66 to 0.24)	Ref	1.39 (0.06 to 2.73)	1.27 (−0.68 to 3.22)	<.001 (.001)
28 y (n = 1126)	−3.44 (−6.76 to −0.12)	−0.67 (−2.96 to 1.62)	Ref	2.68 (0.38 to 4.98)	2.25 (−1.58 to 6.08)	<.001 (.01)
50 y (n = 1648)	−3.57 (−6.24 to −0.91)	0.16 (−1.72 to 2.05)	Ref	2.32 (0.37 to 4.27)	2.09 (−0.84 to 5.02)	<.001 (.06)

Ref, reference.
[a] P value based on regression analysis using birth weight categories.
[b] Males only.

TABLE 3 Adjusted Mean Differences (95% Confidence Intervals) in Standardized Intelligence Score for Each Birth Weight Category Compared With the Middle Birth Weight Category for Tests at Ages 19, 28, and 50 Years

Birth Weight (kg)	Adjusted Mean Difference[a]	P	Conditional on Gestational Age[b]	P	Conditional on Previous Test Score[c]	P	P for Normal Birth Weight Sample[d]
Age 19 y[e]	n = 2520	<.001	n = 2035	<.001	—	—	<.001/<.001
≤2.5	−3.14 (−5.04 to −1.25)		−5.29 (−7.94 to −2.64)				
>2.5–3.0	−0.80 (−2.28 to 0.67)		−0.63 (−2.31 to 1.05)				
>3.0–3.5	Ref		Ref				
>3.5–4.0	0.77 (−0.60 to 2.14)		1.56 (0.02 to 3.10)				
>4.0	0.35 (−1.64 to 2.34)		1.35 (−0.83 to 3.52)				
Age 28 y	n = 990	.02	n = 896	.03	n = 388	.85	.02/.01/.13
≤2.5	−3.07 (−6.41 to 0.28)		−3.93 (−7.97 to 0.11)		−0.84 (−6.56 to 4.88)		
>2.5–3.0	−0.27 (−2.55 to 2.00)		−0.42 (−2.87 to 2.03)		0.10 (−2.66 to 2.86)		
>3.0–3.5	Ref		Ref		Ref		
>3.5–4.0	1.48 (−0.83 to 3.78)		1.41 (−1.06 to 3.87)		0.63 (−1.92 to 3.17)		
>4.0	0.46 (−3.36 to 4.29)		−0.03 (−4.05 to 4.00)		0.15 (−3.83 to 4.13)		
Age 50 y	n = 1357	.17	n = 1123	.01	n = 253	.70	.25/.02/.63
≤2.5	−1.62 (−4.40 to 1.17)		−1.82 (−5.61 to 1.98)		1.94 (−8.00 to 11.88)		
>2.5–3.0	1.62 (−0.33 to 3.57)		1.27 (−0.91 to 3.46)		−0.02 (−4.12 to 4.09)		
>3.0–3.5	Ref		Ref		Ref		
>3.5–4.0	2.21 (0.23 to 4.20)		3.60 (1.37 to 5.83)		2.95 (−1.60 to 7.49)		
>4.0	1.85 (−1.10 to 4.79)		2.90 (−0.35 to 6.14)		−0.86 (−7.97 to 6.25)		

All P values are based on regression analysis using birth weight categories. Ref, reference; —, not applicable.
[a] Adjusted for: sex, infant SES, mother's age at birth, birth order, and mother's smoking in last trimester.
[b] Adjusted for all factors listed above as well as for gestational age.
[c] Adjusted for all factors listed above as well as for intelligence score at the previous age.
[d] Normal birth weight defined as 2.50 to 4.00 kg.
[e] Males only.

0.59 kg) and the mean intelligence sum of the raw scale scores in the 3 follow-up assessments was 39.7 (SD: 11.5; range: 4–73) on the BPP, 113.2 (SD: 22.2; range: 29–176) on the WAIS (sum of scaled scores corresponding to a WAIS mean IQ of 102.2 [SD: 15.2]), and 29.3 (SD: 10.2; range: 4–56) on the I-S-T 2000 R. The overlap between the 3 follow-up assessments is illustrated in Fig 1.

Table 1 shows the means of standardized intelligence scores at all 3 follow-up assessments according to the covariates. In addition to birth weight, the mean score increased with increasing birth length, head circumference at birth, infant SES, and maternal age, whereas it decreased with a gestational age <38 and >41 weeks and maternal smoking. The mean birth weight in the 3 samples was 3.3 kg (SD: 0.60 kg), 3.3 kg (SD: 0.54 kg), and 3.2 kg (SD: 0.56 kg), respectively, whereas it was 3.2 kg (SD: 0.60 kg) in the full cohort. The mean infant SES score in the 3 samples was 4.0 (SD: 1.8), 4.7 (SD: 1.9), and 4.3 (SD: 1.9), respectively, whereas it was 4.0 (SD: 1.8) in the full cohort.

TABLE 4 Correlations and Partial Correlations Using Birth Weight as a Continuous Variable (Birth Weights up to 4 kg Included)

	Unadjusted r	Adjusted[a] r	Adjusted[b] r	Explained Variance[b] r (%)
Age 19 y[c]	0.11 (P < .001)	0.08 (P < .001)	0.11 (P < .001)	0.65
Age 28 y	0.12 (P < .001)	0.09 (P = .009)	0.09 (P = .006)	0.90
Age 50 y	0.08 (P = .006)	0.04 (P = .16)	0.09 (P = .005)	1.27

[a] Adjusted for: sex, infant SES, mother's age at birth, birth order, and mother's smoking in last trimester.
[b] Adjusted for all factors listed above, as well as for gestational age.
[c] Males only.

The mean differences in standardized intelligence scores for the 5

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categories of birth weight indicated increasing mean intelligence with increasing birth weight, followed by a decrease in intelligence scores for the highest birth weight category, and this pattern was similar at all 3 follow-up assessments. All *P* values based on regression analyses were significant, except for the *P* value based on the normal birth weight sample at 50 years ($P = .06$) (Table 2). Table 3 shows that adjustment for sex, infant SES, mother's age at birth, birth order, and mother's smoking in the last trimester generally weakened the association between birth weight and intelligence (and at age 50 years, the association became insignificant), whereas additional adjustment for gestational age increased the significance for all ages.

The fully adjusted association between birth weight and intelligence did not seem weaker at age 50 years; hence, the mean score at age 50 years increased by 5.42 IQ points (SE: 2.08 points; $P \leq .01$) for those with a birth weight of 3.5 to 4.0 kg compared with a birth weight of ≤2.5 kg, whereas this increase was 5.34 IQ points (SE: 2.21 points; $P \leq .05$) at age 28 years. Tests of differences in intelligence between the 2 highest birth weight groups showed no significant differences at any follow-up point, thereby indicating a nonlinear relationship and, thus, tests of linear trends using birth weight as a continuous variable in Table 4 were conducted for birth weights up to 4.0 kg. In these analyses, birth weight explained an increasing amount of variance in IQ with increasing age; explaining 0.65% of the variance in IQ at age 19, 0.90% at age 28, and 1.3% at age 50 (Table 4). The explained variance may seem small, but the adjusted differences between the ≤2.5kg birth weight group and the 3.5 to 4.0kg birth weight group at all 3 follow-up assessments were larger than 5 IQ points, corresponding to one-third of a SD. Conditional regression models showed that the influence of birth weight on intelligence at ages 28 and 50 years primarily reflected the effects of intelligence earlier in life. Overall, in both unadjusted and adjusted analyses, the level of significance was not attenuated when analyses were restricted to the normal birth weight categories.

DISCUSSION

In a large Danish birth cohort, birth weight was associated with intelligence through young adulthood and midlife in a general population sample. Birth weight was significantly associated with intelligence at all 3 follow-up assessments with intelligence scores increasing across the 4 lowest birth weight categories for all ages and declining (although nonsignificantly) for the highest birth weight category. The associations remained significant when adjusting for a wide range of confounders, including infant SES, corroborating previous findings suggesting that the association between birth weight and intelligence is independent of family social background.[4] In contrast to most previous studies, we were able to adjust for gestational age. By including gestational age, the adjusted estimates reflect not only growth in general, but also the variance in growth that is independent of gestational age. We found that all associations with intelligence generally increased with the inclusion of this factor, thus underlining the importance of not only birth weight in itself, but especially the importance of birth weight relative to gestational age.[1,23] Notably, the association was observed not only in the full range of birth weights, but also within the normal birth weight range (that is 2.5–4.0 kg) at all ages, which suggests that the significant associations do not reflect extreme birth weights only. In the normal birth weight range, previous studies on the associations between birth weight and intelligence are conflicting.[1] Although several studies found positive associations,[2–4] others concluded that no such relationships were present in normal birth weight samples.[5,6]

The association between birth weight and intelligence was maintained across young adulthood (ages 19 and 28 years) and midlife (age 50 years) in the fully adjusted analyses; hence, the evidence of an association with birth weight was not weaker at age 50 years. These findings of the long-term effects of birth weight are in accordance with a study based on the Helsinki Birth Cohort Study, in which lower birth weight was associated with lower cognitive ability in a sample of 931 men with a mean age of 68 years.[10] It is, however, contrary to studies by Richards et al,[4] who found no significant associations between birth weight and intelligence at age 43 years in the British 1946 birth cohort, and Martyn et al,[7] who found no relationship between birth weight and intelligence in a population of individuals between 48 and 74 years born in 3 different areas in England. However, in our study, conditional regression models showed that the influence of birth weight on intelligence at later ages was explained by the effect of birth weight on intelligence at earlier ages. This finding is in accordance with studies on the stability of intelligence over the life span[24,25] and with previous studies assessing intelligence at a younger age than in the current study.[4]

Limitations of the Study

Some limitations of the current study should be noted. First, caution is needed in the interpretation of the multiple statistical tests of birth weight with different measures of intelligence, especially because the follow-up assessments of intelligence were based on different but overlapping samples of different

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sizes. The fact that 3 different intelligence tests were used at the follow-up assessments is likely to have influenced the conditional regression models, and standardized scores based on different samples of different ages may not be comparable because they assume no change in the psychometric structure of intelligence with age and no age differences in sample variance. However, the midlife participants were about 50 years old, and much evidence suggests that there is little age-related cognitive decline before the age of 60 years.[26]

Secondly, our analyses adjusted for important aspects of early family background, particularly those known to be strongly associated with cognitive development, such as infant SES, maternal smoking in pregnancy, and gestational age. There are, however, several other factors related to family background, such as nutrition, home environment, parental intelligence, and maternal stress. Thus, we cannot rule out the possibility that residual confounding related to family factors remained after statistical adjustment. In addition, it is possible that confounding factors could have affected the comparison of associations between birth weight and intelligence in the 3 samples if they acted differently through the life course and on the different cognitive tests.

For the draft board sample, we know that all Danish men are required by law to appear before the draft board except for men suffering from medical conditions, including intellectual disability. For the 2 other samples, participation may be related to intelligence and thus indirectly to birth weight. To the extent that selective participation has reduced the variance in both birth weight and intelligence, the association between birth weight and intelligence may have been diluted in these samples. In this study, we compare the association between birth weight and intelligence in 3 different follow-up samples, and this comparison may have been influenced by selection factors if selection bias differed between the 3 samples. As mentioned in the Results section, the means and SDs of birth weight among the 3 samples were similar and were also similar to the mean and SD of birth weight for the full cohort. Consequently, it seems unlikely that selection bias could have affected the present results substantially.

Interpretation

In contrast to previous findings, our results suggest that the cognitive effects of birth weight tend to be stable until midlife. Martyn et al[7] suggested that, "by the time a baby reaches adulthood, environmental factors in postnatal life may overshadow any effect of intrauterine experience on cognitive performance." However, the results from the current study imply that the effects of birth weight remained significant in midlife despite exposure to numerous factors influencing cognition throughout the life span. In accordance with studies of the stability of individual differences in intelligence throughout the life span,[25] our results suggest that adaptations made by the individuals in response to retarded growth are not sufficient to compensate for the effect of early brain development.

Some developmental factors are not confounding factors because they only affect birth weight or intelligence. In contrast, the associations between birth weight and intelligence may reflect confounding factors that influence both birth weight and intelligence (eg, genetic factors or aspects of family background). Obviously, birth weight will be affected by factors, such as maternal nutrition during pregnancy and insulinlike growth factors, that influence fetal growth,[27–31] but these factors are also likely to affect brain development, and perhaps a more important issue is whether there is an effect of size at birth on intelligence that is independent of prenatal growth factors. Such an effect may be mediated through recurrent illnesses and aspects of parent-child interaction associated with individual differences in birth weight.

It is not a trivial matter whether the association between birth weight and intelligence reflects confounding or a direct influence of fetal growth and birth weight on the development of intelligence. If the association reflects confounding influence, interventions should be directed at the confounding factors and not birth weight, but if the association primarily reflects an association between fetal growth and intelligence, interventions should target fetal growth, in particular pregnant women at risk for giving birth to a low birth weight infant. Such interventions may be particularly important in less-developed countries given that the level of low birth weight in Europe is 6% whereas it is 19% in the least-developed countries.[32] However, because of the large proportion of normal births, even small shifts in the distribution of birth size in normal-sized infants may have a substantial impact at the population level because even small differences in IQ may have important societal implications[33] related to health, educational, and economic benefits.[34]

CONCLUSIONS

From the perspective of early intervention and preventative programs, it is important to know whether fetal growth has a permanent association with intelligence. Except for parental social class, education, and maternal intelligence, few factors have previously been shown to account for a substantial amount of variance

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in intelligence.[35] Our results suggest that a modest amount (1.3%) of variance in IQ at age 50 years is explained by birth weight, but the results also indicate that differences in mean intelligence among birth weight groups correspond to at least one-third of an IQ SD throughout the life span from young adulthood to midlife. This lasting impact on IQ over a substantial part of the life span cannot be explained by the included potentially confounding factors, and the impact can be observed within the normal birth weight range. Thus, this study provides evidence of life span cognitive consequences of the factors influencing fetal growth and birth weight.

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ABBREVIATIONS

BPP: Børge Priens Prøve
CAMB: Copenhagen Aging and Midlife Biobank
CPC: Copenhagen Perinatal Cohort
I-S-T 2000 R: Intelligenz-Struktur-Test 2000 R
SES: socioeconomic status
WAIS: Wechsler Adult Intelligence Scale

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