

Birth Size and Brain Function 75 Years Later

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KEY WORDS

birth size, education, brain atrophy, cognition, aging

ABBREVIATIONS

AGES—Age Gene/Environment Susceptibility

CI—confidence interval

CSF—cerebral spinal fluid

GM—gray matter

ICV—intracranial volume

PI—Ponderal index

RS—Reykjavik Study

TB—total brain

WM—white matter

WML—white matter lesion

Dr Muller conceptualized and designed the study, drafted the initial manuscript, and carried out the initial analyses; Drs Sigurdsson, Kjartansson, Jonsson, and Garcia designed the data collection instruments of the Age Gene/Environment Susceptibility (AGES)—Reykjavik Study and critically reviewed the manuscript; Dr von Bonsdorff carried out the initial analyses and critically reviewed the manuscript; Drs Gunnarsdóttir and Thorsdóttir designed part of the data collection instruments of the Reykjavik Study and critically reviewed the manuscript; Drs Harris, van Buchem, and Gudnason designed the data collection instruments of the AGES-Reykjavik Study, coordinated and supervised data collection, and critically reviewed the manuscript; Dr Launer conceptualized and designed the study, designed the data collection instruments of the AGES-Reykjavik Study, coordinated and supervised data collection, and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: The fetal origins of adult disease hypothesis proposes that suboptimal fetal development may condition the later risk of disease, particularly cardiovascular disease. However, this hypothesis has never been tested for diseases of the aging brain.



WHAT THIS STUDY ADDS: This first study of its kind provides clinical measures suggesting that small birth size, as an indicator of an adverse intrauterine environment, has lifelong consequences for brain tissue volume and cognitive function. In addition, it shows that the effects of a suboptimal intrauterine environment on late-life cognitive function were particularly present in those with lower educational levels.

abstract



BACKGROUND: There are several lines of evidence pointing to fetal and other early origins of diseases of the aging brain, but there are no data directly addressing the hypotheses in an older population. We investigated the association of fetal size to late-age measures of brain structure and function in a large cohort of older men and women and explored the modifying effect of education on these associations.

METHODS: Within the AGES (Age Gene/Environment Susceptibility)-Reykjavik population-based cohort (born between 1907 and 1935), archived birth records were abstracted for 1254 men and women who ~75 years later underwent an examination that included brain MRI and extensive cognitive assessment.

RESULTS: Adjustment for intracranial volume, demographic and medical history characteristics, and lower Ponderal index at birth (per kg/m³), an indicator of third-trimester fetal wasting, was significantly associated with smaller volumes of total brain and white matter; β s (95% confidence intervals) were -1.0 (-1.9 to -0.0) and -0.5 (-1.0 to -0.0) mL. Furthermore, lower Ponderal index was associated with slower processing speed and reduced executive functioning but only in those with low education (β [95% confidence interval]: -0.136 [-0.235 to -0.036] and -0.077 [-0.153 to -0.001]).

CONCLUSIONS: This first study of its kind provides clinical measures suggesting that smaller birth size, as an indicator of a suboptimal intrauterine environment, is associated with late-life alterations in brain tissue volume and function. In addition, it shows that the effects of a suboptimal intrauterine environment on late-life cognitive function were present only in those with lower educational levels. *Pediatrics* 2014;134:761–770

There are several lines of evidence suggesting that early-life influences may be important to consider when identifying risk factors for pathologic brain aging later in life.¹ To date, these early influences have been captured by head size, as an indirect measure of fetal experience,^{2,3} and by education, which may not only reflect positive neurotropic effects but also risk factors for dementia such as socioeconomic factors and the load of cardiovascular disease.^{4,5}

The fetal origins of adult disease hypothesis proposes that abnormal fetal development, deduced from small birth size, may induce permanent changes in the structure, metabolism, and physiology of fetal organs, for example, through epigenetic mechanisms.^{6,7} These changes in combination with effects of environmental exposures during childhood, such as education, may condition the later risk of disease.⁸ Although these lines of evidence suggest early-life influences on cardiovascular disease, this hypothesis has never been tested for brain disease, which is highly prevalent and debilitating in older populations. Furthermore, several lines of evidence have suggested that higher educational achievement in early life is related to a reduced dementia risk later in life,⁹ which is consistent with the cognitive reserve hypothesis.¹⁰ However, it is unknown if these early-life influences (birth size and education) interact with respect to late-life disease risk.

In this first study of its kind to our knowledge, we investigated the association of birth size to late-age measures of brain structure and cognitive function and explored the modifying effect of education in these associations in a large cohort of older men and women (mean age: 75 years) who participated in the Age Gene/Environment Susceptibility (AGES)–Reykjavik Study (RS).

METHODS

AGES-RS

This analysis is based on the cohort of men and women who participated in

the RS and its follow-up, the AGES-RS. The RS (1967–1996) was initiated by the Icelandic Heart Association to study cardiovascular disease and risk factors in middle age. The cohort included men and women born between 1907 and 1935 and living in Reykjavik in 1967. The midlife data reported here were obtained from the study examination closest to the time that the participants were 50 years of age. The AGES-RS was initiated in 2002 to examine the contribution of genetic susceptibility and gene-environment interaction to conditions common in old age.¹¹ From 2002 to 2006, a random sample of survivors of the original RS cohort was invited to the AGES-RS, and 5764 subjects (72% response rate) participated in the study. All participants in the AGES-RS underwent extensive evaluation, including a standard clinical evaluation, brain MRI, and neuropsychological testing. The protocol was approved by the Icelandic National Bioethics Committee (VSN 00-063), the Icelandic Data Protection Authority, and by the institutional review board of the National Institute of Aging; all participants provided written informed consent.

Birth Size

Original midwives' birth records on cohort members born in the greater Reykjavik area were stored at the National Archives of Iceland, Reykjavik. Birth records were found and matched for 4828 individuals who participated in the RS. Data on birth size were abstracted by 2 researchers and included birth weight and length, as well as information on whether the birth was preterm (defined at that time as birth length <48 cm), singleton, or multiple¹²; data on gestational age were not recorded. Birth weight was recorded to the nearest 0.05 kg and length in centimeters from crown to heel. Ponderal index (PI) was calculated as birth weight (kg) divided by cubic length (m³). Low PI indicates having soft tissue mass below normal for the stage of skeletal development.

This measure generally reflects impaired fetal growth in late gestation, leading to disproportionate fetal growth, and is an indicator of fetal wasting.^{6,13}

Late-Life Brain Structure

Magnetic resonance images were acquired on a study-dedicated 1.5-T Signa Twinspeed EXCITE system (General Electric Medical Systems, Waukesha, WI) and were acquired during the late-life examination as part of the AGES-RS. The structural image protocol and the processing of the images have been fully described elsewhere.¹³ Briefly, brain tissue volumes (mL), including gray matter (GM), white matter (WM), cerebral spinal fluid (CSF), and white matter lesions (WMLs), were generated by using the multispectral magnetic resonance images and a high-throughput automatic image analysis pipeline. The pipeline, described previously, was based on the Montreal Neurologic Institute pipeline and optimized for use in the AGES-RS.^{14,15} Tissue classification was achieved with an artificial neural network classifier in the 4-dimensional intensity space defined by the 4 sequences (fluid attenuation inversion recovery and T1-, proton density-, and T2-weighted). Quality control was based on visual inspection of a verification image for each subject including 14 a priori selected slice locations from each of the pulse sequences (T1, proton density, T2, and fluid attenuation inversion recovery), evenly distributed across the entire brain in the axial, coronal, and sagittal planes. Total brain (TB) volume was computed as the sum of GM, WM, and WML. Total intracranial volume (ICV) was computed as the sum of TB and CSF.

Late-Life Cognitive Function

A battery of 6 different cognitive tests was administered to all participants as described earlier.¹⁶ Interrater reliability for all tests was excellent (Spearman correlations range: 0.96–0.99). From

these tests, 3 cognitive domain composite scores were calculated to form reliable and valid cognitive domain measures and to increase precision and were based on a theoretical grouping of tests, similar to other population-based studies^{17,18}: (1) the memory composite score includes the immediate and delayed recall sections of the modified version of the California Verbal Learning Test; (2) the processing speed composite includes the Figure Comparison Test, Digit Symbol Substitution Test, and the Stroop Test 1 (word reading) and 2 (color naming); and (3) the executive function composite includes a short version of the Cambridge Neuropsychological Test Automated Battery Spatial Working Memory Test, the Digits Backward Test, and Stroop Test 3 (word-color interference). A confirmatory factor analysis was used to check the fit of the composites to the data; results indicated that the 3-factor structure fit the data reasonably well.¹⁶ Composite measures were computed by converting raw scores to standardized z scores and averaging them across the tests in each composite. Interrater reliability for all tests was excellent (Spearman correlations range: 0.96–0.99).

Covariates

Body weight and height were measured at midlife and late-life. As part of the AGES-RS, participants were administered a standardized questionnaire that included questions about education, childhood environment, and their lifetime education. Education was categorized into low (primary school) versus high (secondary school/college/university). Occupation was categorized into “homemaker/miscellaneous,” “manual,” “service workers,” and “professional.”¹⁹ Lifestyle factors and cardiovascular risk/disease developed during adulthood may explain any association we find between birth size and brain.^{6–8} Therefore, we considered in our analyses

the following factors: smoking and alcohol consumption categorized as current/former/none; hypertension defined as antihypertensive treatment and/or systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg; diabetes defined as having a history of diabetes, using glucose-modifying medication, or with a fasting glucose of ≥ 126 mg/dL; dyslipidemia defined as total cholesterol ≥ 240 mg/dL or use of statins; and prevalent coronary artery disease based on self-reported history, angina pectoris on the Rose questionnaire, or evidence on electrocardiogram of possible or probable myocardial infarction.

Analytical Sample

Of the 4828 original Reykjavik cohort participants with available birth records, 1682 (35%) participated in the AGES-RS, including 1254 individuals with brain volume and cognition data. Compared with data published for the whole Reykjavik population with birth record data ($N = 4828$), the individuals in the analytical sample of this study had similar birth size and midlife body size.¹² Compared with the total AGES-RS sample with brain MRI ($N = 4614$), the individuals in the analytical sample were younger (75 vs 76 years), had more years of education (% with low education: 18% vs 24%), and had somewhat larger ICV (1511 vs 1501 mL) and TB volume (1087 vs 1079 mL).

Data Analysis

Subject characteristics at birth, midlife, and late life were calculated for the total population ($N = 1254$) and for descriptive purposes according to categories of PI (≤ 23.0 , 23.1–27.0, and >27.0 kg/m³) to create low (<25%), normal (25%–75%), and high (>75%) PI. Statistical differences across PI categories were calculated by using analysis of covariance for continuous measurements and χ^2 for categorical variables. Linear regression adjusted for age and gender was used to

investigate the association of continuous birth size measures (weight, length, and PI) to late-life ICV, absolute brain volumes (TB, GM, WM, WML, and CSF), and cognitive function (memory, processing speed, and executive functioning) (model 1). All outcome variables were normally distributed except for WML volume, which was log (ln) transformed. For ICV and brain volumes, additional adjustments were made for education (model 2) and for midlife weight and height, because birth size and head size are both strongly related to adult body size (model 3). Analyses for brain tissue were adjusted for ICV (model 4), because absolute brain tissue is strongly related to head size and to obtain relative brain volumes as indicators of brain atrophy. In addition, to examine if the effect of education on the “birth size–brain aging” relation was explained by socioeconomic status, additional adjustments were made for occupation. Finally, to examine whether relations between birth size measures and brain structure and function were explained by lifestyle and cardiovascular risk factors, additional adjustments were made for history of smoking, alcohol, hypertension, diabetes, hyperlipidemia, and coronary artery disease.

We a priori assessed whether the relationship between birth size and brain structure and function differed across educational level by adding interaction terms between birth size measures (continuous) and education (high versus low) to the regression models. Because interaction tests have less power than main effect tests, we followed the customary approach of taking the more liberal P value ($P < .10$). To better visualize the results and to check for nonlinearity, adjusted mean differences (95% confidence intervals [CIs]) (according to model 4) in brain volumes and cognition z scores were calculated by birth size categories by using analysis of covariance, and when a linear relation was observed a P -trend across

TABLE 1 Characteristics of the Total Population and Those in the Lowest, Middle, and Highest Quartiles of PI at Birth

	PI			P	Total (N = 1254)
	≤23.0 kg/m ³ (n = 202)	23.1–27.0 kg/m ³ (n = 663)	>27.0 kg/m ³ (n = 389)		
General and birth characteristics					
Gender, % female	53	59	58	.09	57
Education, %				.25	
Primary	17	19	19		18
Secondary	54	53	47		52
College/university	29	28	34		30
Occupation, %				.27	
Homemaker/miscellaneous	40	45	45		44
Manual	12	16	15		15
Services	26	23	23		24
Professional	22	16	17		17
Birth weight, mean (SD), kg	3.4 (0.6)	3.7 (0.5)	4.0 (0.5)	<.001	3.7 (0.5)
Birth length, mean (SD), cm	54.2 (3.1)	52.7 (2.1)	51.3 (2.2)	<.001	52.5 (2.5)
Parity, mother, %				.04	
0	39	30	23		30
1–2	36	41	41		40
≥3	25	29	36		30
Midlife characteristics					
Age, mean (SD), y	49 (6)	50 (6)	51 (6)	<.001	50 (6)
Height, mean (SD), cm	173 (9)	171 (9)	171 (9)	.04	171 (9)
Weight, mean (SD), kg	73 (13)	74 (13)	74 (13)	.87	74 (13)
BMI, mean (SD)	24.6 (3.4)	25.2 (3.5)	25.3 (3.3)	.03	25.1 (3.4)
Late-life characteristics					
Age, mean (SD), y	74 (5)	75 (5)	76 (5)	<.001	75 (5)
Height, mean (SD), cm	170 (10)	168 (9)	167 (9)	.02	168 (9)
Weight, mean (SD), kg	78 (15)	77 (14)	77 (15)	.83	77 (15)
BMI, mean (SD)	26.8 (4.4)	27.4 (4.3)	27.4 (4.5)	.26	27.3 (4.4)
Lifestyle and cardiovascular risk factors, %					
Smoking: current/former	62	62	55	.07	59
Alcohol : current	69	71	72	.74	71
Hypertension	74	81	79	.25	79
Diabetes	11	15	10	.18	13
Hyperlipidemia	52	47	50	.42	48
Coronary artery disease	24	29	29	.34	28

these categories was calculated. Analyses were carried out with IBM SPSS Statistics 18.0 (SPSS, Inc, Chicago, IL).

RESULTS

The 1254 participants had a mean age of 75 years (10th–90th percentile: 69–82 years) at the late-life examination and 50 years (10th–90th percentile: 42–58 years) at the midlife examination; 57% were women. The mean (SD) birth weight was 3.7 (0.5) kg, birth length was 52 (2.5) cm, and PI was 25.9 (3.4) kg/m³. Compared with individuals with a higher PI at birth, those with a lower PI were more often first-borns, younger at midlife and late-life examinations, and were more often men and smokers. Education was not different across the PI groups (Table 1).

At late life, mean (SD) ICV was 1510 (145) mL and mean (SD) TB volume was 1087 (101) mL, which is 72% of ICV. Mean (SD) WM, GM, WML, and CSF volumes were 388 (48), 679 (63), 20 (19), and 425 (83) mL, respectively.

Birth Size and Late-Life Brain Structure

Lower birth weight, birth length, and PI were associated with smaller ICV, smaller absolute brain volumes, and larger absolute CSF volume later in life (Table 2, model 1). After adjusting for ICV, the associations of lower birth weight and lower birth length to late-life brain volumes (model 3) were not significant. However, lower PI remained significantly associated with smaller relative TB (and larger CSF) and WM

volumes, but not with GM and WML volumes (model 3). Per each kg/m³ decrease in PI, mean (95% CI) relative TB and WM volumes decreased by −1.0 (−1.8 to −0.1) and −0.5 (−0.9 to −0.1) mL, respectively. Further adjustment for lifestyle and cardiovascular risk factors (model 4) did not change these effect estimates: −1.0 (−1.9 to −0.0) and −0.5 (−1.0 to −0.0) mL, respectively.

The relation between PI and brain volumes was linear (Fig 1; *P*-trend = .03). Adjusted mean differences between low PI (≤23.0 kg/m³) and high PI (>27.0 kg/m³) were significant for volumes of ICV-adjusted TB, WM, and CSF (β [95% CI]: −9.4 [−18.4 to −0.3], −3.4 [−6.9 to −0.7], and 9.4 [0.3 to 18.4] mL, respectively. Education did not modify the

TABLE 2 Association of Birth Size Measures With Late-Life ICV and Brain Volumes (in mL) in 1254 Older Participants

	ICV	TB Volume	WM Volume	GM Volume	CSF Volume	Ln WML Volume
Birth weight (per SD decrease)						
Model						
1	-25.9 (-32.0 to -19.8)**	-17.6 (-22.3 to -12.9)**	-7.5 (-9.7 to -5.2)**	-9.8 (-12.9 to -6.8)**	-8.3 (-12.1 to -4.5)**	-0.02 (-0.06 to 0.03)
2	-25.0 (-31.1 to -19.0)**	-17.1 (-21.7 to -12.4)**	-7.2 (-9.4 to -4.9)**	-9.6 (-12.6 to -6.6)**	-8.0 (-11.8 to -4.2)**	-0.01 (-0.06 to 0.04)
3	-20.3 (-26.5 to -14.1)**	-13.4 (-18.2 to -8.6)**	-5.9 (-8.2 to -3.6)**	-7.2 (-10.3 to -4.1)**	-6.9 (-10.8 to -2.9)**	-0.02 (-0.07 to 0.04)
4	NA	-1.3 (-4.4 to 1.7)	-0.5 (-2.1 to 1.1)	-1.0 (-3.6 to 1.5)	-1.3 (-4.4 to 1.7)	0.02 (-0.03 to 0.07)
Birth-length (per SD decrease)						
Model						
1	-18.8 (-25.1 to -12.6)**	-10.7 (-15.5 to -5.9)**	-4.5 (-6.8 to -2.2)**	-5.9 (-9.0 to -2.8)**	-8.2 (-12.0 to -4.3)**	0.00 (-0.05 to 0.05)
2	-18.2 (-24.3 to -12.0)**	-10.3 (-15.0 to -5.5)**	-4.3 (-6.5 to -2.0)**	-5.8 (-8.8 to -2.7)**	-8.0 (-11.7 to -4.1)**	0.00 (-0.05 to 0.05)
3	-13.3 (-19.5 to -7.0)**	-6.4 (-11.2 to -1.5)*	-2.8 (-5.1 to -0.5)*	-3.4 (-6.5 to -0.3)*	-6.9 (-10.8 to -2.9)**	0.01 (-0.05 to 0.06)
4	NA	1.6 (-1.5 to 4.6)	0.8 (-0.8 to 2.4)	0.7 (-1.8 to 3.1)	-1.6 (-4.6 to 1.5)	0.03 (-0.02 to 0.08)
PI (per SD decrease)						
Model						
1	-8.5 (-14.9 to -1.9)*	-8.9 (-14.1 to -3.8)**	-4.1 (-6.6 to -1.7)**	-4.8 (-8.1 to -1.5)**	-0.4 (-4.6 to 3.8)	-0.02 (-0.07 to 0.04)
2	-8.2 (-14.6 to -1.9)*	-8.8 (-13.9 to -3.7)**	-4.1 (-6.5 to -1.7)**	-4.8 (-8.1 to -1.5)**	-0.3 (-4.5 to 3.8)	-0.02 (-0.07 to 0.04)
3	-7.5 (-13.7 to -1.3)*	-8.2 (-13.2 to -3.2)**	-4.0 (-6.4 to -1.6)**	-4.2 (-7.5 to -1.0)*	-0.1 (-4.3 to 4.1)	-0.02 (-0.07 to 0.03)
4	NA	-3.3 (-6.5 to -0.1)*	-1.8 (-3.5 to -0.1)*	-1.7 (-4.3 to 0.8)*	3.3 (0.1 to 6.5)*	-0.01 (-0.06 to 0.05)

Data are presented as β s (95% CIs). Birth weight SD = 545 g; birth length SD = 2.5 cm; PI SD = 3.4 kg/m³. Model 1: adjusted for age and gender; model 2: additionally adjusted for education; model 3: additionally adjusted for midlife weight and height; and model 4: additionally adjusted for ICV. * $P < .05$; ** $P < .01$. Ln, log normal; NA, not applicable.

association of birth size measures with brain volumes (P -interaction $> .10$).

Birth Size and Late-Life Brain Function

Lower birth weight, birth length, and PI were not directly associated with late-life memory performance, processing speed, or executive functioning after controlling for age, gender, and education (Supplemental Table 1). However, the interaction between PI and education was significant for processing speed and executive function but not for memory (P -interaction = .04 and .007, respectively).

Stratified analysis showed that lower PI (per SD) was significantly associated with slower processing speed and poorer executive functioning in participants with low education ($\beta = -0.136$ [95% CI: -0.235 to -0.036], $P = .008$, and $\beta = -0.077$ [95% CI: -0.153 to -0.001], $P = .04$) but not in those with higher education ($\beta = 0.007$ [95% CI: -0.033 to 0.047] and $\beta = 0.038$ [95% CI: -0.004 to 0.077]). To better visualize the interaction, we present the low- and high-education effects by tertiles of PI (Fig 2). Further adjustment for occupation and lifestyle and cardiovascular risk factors yielded similar results as presented (data not shown). TB and WM volumes were correlated with processing speed and executive functioning but not with memory performance; correlation coefficients for TB volume were 0.21 ($P < .001$), 0.21 ($P < .001$), and 0.03 ($P > .05$) and for WM volume were 0.22 ($P < .001$), 0.23 ($P < .001$), and 0.03 ($P > .05$). When including WM volume and ICV in the model, the associations between PI and processing speed and executive functioning in the low-education group were attenuated ($\beta = -0.032$ [95% CI: -0.060 to -0.004] and $\beta = -0.020$ [95% CI: -0.045 to 0.004]). Education did not modify the association of birth weight or length with cognitive function (P -interaction $> .10$).

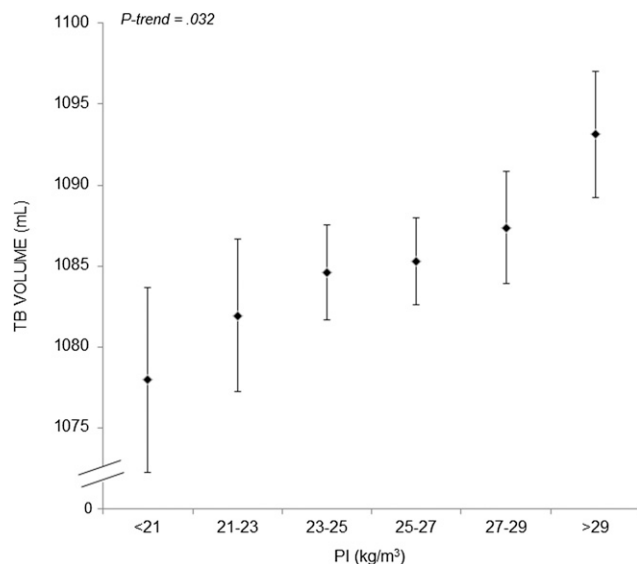


FIGURE 1

PI at birth and late-life TB volume. Values are mean (SE) brain volumes, adjusted for age, gender, midlife weight and height, and late-life ICV, for categories of PI in 1254 participants.

There was no change in the associations after excluding preterm births ($n = 24$), excluding individuals with prevalent dementia ($n = 34$), or after adjusting for birth year. Also, to investigate whether being small for gestational age explained our findings, analyses were repeated relating birth weight <10th percentile²⁰ (≤ 3.0 kg) to the outcome measures, and we found no relation.

DISCUSSION

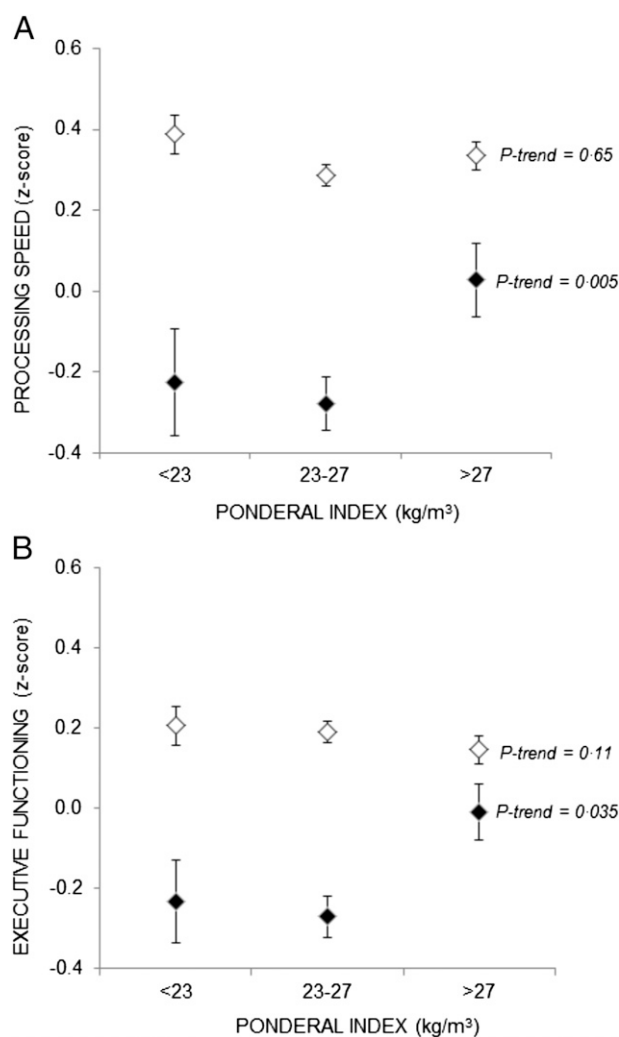
In this study we provide unique data linking 2 current hypotheses about risk factors for pathologic changes in brain characteristics during life: (1) there are early origins of late-life brain aging (alterations in brain structure and function) and (2) education reduces risk of cognitive impairment in multiple pathways. We found that small birth size, indicated by lower birth weight, shorter birth length, and lower PI were all strongly associated with smaller head size (ICV) and smaller absolute brain tissue volumes in late life. When taking into account head size, lower PI, as an indicator of disproportionate growth retardation, was associated with smaller

late-life relative brain volumes, specifically with smaller relative TB and WM volumes. This finding was reflected in cognitive performance; lower PI was associated with slower late-life processing speed and reduced executive functioning but only in those with lower educational levels.

This population-based study with a large sample has several unique strengths related to the availability of recorded data across the life span. Birth size data were abstracted from midwife records, which were not available in previous studies on early-life risk factors for late-age evidence of brain pathology.¹ We used an extensive range of cognitive tests, quantitatively assessed total and tissue-specific brain volumes, and were able to control for ICV, midlife body size, and cardiovascular risk to estimate the independent effect of small birth size on late-life brain volumes. Furthermore, the subset of participants included in these analyses did not differ in birth size from those who were not in the AGES follow-up. A limitation of this study is that we were not able to specifically study the effect of preterm birth and being small for gestational age, which

resulted in proportional growth retardation, as opposed to disproportional retardation reflected by PI. Furthermore, although we adjusted for both adult body and head size to account for the strong correlation between body and brain size present at birth, we cannot rule out residual confounding. Another limitation is that no data were available on neonatal head circumference, which could have helped, at least in part, to unravel the mechanisms involved in the birth size–brain pathology connection. Finally, education usually is highly correlated with socioeconomic status and therefore difficult to disentangle from one another. However, additional adjustment for occupation, as a proxy for socioeconomic status, showed that the effect of low PI on reduced cognitive performance in the low-education group was not explained by occupation.

Although we found that all measures of birth size were strongly associated with late-life head size, only PI, as an indicator of fetal wasting, revealed an association with brain volumes, particularly WM volume. Clinical observations have shown that growth inhibition in early pregnancy produces a proportionally undersized fetus that affects both length and weight, so PI is normal.⁶ Growth inhibition in late pregnancy has less effect on fetal length but could result in disproportionate thinness at birth (low PI).⁶ Our findings therefore suggest that the critical period of impaired fetal growth for our outcomes occurred in late pregnancy, which is when the organs and tissues undergo critical periods of development.²¹ Normal brain development in this critical period of late pregnancy involves both development of GM and WM. However, the formation of WM and myelination starts in the second half of pregnancy and oligodendrocyte differentiation occurs during the last gestational weeks of prenatal development and therefore is severely compromised in several

**FIGURE 2**

PI at birth and late-life cognitive functioning within strata of education. Values are mean (SE) z scores of speed of processing (A) and executive functioning (B) for categories of PI and stratified for education. Values are adjusted for age and gender. ◆, Low education, $n = 231$; ◇, high education, $n = 1023$.

conditions affecting fetal nutrition in this critical period.^{22,23} That the last gestational weeks are critical for brain development is confirmed by human MRI studies showing that preterm-born individuals have abnormally altered brain structures, particularly the WM,^{24–29} and that lower placental weight is associated with altered late-life WM integrity in older individuals.³⁰

Our second finding is that small birth size contributed to reduced late-life cognitive performance only in participants with lower educational achievement during early life. The association

was clearest in the processing speed and executive functioning tests that rely on WM integrity to transmit signals throughout the brain. Our findings are in line with a study showing that late-middle-aged persons, affected by exposure to famine before birth, had poorer executive functioning than those not affected.⁵¹ Better than expected cognitive performance in the presence of brain pathology has been observed in the context of the cognitive reserve hypothesis.¹⁰ The concept of cognitive reserve provides an explanation for differences between individuals in susceptibility to age-

related brain changes or pathology, whereby some people, for example, those with higher educational achievement, can tolerate more of these changes than others and maintain function.

Thus, suboptimal pre- and postnatal environments could result in a delay in myelination affecting axonal conduction velocity and could conceivably underlie long-term cognitive performance.²³ We know that in an environment of impaired fetal growth, the brain is preferentially perfused to maintain oxygen supply.³² Of particular interest is that the observed variations in birth anthropometric measures are likely to be physiologic in this sample. Also, the mean birth weight in the North Atlantic, which is among the highest in the world¹² and the high level of education in Iceland, with a widespread literacy rate since the end of the 18th century, suggest that even subtle normal variations in intrauterine environment and educational levels may lead to differences in postnatal brain structure and function. Because our study sample had more years of education than the total AGES-RS cohort, it is expected that effect sizes would increase when studying this relation in populations with proportionately smaller birth sizes and lower educational levels.

Possible pathways exist to link these suboptimal pre- and postnatal environments to smaller brain volumes and reduced cognitive functioning in late life (Fig 3). A chain of events triggered by abnormal or suboptimal fetal development, through, for example, maternal malnutrition or placental insufficiency, leading to small birth size, lower socioeconomic status, an unhealthy life style, and increased cardiovascular risk could explain our findings. Our study revealed that individuals with lower birth PI were more likely to smoke during adult life. Because there is a strong

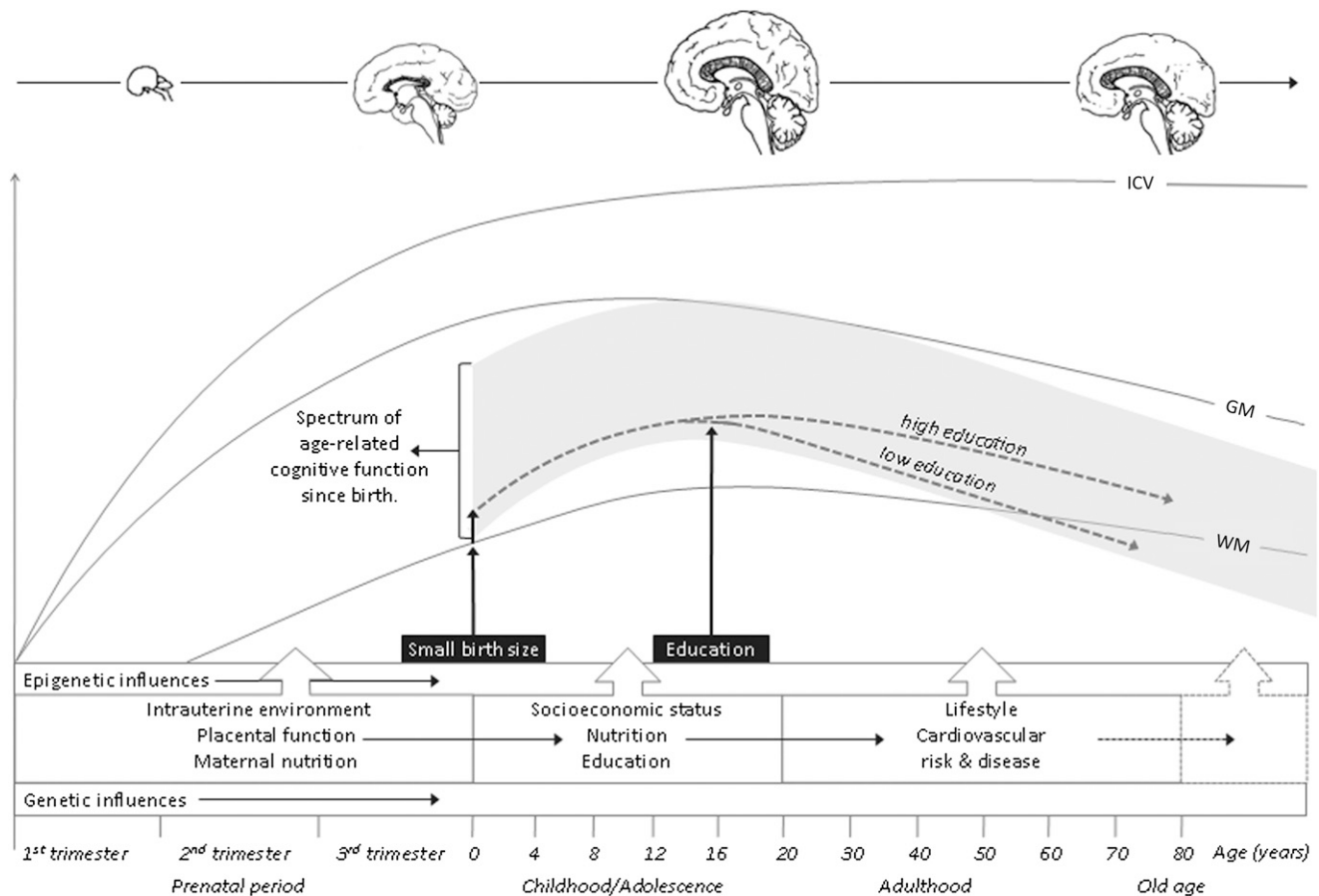


FIGURE 3 Hypothesized model on the origins and life course of brain aging. Several “critical periods” (prenatal period, childhood/adolescence, adulthood, and old age) are identified during which an individual is at greatest risk of damage if exposed to putative risk factors. Normal development of ICV and brain volumes (GM and WM) is presented for these critical periods, and the possible different risk factors influencing brain development throughout these periods are described. Allegedly, genetics and epigenetic influences could alter brain structure and function throughout life, but their impact would probably fade with age. In addition, the spectrum of age-related cognitive ability from birth to old age is presented in this figure, with a schematic view of our findings that small birth size is related to poor cognitive functioning only in those with lower educational levels.

relation between smoking behavior of parents and children, this finding could reflect that the mothers of individuals with lower PI smoked more during their pregnancy. However, adjusting for smoking and other measures of socioeconomic status and lifestyle factors did not change our results. Another possibility is that fetal undernutrition directly affects neurodevelopment or accelerated brain aging.¹ In our study, small birth size was not only related to reduced late-life head size but also to smaller late-life relative brain volumes. And, although brain volumes and cognitive function were measured at 1 point in time, this finding could suggest that suboptimal

fetal development is involved in the disruption of optimal brain growth as well as in neurodegenerative processes and loss of brain tissue. Although this is a genetically homogenous population, genetic influences could explain, at least in part, the relation between birth size and brain development.^{33,34} Epigenetic changes may also play an important role in propagating these trajectories. Recent investigations give insight into how epigenetic changes in the fetal environment, such as alterations in methylation of genes involved in regulating cortical development, may have lasting effects on developmental and aging processes, through influencing the expression of key regulatory genes

or progenitor cells.^{7,35,36} For instance, it has been hypothesized that fetal undernutrition affects the differentiation of progenitors into myelin-forming oligodendrocytes, which occurs during the last gestational weeks of human development.²² In addition, it has been shown that early-life socioeconomic status, including education, contributes to DNA methylation variation.³⁷

CONCLUSIONS

This study is the first to our knowledge that shows that small birth size is associated with smaller late-life brain volumes and that higher levels of education, as an indicator of cognitive

reserve, may minimize the effects of a suboptimal intrauterine environment on late-life cognitive function (Fig 3). These study results provide a framework for linking several actively pursued areas of research on

the origins of chronic disease, including dementia, and studies investigating the contribution to dementia risk of education, small head size, and cognitive reserve. A clinical implication of our findings is that interventions to boost

cognitive reserve throughout childhood and adult life, for example, by increasing educational levels, hold promise to prevent late-life cognitive impairment, particularly in those with small birth size.

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