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Association between birthweight and cognitive function in middle age: the ARIC study

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Abstract

PURPOSE—We aimed to examine the relationship of birthweight to cognitive performance in middle aged participants of the Atherosclerosis Risk in Communities Study (ARIC).

METHODS—Cognitive function, assessed by means of three neuropsychological tests - the Delayed Word Recall Test (DWR), the Digit Symbol Subtest of the Wechsler Adult Intelligence Scale-Revised (DSS/WAIS-R) and the Word Fluency (WF) Test, was evaluated in relation to birthweight, as recalled through standardized interviews, using data from the second and fourth follow-up visits of the ARIC study cohort (1990 to 1992 and 1996 to 1998, respectively). Overall, 6785 participants satisfied the inclusion criteria and were included in the analysis.

RESULTS—After adjusting for adult socio-demographic factors, childhood socio-economic environment and parental risk factors, and adult anthropometric, health status related and behavioral variables, linear trends were observed for the relationship of birthweight to WF scores, although the trend was statistically significant only for those reporting exact birthweights (p for trend= 0.004). For the other cognitive test results, results were either null or inconsistent with the a priori hypotheses.

CONCLUSIONS—Except for WF in those reporting exact birthweights, our study does not support the notion that birthweight influences cognitive function in adults.

Keywords

birthweight; cognition disorders; fetal programming; cohort studies

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INTRODUCTION

The association between birthweight and cognitive development has been consistently observed in European cohorts born during different periods in the 20th century (1). In the Aberdeen Children of 1950's cohort study, growth in utero and during childhood were correlated with later cognition scores (2). Birthweight was positively associated with cognitive performance at age 20 years in a historical cohort of Danish men (3), and in a very preterm or very low birthweight Dutch birth cohort (4).

As reported by Richards et al. (5), the association between birthweight and later cognition was evident across the whole spectrum of birthweight. This association, which is seen through childhood, adolescence and early adulthood, has not been found to be due to confounding by social factors and postnatal growth (1, 6). Such findings imply a role for childhood nutrition (5, 6), which is known to affect neurological, cognitive and emotional development (7–10). The association between fetal growth and cognitive function in later adult life, however, remains uncertain (5, 6, 9).

In the Atherosclerosis Risk in Communities (ARIC) cohort study, data on birthweight and cognitive performance at ages 48–67 and 54–73 years were assessed according to standardized protocols. The aim of the present study was to examine the relationship of birthweight to cognitive performance in middle aged ARIC cohort participants.

METHODS

ARIC is a multi-center cohort study described in detail elsewhere (11). Briefly, 15,792 participants from four US communities, aged 45 to 64 years, were included, and first examined from 1987 through 1989. Three subsequent evaluations at three year intervals followed this baseline examination (visits 2, 3 and 4).

Cognitive function was assessed at visits 2 (1990 to 1992; n = 14,128) and 4 (1996 to 1998; n = 11,265) by means of three neuropsychological tests: the Delayed Word Recall Test (DWR) (12), the Digit Symbol Subtest of the Wechsler Adult Intelligence Scale-Revised (DSS/WAIS-R) (13) and the Word Fluency Test (WF) (14) of the Multilingual Aphasia Examination (15). The DWR test is a test of verbal learning and recent memory. The DSS/WAIS-R measures psychomotor performance and is relatively unaffected by intellectual ability, memory or learning for most adults (13). The WF test is particularly sensitive to linguistic impairment (14, 16) and early mental decline in older persons (17); it is also a sensitive indicator of damage to the left lateral frontal lobe (14, 16). Overall, data on all three cognitive test scores at visits 2 and 4 were available for 11,030 participants.

The DWR and WF tests were administered by trained interviewers. The DSS/WAIS-R test is a timed test, and was self-administered following standardized instruction. Interviewer performance in ARIC was monitored by tape recording and review of a random sample of taped interviews by an experienced interviewer. No systematic departures from the protocol were detected by listening to the tapes, and mean scores obtained by different interviewers were found to be similar. A detailed description of cognitive assessment in ARIC has been presented elsewhere (18, 19).

Information on birthweight (exposure variable) was obtained through standardized interviews at visit 4 (1996 through 1998). Participants were first asked to recall their exact birthweights (in pounds and ounces) or, when unable to do so, to inform whether it was low (<5.5 lbs), medium (5.5–9.0 lbs) or high (>9.0 lbs). Overall, exact and non-exact birthweight values were recalled by 5350 and 5810 participants, respectively, and 496 participants did not recall their birthweights.

Eligibility was determined by availability of information on birthweight, (either exact or approximate) at visit 4, and cognitive function testing at visits 2 and 4, comprising 10,706 out of 11,656 visit 4 participants. Participants who reported stroke, transient ischaemic attack (TIA) or myocardial infarction either prior or subsequent to the baseline visit (n = 1868), and those using medications with known central nervous system effects, such as antidepressants and anti-psychotics (n = 2681), were excluded. Additional exclusion criteria were being a twin (n = 343) and missing information on educational level (n = 17). In addition, we excluded premature birth (n = 930) as our hypothesis focused on low birthweight due to growth restriction, and not to prematurity. As there were very few cohort participants of Asian or Indian ethnic origin (n = 31) as well as non-whites in the Minneapolis and Washington County Field Centers (n = 30), these groups were also excluded. A total of 3921 participants were excluded due to at least one exclusion criterion.

Recalled exact birthweight (in pounds and ounces) was converted to kilograms (kg) as well as to birthweight categories: <2.5 kg: low; 2.5 to 3.9 kg: medium; and ≥4.0 kg: high. Cognitive function (outcome variable) was assessed as the mean score of visits 2 and 4 tests for each of the three neuropsychological tests. Analyses were done separately according to how birthweight data were obtained (exact or non-exact). Additional analyses were carried out excluding participants who recalled either very low (<1.5 kg) or very high exact birthweights (>4.5 kg). The latter group was excluded because, as previously reported (20), the proportion of participants reporting birthweights >4.5 kg in ARIC (9%) was found to be much higher than that expected based on 1950 population data (2%) from the US National Center for Health Statistics (21).

Potential confounding factors and effect modifiers were considered, including adult socio-demographic factors, childhood socio-economic environment and parental risk factors, and adult anthropometric, health status related and behavioral variables. Variables measured in the first visit included gender, educational level (≤8th grade, 9th to 12th grade, vocational school or college), ethnic background (Black or White), parental history of diabetes, stroke and ischemic heart disease (yes/no) and self reported health status (excellent, good and fair or poor). Vital exhaustion was measured in the second visit. Variables measured in the fourth visit included marital status at visit 4 (single, married, divorced/separated, widowed), maximum parental education at participant’s birth, or maximum education of the two adults who took care of the participant during childhood (<4th grade, 4th to 8th grade, 9th to 11th grade, ≥12th grade). Variables for which means of values obtained in the second and fourth visits were calculated included age (classified into age groups: <55, 55 to 59, 60 to 64 and ≥ 65 years old), adult body mass index (BMI - kg/m^2), HDL and LDL cholesterol levels (mg/dl) and sports index values. Variables based on values assessed at visits 2 and 4 were field center (Forsyth County, North Carolina; Jackson, Mississippi; Minneapolis, Minnesota; Washington County, Maryland), use of cholesterol lowering medication (yes/no), presence of hypertension (systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg) and diabetes (fasting glicemia ≥126 mg/dl), smoking status and alcohol consumption (current, former, never, unknown).

Vital exhaustion was assessed by the Maastricht Questionnaire, a 21-item, pencil-and-paper test that assesses mental and physical exhaustion, hopelessness, and symptoms of depression (22). The sports index, used as a measure of physical activity during leisure time, was assessed by a modified version of the questionnaire of Baecke et al. (23).

Statistical analysis

Unadjusted mean and percentile values of cognitive test scores were examined in relation to birthweight. The distribution of potential confounders according to recalled birthweight values was examined by comparing means and proportions across groups. Linear regression modeling was used to analyze the association between birthweight and cognitive function, adjusted for potential confounding variables. Covariates were added to the univariate models, according to a standard sequence: first, adult socio-demographic factors, followed by childhood socio-economic environment and parental risk factors, and adult anthropometric, health status related and behavioral variables. Each group of covariates was added simultaneously. When exact birthweight was the exposure, models provided estimates of the average change in mean cognitive scores for a change of 100 g in birthweight. When non-exact birthweight was the exposure, estimates of the average difference in mean scores of each cognitive test between medium and high birthweight categories relative to low birthweight were obtained. Linear trends were examined using the Wald statistic for the regression coefficient corresponding to birthweight converted into a single ordinal term, with values 0, 1 and 2 representing the birthweight categories, low, medium and high, respectively. For each model, the amount of variation of mean cognitive function scores explained by all covariates was obtained by calculating the r-square statistic. Statistical significance was set at the two-tailed 5% level ($p < 0.05$). Stata version 8 (Stata Corporation) was used for all analyses.

In order to evaluate the possibility of bias in reporting birthweight associated with poorer cognitive performance, all analyses were repeated excluding participants who scored less than the 5^{th} percentile on any of the three cognitive test mean scores distributions. Additionally, we compared the distributions of cognitive tests scores across birthweight categories between those who reported and those who did not report exact birthweights.

RESULTS

Overall, 6785 participants satisfied the inclusion criteria. The exact birthweight was recalled by 3292 (48.5%) participants. Mean birthweight was 3.5 kg (SD: 0.7 kg) for those who recalled it exactly (Table 1). Medium birthweights (2.5 to 3.9 kg) were more frequently recalled by all participants, particularly by those who only reported birthweight categories. Mean scores for all cognitive tests at visits 2 and 4 were only slightly higher for participants who recalled exact birthweights. Female gender, white ethnicity and college education and were more frequent in participants who recalled exact birthweights. In addition, parents of those in the exact birthweight group had a higher educational level than in the non-exact group. The exact group also had a slightly better morbidity profile and a higher proportion of current drinkers. BMI, sports index and current smoking differed little between groups (Table 1).

Cognitive test scores were uniformly higher in those reporting exact birthweights across all birthweight categories (Table 2). Higher cognitive test scores were observed among participants who reported medium birthweights (ranging from 2.5 up to 3.9 Kg), both in those reporting exact and non-exact birthweights, except for the DWR test in those reporting exact birthweight, in whom an inverse monotonic relationship between birthweight and cognitive function was found.

The multivariable adjusted relationships of birthweight to cognitive test scores are presented in table 3.

An increment of 100 g in (exact) birthweight was found to be related to an average increase of 0.752 words (95% confidence interval: 0.174, 1.331) in the Word Fluency test score. Linear trends were observed for the relationship of both exact and non-exact birthweights to WF scores, although the trend was statistically significant only for those reporting exact birthweights (p for trend= 0.004). For the other cognitive test results, results were either null or inconsistent with the a priori hypotheses (Table 3).

Similar results were observed in both univariate and multivariate analyses after excluding participants who recalled exact birthweights <1.5 kg or ≥4.5 kg, as well as those who scored less than the 5^{th} percentile on any of the three cognitive tests (data not shown).

Results of the residual analysis showed that the linearity assumption as well as all other assumptions underlying the multiple regression were met.

DISCUSSION

The association between size at birth and the risk of chronic diseases later in life has been observed in previous studies (8, 24). Evidence from experimental studies with animals suggest that under-nutrition during fetal life affects brain development (7), making it plausible, by analogy, to hypothesize an association between fetal growth restriction and cognitive impairment in humans.

In our study, birthweight was positively associated with the WF test in a graded fashion, although, after adjusting for covariates, significance was only achieved for exact birthweight, evaluated both as a categorical and as a continuous variable. No consistent associations or trends were found of birthweight with either the DWR or the DSS test. Thus, the results of the present study do not strongly support the hypothesis that birthweight is associated with cognitive performance in individuals aged 51 to 70 years. Similar results were reported elsewhere, based on the assessment of other domains of cognitive function (9).

In ARIC, the associations of the WF test score with other variables were previously evaluated. Cross-sectionally, in surgically menopausal women aged 48–57 years examined at visit 2, adjusted mean WF scores were slightly greater in estrogen replacement therapy (ERT) current users than in never users; and within current users, adjusted WF scores increased with duration of ERT use (25). However, after adjusting for multiple covariates, no consistent patterns of cognitive changes during a six year interval - between cohort visits 2 and 4 - could be detected according to current use or duration of ERT use (26). As reported by Wong et al. (27), persons with severe cognitive impairment based on WF test scores were 1.6 times more likely to have early age-related maculopathy than those without severe impairment, after multiple adjustment. Additionally, presence of diabetes at baseline was associated with greater decline in scores of both the WF and DSS tests between visits 2 and 4 (19).

Because DWR and DSS test results obtained at visit 2 were related to all-cause 6-year mortality (28) and because, in addition, only individuals who participated in visits 2 and 4 were eligible for the present analysis, selection bias cannot be ruled out as an explanation for our largely null findings. In addition, those eligible for inclusion in the study population when the ARIC study was started in 1987 were survivors of cohorts born between 1923 and 1944, which represents another potential source of selection bias (9).

A problem in our study is the possible inaccuracy of birthweight recall in those with low cognitive functioning at visit 4. Indeed, poorer performances in all three cognitive tests were observed in those who recalled non-exact birthweight categories, particularly in the low birthweight strata (table 2). On the other hand, although the relationship of birthweight to WF test score was only statistically significant in the exact group, trends were similar in both the non-exact and the exact groups.

In addition, although a mental status measure is not available in ARIC, the Delayed Word Recall was originally developed as a dementia screening tool with a preferred cut-off point of 3, below which we only observed 0.88% and 0.94% of participants who recalled exact and approximate birthweights, respectively. Moreover, after excluding participants at the bottom of any of the three cognitive score distributions (mean scores less than the 5 th percentile), no significant changes were observed in the associations of birthweight with cognitive performance. Thus, it is unlikely that our results can be explained by recall bias.

As observed in previous studies (9, 18, 28), adult cognitive function seems to be highly dependent on individual demographic and socio-economic factors. Indeed, adjustment for these variables accounted for almost the entire variation in the cognitive function test mean scores. It should be pointed out that, although a higher educational level has been found to be positively associated with cognitive performance (18, 28, 29), it is an imperfect surrogate of social class (30). If the overall construct, social class, is responsible for the association of education with cognitive function, adjustment for educational level without considering other components of social class may still result in residual confounding.

The strengths of our study included a large sample size, stringent quality control measures and adjustment for multiple confounding variables.

In sum, except for WF in those reporting exact birthweights, our study does not support the notion that birthweight influences cognitive function in adults. Determinants other than those restricted to fetal life would seem to influence cognitive function in adult life.

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LIST OF ABREVIATIONS

ARIC	Atherosclerosis Risk in Communities
BMI	Body mass index
CI	Confidence interval
DSS/WAIS-R	Digit Symbol Subset of the Wechsler Adult Intelligence Scale-Revised
DWR	Delayed Word Recall Test
ERT	Estrogen replacement therapy
HDL	High density lipoprotein
kg	kilogram
LDL	Low density lipoprotein
SD	Standard deviation
TIA	Transient ischaemic attack
US	United States
WF	Word Fluency Test

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Table 1

Distributions of selected variables according to exactly and non-exactly recalled birthweight and in the total cohort, the ARIC Study

Variables	Recalled birthweight: Exact (n = 3292)		Recalled birthweight: Non exact (n = 3493)		Total cohort (n=11,656)	
	Mean (SD[1])	%	Mean (SD[1])	%	Mean (SD[1])	%
Birthweight******						
Exact (kg)	3.5 (0.7)		---		3.4 (0.8)	
Low (<2.5 kg)[2]		4.6		2.3		6.8
Medium (2.5 to 3.9 kg)[2]		82.4		95.5		82.8
High (≥4.0 kg)[2]		13.0		2.2		10.4
Cognitive function scores						
DWR[1]***	6.8 (1.3)		6.6 (1.3)		6.6 (1.3)	
DSS[1]***	47.5 (12.0)		44.5 (12.9)		45.0 (12.9)	
WF[1]***	35.4 (11.4)		33.4 (11.5)		33.8 (11.7)	
Sociodemographic variables						
Female sex*		56.4		48.6		55.8
Age (years)***	59.2 (5.6)		60.1 (5.6)		59.8 (5.7)	
White ethnic group*		85.1		74.8		76.9
Married******		78.9		78.6		75.0
Incomplete College or College Completion*		45.4		38.8		38.6
Childhood socioeconomic environment and parental risk factors						
Highest education level of parents (grades 12+)******		45.9		35.9		37.7
Family history of stroke*		27.9		30.6		29.5
Family history of coronary heart disease*		41.0		38.9		40.3
Family history of diabetes*		23.4		23.9		24.4
Anthropometric and health status related risk factors						
Body mass index (kg/m^2)***	28.2 (5.2)		28.3 (5.1)		28.3 (5.3)	
HDL[1] cholesterol (mg/dl)***	50.3 (15.9)		48.7 (14.7)		49.8 (15.6)	

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Variables	Recalled birthweight					
	Exact (n = 3292)		Non exact (n = 3493)		Total cohort (n=11,656)	
	Mean (SD[1])	%	Mean (SD[1])	%	Mean (SD[1])	%
LDL[1] cholesterol (mg/dl)***	126.8 (30.1)		128.8 (30.2)		127.8 (30.8)	
Cholesterol lowering medication use****		14.4		15.1		15.9
Hypertension****		44.7		48.3		50.2
Diabetes****		15.3		17.3		18.5
Excellent or good self reported health status*		88.9		84.9		81.5
Vital exhaustion (score)**	4.8 (4.9)		5.3 (5.2)		6.2 (5.8)	
Behavioral risk factors						
Sport index***	2.6 (0.7)		2.5 (0.7)		2.5 (0.7)	
Current smoker****		13.3		12.4		14.9
Current drinker****		55.6		51.1		48.9

* Gender, educational level, race/colour, family history of stroke, coronary heart disease and diabetes, and self reported health status assessed at visit 1.

** Vital exhaustion score assessed at visit 2.

*** DWR, DSS and WF scores, age, sport index, body mass index, LDL and HDL cholesterol: mean values assessed at visits 2 and 4.

**** Smoking and drinking status, and reported cholesterol lowering medication use assessed at visits 2 and 4.

***** Hypertension and diabetes diagnosed prior to or at visits 2 and/or 4.

****** Birthweight, higher parental educational level and marital status assessed at visit 4.

[1] SD: standard deviation; DWR: Delayed Word Recall Test; DSS: Digit Symbol Subtest; WF: Word Fluency Test HDL: high density lipoprotein; LDL: low-density lipoprotein

[2] For participants who recalled exact birthweight, it was converted into birth weight categories

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Table 2

Mean scores of cognitive function according to type of birthweight recall, the ARIC Study

		Birthweight recall			
		Exact		Non exact	
Cognitive function test*	Birth weight Categories**	Mean	(95% CI*)	Mean	(95% CI*)
	Low	7.1	(6.9–7.3)	6.2	(5.8–6.5)
DWR	Medium	6.9	(6.8–6.9)	6.7	(6.6–6.7)
	High	6.6	(6.5–6.7)	6.2	(5.9–6.5)
	Low	47.7	(45.7–49.6)	36.4	(33.4–39.3)
DSS	Medium	48.0	(47.5–48.5)	44.7	(44.3–45.2)
	High	45.7	(44.9–46.5)	41.7	(38.8–44.6)
	Low	33.7	(31.9–35.4)	28.9	(26.3–31.6)
WF	Medium	35.7	(35.2–36.1)	33.6	(33.2–33.9)
	High	34.6	(33.8–35.5)	33.2	(31.0–35.5)

* DWR: Delayed Word Recall Test; DSS: Digit Symbol Subtest; WF: Word Fluency Test; CI: confidence interval

** Low (<2.5 kg); Medium (2.5 to 3.9 kg); High (≥4.0 kg)

Table 3

Relationships between birthweight and cognitive function mean scores, the ARIC Study

Recalled birthweight	Linear regression model[1]	DWR[2] Linear regression coefficient (95% CI[2])	DSS[2] Linear regression coefficient (95% CI[2])	WF[2] Linear regression coefficient (95% CI[2])
Exact (n = 3292)	Birthweight (unit of 100 g)	0.028 (−0.038 to 0.094)	−0.067 (−0.565 to 0.431)	0.752 (0.174 to 1.331)
Exact[3] (n = 3292)	Low birthweight (< 2.5 kg)	Reference	Reference	Reference
	Medium birthweight (2.5 to 3.9 kg)	−0.076 (−0.286 to 0.133)	0.004 (−1.570 to 1.578)	1.078 (−0.749 to 2.905)[5]
	High birthweight (≥4.0 kg)	−0.051 (−0.291 to 0.189)	0.170 (−1.637 to 1.978)	2.608 (0.511 to 4.706)[5]
Non exact[4] (n = 3493)	Low birthweight (< 2.5 kg)	Reference	Reference	Reference
	Medium birthweight (2.5 to 3.9 kg)	0.281 (−0.031 to 0.592)	2.928 (0.590 to 5.266)	2.515 (−0.186 to 5.216)[6]
	High birthweight (≥4.0 kg)	−0.046 (−0.465 to 0.373)	1.825 (−1.321 to 4.970)	2.961 (−0.673 to 6.594)[6]

[1]Multivariate linear regression model of mean scores of cognitive function tests on birthweight, adjusted for sociodemographic factors (age, gender, race, education, marital status and field center), childhood socioeconomic environment (parental education), parental risk factors (family history of stroke, coronary heart disease and diabetes), health status related variables (body mass index, hypertension and diabetes. LDL and HDL cholesterol, reported cholesterol lowering medication and self reported health status) and behavioral variables (sport index, smoking and drinking status and vital exhaustion).

[2]DWR: Delayed Word Recall; DSS: Digit Symbol Subtest of the Wechsler Adult Intelligence Scale Revised; WF: Word Fluency Tests; CI: confidence interval.

[3]Participants who recalled exact birth weight, converted to birthweight categories

[4]Participants who recalled non exact birthweight

[5]p for trend = 0.004

[6]p for trend= 0.131