DOI: 10.1093/brain/awg225 Advanced Access publication June 23, 2003 *Brain* (2003), **126,** 2273–2278

Foetal and postnatal head growth and risk of cognitive decline in old age

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Summary

Studies of elderly people have shown that scores on tests of cognitive function tend to be higher in those with larger head circumferences. One explanation for these findings is that optimal brain development *in utero* and in the first years of life may protect against cognitive decline in old age, though the relative importance of these two periods of brain growth is unclear. We assessed change in cognitive function over a 3.5-year period in 215 men and women aged 66–75 years whose head circumference had been recorded at birth and as adults. Cognitive function was tested in the initial study and at follow-up with the AH4 intelligence test and the Wechsler Logical Memory test. We found no associations between head circumference at birth and score on the cognitive function tests or change in score over time. However, people who had a larger head circumference as an adult gained significantly higher scores on the intelligence test on both testing occasions and were less likely to show a decline in memory performance over the follow-up period. People whose head circumference was in the top quarter of the distribution had an odds ratio for decline in immediate recall on the Logical Memory test of 0.2 (95% confidence interval 0.1–0.6) and an odds ratio for decline in delayed recall of 0.3 (95% confidence interval 0.1–0.9) compared with those whose head circumference was in the bottom quarter, after adjustment for age, sex and potential risk factors. These results suggest that brain development during infancy and early childhood is important in determining how well cognitive abilities are preserved in old age.

Keywords: head circumference; cognitive decline; foetal growth; postnatal growth

Introduction

There is evidence from studies of elderly people that men and women with larger head circumferences perform better on tests of cognitive function (Reynolds *et al*., 1999; Tisserand *et al*., 2001). As adult head circumference is known to provide an accurate estimate of maximal attained brain size (Wickett *et al*., 2000) these findings have been interpreted as evidence in support of the theory that optimal neurological development in early life may provide a buffer against pathological processes that can affect cognitive performance in old age (Stern, 2002). But as brain size is related to intelligence test scores in young adults (Wickett *et al*., 2000), it is possible that the associations found between head circumference and cognitive performance in elderly people are simply a reflection of the long-term stability of individual differences in mental ability (Deary *et al*., 2000).

The brain begins its growth spurt in the last trimester of pregnancy. This is the period when glial cells start to develop, axons grow, dendrites branch and synapses are formed. As myelination proceeds, brain volume increases and head circumference expands rapidly from ~25 cm at 28 weeks gestation to ~35 cm at term. Head circumference at birth provides an indicator of brain growth during foetal life (Cooke *et al*., 1977). Postnatally, the velocity of head growth remains high, particularly in the first few months (Ulijaszek *et al*., 1998). The brain doubles its birth weight in the first year and triples it by age six (Sinclair and Dangerfield, 1998). Head circumference at this age is ~93% of its final size, so measurements of head circumference made in adults are largely a reflection of brain growth during the first few years of postnatal life.

The relative importance of foetal and postnatal head growth in determining how well cognitive abilities are preserved in old age is unknown. We assessed change in cognitive function over a 3.5-year period in a group of elderly men and women whose head circumference had been recorded at the time of their birth and as adults. Our aim was to investigate whether brain growth in foetal or postnatal life, as indicated by head circumference, affected the risk of cognitive decline in old age.

Methods

Participants

Midwives at the Jessop Hospital for Women, Sheffield, kept a standard record for each woman admitted. Details included the baby's birth weight, head circumference, crown–heel length and date of the mother's last menstrual period. We asked the National Health Service Central Register to trace all 4793 people who had been born in the hospital between 1922 and 1930. Only those still living in Sheffield were eligible to take part in the study. A stratified sample of 746 people, comprising all 236 subjects from the highest and lowest fifths of birth weight and 85 randomly chosen subjects of each sex from each of the three intervening fifths of birth weight, was selected. In 1997–1998, having obtained permission from their general practitioners, we wrote to 660 men and women who were still living in Sheffield to ask whether we could interview them at home. Four hundred and twelve (62%) agreed and were interviewed at home by a research nurse. Of these, 392 were willing to attend a clinic for examination. Some of the findings from this study have been described previously (Hall *et al*., 2002).

In 2000–2001, we asked the general practitioners of the 392 men and women who had attended our clinic as part of the initial study for permission to invite them to take part in further research. Of the 392 former participants, 21 had died, 11 had moved out of the area and six were too ill to be approached. We were therefore able to write to 354 men and women. Of these, 242 (68%) agreed to be visited at home by a research nurse.

Measurements

During the initial study, the research nurse asked about any history of cardiovascular disease, education and father's occupation at the time of the participant's birth. Reports of a history of stroke or transient ischaemic attack were subsequently confirmed from the general practitioners' records. Height was measured with a portable stadiometer.

The research nurse administered two tests of cognitive function. The AH4 test provides a measure of logical, verbal and numerical reasoning (Heim, 1968) The Logical Memory subtest of the Wechsler Memory Scale assesses the ability to recall ideas presented in two short stories (Wechsler, 1987). Participants also completed the Nottingham Health Profile, a questionnaire that measures perceived health status on six dimensions (energy, pain, emotional reactions, sleep, social isolation and physical mobility) (Hunt *et al*., 1980). Scores on the emotion subscale have been shown to provide a valid indicator of the presence of depression (Ebrahim *et al*., 1986).

During the follow-up interview, the research nurse re-administered the two tests of cognitive function and asked the participants to complete the Nottingham Health Profile. She also measured their head circumference. A tape measure was passed around the head and placed on the most anterior protuberance of the forehead and the most posterior protuberance of the back of the head. The tape measure was pulled tight to compress the hair and measurements were made to the nearest 0.1 cm.

Twenty-seven participants were excluded from the analysis because of missing data on head circumference, either at birth or as an adult ($n = 22$) or because they experienced problems during the cognitive function testing due to interruption or deafness ($n = 5$). The analyses that follow are therefore based on 215 participants (61% of those invited to participate).

The initial and follow-up studies were approved by the South Sheffield Research Ethics Committee. The research followed the tenets of the Declaration of Helsinki. All participants gave their written informed consent.

Statistical analysis

We used analysis of variance to examine the relation between mean scores on the AH4 intelligence test and Wechsler Logical Memory test and the two measures of head circumference, with adjustment for other potential risk factors. We divided each head circumference measure into quarters of the distribution, treating men and women separately. The P values for trend shown in Table 2 were calculated in linear regression using head circumference as a continuous variable. We calculated change in scores on the two cognitive function tests by subtracting the score at initial testing from the score at follow-up. We studied the relation between change in test score and measures of head circumference in two ways. First, we examined change in score on each test as a continuous variable, using partial correlation coefficients to investigate the relation between change in test score and the two measures of head circumference, with adjustment for other potential risk factors. Secondly, we examined change in score as a categorical variable, divided into two groups (cognitive decline or no decline). Cognitive decline was defined as a drop in score on the AH4 intelligence test or the Wechsler Logical Memory test of half a standard deviation or more. Decline on the AH4 intelligence test meant a drop of $\geqslant 4$ points; decline on the Wechsler Logical Memory test meant a drop of $\geqslant 3$ points on either immediate or delayed recall. We used logistic regression to examine the relation between risk of decline and head circumference. Odds ratios (with 95% confidence intervals) are shown according to fourths of the distribution of head circumference. P values are given for the trend in the odds ratio across the groups.

Results

Table 1 shows the characteristics of the 215 men and women included in the analysis and their mean scores on the tests of cognitive function at the time of the initial study. Comparison of these individuals with the 197 people who were interviewed as part of the initial study but who are not included in the analysis because of loss to follow-up or missing data showed that the latter group were less likely to have stayed at school after the age of 14 years ($P = 0.02$) and had performed less well on the cognitive function tests in the initial study. Mean scores on the AH4 intelligence test were 19.2 compared with 24.0 ($P < 0.001$) and on immediate recall on the Logical Memory test 20.0 compared with 23.6 ($P < 0.001$). There were no significant differences between the two groups in age, sex, head circumference at birth, father's social class, height, history of cerebrovascular disease or Nottingham Health Profile emotion subscale score. We had no data on the adult head circumference of those who did not take part in the follow-up study, but it seems unlikely that they differed in this respect from those who were followed up, as the two groups were similar in height and this was highly correlated with head circumference ($r = 0.73$, $P < 0.001$).

Table 1 *Characteristics of the study participants*

Characteristic	*n* = 215
Female: *n* (%)	99 (46.0)
Head circumference at birth (cm)	34.7 (1.7)
Social class of father (non-manual): *n* (%)	26 (12.1)
Education (stayed at school beyond age 14 years): *n* (%)	46 (21.4)
Head circumference as adult (cm)	57.3 (1.3)
Height (cm)	164.9 (9.0)
History of cerebrovascular disease: *n* (%)	9 (4.2)
Nottingham Health Profile emotion subscore	8.1 (16.3)
Age (years)	69.8 (2.0)
AH4 intelligence test score	24.0 (9.4)
Wechsler Logical Memory test score	
Immediate memory	23.6 (6.7)
Delayed memory	18.2 (7.2)

Values are mean (SD) unless stated otherwise.

Men and women with larger head circumferences gained higher scores on the AH4 intelligence test at the time of initial testing and at follow-up ~3.5 years later. These associations remained statistically significant after adjustment for age, sex, education, father's social class, history of cerebrovascular disease and Nottingham Health Profile emotion subscale score (Table 2). Tallness was associated with higher intelligence test scores in univariate analysis, but this relation ceased to be statistically significant once we adjusted for head circumference. [After adjustment for head circumference and the other risk factors, for example, AH4 intelligence test score at follow-up rose by 0.177 points (95% confidence interval –0.04 to 0.39) for each centimetre increase in height ($P = 0.111$).] Performance on the Logical Memory test differed little by head circumference at initial testing, but at the follow-up examination scores tended to rise with increasing head size, though only the relation with immediate recall was statistically significant (Table 2).

We found no association between scores on either of the tests of cognitive function and head circumference at birth (Table 2). When we examined whether adjusting for head size at birth had any influence on the relation between adult head circumference and cognitive performance, the results remained unchanged. We investigated whether birth weight or length at birth was related to cognitive function test scores,

Table 2 *Mean scores on the AH4 intelligence test and Wechsler Logical Memory test during the initial and follow-up studies according to adult head circumference and head circumference at birth*

	AH4 intelligence test		Logical Memory Test: Immediate recall		Logical Memory Test: Delayed recall	
	Initial score*	Follow-up score*	Initial score*	Follow-up score*	Initial score*	Follow-up score*
Adult head circumference†						
1	22.0	23.2	23.2	22.0	18.3	18.2
2	24.5	25.5	22.4	20.7	17.1	16.5
3	25.8	28.3	25.2	25.4	19.6	21.2
4	26.6	27.1	23.4	24.2	17.9	20.0
	P for trend = 0.011	*P* for trend = 0.005	*P* for trend = 0.632	*P* for trend = 0.033	*P* for trend = 0.819	*P* for trend = 0.124
Head circumference at birth‡						
1	23.6	26.2	23.7	23.6	18.7	19.6
2	23.4	26.1	24.4	24.2	18.4	20.4
3	23.6	25.6	23.8	23.2	18.2	17.8
4	25.1	25.8	23.8	22.2	18.0	18.7
	P for trend = 0.376	*P* for trend = 0.943	*P* for trend = 0.746	*P* for trend = 0.508	*P* for trend = 0.745	*P* for trend = 0.776

*Adjusted for age, sex, education, social class at birth, history of cerebrovascular disease and Nottingham Health Profile emotion subscale score. Scores according to head circumference at birth are also adjusted for gestational age. †Adult head circumference groups 1–4 (cm), ⩽56.4, 56.5–57.2, 57.3–58.1 and ⩾58.2, respectively, for men and ⩽53.7, 53.8–54.7, 54.8–55.8 and ⩾55.9 for women;
‡Head circumference at birth groups 1–4 (cm), ⩽33.0, 33.1–35.2, 35.3–36.3 and ⩾36.4, respectively, for men and ⩽33.0, 33.1–34.3, 34.4–35.4 and ⩾35.5 for women.

Table 3 *Risk of decline in performance on the Wechsler Logical Memory test according to adult head circumference*

Adult head circumference†	Immediate recall			Delayed recall		
	No. (%) with decline	OR (95% CI), unadjusted	OR (95% CI), adjusted*	No. (%) with decline	OR (95% CI), unadjusted	OR (95% CI), adjusted*
1	23 (41.1)	1.0	1.0	21 (37.5)	1.0	1.0
2	23 (46.9)	1.3 (0.6–2.8)	1.1 (0.5–2.9)	13 (26.5)	0.6 (0.3–1.4)	0.6 (0.2–1.6)
3	20 (36.4)	0.8 (0.4–1.8)	0.5 (0.2–1.2)	15 (27.3)	0.6 (0.3–1.4)	0.4 (0.2–1.1)
4	11 (20.0)	0.4 (0.2–0.8)	0.2 (0.1–0.6)	12 (21.8)	0.5 (0.2–1.1)	0.3 (0.1–0.9)
		P for trend = 0.013	*P* for trend = 0.001		*P* for trend = 0.086	*P* for trend = 0.026

*Adjusted for age, sex, education, social class at birth, history of cerebrovascular disease, Nottingham Health Profile emotion subscale score and initial memory test score. †Adult head circumference groups 1–4 (cm) ⩽56.4, 56.5–57.2, 57.3–58.1 and ⩾58.2, respectively, for men and ⩽53.7, 53.8–54.7, 54.8–55.8 and ⩾55.9 for women. CI, confidence interval.

but found no significant associations. [For example, after adjustment for gestational age and the other risk factors, AH4 intelligence test score at follow-up rose by 0.634 points (95% CI, –1.33 to 2.60) for each kilogram increase in birth weight (P = 0.525) and fell by 0.039 points (95% CI, –0.49 to 0.41) for each centimetre increase in length at birth (P = 0.863). Score on immediate recall in the Logical Memory test at follow-up rose by 0.648 points (95% CI, –0.88 to 2.17) for each kilogram increase in birth weight (P = 0.404) and by 0.006 points (95% CI, –0.35 to 0.36) for each centimetre increase in length at birth (P = 0.973).]

When we examined how scores on the AH4 intelligence test had changed over the follow-up period, we found that 70% of the participants gained a score at follow-up that was the same or higher than at initial testing. The mean score increased by 2 points. There was no significant linear relation between change in score, treated as a continuous variable, and either head circumference at birth (r = –0.09, P = 0.20) or adult head circumference (r = –0.05, P = 0.51). Only 21 participants (10%) met our definition of decline on this test, a follow-up score 4 ($\frac{1}{2}$ SD) or more points below the initial score.

We examined the relation between anthropometric measures and change in score on the memory test, treating this as a continuous variable. Head size at birth was not associated with change in score, either at immediate recall (r = –0.013, P = 0.857) or at delayed recall (r = 0.052, P = 0.454). There was also no significant relation between change in the memory test score and either birth weight or length at birth (data not shown). There was evidence, however, to suggest that people with a larger adult head circumference tended to gain the same or slightly higher scores at follow-up, while those with a smaller head tended to get a lower score than in the initial study. The partial correlation coefficient between adult head circumference and change in score at immediate recall was r = 0.151, P = 0.034, and at delayed recall it was r = 0.126, P = 0.07 after adjustment for age, sex, education, father's social class, history of cerebrovascular disease, Nottingham Health Profile emotion subscale score and initial memory test score.

When we treated the change in score as a dichotomous variable, 77 (36%) participants met our definition of cognitive decline [scoring 3 ($\frac{1}{2}$ SD) or more points below their initial score] on immediate recall in the Logical Memory test, and 61 (28%) met our condition of cognitive decline on delayed recall. We calculated the odds ratios for a decline in memory performance (a drop in score of ⩾3) over the follow-up period according to adult head circumference. Men and women with larger head circumferences were significantly less likely to have experienced a decline in memory performance (Table 3). Compared with those whose head circumference was in the bottom quarter of the distribution, people whose head circumference was in the top quarter of the distribution had an odds ratio for decline in immediate recall of 0.2 (95% confidence interval 0.1 to 0.6) and an odds ratio for decline in delayed recall of 0.3 (95% confidence interval 0.1 to 0.9) after adjustment for age, sex, other risk factors and initial score. Height was not associated with risk of decline in memory performance and its inclusion in the multivariate model had little effect on these estimates of risk (data not shown).

Discussion

In this study of men and women aged 66–75 years, we found no associations between head circumference at birth and scores on the AH4 intelligence test or the Wechsler Logical Memory test. However, people who had a larger head circumference as an adult gained higher scores on the intelligence test and were less likely to show a decline in memory performance on immediate and delayed recall over the 3.5-year follow-up period. On the basis of their scores at immediate recall, there was a five-fold difference in the risk of decline between people with the smallest and largest adult head size.

Our study has some limitations. Although head circumference was routinely recorded in the birth records of our participants, the clumping of the data points suggests that the midwives often rounded the measurement to the nearest half-inch. The lack of association between cognitive performance and head circumference at birth may be due to this inaccuracy, though this seems unlikely as there was a similar lack of association between cognitive performance and the more precise measure of birth weight, which was highly correlated with head size (r = 0.71). As is common in longitudinal studies of elderly people, participants who were lost to follow-up had lower mean cognitive test scores in the initial study than those who took part in the repeat testing. However, studies that have examined the effects of such attrition have demonstrated that it does not bias estimates of cognitive change and has little effect on the strength of associations between variables (Norris, 1987; Deeg, 2002; Van Beijsterveldt *et al*., 2002). The fact that we had data on cognition at only two points in time means that our estimates of the extent of cognitive change in our elderly participants need to be treated with caution. Random variation or regression to the mean may account for some of the observed change in cognitive test scores, though it seems unlikely that this could have produced the dose–response relation between adult head size and risk of decline in memory performance. Improvements due to practice may have masked any evidence of decline on the AH4 intelligence test.

Our finding that elderly men and women with larger head circumferences gained higher scores on an intelligence test confirms the results of previous studies. Larger head size was associated with better performance on tests of intelligence, speed of information processing and global cognitive functioning in 818 non-demented people aged 50–81 years (Tisserand *et al*., 2001) and with a reduced likelihood of poorer scores on the Mini-Mental State Examination in 825 non-demented people aged ⩾70 years (Reynolds *et al*., 1999). Similar associations have recently been reported between intracranial capacity, assessed by MRI, and scores on a range of cognitive tests in a group of elderly men (MacLullich *et al*., 2002). A new finding from our study is that it is the extent of head growth during postnatal life rather than during foetal development that seems to be important. In our data, there were no significant relations between head circumference at birth and any measure of cognitive function—a result that mirrors the findings of a previous study of size at birth and cognition in later life (Martyn *et al*., 1996)—nor was there any indication that the association between adult head size and cognitive performance was modified by the size of the head at birth. It is possible, of course, that a larger adult head size and greater intelligence are both consequences of a favourable environment during infancy and early childhood, and that the link between them is due to confounding by nutritional factors or parental influences rather than being causal. Findings in a recent case–control study that the risk of Alzheimer's disease rose with increasing number of siblings add to the evidence that the early environment may affect susceptibility to neurodegeneration, though whether this relation was due to poorer brain growth rates in larger families is unclear (Moceri *et al*., 2000). We had limited information on our participants' environment in the first few years of life, but the associations found here between head size and cognitive function persisted after adjustment for the father's social class at the time of birth.

Brain size is related to intelligence test scores in young adults (Wickett *et al*., 2000), so the associations found between head circumference, or intracranial capacity, and cognitive test scores in elderly people may reflect the long-term stability of individual differences in mental ability (Deary *et al*., 2000). However, the observation in our study that elderly people with a larger head circumference were less likely to show a decline in memory performance over a 3.5-year follow-up period suggests that optimal brain development during early life may also protect against cognitive decline. This finding is consistent with results from some other studies that suggest that a larger brain may protect against the clinical manifestations of dementia. In a cross-sectional study of over 600 elderly people, the risk of Alzheimer's disease was highest in those with the smallest head circumferences (Schofield *et al*., 1997). Small head circumference was associated with an increased incidence of Alzheimer's disease in a cohort of around 2000 people, though only in those who had the APOE ε4 allele (Borenstein Graves *et al*., 2001). A smaller premorbid brain size, as estimated by cross-sectional area on CT sections, was associated with a younger age at onset of symptoms of Alzheimer's disease in a retrospective case series (Schofield *et al*., 1995). Two case–control studies, however, have found no association between total intracranial volume, as measured by MRI, and Alzheimer's disease (Jenkins *et al*., 2000; Edland *et al*., 2002).

The results of this study suggest that brain development during infancy and early childhood is more important than foetal growth in determining how well cognitive abilities are preserved in old age. Factors that promote brain growth during this period may help to protect against cognitive decline.

Acknowledgements

We are grateful to the men and women who took part in our study. The study was funded by the Wellcome Trust, the Medical Research Council and the Sir Jules Thorn Trust.

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Received February 25, 2003. Revised April 28, 2003.
Accepted May 7, 2003