Articles

An association between head circumference and Alzheimer's disease in a population-based study of aging and dementia

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Article abstract—We investigated the association between head circumference (HC) and Alzheimer's disease (AD) in a cross-sectional population-based study of aging in North Manhattan. Six hundred forty-nine subjects underwent neurologic, neuropsychological, and anthropometric evaluations; apolipoprotein E (apoE) genotype was available for a subsample of 300 individuals. Logistic regression analyses were performed with AD the outcome of interest to evaluate any association between HC and AD. In these analyses, HC evaluated as a continuous variable was associated with AD (OR 0.8, 95% CI 0.7–0.9) after adjusting for age, education, and ethnicity, gender, and height. Analyses suggested that increased risk resided mainly in those with smallest HC. Thus, women whose HC was within the lowest quintile of HC for women were 2.9 (95% CI 1.4–6.1) times more likely to have AD, after adjusting for age, education, and ethnicity; and men in the lowest quintile of HC (for men) were 2.3 times more likely to have AD (95% CI 0.6–9.8). There was no confounding by height, weight, or apoE genotype. The results are consistent with previous studies that suggest that premorbid brain size may influence the age-specific risk for AD. Future epidemiologic studies seeking environmental risk factors for AD may benefit by making HC measurements on all subjects to decrease the variance associated with other potential risk factors.

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The results from several studies suggest that risk for Alzheimer's disease (AD) may be associated with premorbid brain size. In a study of nursing home residents who underwent regular neuropsychological evaluations, Katzman et al.[1] identified a subgroup with larger brains who had normal cognition prior to death, despite autopsy evidence of underlying AD. The finding suggested that brain size might be an important determinant of "reserve" influencing the timing of onset of clinical disease in patients with AD. In a study conducted on a convenience sample of 28 white and African-American women, all with AD, we found that the age at onset of symptoms of AD correlated significantly with an index of premorbid brain size derived from CT scans: subjects with larger brains had later onset of symptoms, perhaps a reflection of increased "reserve."[2] In a recent study of 1,985 Japanese-Americans over 65 years of age who underwent screening with the Cognitive Screening Abilities Instrument (CASI),[3] Graves et al.[4] obtained subjects' head circumference (HC) measurements as a correlate of premorbid brain size. Analyses adjusted for age, gender, and education showed that subjects with AD and smaller HC performed more poorly on the CASI than subjects with AD and larger HC, consistent with the hypothesis that premorbid brain size may influence the clinical course of the disease.

In the present study, we assessed premorbid brain size as a possible risk factor for AD; to this end, we used HC as an index of premorbid brain size, a somewhat imprecise measure, but one adequate for our purposes.[5] By contrast with our earlier study, which was based on a highly select sample of women from a memory disorders clinic,[2] the current study employed data from a large, representative sample, including men and women, three different ethnic groups, and control subjects derived from the same population base.

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Methods. *Subjects.* Data were derived from the North Manhattan Aging Project.[6] Subjects evaluated in the survey component of this study comprise a random sample of medicare recipients aged 65 years or more who reside within a well-defined geographic region in upper Manhattan. Ethnicity was determined by self report, or report from a close relative in cases of dementia, according to guidelines proposed by the bureau of census.[7]

Anthropometric measures. HC was measured to the nearest 0.5 cm by placing a flexible fabric tape measure around the head, above the eyebrows and over the occipital protuberance. Measurements were made by testers who did not participate in subjects' cognitive evaluations. Height was measured using a stadiometer. When subjects were unable to stand because of frailty or other reasons, the knee length was measured, and an estimated height calculated using the formula of Chumlea et al.[8] Weight was measured using a scale-tronix 5600 portable stand-on scale.

ApoE status. ApoE allele type was determined by a previously reported method.[9]

Diagnostic evaluation. All subjects in the survey sample were assessed at entry into the study with a cognitive screening evaluation,[10] based on the Comprehensive Assessment and Referral Interview,[11] and subsequently subjects also underwent a neuropsychological evaluation, which has been described in more detail elsewhere.[12,13] Briefly, the neuropsychological evaluation includes tests of short- and long-term memory,[14,15] orientation, abstract reasoning,[16,17] language,[18-20] and construction.[21] All subjects who meet neuropsychological criteria for dementia, based on a rigidly defined paradigm of test cut scores, are also referred for evaluation by a clinician who determines if there is evidence of functional impairment due to cognitive decline, an additional requirement for a definitive diagnosis of dementia. In addition, all subjects scoring three or more on the cognitive screen, and a randomly selected 25% of subjects who score two or less, are also referred for evaluation by a clinician.[13] All data from neuropsychological and clinical evaluations are reviewed at a consensus conference at which the definitive diagnoses are determined. The diagnosis of probable or possible AD is made according to the guidelines of the NINCDS-ADRDA,[22] and each subject is assigned a Clinical Dementia Rating (CDR)[23] to reflect the severity of cognitive impairment (nondemented CDR = 0, mildly demented CDR = 1, moderately demented CDR = 2, etc.). Subjects were included in the current study if they had a completed diagnostic evaluation, a CDR score, HC measurement, and if they were of Hispanic, African-American, or white ethnicity.

Statistical analyses. We used t tests or chi-square to compare the mean age, years of education, height, weight, head circumference, and the frequency of dementia and of AD specifically, in the three ethnic groups, separately in men and women. To evaluate the association between HC and AD we used two analytic strategies: first, with HC as a categorical variable, second with HC as a continuous variable. In all analyses, all nondemented subjects in the sample under study were used as controls.

HC as a categorical variable. For each study sample under analysis we created quintiles, defined by HC (explained in greater detail later). We performed chi-square analyses initially, then logistic regression analyses with AD the outcome, to assess the association between HC (as a categorical variable) and AD. The logistic analyses were performed separately in men and women, and then, in addition, separately within ethnic-gender strata. All logistic models included age (as a continuous variable) and education (years of formal education) as potential confounders and, whenever appropriate, gender and ethnicity, as specified in the results section. Additional logistic models were also constructed to evaluate weight, height, and apoE status as potential confounders.

HC as a continuous variable. We assessed the association between HC and AD in an analysis of covariance (ANCOVA), and then in logistic regression analyses. We used the ANCOVA to compare the group mean HC of AD cases with the group mean HC of nondemented subjects, adjusted for age, education, gender, and ethnicity. We used logistic analyses to obtain adjusted risk estimates for AD associated with HC, and to evaluate age, education, gender, height, weight, and apoE as potential confounders of the association between HC and AD.

Results. Of the 2,128 subjects who took the cognitive screening evaluation, at the time of this study 677 had completed a diagnostic assessment. Twenty-eight of these subjects were excluded from subsequent analyses because of unknown CDR (n = 16), HC (n = 7), or ethnicity (n = 5). The current study is based on the remaining 649 subjects, of whom 375 underwent a clinician's evaluation in addition to the neuropsychological assessment. A total of 71% of subjects were female. The sample comprised 44% Hispanics, 35% African-Americans, and 21% whites; Hispanics had fewer years of education than whites. The mean age of the sample was 78.3 years (SD, 6.4) (table 1). Dementia was present in 84 (11%) subjects, and could not be determined in one subject because of aphasia. Dementia was due to probable AD in 59 subjects and possible AD in 16. Demented subjects were older (84.0 versus 77.8 yr, $p < 0.001$) had fewer years of schooling (5.8 versus 8.9, $p < 0.001$), and were more likely to be Hispanic (chi-square $p < 0.01$) than nondemented subjects. Because we were interested in the association between HC and AD, nine subjects with non-AD dementia were excluded from the subsequent analyses. We combined probable and possible AD cases into a single diagnostic category because both categories shared a similar relation to HC in our data, as indicated later.

For anthropomorphic measures, there were significant gender and ethnic differences with respect to height, weight, and head circumference (see table 1). Subjects with AD were significantly shorter ($p < 0.01$), lighter ($p < 0.001$) and had smaller HC ($p < 0.001$) than nondemented subjects.

Head circumference (categorical) and dementia: univariate analyses. Because of significant gender differences in HC, we performed univariate analyses within strata defined by gender. For each gender, we divided the population into approximate quintiles based on HC, and determined the frequency of AD within each quintile (figure). Among women, there was a highly significant trend toward increasing frequency of AD from the quintile of greatest HC to the quintile of smallest HC (Mantel-Haenszel [MH] test for linear association $p < 0.001$). In a similar analysis among men, there was no significant trend (MH test for linear association $p = 0.18$). Because of

***Table 1** Subject characteristics*

	Females (n = 462)			Males (n = 187)			
	White (n = 88)	African-American (n = 159)	Hispanic (n = 215)	White (n = 46)	African-American (n = 70)	Hispanic (n = 71)	All (n = 649)
Age (yr) mean (SD)	79.5 (7.5)	79.3 (6.7)	77.9 (6.3)	77.0 (5.7)	77.1 (4.9)	77.3 (5.9)	78.3 (6.4)
Ed (yr) mean (SD)	12.0 (3.4)	9.7† (3.8)	6.1*† (4.0)	12.3 (3.9)	9.4† (3.9)	6.6*† (4.0)	8.6 (4.5)
HC (cm) mean (SD)	54.9* (1.9)	55.5 (1.9)	54.1*† (1.7)	56.8 (1.7)	57.6 (1.8)	56.2* (1.9)	55.4 (2.2)
Height (cm) mean (SD)	154.7* (7.4)	159.0 (6.4)	153.4* (6.5)	170.8 (6.1)	174.5 (10.5)	169.9* (14.1)	160.3 (11.3)
Weight (lb) mean (SD)	145.7* (46.4)	158.6 (37.3)	145.2* (29.3)	170.0 (25.6)	178.1 (36.8)	158.1* (21.0)	155.3 (35.7)
Dementia no. (%)	4 (5)	21 (13)	42 (20)‡	1 (2)	6 (9)	10 (14)	84 (12.9)
AD no. (%)	4 (5)	19 (12)	37 (18)‡	1 (2)	5 (7)	9 (13)	75 (11.6)

* Significantly lower/less than for African-Americans of same sex; Bonferroni correction $p < 0.05$.
† Significantly lower/less than for whites of same sex; Bonferroni correction $p < 0.05$.
‡ Chi-square $p < 0.01$ (conducted separately within men and women).

Ed = education; HC = head circumference; AD = probable or possible Alzheimer's disease.

ethnic differences in AD frequency and mean HC, we repeated our analyses after further stratifying by ethnicity. For these analyses, approximate quintiles of HC were uniquely determined from the data for each gender-ethnic stratum. Subjects were then reclassified on the basis of their HC into the appropriate quintile of HC, given their gender and ethnicity. Of the 129 subjects in the quintile of lowest HC for their gender and ethnic group, 25 (19%) had AD, compared with 11% with AD in the second, 12% in the third, 11% in the fourth, and 6% in the fifth quintile of largest HC (chi-square $p = 0.02$, MH test for linear association $p = 0.002$).

Head circumference (categorical) and AD: multivariate analyses. To obtain adjusted risk estimates for the association between HC and AD, we undertook logistic regression analyses with the outcome AD. We performed separate analyses for men and women, always adjusting for age and education, and adjusting for ethnicity in all analyses not restricted to a single ethnic stratum. In a preliminary logistic analysis restricted to all women, in which the quintile of largest HC defined the referent group, risk of AD was increased for the quintile of smallest HC (OR 2.5, 95% CI 0.8–7.4), but not for the second smallest (OR 0.8), third (OR 0.8), or fourth quintiles (OR 0.8). These results suggested that increased risk for AD lay predominantly within the quintile of smallest HC and that it would be appropriate to combine subjects in the upper four quintiles of HC into a single referent category in subsequent analyses. In logistic regression analyses, women in the quintile of smallest HC were 2.9 times more likely to have AD (OR 2.9, 95% CI 1.4–6.1) than those in the upper four quintiles. In a separate analysis among men, lowest quintile of HC was associated with 2.3 times the risk for prevalent AD compared with the upper four quintiles; however, this was not statistically significant (OR 2.3, 95% CI 0.6–9.8). We then performed similar logistic analyses separately within each of the six strata defined by both gender and ethnic group. In each logistic analysis, the referent group comprised subjects whose HC lay within the upper four quintiles of HC determined uniquely for the restricted sample under study—a division that was approximate, however, because HC had been recorded to the nearest 0.5

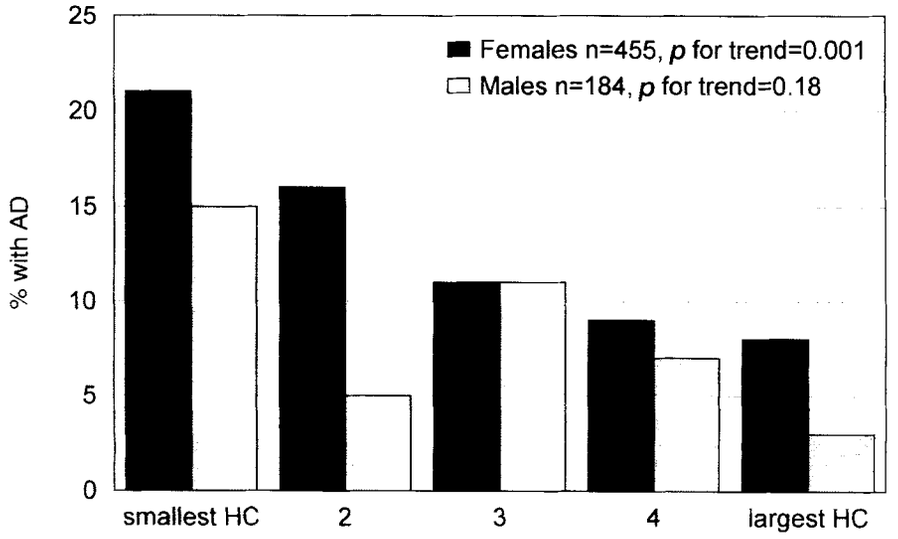

Figure. Frequency of Alzheimer's disease according to head circumference (HC) by gender.

Table 2 *Odds ratio for Alzheimer's disease associated with lowest quintile of head circumference* vs upper four quintiles, adjusted for age, education*

Analytic sample	Head circ* (cm)	Number‡ (%)	OR (95% CI) for AD	OR (95% CI) for AD CDR = 1
All women†	≥53.5	349 (77)	1 (reference)	1 (reference)
	<53.5	106 (23)	2.9 (1.4–6.1)	2.4 (1.1–5.6)
African-American women	≥54.5	117 (75)	1 (reference)	1 (reference)
	<54.5	40 (25)	2.1 (0.7–6.6)	2.4 (0.6–9.6)
White women	≥53.5	69 (78)	1 (reference)	1 (reference)
	<53.5	19 (22)	4.5 (0.2–100.5)	4.5 (0.2–100.5)
Hispanic women	≥53.0	166 (79)	1 (reference)	1 (reference)
	<53.0	44 (21)	3.1 (1.2–8.1)	2.1 (0.7–6.7)
All men†	≥55.5	151 (82)	1 (reference)	1 (reference)
	<55.5	33 (18)	2.3 (0.6–9.8)	4.0 (0.9–18.3)
African-American men	≥56	53 (78)	1 (reference)	1 (reference)
	<56	15 (22)	1.0 (0.1–9.8)	1.0 (0.1–9.8)
White men	≥55.5	36 (78)	1 (reference)	1 (reference)
	<55.5	10 (22)	No estimate	No estimate
Hispanic men	≥55.5	50 (71)	1 (reference)	1 (reference)
	<55.5	20 (29)	4.3 (0.8–22.5)	13.2 (1.3–132)

* Lowest quintile for the population strata included in the analysis.
† Adjusted for ethnicity.
‡ Number of subjects in analyses for AD of any severity.

AD = probable or possible Alzheimer's disease; CDR = Clinical Dementia Rating.

cm. The results of these analyses are presented in table 2. For each analytic sample (e.g., African-American) we specify the HC that defined the referent group (e.g., for African-American women it was HC ≥ 54.5) and what proportion of the analytic sample the referent group represented (e.g., for African-American women it was 75%). Estimates of risk for AD associated with the lowest (approximate) quintile of HC compared with the risk for subjects in the upper (approximate) four quintiles of HC were similar among African-American women (OR 2.1, 95% CI 0.7–6.6), white women (OR 4.5, 95% CI 0.2–100.5), and Hispanic women (OR 3.1, 95% CI 1.2–8.1) (see table 2). Among men, the analyses were limited by small numbers. Risk associated with lowest quintile HC was not elevated in African-Americans, could not be calculated because of insufficient data in whites, but was elevated in Hispanics. Because of possible confounders, we repeated our analyses including nondemented subjects and only AD cases with CDR of one—our best available index of incident cases—but there was little change in the risk estimates compared with those obtained in the entire prevalent sample (see table 2). Because the relationship between HC and AD might have been driven by inclusion of subjects with unrecognized mild mental retardation, with HC smaller than cognitively normal subjects,[24,25] we performed analyses restricted to women who had completed at least 9 years of formal education; the risk associated with lowest quintile of HC remained significantly elevated (OR 5.9, 95% CI 1.5–24.5). As an alternative means of excluding potential cases with mild static encephalopathy we excluded cases of AD with CDR 1. Once again, the risk in women associated with lowest quintile HC remained significantly elevated (OR 4.1, 95% CI 1.4–11.6).

HC is strongly correlated with height and weight,[26] which might have been confounders in our analyses. Because AD is also associated with weight loss,[27,28] it would have been inappropriate to evaluate current weight in all subjects as a risk factor or confounder for the association between HC and AD. Fortunately, we had a history of recent weight loss or no recent weight loss from 544 subjects, and the usual weight by history of those who reported weight loss. We defined "common weight" as the measured weight in subjects with no recent weight loss, and the reported usual weight in subjects with recent weight loss. In logistic analyses adjusting for age, education, ethnicity, height, and common weight there was no association between common weight or height and prevalent AD, and the risk associated with lowest quintile of HC remained similar to previous estimates in both men (OR 2.7, 95% CI 0.6–12.8) and women (OR 2.4, 95% CI 1.0–5.6). Next, we performed logistic analyses among all women subjects with a history of no weight loss. In these analyses, lowest quintile HC remained a significant risk factor for prevalent AD (OR 2.9, 95% CI 1.1–7.4). In a separate analysis restricted to the 52 women subjects with a known history of weight loss, the point estimate for risk was higher, but did not reach statistical significance (OR 3.8; 95% CI, 0.8–18.5).

Recent studies have demonstrated a significant association between IQ and brain size measured by MRI within young adult populations.[26,29-31] If premorbid IQ were related to HC in our population, it might confound the asso-

Table 3 Results of logistic regression analyses predicting AD (possible or probable)

Variable	All subjects with known height (n = 628)		Subjects in whom common weight and apoE genotype known (n = 192)	
	Univariate odds ratio (95% CI)	Adjusted odds ratio (95% CI)	Univariate odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age	1.2 (1.1–1.2)	1.2 (1.1–1.2)	1.2 (1.1–1.2)	1.2 (0.6–9.3)
Gender				
Male	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Female	1.7 (1.0–3.1)	0.6 (0.2–1.4)	2.2 (0.8–6.2)	2.2 (0.2–30.8)
Education (yr)	0.9 (0.8–0.9)	0.9 (0.8–1.0)	0.9 (0.8–1.0)	0.9 (0.8–1.1)
Ethnicity				
White	1 (reference)	1 (reference)	1 (reference)	1 (reference)
African-American	3.0 (1.2–8.3)	4.5 (1.4–15.0)	4.5 (0.9–21.4)	4.6 (0.4–48.1)
Hispanic	5.1 (2.0–13.1)	4.9 (1.4–16.4)	6.00 (1.3–27.4)	6.0 (0.5–69.1)
Head circumference (cm)	0.8 (0.7–0.9)	0.8 (0.7–1.0)	0.8 (0.7–1.0)	0.8 (0.6–1.3)
Height (cm)	0.9 (0.9–1.0)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.0 (0.9–1.1)
Common weight (lb)*			1.0 (1.0–1.0)	1.0 (1.0–1.0)
ApoE				
No $\epsilon 4$			1 (reference)	1 (reference)
One or two $\epsilon 4$			2.0 (0.8–4.5)	2.4 (0.6–9.3)

* Common weight = measured weight if no recent weight loss, otherwise = reported usual weight.

ciation between HC and AD. To explore this possibility, we evaluated the relationship between performance on the Similarities subtest of the WAIS-R (the only WAIS-R test item in our neuropsychological test battery) and HC among nondemented subjects. In ANCOVAs adjusted for age, education, and ethnicity, the adjusted group mean performance on the Similarities subtest did not differ for lowest quintile HC subjects compared with those from the upper four quintiles of HC in either men or women, providing limited evidence that premorbid cognitive ability could not be a confounder in our analyses.

ApoE genotype was available for a subsample of 300 subjects. ApoE status was not a confounder of HC in logistic analyses that evaluated risk for AD associated with lowest quintile of HC adjusted for age, education, and ethnicity.

Head circumference (continuous variable). In an ANCOVA adjusted for age, gender, education, and ethnicity, the group mean HC of AD cases was 0.62 cm less than that of controls ($p = 0.01$). When the ANCOVA was restricted to nondemented subjects and AD subjects with CDR of 1, the adjusted group mean difference in HC was 0.57 cm ($p = 0.04$). If weight loss, more common in patients with AD, caused loss of subcutaneous scalp fat, this might explain a smaller mean HC in subjects with AD. To explore the possibility that weight loss might decrease the HC, we performed analyses among nondemented subjects. In ANCOVAs adjusted for age, gender, education, and ethnicity, a history of weight loss was associated with a significant group mean difference in (measured) weight (−13.8 lb, $p = 0.004$), but no significant group mean difference in HC (−0.27 cm, $p = 0.26$). This result, together with the results of the previous separate logistic analyses of subjects with and without a history of weight loss, indicates that the association between smaller HC and AD was not an artifact of weight loss secondary to AD.

Although our analyses suggested that AD was most associated with lowest quintile HC and that the "categorical HC" approach to analysis was more appropriate, we also performed logistic regression analyses with HC as a continuous variable. This permitted us to pool data from both sexes in a single logistic model, and to re-evaluate potential confounders. We also used this approach to assess HC as a predictor, separately, of possible AD, and probable AD; we obtained similar point estimates of risk in both models, adjusted for age, education, gender, and ethnicity (OR for possible AD 0.8, 95% CI 0.5–1.2, OR for probable AD 0.8, 95% CI 0.7–1.0). The results of other analyses are presented in table 3. Because common weight and apoE status were unknown for many subjects, statistical power was significantly reduced for the most complete logistic regression model, which included both these variables. Therefore, we present the results of the logistic regression analysis conducted in the full population, which does not include these variables, and also the results from the most complete model, which derives from a much smaller sample. Risk estimates for univariate and adjusted logistic models are presented in each table. The risk associated with HC was similar in univariate and adjusted analyses, and in less complete multivariate models not presented here, indicating a lack of confounding by other variables according to the criteria of Kleinbaum et al.[32]

Discussion. In a cross-sectional analysis, we have demonstrated an association between small HC and increased prevalence of AD. The result suggests that small premorbid brain size may be a significant risk

factor for AD but to sustain this view, we need to resolve some important questions.

Does HC remain constant over time, or could AD cause a decrease in HC, explaining the association we observed and invalidating HC as a potential risk factor in cross-sectional studies? Unfortunately, we are aware of no longitudinal studies in which the HC of fully grown adults was measured repeatedly. We demonstrated that weight loss, more common in AD, seems unassociated with significant reductions in HC. But, could the *bony* cranial dimensions of subjects with AD actually decrease as a consequence of the cerebral atrophy that accompanies the disease? Longitudinal CT studies of AD subjects have not suggested that the cranial dimensions decrease with progression of the disease.[33-35] Nevertheless, if AD caused a slight reduction in skull size, a small mean difference in HC between cases and controls might arise. In our study, however, AD was particularly associated with the lowest quintile of HC. Very substantial reductions in skull size due to AD would be necessary to produce this result, if premorbid HC were unrelated to AD risk, and such changes should have been detected by longitudinal quantitative imaging studies.

Is HC a satisfactory proxy for premorbid brain size? Estimates of the correlation between HC and brain size lie between 0.2 and 0.8.[5,26] Skull thickness may differ by gender and ethnicity,[36,37] so the scaling factor between HC and brain size probably differs by gender and ethnicity also. Because of this we stratified our analyses. The correlation between HC and brain size may be less in men than in women,[29] and nondifferential misclassification of brain size by HC may therefore have been greater among men, perhaps accounting for the somewhat lower risk estimates associated with lowest quintile HC for men compared with women. Because there were fewer men in the analyses, our power to detect an effect in men was also less.

Did we overlook important potential confounders? Neither ethnicity, height, weight, educational attainment, nor apoE status were confounders in the association between HC and AD. Premorbid cognitive capacity was a potential confounder for which it was more difficult to control. Subjects with AD, but high premorbid IQ, might maintain neuropsychological test performance within a nondemented range longer into the illness, delaying the diagnosis of dementia in our study. High premorbid cognitive ability might thus function as a protective factor and, because of the known association with brain size, meet criteria as a potential confounder. In previous studies, the correlation between HC and measures of intelligence has ranged from 0.08 to 0.22.[38] In our study, analyses restricted to the nondemented subjects showed no association between HC and performance on a WAIS-R subtest; this suggests that HC and cognitive capacity were not significantly associated in our population.

In their study of 1,985 Japanese-Americans, of whom 382 received clinical and neuropsychological evaluations, Graves et al.[4] found that HC predicted severity of dementia in subjects with probable AD, with smallest HC predicting greatest impairment. However, HC was not associated with AD within their entire study sample after adjustment for age, gender, and educational attainment, a finding contrary to their expectations and at variance with our results. The authors speculated that excess mortality in AD subjects with smaller HC, relative to AD subjects with larger HC, might account for this negative finding in their study, which included prevalent cases of AD. In support of this interpretation, they cite evidence suggesting that smaller, lighter people experience excess mortality compared with taller, heavier individuals (who might be expected to have greater HC).[39] We cannot readily explain the discrepancy between the results of this study and ours, although ethnic and other demographic differences may have been important.

Certainly, all studies, such as ours, that assess risk factors in relation to prevalent cases of disease may be biased by differential mortality. For instance, small HC might appear to be a risk factor for AD if it were associated with a survival advantage to individuals with AD (Graves et al.[4] argued that the reverse was actually probable). Studies of incident disease avoid this problem of interpretation. Although we did not have incident data in the current study, we performed one set of analyses that included cases with mild AD only (CDR = 1) and obtained risk estimates associated with HC similar to those obtained in the entire prevalent sample. We conclude that differential mortality by HC is unlikely to account for our findings.

Our results are compatible with at least three different mechanisms. First, small brain size might be a trait determined by genetic factors that also increase susceptibility to AD. In this study we sought, but found no evidence for, an association between HC and the presence of the apoE $\epsilon 4$ allele, the genetic marker most strongly associated with risk for AD.[40] Second, small brain size might reflect exposures to environmental factors that occur during the period of brain maturation and growth and increase risk of AD independently of their effect on brain size. Previous investigators have identified low educational attainment as a possible risk factor for AD.[41-47] Some have suggested that low educational attainment may be a proxy for early life exposure to nutritional deprivation or other factors that increase risk for AD.[48,49] The association between brain size and AD might be interpreted similarly. In our study, the association between brain size and AD was present after adjusting for educational attainment: if brain size and educational attainment are proxies for early life exposures, the nature of these exposures might be different. Finally, brain size might determine "reserve," as suggested by the findings of Katzman et al.[1] and Schofield et al.,[2] and early life exposures might increase risk for clinically apparent AD as a

direct consequence of their impact on brain growth and development.

In this study, there was no association between HC and either educational attainment or (our index of) premorbid cognitive capacity, two characteristics that might determine "reserve," because they influence the level of premorbid cognitive performance. Because HC did not appear to be a proxy for premorbid cognitive ability in our sample—at least to the limited extent that we could assess this—our results suggest that brain size might mediate reserve by an independent mechanism based on structure. In a direct sense, brain size might determine reserve because more neurons, more synapses, or more neural pathways might permit function longer into the illness. Some other structural characteristic of larger brains might be protective, however, such as a higher ratio of glia to neurons.[50-52]

Structural brain reserve might be important at one or more phases of the disease. Low reserve might abbreviate the preclinical phase or increase the rate of cognitive decline once this becomes apparent, or both. In future studies, we plan to investigate whether the rate of cognitive decline differs according to an index of premorbid brain size in individuals with cognitive impairment or AD.

Increased risk for AD was associated with lowest quintile HC, perhaps reflecting low "structural brain reserve." Investigators who seek new risk factors for AD in large epidemiologic studies might benefit by obtaining HC measurements in all study subjects. HC measurements may provide an important index of risk for AD, and help investigators estimate the risk associated with other factors with greater precision.

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