Knee height and arm span: A reflection of early life environment and risk of dementia

T. L. Huang, M. C. Carlson, A. L. Fitzpatrick, L. H. Kuller, L. P. Fried and P. P. Zandi

Neurology 2008;70;1818-1826
DOI: 10.1212/01.wnl.0000311444.20490.98

Knee height and arm span

A reflection of early life environment and risk of dementia

T.L. Huang, PhD
M.C. Carlson, PhD
A.L. Fitzpatrick, PhD
L.H. Kuller, MD, DrPh
L.P. Fried, MD, MPH
P.P. Zandi, PhD

Address correspondence and reprint requests to Dr. Tina L. Huang, Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Dietary Assessment & Epidemiology Research Program, 9th Floor, 711 Washington St., Boston, MA 02111
tina.huang@tufts.edu

ABSTRACT

Objectives: To determine if anthropometric measures, as markers of early life environment, are associated with risk of dementia, Alzheimer disease (AD), and vascular dementia (VaD).

Methods: A total of 2,798 subjects were followed as part of the Cardiovascular Health Cognition Study for an average of 5.4 years; 480 developed dementia. Knee height was measured 3 years prior to and arm span 4 years after the study's baseline. Cox proportional hazard models were used to examine their association with subsequent risk of dementia, AD, and VaD.

Results: Among women, greater knee height and arm span were associated with lower risks of dementia (knee height: HR per 1-inch increase 0.84; 95% CI 0.74–0.96; arm span: HR per 1-inch increase 0.93; 95% CI 0.88–0.98) and AD (knee height: HR per 1-inch increase 0.78; 95% CI 0.65–0.93; arm span: HR per 1-inch increase 0.90; 95% CI 0.85–0.96). Women in the lowest quartile of arm span had ~1.5 times greater risk of dementia (HR 1.45; 95% CI 1.03–2.05) and AD (HR 1.70; 95% CI 1.10–2.62) than other women. Among men, only arm span was associated with lower risks of dementia (HR per 1-inch increase 0.94; 95% CI 0.89–1.00) and AD (HR per 1-inch increase 0.92; 95% CI 0.84–1.00). For each gender, knee height was not associated with VaD, while arm span was associated with a nonsignificant lower risk of VaD.

Conclusions: Our findings with knee height and arm span are consistent with previous reports and suggest early life environment may play an important role in the determination of future dementia risk. ***Neurology*® 2008;70:1818–1826**

GLOSSARY

3MSE = Modified Mini-Mental State Examination; **AD** = Alzheimer disease; **ADDTC** = Alzheimer's Disease Diagnostic and Treatment Centers; **CHS** = Cardiovascular Health Study; **DSM-IV** = *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition; **MMSE** = Mini-Mental State Examination; **NINCDS-ADRDA** = National Institute of Neurological and Communicative Diseases and Stroke–Alzheimer's Disease and Related Disorders Association; **NINDS-AIREN** = National Institute of Neurological Diseases and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences; **VaD** = vascular dementia.

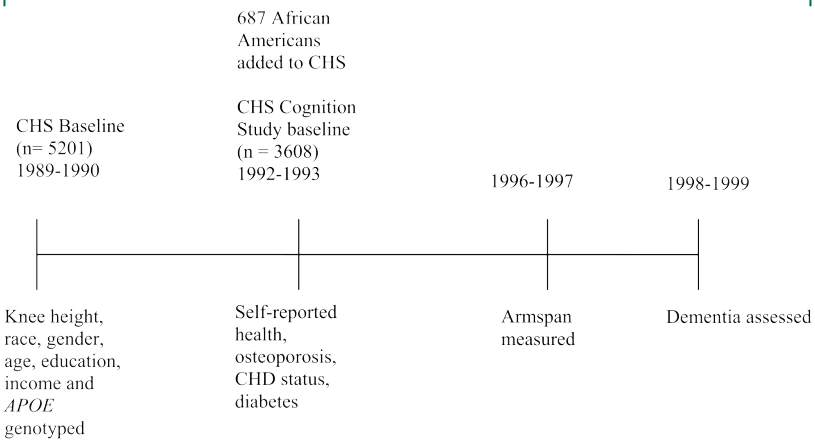
Several studies have suggested that early life environment plays a role in susceptibility to chronic disease in later life.[1] Small size at birth and during childhood is associated with cardiovascular disease, hypertension, and type 2 diabetes.[1-7] Early life environment may also modify an individual's risk for developing neurologic disorders, such as Alzheimer disease (AD). Studies using census data, birth certificates, or information from proxies to characterize early life exposures showed that people whose fathers were unskilled laborers,[8] as well as those who came from homes with a greater number of dependents,[8,9] had a higher risk of developing AD. Growing up in the suburbs prior to age 18 was also associated with a lower risk of AD.[9] While these indicators of socioeconomic status are unlikely to be the direct cause of AD, they may be markers for underlying risk factors during growth and critical brain development throughout adolescence. Both behavioral and

From Jean Mayer USDA Human Nutrition Research Center on Aging (T.L.H.), Boston, MA; Johns Hopkins Bloomberg School of Public Health (M.C.C., P.P.Z.), Baltimore, MD; Department of Mental Health, University of Washington (A.L.F.), Seattle; University of Pittsburgh (L.H.K.), PA; and Johns Hopkins Department of Medicine (L.P.F.), Baltimore, MD.

T.L.H. was supported by NIH grant T32-MH14592 and NIH/NIDDK grant T32 DK75610, a grant from the Charles A. King Trust, Bank of America, Co-Trustee (Boston, MA), and by the USDA Agricultural Research Service under contract no. 53-3K06-5-10. The research reported in this article was supported by contracts N01-HC-85079 through N01-HC-85086, N01-HC-35129, and N01 HC-15103 from the National Heart, Lung, and Blood Institute, and grant AG15928 from the National Institute on Aging.

Disclosure: The authors report no conflicts of interest.

Figure Timeline of the Cardiovascular Health Study



postmortem data suggest that the pathology of AD may begin early in life.[10,11] Markers of linguistic ability in the diaries of nuns in their early 20s were associated with a decreased risk of the disease,[10] and in a separate study where neuropathologic hallmarks of AD were measured by age, neurofibrillary tangles and amyloid deposits were evident in young adults.[11] Thus deficits or injury in childhood or adolescence may predispose a person to neurodegeneration in later life.

Given that risks associated with dementia may occur early in life, researchers have looked for biologic indicators of early deficits, such as anthropometric measures. Shorter leg length, arm span, and maximal adult height have already been shown to be associated with cognitive impairments in late life in several studies.[12-17] Differences in these anthropometric measures may reflect nutritional or other deficits throughout childhood.[14] Thus, these studies suggest that deprivation during the critical growing years has the potential to place an individual at greater risk for cognitive deficits in later life.

Three previous studies that specifically examined the association of leg length and arm span with dementia were in populations from Asia.[14-16] We further sought to examine these relationships in an American population followed as part of the Cardiovascular Health Study (CHS). This study offers a large national sample of both men and women with a long period of follow-up, enabling us to address how differences in knee height and arm span may be related to risk of developing dementia in late life.

METHODS

Study overview. The CHS is a multisite prospective, observational study designed to investigate risk factors for cardiovascular disease in adults aged 65–101 at baseline.[18] The CHS recruited 5,888 participants from age-stratified Medicare eligibility lists in four US communities: Forsyth County, NC, Washington county, MD, Sacramento County, CA, and Pittsburgh, PA.[19] The original cohort of 5,201 participants was recruited in 1989–1990 and an additional 687 African Americans were recruited in 1992–1993 at three of the sites (Forsyth County, Sacramento, and Pittsburgh) (see the figure for clarification of timeline). The CHS Cognition Study, an ancillary study of CHS to investigate risk factors for dementia, included the subset of 3,608 participants who underwent MRI during 1992–1993 and a concurrent Mini-Mental State Examination (MMSE)[20] to assess global cognition. The institutional review board at each center approved the study, and all participants signed an informed consent at entry and at specified intervals during the course of the study.

Assessment of exposures. As part of the CHS, participants came into the clinical centers for up to 11 annual examinations through 1998–1999 (figure). Data collected at these examinations included demographics, anthropometry, blood pressure, medical history and behaviors, physical function, medications, and psychosocial interviews to assess depression.[18] Cognitive function was measured using the MMSE at baseline and the Modified Mini-Mental State Examination (3MSE) at all follow-up examinations.[21] Cerebral MRI were completed twice, in 1992–1993 and again in 1997–1998.[22] Phlebotomy was done at several examinations during the study, and after collecting informed consent for use of DNA, *APOE* genotype was determined from the 91.5% of subjects who consented to DNA analysis. Surveillance of mortality, cardiovascular outcomes, and all hospitalizations were conducted throughout study follow-up.[23]

Knee height was measured in 1989–1990, and arm span was measured in 1996–1997 (figure). Knee height was defined as the distance from the sole of the foot to the anterior surface of the thigh, with the ankle and knee each flexed to a 90-degree angle. It was measured on each of the participants while supine on the examination table using a sliding caliper on the left leg. Arm span was measured with the participant standing with arms outstretched to either side of the body parallel to the floor, and was defined as the distance between fingertips.

Evaluation of dementia. Detailed methods for classifying dementia in the CHS Cognition Study have been reported elsewhere.[24] In brief, in 1998–1999, participants were screened as being at high risk for dementia using the 3MSE, medical records review, and several other cognitive tests gathered throughout the study. At three of the four sites, all individuals considered at high risk of dementia, all minority participants, those with a history of stroke, and those residing in nursing homes were included for additional data collection to assess cognitive status. Participants were invited to come into the clinic for neuropsychological testing or were

Table 1 Anthropometric measures by characteristics, mean inches (SD)

	Men				Women			
Age, y	No.	Knee height	No.	Arm span	No.	Knee height	No.	Arm span
60–70	405	20.90 (1.11)*	329	68.71 (3.00)*	700	19.07 (1.01)*	612	62.62 (3.12)*
70–80	637	20.77 (1.12)	458	67.96 (3.26)	821	19.00 (1.12)	632	62.02 (3.31)
80–90	98	20.68 (1.09)	54	66.66 (4.23)	120	18.81 (0.98)	62	61.30 (3.31)
Race†								
White	1037	20.77 (1.10)*	763	67.98 (3.19)*	1450	18.97 (1.05)*	1147	61.96 (3.10)*
Black	98	21.21 (1.14)	74	70.20 (3.47)	184	19.38 (1.07)	154	64.56 (3.40)
Education‡								
8th grade or less	114	20.44 (1.05)*	76	67.98 (2.91)*	150	18.69 (1.14)*	112	61.71 (3.53)*
9th–12th grade/GED	394	20.66 (1.09)	282	67.88 (3.30)	735	18.90 (0.99)	593	62.22 (2.98)
Vocational school	92	20.69 (1.07)	74	67.89 (3.52)	161	19.15 (1.17)	127	62.20 (3.41)
College	356	20.97 (1.14)	268	68.26 (3.26)	447	19.19 (1.04)	351	62.34 (3.48)
Graduate school	184	21.13 (1.05)	141	68.85 (3.24)	143	19.29 (1.09)	119	62.87 (3.16)
APOE§								
No ε4	806	20.83 (1.11)	591	68.21 (3.13)	1128	19.03 (1.07)	896	62.38 (3.23)*
Any ε4	234	20.85 (1.18)	172	68.26 (3.35)	368	18.96 (1.07)	292	61.95 (3.21)
Income¶								
<$12K	115	20.74 (1.06)*	82	68.52 (3.08)	397	18.85 (1.15)*	301	62.12 (3.60)*
$12–25K	383	20.68 (1.11)	271	68.03 (3.30)	542	18.99 (1.03)	434	62.06 (3.11)
$25–35K	225	20.84 (1.13)	171	68.46 (3.33)	243	19.09 (1.02)	201	62.69 (3.26)
$35–50K	143	20.84 (1.05)	109	68.01 (3.36)	152	19.21 (1.04)	127	62.72 (3.02)
>$50K	226	20.99 (1.17)	177	68.16 (2.94)	198	19.28 (1.01)	159	62.57 (3.20)
Health								
Excellent	212	21.01 (1.08)*	174	68.65 (2.93)*	255	19.10 (1.13)*	214	62.56 (2.97)
Very good	325	20.84 (1.15)	256	68.38 (3.30)	470	19.13 (1.02)	393	62.37 (3.07)
Good	415	20.72 (1.11)	301	67.86 (3.40)	606	18.95 (1.10)	486	62.21 (3.40)
Fair	170	20.68 (1.07)	97	67.67 (3.28)	281	18.94 (0.98)	194	62.04 (3.33)
Poor	15	21.25 (0.96)	12	68.80 (3.36)	28	18.77 (0.82)	18	61.48 (2.40)

*$p < 0.05$ with *t* test for dichotomous variables and linear test for trend for polychotomous variables.
†There were 5 men and 7 women who were not considered in either ethnic group represented in table 1.
‡There were 5 women missing education.
§There were 100 men and 146 women missing APOE status.
¶There were 49 men and 109 women missing income.

offered in-home testing. If a participant failed tests for memory or tests in more than one other cognitive domain (premorbid intelligence, language, visuoperceptual/visuoconstructional, executive function, or motor), further testing was done by a neurologist. If a participant refused or was deceased, dementia was assessed using the prospectively collected data from the annual clinic examination supplemented with data from medical records, physician questionnaires, and informant/proxy interviews. At one site (Pittsburgh), all living participants at the clinic were evaluated to ascertain screening bias. Twelve participants who screened normal were found to have dementia, and thus it was estimated that 56/1,492 white participants classified as normal may have had dementia.[25]

Based on all information available, a committee of neurologists and psychiatrists (one from each site) classified dementia status for all CHS Cognition Study participants, including those who were deceased by 1998–1999. The clinical diagnosis of dementia was based on a progressive or static cognitive deficit of sufficient severity to affect the subjects' activities of daily living, and history of normal intellectual function before the onset of cognitive abnormalities, and approximated *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) criteria. Participants were also required to have impairments in two cognitive domains, which did not necessarily include memory.[24]

Type of dementia was determined using several criteria including the DSM-IV,[26] the National Institute of Neurological and Communicative Diseases and Stroke–Alzheimer's Disease and Related Disorders Association (NINDS-ADRDA),[27] State of California Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC),[28] and National Institute of Neurological Diseases and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN).[29] The classification of specific types of dementia was completed after the review of the MRI.

Analytic sample. Of the 3,608 participants in the CHS Cognition Study, 6 were determined to lack sufficient information for dementia classification. From the remaining 3,602, we excluded 227 participants with prevalent dementia and 577 subjects with mild cognitive impairment at the baseline of CHS Cognition Study in 1992–1993. Thus, 2,798 participants were included in the present analyses. Of these, 480 subjects developed dementia between 1992 and 1999 (incidence rate of 31.9 per 1,000 person-years). Over the course of follow-up, 245 subjects (83 men and 162 women) developed possible or probable AD by NINCDS-ADRDA criteria and no other dementia diagnosis (incidence rate of 16.3 per 1,000 person-years), and 213 subjects (98 men and 115 women) developed possible or probable vascular dementia (VaD) by ADDTC criteria either alone or mixed with another dementia diagnosis (incidence rate of 14.2 per 1,000 person-years), and 22 developed other dementias. We included the mixed dementias with VaD due to the relatively small numbers of pure VaD cases.

Statistical methods. Trend tests and analysis of variance followed by Tukey post-test for multiple comparisons were used to compare anthropometric measurements stratified by gender across several sociodemographic variables shown in table 1. Cox proportional hazards models were then used to examine the associations of knee height and arm span with risk of dementia, AD, and VaD. Subjects with VaD were excluded in the analyses of AD, and vice versa in the analyses of VaD. The time axis was years of study from the baseline of the CHS Cognition Study in 1992–1993. All analyses were stratified by gender to allow for comparability with previously published articles[14-16] acknowledging that men and women differ in height, rate of growth, and timing of growth. For the primary analyses, we modeled anthropometric measures as continuous variables. In addition, we examined these variables in quartiles, and because potential threshold effects were noted, we presented the results with the lowest vs the remaining quartiles. Because 651 subjects were missing arm span (as compared to only 17 for knee height), we included a "missing" group in our comparison across quartiles of arm span. The "missing" group included subjects who were not able to provide a measurement in 1996–1997 because they were lost to follow-up either due to death (238) or other reasons. In all analyses, we controlled for other covariates that were found to differ with respect to the anthropometric measures (table 1) and were associated with dementia in the Cox models as indicated by likelihood ratio tests. These covariates were included in two different sets of models. The first (baseline) set of models included those covariates that were predetermined before the period of limb development and included age (at baseline), race (white vs minority status), and *APOE* genotype (any vs no $\varepsilon 4$ alleles). The second (full) set of models included these covariates plus others that were potentially established after the period of limb development and included education, income, and self-reported health. Education was modeled as the number of years in school, excluding vocational school. Income was based on income at baseline and was divided into eight categories ranging from under $5,000 to over $50,000. Self-reported health was determined in 1992–1993 and modeled as shown in table 1. We examined other covariates such as clinic site, physical activity, age at menopause, and chronic diseases, including coronary heart disease, osteoporosis, and diabetes. None of these significantly altered our main results, and were thus not retained in the final models. Forward and backward stepwise regression was used to verify the completeness of the models. Finally, interactions between each anthropometric measure and gender using the whole sample were examined to formally test for differences across gender. In further exploratory analyses, we also examined interactions between each anthropometric measure and age, race, or *APOE* genotype. Each of the interactions was tested separately building on the baseline models. All analyses were performed using STATA 8.0.

RESULTS The average age of the subjects in our study was 72 years. Approximately 41% of the subjects were male, while 89.5% were white, 10.1% black, and 0.4% other ethnic backgrounds. The mean knee height and arm span across various sociodemographic characteristics are provided for each gender in table 1. There were significant trends of decreases in both anthropometric measurements with increasing age and increases with additional years of education. Black subjects had significantly greater knee height and arm span than white subjects. Women without an *APOE* $\varepsilon 4$ allele had significantly longer arm spans than those with the high-risk allele. Although there was a trend of greater knee height and arm spans with higher income among women, a similar trend was only apparent for knee height among men. For both genders, there was a trend of greater knee height and arm span with increasing satisfaction with one's health. Those missing arm span were significantly older (men: 73.2 vs 71.6; women: 72.7 vs 71.1), had less education (men: 12.7 vs 13.2 years; women: 12.2 vs 12.5 years), and scored lower on self-reported health, but they were not different in terms of minority status, *APOE* status, and income. Women missing arm span had significantly shorter knee heights (18.90 vs 19.06 in, $p < 0.01$), but there were no statistical differences in knee height for men missing those same measures. Correlations between knee height and arm span were 0.56 for men, and 0.60 for women.

Although there was a trend toward lower risk of dementia with greater knee height for men, the effect was only significant for women (table 2). After controlling for age, race, and *APOE* genotype, each 1-inch increase was associated with 16% less risk for women (HR per 1-inch increase: 0.84; 95% CI 0.74–0.96). Separate analysis of AD and VaD in women revealed that the lower risk was more apparent for AD (HR per 1-inch increase: 0.78; 95% CI 0.65–0.93) than VaD (HR per 1-inch increase: 0.91, 95% CI 0.74–1.11). Examination of women in the lowest quartile of knee height (<18.28 inches) revealed they had

Table 2 Relative risks of dementia, Alzheimer disease (AD), and vascular dementia (VaD) by knee height

	Cases/ person-years	Model 1* HR (95% CI)	Model 2† HR (95% CI)
Men			
Dementia			
Continuous	164/5,481	0.93 (0.81–1.07)	0.95 (0.83–1.10)
Dichotomous (in)			
>20.05	121/5,481	1.0	1.0
<20.05	43/5,481	1.18 (0.83–1.67)	1.11 (0.78–1.58)
AD			
Continuous	69/5,208	0.89 (0.72–1.10)	0.95 (0.76–1.18)
Dichotomous (in)			
>20.05	53/5,208	1.0	1.0
< 20.05	16/5,208	0.97 (0.56–1.71)	0.80 (0.45–1.43)
VaD			
Continuous	87/5,236	0.96 (0.79–1.16)	0.96 (0.79–1.17)
Dichotomous (in)			
>20.05	62/5,236	1.0	1.0
<20.05	25/5,236	1.34 (0.84–2.15)	1.34 (0.84–2.16)
Women			
Dementia			
Continuous	248/8,167	0.84 (0.74–0.96)	0.88 (0.77–1.00)
Dichotomous (in)			
>18.28	178/8,167	1.0	1.0
<18.28	70/8,167	1.26 (0.95–1.67)	1.20 (0.90–1.59)
AD			
Continuous	138/7,833	0.78 (0.65–0.93)	0.82 (0.69–0.97)
Dichotomous (in)			
>18.28	95/7,833	1.0	1.0
<18.28	43/7,833	1.39 (0.96–2.00)	1.29 (0.89–1.86)
VaD			
Continuous	104/7,716	0.91 (0.74–1.11)	0.94 (0.77–1.16)
Dichotomous (in)			
>18.28	78/7,716	1.0	1.0
<18.28	26/7,716	1.07 (0.68–1.67)	1.02 (0.65–1.60)

*Controlling for age at baseline, race, and *APOE* genotype.
†Controlling for age at baseline, race, *APOE* genotype, education, income, and self-reported health.

greater risk of dementia and AD than other women, but the effects were not significant.

Greater arm span was associated with lower risk of dementia among both men and women, after controlling for age, race, and *APOE* genotype (men: HR per 1-inch increase 0.94; 95% CI 0.89–1.00; women: HR per 1-inch increase 0.93; 95% CI 0.88–0.98) (table 3). Arm span was also associated with lower risk of AD (men: HR per 1-inch increase 0.92; 95% CI 0.84–1.00; women: HR per 1-inch increase 0.90; 95% CI 0.85–0.96), but the effect with VaD was not statistically significant. Interestingly, for women only, those in the lowest quartile of arm span (<60.2 inches) had significantly greater risk of dementia (HR per 1-inch increase 1.45; 95% CI 1.03–2.05) and AD (HR per 1-inch increase 1.70; 95% CI 1.10–2.62) compared to others.

In other models, we included interaction terms between each anthropometric measure and gender to formally test whether the relationships with dementia differed for men and women. The interaction terms with sex were not significant in any of these models (data not shown). We further considered other interactions with age, race, and *APOE* genotype, and none of these were significant either. Additionally, in order to more closely examine the potential mediating effect of education, income, and self-reported health on the relationship between these anthropometric measures and dementia, we compared models with and without these covariates (see tables 2 and 3). The results were similar before and after including these covariates.

DISCUSSION We found that shorter knee heights and arm spans were associated with an increased risk of dementia. Although interaction terms between each anthropometric measure and gender did not reach significance, we did observe differences between the sexes. Among women, both knee height and arm span significantly predicted dementia risk, while among men only arm span did. The associations with knee height and arm span were stronger with AD, and only with arm span did we observe a trend for lower risk of VaD. The results were similar whether or not we controlled for education, income, and self-reported health, suggesting that the relationships between the two anthropometric measures and dementia were independent of each of these factors.

Our findings appear to be largely consistent with those from three previous studies in two different elderly Korean populations conducted by the same group of investigators. Two of these studies[15,16] reported that shorter leg length was associated with greater risk of dementia specifically among women in Kwangju, South Korea. The other study,[14] using a separate population from the Jeonbuk province in South Korea, found that shorter arm length was associated with greater risk of dementia independent of gender. The consistency of findings across studies lends support to the contention that these anthropometric measures are associated with dementia risk and the associations with knee height differ by gender.

Table 3 Relative risks of dementia, Alzheimer disease (AD), and vascular dementia (VaD) by arm span

	Cases/ person-years	Model 1* HR (95% CI)	Model 2† HR (95% CI)
Men			
Dementia			
Continuous	100/4,479	0.94 (0.89–1.00)	0.94 (0.89–1.00)
Dichotomous (in)			
>65. 9	72/5,507	1.0	1.0
<65. 9	28/5,507	1.18 (0.76–1.84)	1.12 (0.71–1.75)
Missing‡	64/5,507	2.53 (1.79–3.59)	2.40 (1.68–3.42)
AD			
Continuous	48/4,302	0.92 (0.84–1.00)	0.93 (0.85–1.01)
Dichotomous (in)			
>65. 9	33/5,235	1.0	1.0
<65. 9	15/5,235	1.40 (0.76–2.61)	1.23 (0.65–2.33)
Missing‡	21/5,235	1.94 (1.11–3.38)	1.75 (0.99–3.10)
VaD			
Continuous	47/4,303	0.94 (0.87–1.02)	0.93 (0.85–1.01)
Dichotomous (in)			
>65. 9	35/5,263	1.0	1.0
<65. 9	12/5,263	1.07 (0.55–2.07)	1.07 (0.55–2.10)
Missing‡	40/5,263	3.11 (1.94–4.99)	3.05 (1.89–4.93)
Women			
Dementia			
Continuous	155/6,975	0.93 (0.88–0.98)	0.94 (0.89–0.99)
Dichotomous (in)			
>60.2	103/8,231	1.0	1.0
<60.2	52/8,231	1.45 (1.03–2.05)	1.42 (1.01–2.00)
Missing‡	93/8,231	2.73 (2.03–3.68)	2.51 (1.85–3.41)
AD			
Continuous	92/6,757	0.90 (0.85–0.96)	0.91 (0.85–0.97)
Dichotomous (in)			
>60.2	58/7,898	1.0	1.0
<60.2	34/7,898	1.70 (1.10–2.62)	1.72 (1.12–2.64)
Missing‡	46/7,898	2.52 (1.68–3.78)	2.30 (1.52–3.49)
VaD			
Continuous	60/6,645	0.94 (0.87–1.03)	0.96 (0.88–1.04)
Dichotomous (in)			
>60.2	42/7,781	1.0	1.0
<60.2	18/7,781	1.27 (0.72–2.24)	1.24 (0.71–2.19)
Missing‡	44/7,781	3.05 (1.94–4.80)	2.77 (1.73–4.43)

*Controlling for age at baseline, race, and *APOE* genotype.
†Controlling for age at baseline, race, *APOE* genotype, education, income, and self-reported health.
‡Missing anthropometric measures due to loss of follow-up.

However, as noted above, formal interaction tests of differences by gender were not significant in the current study. Therefore, more studies are needed to confirm if there are indeed gender differences, and the biologic significance of any observed differences.

The current study differs from one of the previous studies carried out in the Korean populations[16] in that we did not find strong evidence for association of these anthropometric measures, especially knee height, with VaD. However, in a subsequent article drawing from an updated sample of the same population,[15] leg length was no longer significantly associated with VaD in women. In both Korean studies, as well as ours, sample sizes of subjects with VaD were small, thus more studies are needed before conclusions can be made regarding the association of limb length with VaD. Overall, our findings suggest that as they do in the Korean populations, anthropometric measures of short stature, even as defined by Western standards, similarly predict risk for dementia.

The relationship of knee height to dementia in our study is particularly interesting given the findings of a British national cohort study of individuals followed since birth in 1946.[30] This study examined the associations of leg and trunk length at age 43 with childhood factors including breastfeeding, early nutrition, health/disease status, socioeconomic circumstances, and emotional trauma. Leg length was most closely associated with breastfeeding and energy intake at 4 years. They concluded that it was most closely associated with environment and diet in early life, corresponding to the periods of most rapid leg growth.

Differences in limb length could reflect differences in genetics, environment, or both. While heritability of height is estimated to be 80% in the United States and Western countries after World War II, the proportion of variation due to the environment is stronger in developing nations and when there is greater environmental stress.[31] Thus, there have been universal secular increases in height, and there is a strong correlation between socioeconomic background and height.[32,33] Interestingly, these secular trends are already reflected during the first 2 years of life.[34] In our population, as well as others, those with longer anthropometric measurements also received more years of education[13,16] and height has been shown to correlate with intelligence.[35-37] Sixty-five percent of the correlation between height and intelligence is due to environmental rather than genetic factors.[38] Adverse conditions, especially during early years of life, lead to stunting (reduced height-for-age).[39] Although there may be some catch-up during later growth, it is not completely

restorative.[39] Primary causes of stunting include nutrition, infection, mother's height and birthweight, the birthweight of the baby, lactation, and childcare.[40,41] The quality of nutrition (the variety of nutrients, the amount of protein) has a much larger influence on growth than does total energy consumption.[42] Infection is important due to its relationship with nutrition. An infection interferes with the ability to properly absorb nutrients, and better nutrition can ameliorate some of the detrimental effects.[31,39,40] Quality of childcare can be affected by family size, birth order, number of younger siblings, overcrowding, social class, parent's education, and economic resources.[40] These risk factors are thought to be related to height through their influence on adequate feeding and ability to deliver a well-balanced diet to the infant.[40]

Correspondingly, physiologic processes that regulate growth and brain development occur within the same time window that environmental influences play the most important role. Differences in knee height and maximal adult height are primarily determined in the first 2 years of life,[40] coinciding with the expression of growth hormone receptors, which are believed to act primarily on the growth plate of long bones.[40,41] In the brain, the hippocampus reaches its full size by 7–10 months, but extensive differentiation of the dendritic spines in the CA-3 region continues through the second year of life.[43] Thus, it is possible that early nutritional deficits, exposure to environmental toxins, or other unaccounted for residual confounders could influence intelligence, cognitive functioning, level of educational attainment, or vulnerability to dementia. Therefore, knee height and arm span may be effective surrogate markers of the effects of nutrition or other early life exposures on brain development.

A limitation of our study is that arm span was measured 4 years after the baseline. Consequently, approximately one fourth of the values for arm span were missing, primarily for subjects who were lost to follow-up before the measurement was taken. Subjects missing arm span measures were more likely to have dementia. Additionally, women missing arm span measures were more likely to have shorter knee heights, while men missing these measures showed no differences in knee height. Given the high correlation between arm span and knee height, it seems likely that women with missing measurements may have had shorter arm spans. Thus, if these subjects had not been missing, our findings may have in fact been strengthened.

The timing of the arm span measurement raises another difficulty for the interpretation of the inverse association with dementia. It is possible that the pathogenesis of dementia, or something related to it, causes shrinking of arm span rather than shorter arm span reflecting a vulnerability to dementia. The same difficulty holds true for the measurement of knee height, which was taken only a couple of years prior to the baseline of the study. Ideally, these anthropometric measurements should be taken in midlife or earlier, many years prior to the onset of dementia, in order to more confidently establish the temporality with the outcome. However, doing this is typically not feasible. There is strong evidence that knee height and arm span are largely determined by early life factors. This is consistent with the use in the literature of knee height as surrogate measure of early life environment[30] and arm span to determine maximal adult height[44] because it is thought not to shrink with aging. However, there is some evidence that limbs do in fact shrink with aging,[45] and we cannot entirely rule out the possibility that this is exacerbated with dementia. It is comforting that when we tried to control for late life factors that could conceivably mediate a relationship between dementia and shrinking limbs, such as cardiovascular disease, osteoporosis, or physical activity, our results did not change. Still, further research with long-term longitudinal studies is needed to confirm the direction of the relationship between these anthropometric measurements and dementia risk.

A final limitation is the possibility of misclassification of the dementia outcome. Subjects at three sites of the study were screened for dementia, and a substudy at the fourth site suggested that the screening was not completely sensitive.[25] As a result, some subjects with dementia may have been misclassified as normal. There is no reason to believe this misclassification would be related to the anthropometric measurements. Non-differential misclassification of this sort tends to bias results toward the null, which means our findings may have underestimated the true association between the anthropometric measurements and dementia.

The strengths of our study include length of follow-up, its longitudinal prospective design, and state-of-the-art adjudication of incident dementia, Alzheimer, and vascular dementias. There were a high number of dementia cases (480) in this sample, and because a variety of methods were used to follow up with subjects who did not return to the clinic, there was no loss to follow-up

with regards to adjudication of dementia status. Sensitivity of screening methods was carefully determined and diagnosis was based on well-established criteria. Two different anthropometric measures, each assessed by standardized methods, allowed us to examine the relationship of each separately to different dementia outcomes. These reasons, plus the fact that our studies have now replicated previous findings, increase our confidence in concluding that, the shorter a woman's knee height or the shorter the arm span of either gender, the greater the risk of developing dementia or AD. However, more longitudinal studies that examine change in anthropometric measures with aging and dementia, and further studies to clarify separate associations of knee height and arm span with dementia between genders, are warranted.

ACKNOWLEDGMENT

For a full list of participating CHS investigators and institutions, see "About CHS: Principal Investigators and Study Sites" at http://www.chs-nhlbi.org. The authors thank Esther Boody-Alter for help with editing.

Received December 14, 2005. Accepted in final form August 14, 2007.

REFERENCES

1. Robinson SM, Barker DJ. Coronary heart disease: a disorder of growth. Proc Nutr Soc 2002;61:537–542.
2. Eriksson J, Forsen T, Tuomilehto J, Osmond C, Barker D. Fetal and childhood growth and hypertension in adult life. Hypertension 2000;36:790–794.
3. Eriksson JG, Forsen T, Tuomilehto J, Osmond C, Barker DJ. Early adiposity rebound in childhood and risk of Type 2 diabetes in adult life. Diabetologia 2003;46:190–194.
4. Eriksson JG, Forsen T, Tuomilehto J, Winter PD, Osmond C, Barker DJ. Catch-up growth in childhood and death from coronary heart disease: longitudinal study. BMJ 1999;318:427–431.
5. Barker DJ, Eriksson JG, Forsen T, Osmond C. Fetal origins of adult disease: strength of effects and biological basis. Int J Epidemiol 2002;31:1235–1239.
6. Barker DJ, Lackland DT. Prenatal influences on stroke mortality in England and Wales. Stroke 2003;34:1598–1602.
7. Michels KB. Early life predictors of chronic disease. J Womens Health (Larchmt) 2003;12:157–161.
8. Moceri VM, Kukull WA, Emanual I, et al. Using census data and birth certificates to reconstruct the early-life socioeconomic environment and the relation to the development of Alzheimer's disease. Epidemiology 2001;12:383–389.
9. Moceri VM, Kukull WA, Emanuel I, van Belle G, Larson EB. Early-life risk factors and the development of Alzheimer's disease. Neurology 2000;54:415–420.
10. Snowdon DA, Kemper SJ, Mortimer JA, Greiner LH, Wekstein DR, Markesbery WR. Linguistic ability in early life and cognitive function and Alzheimer's disease in late life: findings from the Nun Study [see comments]. JAMA 1996;275:528–532.
11. Braak H, Braak E. Frequency of stages of Alzheimer-related lesions in different age categories. Neurobiol Aging 1997;18:351–357.
12. Beeri MS, Davidson M, Silverman JM, Noy S, Schmeidler J, Goldbourt U. Relationship between body height and dementia. Am J Geriatr Psychiatry 2005;13:116–123.
13. Abbott RD, White LR, Ross GW, et al. Height as a marker of childhood development and late-life cognitive function: the Honolulu-Asia Aging Study. Pediatrics. 1998;102(3 Pt 1):602–609.
14. Jeong SK, Kim JM, Kweon SS, Shin MH, Seo MW, Kim YH. Does arm length indicate cognitive and functional reserve? Int J Geriatr Psychiatry 2005;20:406–412.
15. Kim JM, Stewart R, Shin IS, Kim SW, Yang SJ, Yoon JS. Associations between head circumference, leg length and dementia in a Korean population. Int J Geriatr Psychiatry 2008;23:41–48.
16. Kim JM, Stewart R, Shin IS, Yoon JS. Limb length and dementia in an older Korean population. J Neurol Neurosurg Psychiatry 2003;74:427–432.
17. Mak Z, Kim JM, Stewart R. Leg length, cognitive impairment and cognitive decline in an African-Caribbean population. Int J Geriatr Psychiatry 2006;21:266–272.
18. Fried LP, Borhani NO, Enright P, et al. The Cardiovascular Health Study: design and rationale. Ann Epidemiol 1991;1:263–276.
19. Tell GS, Fried LP, Hermanson B, Manolio TA, Newman AB, Borhani NO. Recruitment of adults 65 years and older as participants in the Cardiovascular Health Study. Ann Epidemiol 1993;3:358–366.
20. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.
21. Teng EL, Chui HC. The Modified Mini-Mental State (3MS) examination. J Clin Psychiatry 1987;48:314–318.
22. Bryan RN, Manolio TA, Schertz LD, et al. A method for using MR to evaluate the effects of cardiovascular disease on the brain: the cardiovascular health study. AJNR Am J Neuroradiol 1994;15:1625–1633.
23. Ives DG, Fitzpatrick AL, Bild DE, et al. Surveillance and ascertainment of cardiovascular events: The Cardiovascular Health Study. Ann Epidemiol 1995;5:278–285.
24. Lopez OL, Kuller LH, Fitzpatrick A, Ives D, Becker JT, Beauchamp N. Evaluation of dementia in the cardiovascular health cognition study. Neuroepidemiology 2003;22:1–12.
25. Fitzpatrick AL, Kuller LH, Ives DG, et al. Incidence and prevalence of dementia in the Cardiovascular Health Study. J Am Geriatr Soc 2004;52:195–204.
26. American Psychiatric Association. DSM-IV Diagnostic and Statistic Manual of Mental Disorders. Fourth Edition ed. Washington, DC: American Psychiatric Association; 1994.
27. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Hu-

man Services Task Force on Alzheimer's Disease. Neurology 1984;34:939–944.
28. Chui HC, Victoroff JI, Margolin D, Jagust W, Shankle R, Katzman R. Criteria for the diagnosis of ischemic vascular dementia proposed by the State of California Alzheimer's Disease Diagnostic and Treatment Centers. Neurology 1992;42(3 Pt 1):473–480.
29. Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology 1993;43:250–260.
30. Wadsworth ME, Hardy RJ, Paul AA, Marshall SF, Cole TJ. Leg and trunk length at 43 years in relation to childhood health, diet and family circumstances; evidence from the 1946 national birth cohort. Int J Epidemiol 2002;31:383–390.
31. Silventoinen K. Determinants of variation in adult body height. J Biosoc Sci 2003;35:263–285.
32. Walker M, Shaper AG, Wannamethee G. Height and social class in middle-aged British men. J Epidemiol Community Health 1988;42:299–303.
33. Marmot MG, Smith GD, Stansfeld S, et al. Health inequalities among British civil servants: the Whitehall II study. Lancet 1991;337:1387–1393.
34. Barker D. Mothers, babies and disease in later life. London: BMJ Publishing Group; 1994.
35. Tuvemo T, Jonsson B, Persson I. Intellectual and physical performance and morbidity in relation to height in a cohort of 18-year-old Swedish conscripts. Horm Res 1999;52:186–191.
36. Teasdale TW, Owen DR, Sorensen TI. Intelligence and educational level in adult males at the extremes of stature. Hum Biol 1991;63:19–30.
37. Johnson FW. Biological factors and psychometric intelligence: a review. Genet Soc Gen Psychol Monogr 1991;117:313–357.
38. Sundet JM, Tambs K, Harris JR, Magnus P, Torjussen TM. Resolving the genetic and environmental sources of the correlation between height and intelligence: a study of nearly 2600 Norwegian male twin pairs. Twin Res Hum Genet 2005;8:307–311.
39. Branca F, Ferrari M. Impact of micronutrient deficiencies on growth: the stunting syndrome. Ann Nutr Metab 2002;46 (suppl 1):8–17.
40. Cole TJ. Secular trends in growth. Proc Nutr Soc 2000; 59:317–324.
41. Waterlow JC. Introduction: causes and mechanisms of linear growth retardation (stunting). Eur J Clin Nutr 1994;48 (suppl 1):S1–4.
42. Allen LH, Uauy R. Guidelines for the study of mechanisms involved in the prevention or reversal of linear growth retardation in developing countries. Eur J Clin Nutr 1994;48 (suppl 1):S212–216.
43. Herschkowitz N. Neurological bases of behavioral development in infancy. Brain Dev 2000;22:411–416.
44. Eveleth PB, Andres R, Chumlea WC, et al. Uses and interpretation of anthropometry in the elderly for the assessment of physical status: Report to the Nutrition Unit of the World Health Organization: the Expert Subcommittee on the Use and Interpretation of Anthropometry in the Elderly. J Nutr Health Aging 1998; 2:5–17.
45. Borkan GA, Hults DE, Glynn RJ. Role of longitudinal change and secular trend in age differences in male body dimensions. Hum Biol 1983;55:629–641.