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Height and Risk of Incident Intraparenchymal Hemorrhage: Atherosclerosis Risk in Communities and Cardiovascular Health Study Cohorts

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Abstract

Background—Height is inversely associated with incident coronary disease and total stroke, but few studies have examined the association between height and intraparenchymal hemorrhage. We hypothesized height would be inversely associated with incident intraparenchymal hemorrhage in the combined cohorts of the Atherosclerosis Risk in Communities Study and the Cardiovascular Health Study.

Methods—Data on Caucasian and African American participants were used to estimate the association of height at baseline with incident intraparenchymal hemorrhage verified by MD review of medical records and imaging reports. Sex-specific Cox proportional hazards regression models were used to calculate hazard ratios.

Results—A total of 20,983 participants initially free of stroke (11,788 women, 9,195 men) were followed for an average of 15.9 years (SD = 5.1 years). Incident intraparenchymal hemorrhage occurred in 115 women and 73 men. Sex, but not age, race, study or blood pressure, modified the association, p = 0.03. After adjustment for risk factors (age, systolic blood pressure, triglycerides, LDL-cholesterol, fibrinogen and race), among women, height was significantly inversely associated with incident intraparenchymal hemorrhage [hazard ratio per standard deviation (6.3 cm) = 0.81, 95% CI (0.66 – 0.99)], p = 0.04. The hazard ratio (95% CI) for tertile 3 versus 1 in women was 0.63 (0.37–1.08). Among men, height was not linearly associated with incident intraparenchymal hemorrhage [hazard ratio per standard deviation (6.7 cm) = 1.09, 95% CI (0.84 – 1.40)], p = 0.52.

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Conclusions—This large prospective study provides evidence that shorter height may be a risk factor for incident intraparenchymal hemorrhage in women.

Background

Short height is a risk factor for several cardiovascular diseases but whether height is associated with incident intraparenchymal hemorrhage (IPH) is unclear.[1–3] Two of three previous studies found short height associated with a higher incidence of total hemorrhagic stroke (IPH plus subarachnoid hemorrhage).[4,5] The Nurses' Health Study reported no association.[6] Only three previous studies have examined the association specifically between height and incident IPH.[7–9] All found an inverse association, but one was based on a total of 23 events, one was restricted to men, and one was unable to examine if the association was similar in men and women. Based on this prior research, we hypothesized that height would be inversely associated with incident IPH in the combined cohorts of the Atherosclerosis Risk in Communities Study (ARIC) and the Cardiovascular Health Study (CHS).

Methods

Study Sample

The ARIC cohort comprises a population sample of 15,792 participants age 45–64 at baseline (1987 – 1989) in four communities: Washington County, MD; the northwest suburbs of Minneapolis, MN; Jackson, MS (African Americans only); and Forsyth County, NC.[10] CHS comprises a population sample of 5,888 participants ≥ 65 years of age at baseline selected from Health Care Financing Administration (Medicare) eligibility lists from four communities: Sacramento County, CA; Washington County, MD; Forsyth County, NC; and Pittsburgh, PA.[11] Of the 5,888, 5,201 participants were recruited from 1989 – 1990, and 687 African Americans were recruited from 1992 – 1993. Each center's institutional review committee approved the study, and all participants provided informed consent.

Data Collection

As previously described, ARIC and CHS measured many stroke risk factors using comparable methods at baseline.[10–15] Height was measured without shoes at baseline in centimeters (cm) utilizing a vertical height ruler or stadiometer. The between-technician repeatability coefficient for height measurements at ARIC visits was 0.99.

ARIC outcomes were ascertained through annual phone interviews, three triennial follow-up examinations, community hospital surveillance, and reports of deaths. Acute stroke hospitalizations were screened for eligibility: a discharge diagnosis code of cerebrovascular disease (ICD-9, codes 430–438) or a discharge summary mentioning either a cerebrovascular procedure or acute cerebrovascular disease on neuroimaging. Hospitalized strokes and out-of-hospital stroke deaths, but not nonfatal, out-patient strokes, were ascertained in ARIC. ARIC utilized the National Survey of Stroke criteria for defining stroke.[16] Specifically, a definite IPH must have met at least one of the following criteria: 1. CT or MRI evidence of intraparenchymal hemorrhage; 2. Evidence of intraparenchymal hematoma at autopsy or surgery; or 3. At least 1 major or 2 minor neurological deficits; and bloody cerebrospinal fluid on lumbar puncture; and cerebral angiography indicating an avascular mass effect and no evidence of aneurysm or arteriovenous malformation; and no CT or MRI. A probable IPH met criterion 3, other than cerebral angiography, and had a decreased level of consciousness or coma lasting 24 hours or until death. Overall, 98% of strokes in ARIC had neuroimaging.

CHS outcomes were ascertained through semiannual interviews to identify hospitalizations and searches of the Medicare utilization files for ICD-9 codes 430–438.[17,18] Medical records for potential acute stroke events were abstracted. Fatal and nonfatal hospitalized and non-hospitalized strokes were ascertained. CHS defined stroke events based on the Systolic Hypertension in the Elderly Program.[15] A stroke event was defined as IPH if one of the following criteria was met: 1. CT or MRI evidence of intraparenchymal hematoma; 2. Evidence of intraparenchymal hemorrhage at autopsy or surgery; or 3. Bloody cerebrospinal fluid on lumbar puncture with a focal deficit. Neuroimaging was performed in 86% of stroke events in CHS.

Statistical Analysis

The combined cohort consisted of 21,680 participants at baseline. Participants with a history of stroke at baseline (n = 582) or race/ethnicity other than Caucasian or African American (n = 87) were excluded. In addition, participants who did not fast eight hours prior to baseline blood draw or who were missing fasting information were excluded from analyses involving triglycerides (n = 560). Follow-up went from baseline to either IPH occurrence, loss to follow-up, death, or else December 31, 2007.

Crude and age-adjusted incident rates of IPH were calculated using Poisson regression. Crude and age-adjusted hazard ratios (HRs) of baseline risk factors with incident IPH were estimated from sex-specific Cox proportional hazards regression models. The multivariable association between height (continuous) and incident IPH was adjusted for known confounders in this study population. The final model was selected with backward stepwise models, retaining all statistically significant covariates ($\alpha = 0.05$). Pre-specified two-way multiplicative interactions of height with age, sex, race, study (ARIC, CHS) and systolic blood pressure were examined. We considered $p < 0.05$ to be evidence of significant effect modification. All statistical analyses were performed in SAS 9.2.

Results

A total of 20,983 participants initially free of stroke (11,788 women, 9,195 men) were followed for an average of 15.9 years (SD = 5.1 years). The mean height was 161.4 cm (range 124 – 188) for women and 175.4 cm (range 142 – 199) for men. The interaction of height (continuous) with sex was significant ($p = 0.03$); subsequently sex-specific analyses were performed. Short participants were older and had slightly higher frequency of cardiovascular risk factors than tall participants (Table 1).

A total of 188 incident IPH events (115 in women, 73 in men) occurred during 334,642 person-years of follow-up. Table 2 shows the crude IPH incidence rates and age-adjusted relative rates by sex-specific height tertiles. Among women, an inverse monotonic association existed between height and the crude IPH incidence rate. Among men, the incidence rate was highest for intermediate height. The inverse monotonic association for women between sex-specific height tertiles and incident IPH remained after adjustment for age, systolic blood pressure, log triglycerides, low-density lipoprotein cholesterol (LDL-C), fibrinogen and race. Women in the tallest tertile of height had a HR of 0.63 (95% CI: 0.37 – 1.08) compared with women in the shortest height tertile. For each standard deviation increase in height (6.3 cm), the rate of incident IPH decreased by 19 percent (HR = 0.81, 95% CI: 0.66 – 0.99) in women (Table 3). In the multivariable models for men (Table 3) there was no significant association between height and incident IPH.

The interactions of height with age, study, race and systolic blood pressure were not significant. When stratified by age 65 at baseline (i.e., by study) findings were generally

consistent with the main analysis; however, because of fewer events, the precision of the estimates decreased.

In CHS, the occurrence of a hemorrhagic cerebrovascular event while on anticoagulation medication did not prevent a classification of IPH. Thirteen participants potentially taking anticoagulation medication at the time of IPH were excluded in a sensitivity analysis. Excluding these participants had minor impact on the results and thus they were retained in the analyses.

Discussion

In this prospective population-based study, the association between height and incident IPH differed for women and men. Tall height was significantly associated with a reduced risk of IPH incidence among women, but not among men. The association in women was independent of other measured IPH risk factors and was moderately strong.

Four prior cohort studies and one nested case-control study reported that height was inversely associated with incidence of either total hemorrhagic stroke[4,5] or, specifically, IPH.[7–9] A recent Japanese cohort study of middle-aged men and women found that, after multivariable adjustment, the risk of total hemorrhagic stroke decreased 20 percent with each standard deviation increment in height (95% CI: 0.70 – 0.92).[4] An association of similar magnitude was found in a study of middle-aged Scottish adults, with a multivariable relative rate of total incident hemorrhagic stroke of 0.72 per 10 cm increment in height; however, the precision of the estimate was lower and of borderline statistical significance (95% CI: 0.51 – 1.0).[5] In a prospective cohort study of young Norwegians, aged 20–49 at baseline, in whom 23 IPH occurred, after multivariable adjustment, the relative risk of incident IPH for each 5 cm increment of in height was 0.61 (95% CI: 0.45 – 0.82).[7] Due to the small number of events, the possibility that sex modified the association could not be explored. In a cohort of one million Swedish men, of whom 1,431 suffered IPH, the multivariable-adjusted hazard ratio of incident IPH for each standard deviation increment of height was 0.88 (95% CI: 0.83 – 0.94).[8] A prospective study that matched controls to incident IPH cases on age, sex and screening-year, reported an odds ratio of 0.97 (95% CI: 0.95 – 0.998) per cm increment in height in the fully adjusted model. However, because of the matching criteria sex-specific associations could not be considered. Our study included both men and women. We found an inverse association between height and incident IPH among women that was of similar magnitude to the Swedish study. However, we found no association among men. The 95% confidence interval for our estimate in men (0.84 – 1.40) included the point estimate of 0.88 for the hazard ratio in the Swedish study.[8]

Thus, the totality of evidence suggests that shorter adults are at increased risk of IPH. Possible biological mechanisms for this association include that short height reflects (1) poor intrauterine and childhood nutrition or (2) lower socioeconomic status in childhood or adulthood, both of which have been associated with increased risk of cardiovascular diseases.[19,20] A third potential mechanism for the association is that short height is associated with higher heart rate, premature reflection of pressure waves during systole with augmentation of the primary systolic pulse.[21] Each of these components increases left ventricle work while decreasing the duration of diastole and the pressure for coronary filling.[21] One potential reason for the observed heterogeneity between men and women may be due to the small number of events among men in our study, 64 versus 100 in women, and subsequently the results were less precise for men. Alternatively, differences in artery elasticity; women have less elastic large and small arteries compared to men could explain the results.[22] In addition, the distance of the wave reflection is shorter in women, even after

matching on height.[23] How these factors related to adult height and to sex differences would influence the risk of IPH is uncertain but warrants further study.

A limitation of this study was the small number of events. The interaction of sex with height meant we needed to stratify by sex, which decreased precision. Despite the low number of events, very few prospective cohort studies on this topic had a greater number of incident IPH events. We measured and controlled for a number of potential confounding variables, but some mismeasurement of variables associated with height could have led to residual confounding. Height is accurately measured, but the biological construct of height that is important to IPH remains unknown. However, both height and coronary heart disease have strong familial components.[24–26]

Our results, combined with those of prior studies, suggest that shorter height may be a risk factor for incident IPH, at least among women.

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Table 1

Baseline Characteristics of Study Participants by Sex-Specific Height Tertiles, ARIC and CHS

	Height (cm) in Women			Height (cm) in Men		
Characteristics*‡	**< 159.00**	**159.00 – 163.90**	**≥ 164.00**	**< 172.49**	**172.49 – 177.90**	**≥ 178.00**
Age, years	63 ± 11	58 ± 9	56 ± 9	62 ± 11	59 ± 10	57 ± 9
White	3,060 (79.0)	2,729 (74.5)	2,896 (68.1)	2,424 (80.1)	2,218 (80.2)	2,688 (79.0)
Cardiovascular Health Study (CHS)	1,613 (41.7)	911 (24.9)	711 (16.7)	1,038 (34.3)	717 (25.9)	552 (16.2)
SBP, mmHg	129 ± 22	124 ± 21	122 ± 20	128 ± 21	126 ± 20	123 ± 18
Antihypertensive meds	1,403 (36.4)	1,165 (31.9)	1,254 (29.6)	947 (31.4)	795 (28.9)	826 (24.4)
LDL-C, mg/dL	138 ± 40	136 ± 40	133 ± 39	136 ± 37	135 ± 37	135 ± 37
HDL-C, mg/dL	57.9 ± 16.6	58.2 ± 16.9	58.0 ± 17.1	46.1 ± 13.8	44.9 ± 13.8	44.7 ± 13.5
Triglycerides, mg/dL†	118 (85 – 159)	111 (79 – 150)	107 (76 – 144)	122 (86 – 168)	122 (86 – 167)	121 (85– 166)
Diabetes mellitus	501 (13.1)	405 (11.1)	518 (12.3)	435 (14.5)	388 (14.1)	400 (11.8)
Weight, kg	66.6 ± 14.6	71.4 ± 15.5	77.5 ± 16.8	77.0 ± 12.4	83.5 ± 12.4	90.2 ± 14.1
BMI, kg/m^2	27.9 ± 6.0	27.5 ± 5.9	27.5 ± 5.9	27.2 ± 4.2	27.3 ± 4.0	27.2 ± 4.1
Alcohol, g/week†	19 (8 – 71)	30 (15 – 91)	36 (15 – 96)	50 (21 – 158)	60 (26 – 164)	70 (32 – 172)
Smoking, pack-years†	15 (9 – 37)	15 (8 – 34)	15 (8 – 33)	23 (14 – 47)	23 (14 – 46)	23 (14 – 45)
Fibrinogen, mg/dL	319 ± 66	309 ± 67	309 ± 64	310 ± 69	303 ± 67	298 ± 63

*Values are arithmetic mean ± SD or n (%) except where marked with † in which case they are geometric means (interquartile range)

‡Significant p trend (linear trend across ordinal values of height) for all characteristics ($p<0.05$) except HDL-C, diabetes mellitus and smoking for women and race, LDL-C, triglycerides, BMI and smoking for men.

Table 2

Crude Incidence Rates and Age-Adjusted Rate Ratios of Incident IPH by Tertiles of Height

	Height (cm) in Women			Height (cm) in Men		
	< 159.00	**159.00 – 163.90**	**≥ 164.00**	**< 172.49**	**172.49 – 177.90**	**≥ 178.00**
Incident IPH (n/N)	53/3872	36/3664	26/4252	19/3028	33/2765	21/3402
Person-Years of Follow-up	59,754	60,598	72,592	44,121	42,171	55,406
Crude Incidence Rate per 100,000	88.70	59.41	35.82	43.07	78.26	37.90
Age-Adjusted Relative Rate (95% CI)	1.00	0.92 (0.60 – 1.41)	0.73 (0.44 – 1.21)	1.00	2.19 (1.24 – 3.85)	1.66 (0.95 – 2.88)
Multivariable Adjusted Hazard Ratio (95% CI)*	1.00	0.87 (0.55 – 1.39)	0.63 (0.37 – 1.08)	1.00	2.11 (1.16 – 3.85)	1.27 (0.64 – 2.52)

*Adjusted for age, systolic blood pressure, log triglycerides, LDL-C, fibrinogen and race

Table 3

Sex-Specific Multivariable Adjusted Model of incident IPH

WOMEN	**HR**	**95% CI**
Events: 100		
Height, SD = 6.3 cm	0.81	0.66 – 0.99
Age, 10 years	2.18	1.74 – 2.72
SBP, 20 mmHg	1.44	1.21 – 1.72
Triglycerides, 0.5 log mg/dL *	0.67	0.52 – 0.87
LDL-C, 40 mg/dL	0.78	0.63 – 0.98
Fibrinogen, 65 mg/dL	1.21	1.01– 1.46
White	0.67	0.43 – 1.06
Men		
Events: 64		
Height, SD = 6.7 cm	1.09	0.84 – 1.40
Age, 10 years	1.92	1.45 – 2.55
SBP, 20 mmHg	1.45	1.17 – 1.81
Triglycerides, 0.5 log mg/dL *	0.89	0.68 – 1.17
LDL-C, 40 mg/dL	0.71	0.53 – 0.96
Fibrinogen, 65 mg/dL	1.27	1.04 – 1.55
White	0.49	0.28 – 0.85

* Log transformed