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Association of Left Ventricular Hypertrophy with Cognitive Decline and Dementia Risk over 20 years: The Atherosclerosis Risk in Communities - Neurocognitive Study (ARIC-NCS)

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Abstract

Background —Left ventricular hypertrophy (LVH) is an indicator of organ damage largely due to hypertension. We assessed whether LVH was associated with dementia and cognitive function in the Atherosclerosis Risk in Communities study.

Methods —Our analysis included 12,665 individuals (23% black race, 56% female, mean age 57) who attended visit 2 in 1990–92. Cornell voltage (SV3 + RaVL) was derived from 12-lead electrocardiograms and dichotomized as LVH using sex-specific criteria (> 28mm men; >22mm women). Incident dementia was defined by expert review using a predetermined algorithm and cognitive function was measured longitudinally using 3 tests. A Cox model was used to evaluate the association between time-dependent LVH and dementia adjusted for time-varying covariates from 1990–2013. Linear regression models fit with generalized estimating equations were used to evaluate LVH with cognitive function.

Results —During a mean follow-up of 18 years, we identified 544 participants with LVH and 1195 dementia cases. LVH was associated with a higher risk of dementia: multivariable hazard

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ratio = 1.90; 95% confidence interval (CI): 1.47–2.44. Those with LVH had lower cognitive scores at baseline; however there was no difference in the rate of cognitive decline over 20 years in those with LVH vs. those without LVH.

Conclusion —In this population-based study, LVH measured during mid-life was associated with an increased risk of incident dementia; however, LVH was not associated with additional cognitive decline. These results underscore the need for hypertension control to prevent subclinical brain injury.

Keywords

left ventricular hypertrophy; dementia; cognitive function; aging

Background

Left ventricular hypertrophy (LVH) is an indicator of target organ damage mainly due to hypertension.¹ LVH is associated with cardiovascular morbidity and mortality, including myocardial infarction, coronary heart disease (CHD), sudden death, stroke, and congestive heart failure, independent of traditional cardiovascular risk factors.^{2–5} Furthermore, LVH is more prevalent in blacks than in whites, and is an independent predictor of CHD / cardiovascular disease (CVD) survival in blacks beyond traditional risk factors.^{6–8} LVH, measured by 12-lead electrocardiogram (ECG), may serve as a marker for chronicity and degree of blood pressure elevation as an indicator of long-term burden of vascular risk factors.⁹ Additionally, LVH is associated with an increased risk of all-cause cardiovascular events even in non-hypertensive individuals,^{4, 10} and therefore may be an independent risk factor for cognitive function.

An association between blood pressure and cognitive decline has been established,^{11, 12} including an inverse relationship between the magnitude and duration of blood pressure elevation and cognitive performance.¹³ Despite the extensive literature on this area, few studies have explored the association between LVH with cognitive function and dementia. In a cross-sectional study, left ventricular (LV) mass, measured by echocardiography, was associated with lower global cognitive function and increased risk of dementia in the elderly, independent of risk factors including blood pressure.¹⁴ In another cross-sectional study of stroke-free participants with an average age of 57 years, LV mass was associated with cognitive performance after adjustment for blood pressure, but the association was attenuated after additional adjustment of CVD and risk factors, suggesting CVD risk factors play an important role in the relationship between LV mass and cognition.⁹ In the Helsinki Aging Study, LV mass was associated with a 5-year decline in Mini-Mental State Examination scores for 160 elderly participants,¹⁵ indicating the need for additional longitudinal studies to study the association between LVH and cognitive measures.

In this study, we examined the association of LVH with cognitive decline and dementia over time (approximately 20 years) in a bi-racial community sample. The Atherosclerosis Risk in Communities (ARIC) study provides a large sample size, extensive follow-up time, and information on numerous covariates to evaluate whether these associations exist independent of other risk factors.

METHODS

Study population

The ARIC study is a mostly biracial, prospective cohort study of cardiovascular disease and atherosclerosis risk factors.¹⁶ Participants at baseline (1987–1989) included 15,792 men and women aged 45–64, recruited from 4 communities in the US (Washington County, Maryland; the northwest suburbs of Minneapolis, Minnesota; Jackson, Mississippi; and Forsyth County, North Carolina). ARIC participants were mostly white in the Washington County and Minneapolis centers, only African-American in the Jackson center, and included both races in Forsyth County. After the initial assessment, study participants were examined 4 additional times (1990–92 (visit 2), 1993–95 (visit 3), 1996–98 (visit 4), and 2011–13 (visit 5)). Additionally, ARIC participants have received annual follow-up calls (semi-annual after 2012), with response rates of 90% among survivors. Cognitive scores were first measured at visit 2, which was our baseline visit for this analysis.

Of the 14,348 participants who attended visit 2 (1990–92) in the ARIC study, we included 13,925 with ECG measures and cognitive scores. Of those, we excluded individuals who were of a racial group other than white or African-American along with nonwhites in the Minneapolis and Washington County field centers due to low numbers (n=91), those with prevalent dementia at visit 2 (n=3), prevalent stroke at visit 2 (n=236), those with major intraventricular conduction delay on ECG (including complete bundle branch blocks, Wolf Parkinson-White Syndrome and/or QRS duration ≥ 120 ms) (n=337), and those missing covariates (n=593). After exclusions, our study population included 12,665 participants (23% black race, 56% female).

This study was approved by institutional review boards at each participating center and all study participants provided written informed consent.

Dementia and cognitive function ascertainment

Dementia was defined by expert review using a predetermined algorithm, incorporating data from the cognitive evaluations at visits 2, 4 and 5, and consisting of a full neuropsychological assessment (visit 5 only), interviews, informant interviews, hospital discharge codes, or diagnostic codes from death certificates, as previously described.¹⁷ The algorithm was based on the National Institute on Aging-Alzheimer's Association working group formulations of dementia¹⁸ and DSM-5.¹⁹ Dementia diagnoses were established by review of all information by a physician (neurologist or geriatrician) and a neuropsychologist. If the 2 disagreed, a third clinician reviewed the case to arrive at a final diagnosis.¹⁷ The clinician reviewers agreed with the algorithmic diagnosis 94% of the time.¹⁷

At visits 2, 4 and 5, ARIC participants underwent cognitive assessment consisting of 3 main instruments: a delayed word recall test (DWRT),²⁰ digit symbol substitution test (DSST),²¹ and a word fluency test (WFT).^{22,23} Briefly, DWRT is a test of verbal learning and recent memory. Participants were given 10 common nouns that they were asked to use in a sentence. After a 5 minute delay, participants were asked to recall as many of the 10 words as they could in within 60 seconds. The score is the number of words correctly recalled.

DSST is a test of executive function and processing speed. Participants were asked to translate numbers to symbols using a key. The score is the total number of correctly transferred numbers to symbols within 90 seconds, and the range of possible scores is 0–93. WFT is a test of executive function and language and tests the ability to spontaneously generate words beginning with a particular letter. Participants were given 60 seconds for each of the letters ‘F’, ‘A’ and ‘S’. The score is the total number of words generated across the three trials. Additionally, the 3 test scores were combined to create a global score of cognitive function, consistent with previously published ARIC neurocognitive papers.^{12,17,24}

LVH ascertainment

At each ARIC study visit, a standard supine 10-second 12-lead ECG was performed using a MAC PC cardiograph (Marquette Electronics Inc, Milwaukee, WI) and transmitted to the ARIC ECG Reading Center for coding, interpretation and storage. ECG data processing, monitoring and quality control have been described elsewhere.²⁵ We examined associations using the dichotomous (yes/no) LVH sex-specific Cornell voltage criteria ($SV_3 + RaVL > 28\text{mm}$ for men, and $>22\text{mm}$ for women).²⁶ Cornell voltage has sex-specific cut-off points, and additionally is composed of limb and chest lead components unlike several other LVH criteria, making it more stable and less liable to be impacted by changes in body mass over time. LVH was additionally explored as a continuous variable using Cornell voltage, as the association between LVH measures with most CVD is linear.²⁷ In a sensitivity analysis, we alternatively defined LVH using the SokolowLyon index ($SV_1 + RV_5/V_6 \geq 3.5\text{ mV}$ and/or $RaVL \geq 1.1\text{ mV}$).²⁸

Covariate measures

Detailed procedures on covariate measure have been previously published.¹⁶ In brief, baseline information was collected on education level and occupation, and participants underwent a physical exam at every visit. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Blood pressure was measured using a random-zero sphygmomanometer after 5 minutes of rest in the sitting position, and was defined as the average of the 2nd and 3rd measurements taken. The use of anti-hypertensive medications was confirmed by checks on medications brought to each visit by the patient. ARIC participants had *APOE* genotyping performed using the TaqMan assay (Applied Biosystems, Foster City, CA) using blood samples from visit 1. Diabetes mellitus was defined as fasting glucose $\geq 126\text{ mg/dL}$, non-fasting glucose $\geq 200\text{ mg/dL}$, treatment for diabetes mellitus, or self-reported physician diagnosis of diabetes. Participants self-reported current smoking status. Blood samples were collected at each visit following a fast of at least eight hours and sent to the ARIC Central Lipid Laboratory for processing where total plasma cholesterol was determined by enzymatic methods.¹⁶ At each visit, prevalent heart failure (HF) was defined as the reported use of HF medication in the previous two weeks, presence of HF according the Gothenburg criteria (only at the baseline visit), or having developed incident HF from the previous visit.²⁹ Incident HF was defined as the presence of ICD-9-CM code 428 in any hospitalization during follow-up.³⁰ Prevalent CHD was defined as prior cardiovascular revascularization, physician-diagnosed myocardial infarction, or presence of a previous myocardial infarction by ECG and incident CHD was ascertained by the ARIC Morbidity and Mortality Classification Committee using data from follow-up

calls, hospitalization records and death certificates.³¹ Atrial fibrillation was ascertained by three different sources in the ARIC study: ECGs performed at study visits, hospital discharge codes, and death certificates.³² Prevalent stroke was defined as the self-reported physician diagnosis of a stroke prior to visit 1, and following visit 1 was adjudicated from diagnosis codes indicative of cerebrovascular disease.³³ Incident stroke was defined as the first probable or definite hospitalized stroke occurring in a participant free of a history of diagnosed stroke at baseline. A composite CVD risk score was calculated using the Framingham risk score.³⁴

Statistical analysis

The association of LVH with dementia incidence was assessed using a Cox proportional hazards model, allowing for time-dependent LVH and time-varying covariates measured at visits 2, 3 and 4. Time was from visit 2 (1990–92) until dementia, death, loss to follow-up, or administrative censoring on December 31st, 2013, whichever occurred first. Models were adjusted for the baseline variables of sex, race/center (6 levels), APOE genotype (0, 1 or 2 alleles), education (high school graduate vs. not), occupation (categorical), and the time-varying covariates of age (continuous), smoking (current vs. not current), BMI (continuous), systolic and diastolic blood pressure (continuous), anti-hypertensive medication use (yes/no), total cholesterol (continuous), diabetes (yes/no), CHD (yes/no) and heart failure (yes/no). Additionally, model 3 adjusted for time-dependent stroke and atrial fibrillation, which were ascertained continuously through 2013. To visualize the association of LVH and dementia, we calculated the cumulative risk of incident dementia by time-dependent LVH status, taking into account the competing risk of death. We explored the association between continuous Cornell voltage and dementia using restricted cubic splines.

To access the association between cognitive function and LVH, we first calculated cognitive test Z-scores ((test score - mean score) / standard deviation) of the 3 neuropsychological tests and the combined global test at each of the 3 visits. We accessed the association of LVH and cognitive scores at baseline (visit 2) using linear models, adjusted for baseline covariates. To assess the association of LVH and cognitive function over time, we used LVH, covariates and cognitive scores measured at visits 2, 4 and 5. To test the association between LVH and cognitive decline rate, we used linear regression models fit with generalized estimating equations to evaluate associations with cognitive performance trajectories using robust variance and an unstructured correlation matrix. There was an approximate 6 year difference between measures from visit 2 to visit 4, and an approximate 14 year difference between measures from visit 4 to visit 5. To account for the different slopes of decline during the 20 years of total follow-up, models included time modeled using a linear spline with a knot at 6 years (visit 4) and interaction terms between time and LVH status. The association between LVH and cognitive scores was assessed using the same covariates from the 3 models listed above. For this analysis, LVH and covariates were measured at visits 2, 4, and 5 to correspond to the dates of cognitive testing. Interactions between follow-up time and covariates were explored as appropriate. Separate models were run for each cognitive test (DWRT, DSST, and WFT) and the global cognitive score.

Additionally, to account for attrition during follow-up, we conducted a sensitivity analysis using inverse probability of attrition weighting (IPAW).^{24,35} Weights for each individual were calculated at visits 4 and 5, and were the inverse of the estimated probabilities of 1) being alive at time of the follow-up visit, and 2) attending the visit, conditional on being alive at the time of the exam, and the final weights were stabilized by the baseline variables of age, sex, race/center, education, and APOE genotype. In a final sensitivity analysis, we alternatively defined LVH using the Sokolow-Lyon index to assess the association between this measure of LVH and cognitive decline / dementia.

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All statistical analyses were performed with SAS v 9.4 (SAS Inc, Cary, NC) or STATA 14.0, StataCorp LP, College Station, TX.

Results

At baseline (1990–1992), 344 participants were identified as having LVH. Baseline characteristics for ARIC participants by baseline LVH status are shown in Table 1. Participants with prevalent LVH at baseline were more likely to be older, female, black race, and have a higher prevalence of CVD risk factors, including high blood pressure, and be taking anti-hypertensive medications. The unadjusted baseline cognitive scores are much lower in those with LVH; the mean global z-score is 0.69 lower in those with LVH compared to those without LVH.

Dementia

A total of 544 LVH cases were identified by ECG in visits 2, 3 and 4. During a median followup of 20.2 years, we identified 1195 incident dementia cases. The incidence rate of dementia was 5.1 and 8.9 per 1000 person years in participants without LVH and with LVH, respectively. The hazard ratio (HR) and 95% confidence interval (CI) of time-dependent LVH and incident dementia, adjusting for age, sex and race/center was 2.14 (1.67–2.74) (Table 2). After additional adjustment for covariates including stroke and atrial fibrillation, the association between LVH and incident dementia was only partially attenuated and remained significant, HR (95% CI) = 1.90 (1.47–2.44). After further adjustment for the Framingham CVD risk score, the association remained significant, HR (95% CI) = 1.76 (1.36–2.27). There were no significant interactions for sex ($p=0.53$) or race ($p=0.97$) in the fully adjusted model. Figure 1 depicts the cumulative risk of dementia by time-dependent LVH, adjusting for the competing risk of death. Furthermore, the association between baseline Cornell voltage and incident dementia was examined using a restricted cubic spline,

and the association appears linear (Figure 2). Using the continuous variable for LVH, a 5 mm increase in Cornell voltage is associated with a 7% (95% CI 4%–13%) increased risk in incident dementia (Table 2).

Finally, in a sensitivity analysis, we alternatively defined LVH using the Sokolow-Lyon index, and the results are similar to LVH defined using the Cornell voltage. The association with dementia was slightly stronger using the Sokolow-Lyon LVH definition; the fully-adjusted model (model 3) association was significant, HR (95% CI) = 2.06 (1.75–2.42).

Cognitive function

Figure 3 depicts the raw, unadjusted cognitive scores at each visit. In general, the median score value is higher in those without LVH at baseline, and the median score value is similar with regards to LVH status by the last visit.

The cross-sectional association of baseline LVH with baseline cognitive scores is shown in Table 3. After adjustment for age, sex, and race/center, participants with prevalent LVH had significantly lower baseline cognitive scores compared to those without LVH. After further adjustment for cardiovascular risk factors, participants with LVH had significantly lower Global, DWRT, and WFT baseline scores compared to those without LVH.

The association of LVH with the rate of cognitive change over 20 years is shown in Table 4. While there is cognitive decline in both groups over time, there was no difference in the mean rate of decline over 20 years in those with LVH vs. those without LVH. Adjustment for attrition, using IPAW, did not alter the significance of any association. A negative estimate indicates greater 20-year cognitive decline in those with LVH vs. no LVH; however most estimates were positive, and none differed significantly by LVH status, indicating a similar rate of decline. For instance, in the fully adjusted model after adjustment for IPAW, those with LVH had 0.060 (95% CI –0.042 to 0.156) less decline in global z-score over time compared to those without LVH, but this was not statistically significant. LVH was not associated with faster cognitive decline as measured by any of the individual cognitive tests. There were no significant interactions for sex or race in the fully adjusted model in any of the cognitive tests. When we defined LVH using the Sokolow-Lyon index, the association with cognitive function was similar (results not shown).

Discussion

In this population-based study, we observed that LVH measured during mid-life (mean age 57–62) was associated with an increased risk of incident dementia; however, LVH was not associated with additional cognitive decline over time compared to those without LVH. The association with dementia was independent of many time-dependent risk factors, including blood pressure, atrial fibrillation, and stroke, and was similar with regards to sex and black/white race. The significant association between LVH and dementia even after adjustment for blood pressure underscores that LVH reflects either prolonged exposure to hypertension or severe hypertension which is not captured by a single blood pressure measurement.

To our knowledge, this is the first study that reports the longitudinal association between LVH measured by ECG and the risk of incident dementia. One prior cross-sectional study has reported that echocardiography-measured LV mass was associated with an increased risk of dementia in an elderly population, independent of blood pressure.¹⁴ This association should be confirmed in other aging cohorts, and if confirmed, can provide further evidence on the link between the long-term burden of vascular risk factors and an increased risk of dementia.

Growing evidence highlights the impact of cardiovascular risk factors on accelerated brain aging. Hypertension, smoking and diabetes are strong risk factors for dementia risk,³⁶ and have been also associated with faster cognitive decline.^{12, 37} Vascular cognitive impairment and dementia is expected to increase exponentially given prevalent risk factors and the aging of the US population. Therefore, understanding the exact mechanisms through which cardiovascular risk factors influence brain aging is key to develop informed preventive and therapeutic strategies. Studying intermediate phenotypes, such as LVH, can move the field in that direction. One possible mechanism for the observed increased dementia risk in LVH could be chronic increased systemic blood pressure which leads to LVH, impaired ventricular filling, and consequently left ventricular diastolic dysfunction, resulting in hypoperfusion, a purported mechanisms to explain the risk of dementia in cardiac diseases. These processes will also lead to left atrial enlargement and impaired left atrial function, and diastolic dysfunction can also lead to heart failure. Future studies can address the associations between these measures, such as diastolic dysfunction, with incident dementia.

The association between blood pressure and cognitive decline has been established,^{11, 12} including an inverse relationship between the magnitude and duration of blood pressure elevation and cognitive performance.¹³ The association of LVH and cognitive function is mixed: In a cross-sectional study of stroke-free participants with an average age of 57 years, LV mass was associated with cognitive performance after adjustment for blood pressure, but the association was attenuated after additional adjustment for CVD and risk factors, suggesting CVD risk factors may play an important role in the relationship between LV mass and cognition.⁹ In the Helsinki Aging Study, LV mass was associated with a 5-year decline in Mini-Mental State Examination scores for 160 elderly participants.¹⁵ A recent study reported steeper decline in cognitive function of older adults (mean age 75) with LVH after a follow-up of 3 years, independent of CVD risk factors.³⁸ In our study, participants with LVH had significantly lower baseline cognitive scores, and therefore likely had little room for additional decline over time. To provide some context for measures of cognitive function in older adults, a typical cross-sectional cognitive score is approximately 0.04–0.05 standard deviation units lower for each additional year of participant age.^{39–41} That is, a 60-year old would typically have a score that is 0.04–0.05 units lower than a 59-year old. In our study, the baseline fully-adjusted global z-score was 0.16 units lower in those with LVH compared to those without LVH, equating to those with LVH having a score similar to what we would expect in someone approximately 4 years older ($0.16 / 0.04 = 4$). To note, accounting for attrition had little effect on the cognitive decline estimates in our study.

Cognitive decline is a precursor to dementia and our study found an association with incident dementia but not with cognitive decline, suggesting that once LVH develops, we

have already lost the opportunity to prevent dementia. This is in contrast to hypertension, which is related to greater cognitive decline, providing an opportunity to control blood pressure to prevent cognitive decline, and hence prevent dementia. By the time long-term hypertension develops into LVH, the cognitive capacities may have already been altered through vascular dysfunction due to hypertension, enough so that there is negligible additional decline after the date of LVH diagnosis.

Several study limitations should be noted. A time gap exists between 1998 and 2011 in which we are not able to ascertain LVH status, and therefore, we may have misclassification of the exposure and are underestimating the prevalence of LVH and its association with dementia. We do have measures on LVH in 2011–2013; however, since most dementia was diagnosed in this similar time frame, we cannot be certain if LVH or dementia occurred first. Similarly, the date of dementia varies among individuals depending on the severity of symptoms and the date at which expert review assessments were made (i.e. an annual follow-up call made early in the year vs. late in the year). Those with LVH are more likely to be hospitalized and be seen more frequently by a doctor, and therefore may be more likely to be diagnosed with dementia, introducing bias. LVH was ascertained by ECG, which is not considered the gold standard criteria; however Cornell voltage has sex-specific cut-off points, and additionally is composed of limb and chest lead components unlike several other LVH criteria, making it more stable and less liable to be impacted by changes in body mass over time. We do not know whether LVH in all participants was the result of hypertension; although we know from literature that is the case most of the time. As with any observational study, residual confounding may exist, though we have extensively adjusted for time-varying covariates to minimize this bias. Finally, the three cognitive scores measured in ARIC cannot be considered a true measure of global cognitive function since they do not assess all cognitive domains exhaustively.

Despite these limitations, our study has important strengths such as a large, bi-racial sample size, a lengthy follow-up time, numerous LVH and dementia cases, comprehensive cognitive tests, and an extensive list of measured covariates.

In conclusion, in this population-based study, LVH measured during late mid-life (mean age 57–63) was associated with an increased risk of incident dementia. LVH was associated with lower mid-life cognitive scores; however, LVH was not associated with additional cognitive decline over time, likely due to the existing low cognitive scores in those with LVH at the time of diagnosis. The significant association between LVH and dementia even after adjustment for blood pressure indicates that LVH reflects either prolonged exposure to hypertension or severe hypertension which is not captured by a single blood pressure measurement, and underscores the need for long-term hypertension monitoring and control to prevent subclinical brain injury.

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- Left ventricular hypertrophy is associated with an increased risk of dementia
- Left ventricular hypertrophy was measured by electrocardiogram in mid-life
- Results underscore the need for mid-life hypertension control to prevent dementia

Figure 1. Cumulative risk of incident dementia by time-dependent left ventricular hypertrophy (LVH), adjusting for the competing risk of death, ARIC, 1990–2013.

Figure 2:

Association between baseline Cornell voltage and incident dementia, adjusted for baseline variables in the fully adjusted model, ARIC, 1990–2013. The solid line depicts the hazard ratio, the gray area represents the 95% confidence interval (CI) and the histogram illustrates the distribution of baseline Cornell voltage in the ARIC population.

Figure 3.

Raw cognitive score values depicted by LVH status at each visit for Panel A. Delayed Word Recall Test (DWRT); Panel B. Digit Symbol Substitution Test (DSST); Panel C. Word Fluency Test (WFT), ARIC, 1990–2013. The line through each box plot indicates the median value, while the 75th and 25th percentiles are depicted by the edges of each box.

Table 1.

Baseline characteristics of participants by baseline left ventricular hypertrophy (LVH) status, ARIC, 1990–1992

	All (12,665)	No LVH (n=12,321)	LVH (n=344)
Age (years)	56.9 (5.7)	56.9 (5.7)	58.3 (5.8)
Male	5557 (44%)	5430 (44%)	127 (37%)
Race-field center			
White-Minneapolis	3441 (27%)	3401 (27%)	40 (12%)
White-Washington	3305 (26%)	3267 (27%)	38 (11%)
White Forsyth	2947 (23%)	2897 (24%)	50 (15%)
Black-Forsyth	339 (3%)	316 (3%)	23 (7%)
Black-Jackson	2633 (21%)	2440 (20%)	193 (56%)
Education			
Less than High school degree	2630 (21%)	2507 (20%)	123 (36%)
High school, GED, or vocational school	5328 (42%)	5212 (42%)	116 (34%)
College, graduate, or professional school	4707 (37%)	4602 (37%)	105 (31%)
APOE s4 alleles			
0	8774 (69%)	8544 (69%)	230 (67%)
1	3556 (28%)	3452 (28%)	104 (30%)
2	335 (3%)	325 (3%)	10 (3%)
Cigarette smoking status			
Current	2808 (22%)	2728 (22%)	80 (23%)
Former	4778 (38%)	4669 (38%)	109 (32%)
Never	5079 (40%)	4924 (40%)	155 (45%)
Body mass index (kg/m ²)	28.9 (5.4)	27.9 (5.4)	29.1 (5.8)
Systolic blood pressure (mmHg)	121.3 (18.5)	120.8 (18.1)	138.4 (25.2)
Diastolic blood pressure (mmHg)	72.1 (10.2)	71.9 (10.1)	77.7 (12.6)
Hypertensive medication	4002 (32%)	3782 (31%)	220 (64%)
Diabetes mellitus	1819 (14%)	1726 (14%)	93 (27%)
Total cholesterol (mg/dL)	209.9 (39.4)	209.8 (39.2)	215.9 (42.7)
Prevalent coronary heart disease	644 (5%)	616 (5%)	28 (8%)
Prevalent heart failure	545 (4%)	514 (4%)	31 (9%)
Mean cognitive score (SD)			
Global Z score	0.02 (0.99)	0.04 (0.98)	−0.65 (1.1)
DWRT, number of words	6.6 (1.5)	6.7 (1.5)	6.0 (1.7)
DWRT, Z score	0.02 (0.99)	0.03 (0.98)	−0.41 (1.1)
DSST, number of symbols	44.9 (13.8)	45.2 (13.9)	35.1 (15.2)
DSST, Z score	0.02 (0.99)	0.04 (0.98)	−0.67 (1.1)
WFT, Number of words	33.3 (12.5)	33.5 (12.4)	27.7 (12.7)
WFT, Z score	0.01 (1.00)	0.03 (0.99)	−0.44 (1.0)

Values correspond to mean (SD) or N (percentage)

DWRT, delayed word recall test

DSST, digit symbol substitution test

WFT, word fluency test

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Table 2.

Multivariable hazard ratio (95% confidence interval) of incident dementia by left ventricular hypertrophy (LVH), ARIC, 1990–2013

	No LVH (n=12,121)	LVH (n=544)	p-value	Cornell voltage, per 5 mm increase	p-value
# Dementia events	1125	70			
Person-years	221,300	7,875			
Incidence Rate (95% CI) *	5.1 (4.80–5.4)	8.9 (6.9–11.2)			
Hazard Ratio (95% CI), Model 1	1 (REF)	2.14 (1.67–2.74)	<0.0001	1.10 (1.04–1.16)	0.0004
Hazard Ratio (95% CI), Model 2	1 (REF)	1.91 (1.48–2.46)	<0.0001	1.08 (1.02–1.13)	0.007
Hazard Ratio (95% CI), Model 3	1 (REF)	1.90 (1.47–2.44)	<0.0001	1.07 (1.04–1.13)	0.02

* Incidence rate is per 1000 person-years

Model 1 is adjusted for age, sex and race / field center

Model 2: Model 1 and additionally adjusted for education, occupation, apolipoprotein E, smoking, body mass index, systolic blood pressure, diastolic blood pressure, anti-hypertensive medication, total cholesterol, diabetes, prevalent coronary heart disease, prevalent heart failure

Model 3: Model 2 and additionally adjusted for time-dependent stroke and atrial fibrillation

All covariates except sex, race-field center, education, occupation and apolipoprotein E are time-varying variables

Table 3.
Association of baseline cognitive scores with prevalent left ventricular hypertrophy (LVH) ARIC, 1990–1992

		LVH			
		Beta estimate (95% CI)			
	No LVH	Model 1	p-value	Model 2	p-value
Global Z score	0 (Ref)	−0.25 (−0.34 to −0.16)	<0.0001	−0.16 (−0.24 to −0.08)	0.0001
DWRT Z score	0 (Ref)	−0.22 (−0.32 to −0.11)	<0.0001	−0.17 (−0.27 to −0.06)	0.001
DSST Z score	0 (Ref)	−0.14 (−0.22 to −0.05)	0.001	−0.05 (−0.13 to 0.02)	0.15
WFT Z score	0 (Ref)	−0.22 (−0.32 to −0.12)	<0.0001	−0.15 (−0.24 to −0.05)	0.003

Model 1 is adjusted for age (centered at 60), sex and race / center.

Model 2: Model 1 and additionally adjusted for education, occupation, apolipoprotein E, smoking, body mass index, systolic blood pressure, diastolic blood pressure, anti-hypertensive medication, total cholesterol, diabetes, coronary heart disease, heart failure, and atrial fibrillation

A negative estimate indicates a lower cognitive score in those with LVH vs. no LVH

DWRT, delayed word recall test

DSST, digit symbol substitution test

WFT, word fluency test

Table 4.

Additional adjusted 20-Year cognitive change associated with left ventricular hypertrophy (LVH) ARIC, 1990–2013

	Additional Cognitive change in z-score (95% CI)					
	No LVH			LVH		
Un-weighted	Model 1	p-value	Model 2	p-value	Model 3	p-value
Global Z score	0 (Ref)	0.065 (−0.032 to 0.162)	0.19	0.068 (−0.026 to 0.163)	0.16	0.061 (−0.033 to 0.155)
DWRT Z score	0 (Ref)	0.075 (−0.076 to 0.225)	0.33	0.059 (−0.091 to 0.210)	0.44	0.055 (−0.091 to 0.206)
DSST Z score	0 (Ref)	0.032 (−0.048 to 0.112)	0.43	0.044 (−0.033 to 0.120)	0.26	0.035 (−0.041 to 0.111)
WFT Z score	0 (Ref)	0.082 (−0.010 to 0.174)	0.08	0.088 (−0.003 to 0.178)	0.06	0.082 (−0.008 to 0.172)
Adjusted for IPAW	Model 1	p-value	Model 2	p-value	Model 3	p-value
Global Z score	0 (Ref)	0.039 (−0.065 to 0.143)	0.47	0.068 (−0.032 to 0.167)	0.18	0.060 (−0.042 to 0.156)
DWRT Z score	0 (Ref)	0.047 (−0.116 to 0.211)	0.57	0.055 (−0.108 to 0.219)	0.51	0.047 (−0.116 to 0.210)
DSST Z score	0 (Ref)	−0.002 (−0.088 to 0.084)	0.96	0.026 (−0.055 to 0.106)	0.53	0.014 (−0.065 to 0.093)
WFT Z score	0 (Ref)	0.071 (−0.025 to 0.168)	0.15	0.101 (−0.001 to 0.183)	0.05	0.094 (−0.002 to 0.179)

Model 1 is adjusted for age (centered at 60), sex and race / center, time as a linear spline with a knot at 6 years, age by time spline terms, sex by time spline terms, and race / center by time spline terms.

Model 2: Model 1 and additionally adjusted for education, occupation, apolipoprotein E, smoking, body mass index, systolic blood pressure, diastolic blood pressure, anti-hypertensive medication, total cholesterol, diabetes, prevalent coronary heart disease, prevalent heart failure, plus all these variables by time spline terms.

Model 3: Model 2 and additionally adjusted for stroke and atrial fibrillation, plus these variables by time spline terms

IPAW: inverse probability of attrition weighting. This weighting accounts for attrition during follow-up.

A negative estimate indicates greater 20-year cognitive decline in those with LVH vs. no LVH

DWRT, delayed word recall test

DSST, digit symbol substitution test

WFT, word fluency test