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Relation of Elevated Resting Heart Rate in Mid-Life to Cognitive Decline Over 20-years (from the Atherosclerosis Risk in Communities [ARIC] Study)

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Abstract

Resting heart rate (RHR) is independently associated with cardiovascular disease (CVD) risk. We determined whether RHR, measured in mid-life, is also associated with cognitive decline. We studied 13,720 middle-aged white and black ARIC participants without a prior history of stroke or atrial fibrillation. RHR was obtained from a 12-lead resting electrocardiogram at the baseline visit (1990-1992) and categorized into groups as <60 (reference), 60-69, 70-79 and ≥80 bpm. Cognitive scores were obtained at baseline and at up to two additional visits (1996-1998 and 2011-2013). The primary outcome was a global composite cognitive score (Z-score) derived from 3 tests: delayed word recall, digit symbol substitution, and word fluency. The associations of RHR with

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The authors do not report any conflicts of interest.

cognitive decline and incident dementia were examined using linear mixed-effects and Cox hazard models, respectively, adjusting for socio-demographics, CVD risk factors and AV-nodal blockade use. Multiple imputation methods were used to account for attrition over follow-up. Participants had mean±SD age of 58±6 years; 56% were women, 24% black. Average RHR was 66±10 bpm. Over a mean follow-up of 20-years, those with RHR ≥80 bpm had greater global cognitive decline [average adjusted Z-score difference −0.12 (95% Cl −0.21, −0.03)] and increased risk for incident dementia [Hazard Ratio 1.28 (1.04, 1.57)], compared to those with RHR <60 bpm. In conclusion, elevated RHR is independently associated with greater cognitive decline and incident dementia over 20-years. Further studies are needed to determine whether the associations are causal or secondary to another underlying process, and whether modification of RHR can affect cognitive decline.

Keywords

Heart Rate; Cognitive Decline; Risk Factors

Introduction

In an aging population, preservation of cognitive function is a key focus for preventive measures.[1] Cardiovascular diseases (CVD) and cardiovascular risk factors are associated with cognitive decline and with dementia.[2] Resting heart rate (RHR) is an easily measured and independent predictor of mortality and CVD risk.[3,4] It is also potentially modifiable through improved fitness and pharmacological agents. However, despite the established association of RHR with future CVD risk, there are very few studies examining RHR and cognitive decline. One study showed that lower RHR was associated with less cognitive decline in patients with prior ischemic strokes, but little is known about that relationship in the general population.[5] Thus, we used data from the Atherosclerosis Risk in Communities (ARIC) study to examine the cross-sectional and longitudinal associations of RHR with cognitive decline in a community-based cohort. We hypothesized that elevated RHR will be independently associated with lower crosssectional cognitive function and with greater cognitive decline over 20 years.

Methods

The ARIC study is an ongoing prospective epidemiological study that recruited 15,792 men and women aged 44 to 66 years from four U.S. communities (suburbs of Minneapolis, MN; Washington County, MD; Forsyth County, NC; Jackson, MS) from 1987 to 1989 (visit 1). The ARIC design has been previously described.[6] The initial cognitive testing in ARIC was performed at visit 2 from 1990 to 1992, and thus visit 2 represents the baseline for our analysis. Cognitive testing was then repeated at ARIC visits 4 and 5, which took place from 1996 to 1998 and from 2011 to 2013, respectively.

Visit 2 initially included 14,348 participants; however, we limited our analysis to 13,720 participants. We excluded 91 individuals who were neither white nor black and blacks from the MN and MD sites due to small numbers, 272 who had prior history of stroke, 100 with atrial fibrillation/flutter, 56 participants who had missing RHR, and 109 with missing

information on key covariates. Participant inclusions/exclusions and participant flow throughout the study (visits 2 through 5) are shown in Figure 1. The ARIC Study was approved by the Institutional Review Boards at all ARIC centers, and all participants provided written informed consent at each study visit.

RHR was obtained from a standard 12-lead resting electrocardiogram (ECG) at visit 2. The ECG was performed with participants laying supine with arms relaxed at both sides, after participants had abstained at least 1 hour from smoking and caffeine. We only included participants in sinus rhythm at the time of their ECG. We used baseline RHR (visit 2) for the analysis of cognitive change from visit 2 through visit 5.

Cognitive function was assessed with three tests: Delayed Word Recall (DWR)[7], Digit Symbol Substitution (DSS)[8], and Word Fluency (WF)[9] at visits 2, 4, and 5. In DWR, a test for verbal learning and recent memory, participants learned 10 words and used them in 1 or 2 sentences. After a 5-minute delay, they were given 60 seconds to recall the 10 words, and the score was the number of words correctly recalled. In DSS, a test of executive function and processing speed, participants translated numbers to symbols using a key. The score was the number of numbers correctly translated in 90 seconds. In WF, a test of executive function and language, individuals had to spontaneously generate words beginning with a particular letter, excluding proper nouns. Three letters were used, and the score was the number of words created across the three trials. Our primary outcome was a global Z-score, calculated as the average of these 3 individual Z-scores at each study visit and standardized using the visit 2 global Z-score mean and standard deviation (SD). In other words, a Z score of −1 indicates a cognitive performance 1 SD below the mean visit 2 score. This global Z-score has been used in many other ARIC cognitive analyses.[10-13]

Additionally, at the ARIC Neurocognitive Study (ARIC-NCS) visit, which took place at visit 5 (2011-2013), participants underwent more comprehensive neuropsychological testing and an adjudicated diagnoses of incident dementia was made by an expert panel as previously described.[2] Briefly, the diagnosis of dementia was made based on the longitudinal cognitive results from visits 2, 4, and 5, the more extensive neuropsychological tests at visit 5, informant interviews, and from prior discharge records using ICD-9 codes or death certificate recodes for dementia.

Included covariates were obtained from questionnaires, medication inventory, physical exam, and laboratory data obtained from visit 2 (unless otherwise noted), using standardized protocols.[6] In our analysis, we included demographic variables of age (years), age^2, sex (women, men), and race/center (Minnesota-whites; Maryland-whites; North Carolina-whites; North Carolina-blacks; Mississippi-blacks); in addition, education (<high school; high school, GED, vocational school; college, graduate or professional school, ascertained at visit 1), body mass index (BMI, <25 kg/m^2; 25-<30 kg/m^2, ≥30 kg/m^2), smoking (never, former, current), alcohol consumption (never, former, current), physical activity (score range 1-5, using modified Baecke Physical Activity Questionnaire[14], measured at visit 1). Cardiovascular risk factors such as systolic blood pressure (continuous, mmHg), pulse pressure (continuous, mmHg), cholesterol (total and HDL, continuous, mg/dL), use of antihypertensive and lipid lowering medications (yes/no), presence of diabetes (yes/no;

determined by self-report of physician diagnosis, diabetes medication use, fasting blood glucose ≥126 mg/dL, or non-fasting blood glucose ≥200 mg/dL) and coronary heart disease (CHD) (yes/no), and use of AV-nodal blocking medications were also included. APOE genotype (0, 1, or 2 ∈ alleles) was added as a possible predictor.

RHR was categorized into <60 (reference), 60-69, 70-79 and ≥80 bpm, and also evaluated as a continuous variable per increments of 10 bpm. We used multivariable-adjusted linear regression models to assess the cross-sectional and linear mixed effect regression models with random intercepts and slopes to assess the longitudinal associations of RHR with cognitive function (for the global z-score and the 3 individual tests of DWR, DSS, and WF).

As expected, there were key differences in baseline characteristics of participants who did and did not attend visit 5 (which took place approximately 20-years after visit 2) as shown in Supplemental Table 1. Therefore, as per ARIC-NCS recommendations, we addressed this differential attrition and potential selection bias by using multiple imputations by chained equations[15] to account for missing data, imputing for both missing CVD risk factors (in model 3) and missing outcomes (for those who did not return for visit 5). This imputation method used in this present analysis has been previously validated using simulations in a previously published manuscript using the same ARIC data.[16] Supplemental Table 2 presents the numbers imputed for each variable. We also performed 3 sensitivity analyses regarding imputation as follows: 1) a “complete case” analysis which used all available data without imputation; 2) imputing only for covariates (CVD risk factors) but not outcomes; 3) imputing both covariates (CVD risk factors) and outcomes for only those known to be alive at visit 5.

Additionally, we used Cox proportional hazards regression models to determine hazard ratios and their 95% confidence intervals (CI) for incident dementia by RHR group. We verified that the proportionally hazards assumption was not violated by interacting RHR and log follow-up time; results were not significant.

For all of our analyses, we used three progressively adjusted models. Model 1 adjusted for demographic variables (age, age^2, sex, and race/center groups). Model 2 additionally adjusted for socioeconomic and lifestyle variables including education, BMI, smoking, alcohol consumption, and physical activity. Model 3 further adjusted for cardiovascular risk factors (systolic and pulse pressures, HDL and total cholesterol, use of lipid lowering and antihypertensive medications, presence of CHD, diabetes, use of AV-nodal blocking medications, and APOE4 genotype).

Sensitivity analyses were also performed by excluding participants on AV-nodal blocking agents (i.e. drugs which pharmacologically alter heart rates). We also examined for interactions by race/ethnicity and sex. Additionally, we used a demographic-adjusted (Model 1) restricted cubic spline with knots placed at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles to characterize the association between RHR and incident dementia, centered at RHR of 60 bpm.

A 2-sided p value <0.05 was considered statistically significant, and we performed analyses using Stata Version 15.

Results

Baseline participant characteristics at visit 2 (n=13,720) are found in Table 1. Those with higher RHR were more likely to be women, have higher BMI, have lower physical activity scores, be current smokers, have higher blood pressure and use of antihypertensive medications, and more likely to have diabetes and prevalent CHD.

Supplemental Table 3 shows the cross-sectional associations of RHR with cognitive performance at visit 2. After adjusting for CVD risk factors in the fully adjusted model 3, compared to those with those with RHR <60 bpm, those with RHR ≥80 bpm had lower baseline global cognitive Z-score [average difference −0.08 (95% CI −0.13, −0.03)]. This remained essentially unchanged in sensitivity analyses excluding those on AV-nodal blocking medications (Supplemental Table 4).

Over a mean follow-up of 20-years, participants in each RHR group exhibited cognitive decline (Table 2, Part A). However, there was relatively greater global cognitive decline for those with RHR 70-79 and ≥80 bpm compared to <60 bpm (Table 2, Part B). In the fully adjusted model 3, the average difference in global cognitive decline was −0.07 (95% CI −0.13, −0.004) for participants with RHR 70-79 bpm and −0.12 (−0.21, −0.03) for ≥80 bpm, compared to participants with RHR <60 bpm. Results were generally consistent when excluding participants on AV-nodal blockade medications (Supplemental Table 5).

When change in performance on each individualized cognitive test over 20-years was evaluated by RHR groups, the differential cognitive decline in RHR ≥80 bpm vs. <60 bpm was seen for the DSS and WF tests but not for the DWR (Supplemental Table 6). Results were again consistent when excluding those on AV-nodal blocking agents (not shown).

We performed a series of sensitivity analyses to determine the robustness of our findings. First, in complete-case analysis without imputation, findings remained similar to main results (Supplemental Table 7), as they did in imputation only for covariates (but not outcomes) and for imputation for covariates and outcomes only for those who were alive at visit 5 (Supplemental Table 8). Finally, we looked for evidence of effect modification by sex and race. There was no significant interaction of RHR with 20-year global cognitive decline by sex (p interaction=0.95). However, there was an interaction by race (p interaction=0.004). There was a greater cognitive decline over 20-years associated with higher RHR in whites (Supplemental Tables 9) than blacks (Supplemental Tables 10). The adjusted difference in the 20-year change of global cognitive z-score, for those with RHR ≥80 compared to those <60 bpm, was −0.16 (−0.26, −0.06) in whites and 0.01 (−0.16, 0.18) in blacks (model 3).

We also examined the association of RHR at visit 2 with incident dementia. We observed 1,350 cases of incident dementia after 248,437 person-years of follow up. In the fully adjusted model (model 3), the hazard ratios (95% CI) for incident dementia was 1.28 (1.04, 1.57) for those with RHR ≥80 bpm, compared to <60 bpm, and 1.08 (1.02, 1.14) for every 10 bpm increment in RHR (Table 3). There were no interactions by age, sex, and race/center for the outcome of incident dementia (all p>0.05). Excluding participants on AV-nodal blocking medications resulted in weaker associations for incident dementia with hazard ratios (95% CI) of 1.19 (0.94, 1.49) when comparing ≥80 bpm to <60 bpm and 1.06 (0.99,

1.12) for every 10 bpm increment in RHR (Supplemental Table 11). Restricted cubic spline modeling indicated that the association of RHR with incident dementia was approximately linear (Figure 2).

Discussion

Using data from ARIC, a large mostly biracial community-based study, we found an independent association of RHR and cognitive decline over 20-years. Compared to lower RHR, higher RHR at baseline was associated with more cardio-metabolic comorbidities at baseline, suggesting RHR is associated with a poorer health status. However even after adjusting for physical activity and CVD risk factors, a higher RHR was independently associated with a lower cognitive performance at baseline, with greater cognitive decline over 20-years, and with increased risk of incident dementia. Findings remained robust in multiple sensitivity analyses and the relative effect of a higher RHR on cognitive decline appeared greater in whites than in blacks. Our findings are in line with the one study investigating RHR and cognitive decline after an ischemic stroke,[5] but to our knowledge, there have been no prior studies directly looking at RHR and cognitive decline in the general population.

There are many possible explanations for the observed association between RHR and cognitive decline. First, RHR is thought to reflect a balance of sympathetic and parasympathetic nervous systems. In resting states, the parasympathetic system predominates. Thus, elevated RHR can be a sign of decreased parasympathetic and increased sympathetic activity, which has been seen in patients with prevalent cognitive impairment[17,18] and dementia.[19] Higher RHR may be associated with increased blood pressure through increased sympathetic activity, and patients with mild cognitive impairment and dementia have higher arterial stiffness and pulse pressure.[20] Additionally, higher RHR was independently associated with incident hypertension, even among younger individuals.[21] However, we were able to demonstrate that RHR measured in mid-life was associated with decline in cognitive function over 20-years even after taking into account baseline systolic blood pressure, pulse pressure, and use of antihypertensive medication.

An elevated RHR may also stimulate activation of inflammatory pathways. Higher RHR has been associated with higher levels of inflammatory markers such as hs-CRP, IL-6, and fibrinogen.[22] Vagal (parasympathetic) stimulation decreases the release of inflammatory cytokines in stress states.[23] Inflammation has been associated with cognitive decline, and thus it is possible that an inflammatory effect conferred by sympathetic stimulation (or withdrawal of parasympathetic stimulation), as reflected in RHR, could also extend to neurodegeneration.

We also found an interaction of race in the association of RHR and cognitive decline, with the decline more evident in whites than blacks. The reason for this is uncertain, and in the absence of any *a priori* hypothesis to this regard, this should be considered exploratory only and warrants confirmation in other cohorts. Similarly, we are uncertain why we found RHR to be associated with change in DSS and WF but not DWR – findings which also should be

considered with caution in the absence of any hypotheses about why RHR would influence certain cognitive domains over others.

Our study has many strengths including the prospective design utilizing data from the well-characterized ARIC study, which allowed us to rigorously adjust for numerous potentially confounding demographic, lifestyle, and CVD risk factors, the large sample size, and the prolonged time course over 20-years to study the long-term associations between RHR and cognition. However our findings should be interpreted in the context of several limitations. First, it is an observational study and residual confounding may explain the associations seen. An elevated RHR may be just a very good surrogate marker for a poorer health state. Second, there was attrition over 20-years, with less than half of the initial cohort from visit 2 still present at visit 5. Attrition is a common problem in studies on cognitive decline. As is standard in studies using ARIC-NCS data, we used imputation models to attempt to account for any potential bias related to attrition. This imputation method has been previously validated in the same ARIC cohort.[16] Additionally, our findings remained robust in various sensitivity analyses including a complete case analysis. As an additional limitation, our analysis focused on baseline RHR and we were not able to analyze if changes in RHR over time were associated with differential cognitive decline. However, previous ARIC analyses have also highlighted the importance of other vascular risk factors measured in mid-life with future risk of both incident dementia[2] and brain amyloid deposition in late-life.[24]

In summary, we found that elevated RHR was independently linked to worsening cognition over time. RHR can be readily measured at office clinic visits or by the use of personal fitness trackers; however, it remains underutilized for the purpose of CVD risk assessments. Further studies are needed to determine whether the associations we found between RHR and cognitive decline are causal or secondary to another underlying process. If causal, future interventional studies are needed to determine whether modification of RHR can reduce cognitive decline.

Data availability statement

The ARIC cohort participates in the National Heart, Lung, and Blood Institute's Biologic Specimen and Data Repository (BioLINCC). The ARIC data are available upon request, including data from visits 1 to 5, follow-up data, and ancillary data. Requests for data can be made through the following website: https://biolincc.nhlbi.nih.gov/studies/aric/.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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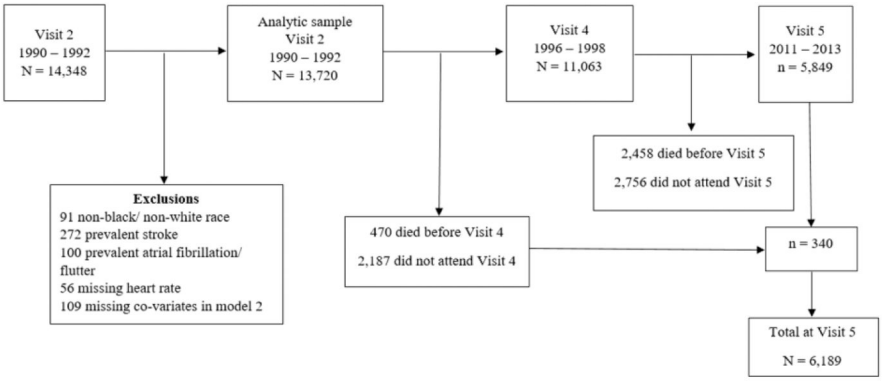

	Visit 2	Visit 4	Visit 5	Total count (for pattern)
Pattern of visit attendance (X=attended)	X	X	X	5,849
	X	X		5,214
	X			2,317
	X		X	340
Total counts (for visit)	13,720	11,063	6,189	

Figure 1.
Participants flow chart including exclusions

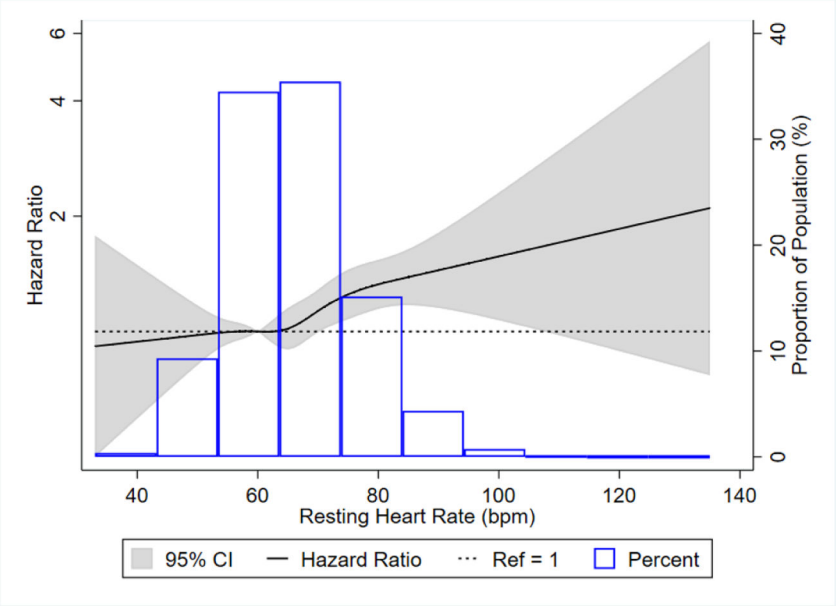

Figure 2:

Associations* of resting heart rate with incident dementia in ARIC, 1990-2013.

*Figure is a restricted cubic spline showing association of resting heart rate with incident dementia in ARIC, 1990-2013. We used resting heart rate of 60 bpm as reference in a Cox proportional hazards model adjusted for age, age^2, sex, and race. The knots were placed at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles.

Table 1.

Baseline Characteristics of Study Participants by Resting Heart Rate Categories, the ARIC Study Visit 2 (1990 -1992)

Baseline Characteristics	Overall	Resting heart rate (bpm)			
		<60	60–69	70–79	≥80
Number of Participants	13,720	3,797	5,490	3,189	1,244
Resting heart rate (beats per minute), mean (SD)	66 (10)	54(4)	64 (3)	74 (3)	86 (6)
Cognitive Test Scores, mean (SD)					
Global Z-Score	0.0 (1.0)	0.0 (1.0)	0.1 (1.0)	0.0 (1.0)	−0.2 (1.0)
Delayed Word Recall Z-Score	0.0(1.0)	0.0 (1.0)	0.1 (1.0)	0.0 (1.0)	−0.2 (1.1)
Delayed Word Recall Raw Score (words)	6.6(1.5)	6.6 (1.5)	6.7 (1.5)	6.6 (1.5)	6.4 (1.6)
Digit Symbol Substitution Z-Score	0.0(1.0)	0.0 (1.0)	0.1 (1.0)	0.0 (1.0)	−0.3 (1.0)
Digit Symbol Substitution Raw Score (points)	44.9 (14.2)	45.2 (14.1)	45.6 (13.8)	44.9 (14.4)	40.6 (14.5)
Word Fluency Z-Score	0.0 (1.0)	0.0 (1.0)	0.0 (1.0)	0.0 (1.0)	−0.1 (1.0)
Word Fluency Raw Score (words)	33.3 (12.5)	33.5 (12.5)	33.5 (12.4)	33.3 (12.6)	31.9 (12.5)
Age (years), mean (SD)	57.5 (5.7)	57.6 (5.7)	57.4 (5.7)	57.2 (5.7)	57.8 (5.8)
Women	7,665 (55.9%)	1,720 (45.3%)	3,154 (57.5%)	1,997 (62.6%)	794 (63.8%)
Race/Center					
Minneapolis, MN Whites	3,696 (26.9%)	1,177 (31.0%)	1,496 (27.3%)	793 (24.9%)	230 (18.5%)
Washington County, MD Whites	3,528 (25.7%)	931 (24.5%)	1,439 (26.2%)	840 (26.3%)	318 (25.6%)
Forsyth County, NC Whites	3,184 (23.2%)	874 (23.0%)	1,306 (23.8%)	750 (23.5%)	254 (20.4%)
Forsyth County, NC Blacks	360 (2.6%)	105 (2.8%)	137 (2.5%)	78 (2.5%)	40 (3.2%)
Jackson, MS Blacks	2,952 (21.5%)	710 (18.7%)	1,112 (20.3%)	728 (22.8%)	402 (32.3%)
Education [†]					
<High School	2,926 (21.3%)	793 (20.9%)	1,080 (19.7%)	712 (22.3%)	341 (27.4%)
High School, GED, or Vocational School	5,716 (41.7%)	1,525 (40.2%)	2,332 (42.5%)	1,348 (42.3%)	511 (41.1%)
College, Graduate, or Professional School	5,078 (37.0%)	1,479 (39.0%)	2,078 (37.9%)	1,129 (35.4%)	392 (31.5%)
Body Mass Index (kg/m^2)					
<25	4,267 (31.1%)	1,318 (34.7%)	1,703 (31.0%)	916 (28.7%)	330 (26.5%)
25-29	5,475 (39.9%)	1,561 (41.1%)	2,256 (41.1%)	1,250 (39.2%)	408 (32.8%)
≥ 30	3,978 (29.0%)	918 (24.2%)	1,531 (27.9%)	1,023 (32.1%)	506 (40.7%)
Physical activity index†, mean (SD) Smoking Status	2.5 (0.8)	2.6 (0.8)	2.5 (0.8)	2.4 (0.8)	2.3 (0.7)
Never	5,474 (39.9%)	1,383 (36.4%)	2,279 (41.5%)	1302 (40.8%)	510 (41.0%)
Former	5,193 (37.9%)	1,600 (42.1%)	2,037 (37.1%)	1,141 (35.8%)	415 (33.4%)
Current	3,053 (22.3%)	814 (21.4%)	1,174 (21.4%)	746 (23.4%)	319 (25.6%)
Alcohol Consumption					
Never	3,081 (22.5%)	742 (19.5%)	1,223 (22.3%)	772 (24.2%)	344 (27.7%)
Former	2,848 (20.8%)	789 (20.8%)	1,081 (19.7%)	682 (21.4%)	296 (23.8%)
Current	7,791 (56.8%)	2,266 (59.7%)	3,186 (58.0%)	1,735 (54.4%)	604 (48.6%)
Systolic Blood Pressure (mmHg), mean (SD)	121 (19)	120 (19)	121 (18)	123 (18)	127 (20)
Pulse Pressure (mmHg), mean (SD)	49 (14)	49 (14)	49 (14)	49 (14)	52 (16)
Use of Hypertension Medications	4,381 (31.9%)	1,208 (31.8%)	1,653 (30.1%)	1,013 (31.8%)	507 (40.8%)

Baseline Characteristics	Overall	Resting heart rate (bpm)			
		<60	60–69	70–79	≥80
Use of atrioventricular-nodal Medications	2,044 (14.9%)	739 (19.5%)	725 (13.2%)	415 (13.0%)	165 (13.3%)
Total Cholesterol (mg/dl), mean (SD)	210 (39)	206 (37)	210 (38)	212 (40)	216 (47)
HDL Cholesterol (mg/dl), mean (SD)	50 (17)	49 (17)	50 (17)	49 (16)	49 (18)
Use of Cholesterol Medications	864 (6.3%)	246 (6.5%)	334 (6.1%)	188 (5.9%)	96 (7.8%)
Diabetes	1,994 (14.6%)	351 (9.3%)	670 (12.3%)	577 (18.2%)	396 (32.0%)
Prevalent Coronary Heart Disease	722 (5.3%)	234 (6.2%)	270 (4.9%)	136 (4.3%)	82 (6.6%)
Apolipoprotein ∈4 Genotype					
TT	9,186 (69.2%)	2,528 (68.6%)	3,694 (69.5%)	2,132 (69.1%)	832 (69.7%)
CT	3,741 (28.2%)	1,048 (28.5%)	1,490 (28.0%)	876 (28.4%)	327 (27.4%)
CC	356 (2.7%)	107 (2.9%)	135 (2.5%)	79 (2.6%)	35 2.9%)

†Measured at ARIC Visit 1 (1987-1989).

Table 2.

Average Adjusted Decline and Difference in Decline over 20-years for the Global Cognitive Z-Score By Resting Heart Rate Groups:[*] the ARIC Study 1990-1992 to 2011-2013.Part A: 20-year Change in Global Cognitive Domain Part B: Relative Difference in the 20-yr by Resting Heart Rate Groups Change of Global Cognitive Z-Scores for Higher Resting Heart Rate Groups Compared to Lowest (Reference)

Resting Heart rate (bpm)	<60	60-69	70-79	≥80	Difference 60-69 vs <60	Difference 70-79 vs <60	Difference ≥80 vs <60
Model 1[†]	−0.88(−0.92, −0.83)	−0.92(−0.97, −0.88)	−0.97(−1.03, −0.91)	−1.05(−1.14, −0.96)	−0.05(−0.09,0.00)	**−0.10(−0.16, −0.04)**	**−0.17(−0.27, −0.08)**
Model 2[‡]	−0.88(−0.93, −0.83)	−0.93(−0.97, −0.88)	−0.97(−1.03, −0.91)	−1.05(−1.14, −0.95)	−0.04(−0.09,0.00)	**−0.09(−0.15, −0.03)**	**−0.16(−0.26, −0.07)**
Model 3[//]	−0.90(−0.94, −0.85)	−0.93(−0.98, −0.89)	−0.96(−1.03, −0.90)	−1.01(−1.10, −0.92)	−0.04(−0.09,0.01)	**−0.07(−0.13, −0.004)**	**−0.12(−0.21, −0.03)**

[*] Results are presented in β coefficients (95% CI) from adjusted linear mixed effect models. Missing covariates and cognitive scores were imputed. Results in bold are statistically significant differences between resting heart rate groups ($p < 0.05$).

[†] Model 1: adjusted for age, age^2, sex, race/center, and interactions between each of these variables and time

[‡] Model 2: Model 1 + education, body mass index, smoking status, alcohol, physical activity, and interactions between each of these variables and time

[//] Model 3: Model 2 + systolic blood pressure, pulse pressure, use of hypertension medication, diabetes, HDL cholesterol, total cholesterol, cholesterol lowering medications, history of prevalent coronary heart disease, use of AV-nodal blocking medications,

APOE4 genotype, and interactions between each of these variables and time

Table 3.

Associations of resting heart rate measured at Visit 2 (1990-1992) with incident dementia through 2013: the ARIC Study

	Resting heart rate (bpm)				Per 10 bpm increment
	<60	**60 – 69**	**70 - 79**	**≥80**	
Number of participants	3,795	5,487	3,188	1,244	13,714
Case	370 (9.8%)	534 (9.7%)	309 (9.7%)	137 (11.0%)	1,350 (9.8%)
Incidence rate (95% CI) *	5.26 (4.75, 5.83)	5.28 (4.85, 5.75)	5.42 (4.85, 6.06)	6.83 (5.78, 8.07)	5.43 (5.15, 5.73)
Hazard Ratios (95% CI)					
Model 1 †	Reference (1)	1.04 (0.91, 1.19)	1.16 (0.99, 1.35)	**1.44 (1.18, 1.75)**	**1.12 (1.06, 1.18)**
Model 2 ‡	Reference (1)	1.05 (0.92, 1.20)	1.15 (0.99, 1.34)	**1.42 (1.17,1.74)**	**1.11 (1.05, 1.17)**
Model 3 ‖	Reference (1)	1.08 (0.95, 1.24)	1.14 (0.97, 1.33)	**1.28 (1.04, 1.57)**	**1.08 (1.02, 1.14)**

* Incidence Rates are per 1,000 person-years

† Model 1: Adjusted for age, age^2, sex, and race/center

‡ Model 2: Model 1 plus education, body mass index, smoking status, alcohol, and physical activity

‖ Model 3: Model 2 plus systolic blood pressure, pulse pressure, use of hypertension medication, diabetes, HDL cholesterol, total cholesterol, cholesterol lowering medications, history of prevalent coronary heart disease, use of AV-nodal blocking medications, and APOE4 genotype