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Midlife vascular risk factors and midlife cognitive status in relation to Prevalence of Mild Cognitive Impairment and Dementia in later life: the ARIC Study

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Abstract

INTRODUCTION—The interplay between midlife vascular risk factors (VRF) and midlife cognitive function with later life mild cognitive impairment (MCI) and dementia (DEM) is not well understood.

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METHODS—In the Atherosclerosis Risk in Communities (ARIC) Study, cardiovascular risk factors and cognition were assessed in midlife, ages 45–64 years. In 2011–2013, 20–25 years later, all consenting ARIC participants underwent a cognitive and neurological evaluation, and were given adjudicated diagnoses of cognitively normal, MCI or DEM.

RESULTS—In 5995 participants with complete covariate data, midlife diabetes, hypertension, obesity and hypercholesterolemia were associated with late-life MCI and DEM. Low midlife cognition was also associated with greater likelihood of late-life MCI or DEM. Both midlife VRF and midlife cognitive function remained associated with later life MCI or DEM when both were in the model.

DISCUSSION—Later life MCI and DEM were independently associated with midlife VRF and midlife cognition.

Keywords

Dementia; mild cognitive impairment; epidemiology; prevalence; diabetes; hypertension; APOE; cognition

Introduction

Low midlife cognitive function [1–6] and midlife vascular risk factors (VRF) [7–14] are both known to be associated with increased risk for later-life cognitive impairment. Mid-life cognition and VRF are themselves associated [15]. The relationship extends even earlier; possession of VRFs as early as the 3rd decade of life [16] has been associated with lower cognitive test scores 20 years later.

The interrelationship between midlife VRF and midlife cognition and later life cognitive disorders has not been addressed within a single cohort to our knowledge. As risk factors for later life cognitive disorders, are they additive or interactive with one another? Which one exerts a greater influence? Is one more important for milder versus more severe cognitive impairment in late life? This is relevant in order to understand the mechanisms by which both convey risk for future cognitive impairment. For example, if effects of low midlife cognition on later life cognitive impairment were attenuated by inclusion of vascular health in the analytic models, that would have different implications for disease mechanisms than if the two had effects on later-life cognition that were largely independent of one another.

We have previously described the prevalence of MCI and dementia from the ARIC visits in 2011–13 [17], and we have previously reported on the relationship of vascular risk factors and dementia [18]. In the current report, we evaluated associations between adjudicated prevalent mild cognitive impairment and dementia at the latest Atherosclerosis Risk in Communities (ARIC) visit, in relation to a VRF profile collected 25 years earlier [19] and to a cognitive assessment performed 20 years earlier [15]. We were particularly interested in whether midlife cognition and midlife VRF were independent or not in their associations with the spectrum of prevalent later life cognitive disorders.

1. Methods

2.1. Participants

Initial enrollment in the ARIC study commenced in 1987 [19]. There were 15,792 men and women, initially aged 45 to 64, who were recruited between 1987 and 1989. The cohort was created using probability samples, employing population-wide lists (mainly driver's licenses) or area sampling from Forsyth County, NC; Jackson, MS; northwestern suburban Minneapolis, MN; and Washington County, MD. Only African-Americans were sampled in Jackson, MS. Approximately 13 percent of the Forsyth County sample was African American. In the other two sites, subjects were virtually all European Americans. The initial evaluation in 1987 to 1989 (referred to as ARIC visit 1, V1) included a full cardiovascular risk factor assessment described below. The response rate was 46% in Jackson Mississippi, and approximately 65% in the other three communities.

The second visit (ARIC visit 2, V2, in 1990–1992) included 14,348 individuals who underwent a cognitive function evaluation described below in addition to a repeat assessment of cardiovascular risk factors. Subsequent ARIC visits in 1993–95 and 1996–98 also included cognitive assessments (only in a subset in 1993–95) and cardiovascular risk factor assessments. Cognitive testing from those visits was used during the diagnostic adjudication in ARIC visit 5 (V5) conducted in 2011–2013.

In 2011–2013 at ARIC V5, all surviving ARIC participants were invited to an examination in which cognitive function was assessed [17]. An informant was sought for all those attending the examinations. Based on the information collected from the informants, including an assessment of daily functioning, and an augmented neuropsychological test battery (described in e-appendix) [17], an expert panel adjudicated diagnoses of cognitively normal (CN), mild cognitive impairment (MCI) and dementia (DEM).

Institutional review boards of each ARIC center have approved the ARIC study protocol over its 30 year existence. Participants provided written informed consent for their participation at each study visit. Consent was obtained from a designated proxy along with the participant's assent in participants with a known diagnosis of dementia, impaired mental status (determined in the examination), or where our trained staff deemed that the participant had diminished capacity to provide informed consent.

1.2. Serial ARIC Cognitive Battery

The cognitive assessments and the baseline performance at ARIC V2 have been presented in detail [15]. The battery included the delayed word recall (DWR) test, the digit symbol subtest (DSS) of the WAIS-R and the first-letter word fluency (WF) test. The tests were administered by trained interviewers in a standardized order during one session in a quiet room. The tests are described in the e-supplement. These three tests were re-administered at all subsequent ARIC visits.

We created a composite of the 3 cognitive tests administered at V2 expressed as a z-score based on averaging the z-scores of each test. Each item was standardized by subtracting the mean and dividing by the standard deviation.

We also used the serial ARIC cognitive battery to assess cognitive decline at the time of V5. Decline was calculated by subtracting the highest prior score from the V5 score for each test. We then derived scores that represented the 10th and 20th percentiles of change.

1.3. Clinical Diagnostic Assessment at ARIC V5

The current analysis includes ARIC participants who were evaluated in person at ARIC V5, and a diagnosis of cognitively normal (CN), mild cognitive impairment (MCI) or dementia (DEM) was rendered by a diagnostic adjudication team that has previously been described [17]. Adjudicators reviewed the cognitive and functional evaluations of all participants with any values outside the normal range, and used an algorithm as a guide for diagnoses. The algorithm was based on the formulations of MCI and dementia laid out in the National Institute on Aging – Alzheimer's Association (NIA-AA) workgroups [20, 21] and DSM-5 [22].

The profile for MCI was defined as at least one V5 cognitive domain score < −1.5 Z (the construction of the cognitive domains is described in the e-appendix [17]), a Clinical Dementia Rating (CDR) [23] sum of boxes >0.5 and ≤ 3, a Functional Activities Questionnaire (FAQ) ≤ 5 [24] and decline <10%ile on one test or < 20thile on two tests in the serial ARIC cognitive battery.

The profile for DEM was defined as >1 V5 cognitive domain score < −1.5 Z and a CDR sum of boxes > 3 and FAQ >5 and decline <10%ile on one test or < 20thile on two tests in the serial ARIC cognitive battery. In addition, a low MMSE score (<21 for European Americans or <19 for African Americans), even in the absence of more complete cognitive testing, was regarded as diagnostic of dementia.

1.4. Demographic and VRF Assessment at ARIC V1

The methodology for defining at ARIC V1 diabetes, hypertension, plasma total cholesterol, cigarette smoking history, prevalent stroke and APOE genotyping has been described in greater detail elsewhere [19], a synopsis of which is presented in an e-supplement.

Hypertension was considered to be present if systolic blood pressure (BP) ≥ 140 mm Hg, or if diastolic BP was ≥ 90 mm Hg, or if antihypertensive medications were being used.

Prevalent diabetes mellitus was defined as a fasting glucose of ≥ 126 mg/dl, non-fasting glucose of ≥ 200mg/dl, a self-reported physician diagnosis of diabetes, or treatment for diabetes. Participants were asked to fast for 12 hours prior to the clinic visit. Blood was drawn from the antecubital vein of seated participants. Serum glucose was assessed by the hexokinase method.

A cerebrovascular etiology for MCI or DEM was described in detail previously [17] based on the presence of a history of stroke, a history of stroke that was temporally related to the onset or substantial worsening of cognitive impairment and infarcts or extensive white matter hyperintensity burden on MR scanning.

1.5. Statistical Methods

Participants with unknown cognitive status at V5 and those with race other than white or black were excluded from analysis, leaving 6456 V5 participants; 5995 (93%) had complete covariate data. A further 230 (4%) had unknown APOE status, which was coded separately in statistical models. V2 cognitive test z-scores were averaged, and grouped into categories based on quartiles of all V2 participants; the 1st quartile was the lowest 25% of scores, the 4th quartile was the highest 25% of scores.

Multinomial logistic regression models were fit to evaluate associations of demographics, V1 VRFs, and V2 cognitive functioning scores with V5 MCI or dementia, each versus normal cognitive functioning. Models included all covariates described above. For each covariate, odds ratios (ORs) for MCI were compared to ORs for DEM with a Wald chi-square test. To investigate the relationship between the VRFs and midlife cognitive functioning in their association with later life cognitive impairment, we fit an additional multinomial model excluding the midlife cognitive functioning covariate. We further assessed the interaction between VRFs and cognitive functioning in a logistic regression model of MCI/DEM stratified by quartiles of midlife cognitive functioning. MCI and DEM were combined in this analysis to maximize the sample size.

We further evaluated interactions between risk factors and APOE (1+ versus no ε4 allele), race (hypothesizing stronger associations in black participants), and sex (hypothesizing similar associations by sex). Analyses were stratified by age at study baseline (44–54 vs 55–64), to determine whether associations were stronger in earlier vs. later midlife. Wald chi-square tests were used to test each interaction separately for MCI and DEM. There were no adjustments for multiple comparisons.

Additional models were fit to evaluate associations of midlife predictors with combined MCI/DEM separated by etiology of disease (cerebrovascular or not cerebrovascular) assessed by adjudicated review. We further evaluated interactions between risk factors and race to evaluate if associations by etiology varied between blacks and whites.

Since approximately 40% of the original V1 sample attended V5, all models were adjusted for attrition from V1 to V5 by inverse probability weighting (IPW). Weights were calculated as the trimmed inverse of the predicted probability of V5 attendance obtained from a logistic regression model of the V1 and V2 covariates plus the square of age and any interactions with $p < 0.10$, and were normalized to the analysis sample size. Missing predictors were first imputed in 20 datasets using multiple imputation with fully conditional specification, and the IPW weight was obtained as the average from the 20 imputations. The average area under the receiver operating characteristic curve (ROC AUC) for the IPW model was 0.75 and the Hosmer Lemeshow test supported goodness of fit with $p > 0.05$ in each of the 20 imputations. A sensitivity analysis was conducted without IPW adjustment.

SAS Version 9.4 was used for all analyses.

2. Results

Table 1 presents the demographic features and VRFs from ARIC V1 (collected 25 years earlier) and cognitive test scores from V2 (collected 20 years earlier) of participants grouped by status at ARIC V5. Those who did not attend V5 or those who died prior to V5 were more likely to be African-American, older and less healthy at V1 (in terms of obesity, current smoking, diabetes, hypertension, coronary heart disease, prevalent stroke) than those who were examined in-person at V5 who were CN or MCI, but more similar to the DEM participants. Those with DEM at V5 had lower V2 cognitive test scores compared to MCI and to CN, as did persons who died before V5. The proportion of APOE e4 carriers was substantially elevated only among those with a V5 DEM diagnosis.

Table 2 shows associations of demographics, carriage of APOE e4 allele, and VRF measured at V1 in models with and without inclusion of cognition as measured at V2 with V5 cognitive status (CN, MCI or DEM). We consider demographics first. In the multinomial, multivariable regression models that did not include V2 cognition, younger age at V1 was protective for MCI and more so for DEM, but education beyond high school was protective only for DEM (contrast with MCI $p<.0001$ for all three risk factors). White race was protective for DEM, but a marginal risk for MCI. Carriage of APOE e4 allele was also associated with a higher risk for both MCI and DEM, but more strongly so with DEM (contrast with MCI $p<.0001$). When V2 cognition was included in the multinomial regression model, the association of African American race with higher DEM prevalence was attenuated and the association of African American race with a *lower* MCI prevalence was stronger.

In the multinomial models, the magnitudes of VRF associations were greater for DEM than MCI, both in models including and those excluding V2 cognitive scores. Diabetes and hypertension in midlife were associated with both MCI and DEM. Associations were stronger, for DEM. Obesity and total cholesterol (>240 mg/dL) were significantly associated with both MCI and DEM, but with similar OR point estimates. Being underweight in midlife was also associated with later life DEM but not MCI. Despite low numbers for stroke and CHD at V1, CHD was associated with DEM. There was no association of cigarette smoking with MCI, but for DEM, lower but not higher cigarette exposure was marginally protective. Associations of VRF with MCI or DEM were not affected by inclusion or exclusion of V2 cognition function (Table 2).

Low cognitive test scores at V2 were strongly associated with increased odds of MCI and DEM at V5 (Table 2). Those in the lowest quartile had higher odds of MCI or DEM with point estimates of 5.3 (95% CI 4.2 – 6.3) and 3.8 (95% CI 2.5 – 6.0) respectively. The ORs for V2 test scores, especially for the lower two quartiles were considerably larger than the ORs for the VRF or APOE e4 carriage. In models stratifying by V2 cognitive function in which MCI and DEM outcomes were combined to ensure adequate power (Table 3), VRF associations were similar across V2 cognitive strata, and no V2 stratum interactions with APOE e4, diabetes and hypertension, or elevated cholesterol for combined MCI or DEM risk were significant. Sensitivity analysis without IPW adjustment yielded similar results (supplemental tables 8 and 9).

We also examined associations stratified by several different features: race (Supplemental Table 1), sex (Supplemental Table 2), APOE e4 carriage (Supplemental Table 3), age (Supplemental Table 4) and presence of an adjudicated “cerebrovascular disease (CVD)” etiology of MCI/DEM (Supplemental Table 5, 6, or 7). There were differences in VRF OR’s in some of the stratified analyses, but no patterns were evident. None of the differences would survive correction for multiple testing.

3. Discussion

Here we show that both midlife lower cognitive functioning and possession of VRFs were associated with MCI and DEM approximately 20 years later. These findings replicate prior studies of VRF [7–14] and of midlife cognition [1–6, 18]. Odds ratios were similar for MCI and DEM with no substantial differences for any of the VRFs. While the different underlying metrics make it difficult to compare odds ratios, being in the lowest quartile of cognitive functioning at V2 doubled the likelihood of MCI or DEM compared to that of being both diabetic and hypertensive in midlife, and nearly twice the risk of carrying an e4 allele of APOE. Midlife cognitive functioning and midlife VRF retained their associations with later life MCI and DEM even when both features were in the models.

Participants with higher cognitive functioning have had a lower burden of VRF across the duration of the ARIC study. VRF were associated cross-sectionally with poorer cognitive performance in midlife (at ARIC V2) [15] and several VRF were associated with subsequent cognitive decline over 6 years [25], 14 years [26], and 20 years [13, 14, 27]. A report from the Scottish Mental Survey 1932 cohort [28] makes a similar point. In that study, those with dementia whose etiology was attributed to cerebrovascular disease had reduced premorbid cognitive ability but there was no difference in premorbid cognitive levels in persons diagnosed with dementia without evidence of cerebrovascular disease. Application of the cognitive reserve hypothesis would suggest that high midlife cognitive functioning should be protective against the cerebrovascular pathologies related to VRF. Or vice versa, a low burden of midlife VRF should mitigate the effects of low midlife cognition.

However, we failed to identify a predilection for later life cognitive impairment as a function of low midlife cognitive status in those with cerebrovascular disease as a contributory etiology (Supplemental Tables 5, 6 and 7). Low V2 cognitive scores were just as strongly associated with non-cardiovascular as with cardiovascular MCI and DEM. We also note that the remarkable strength of the V2 cognitive scores (OR=4.97 (95% CI 3.98 – 6.20) for the lowest quartile, Table 3) was found after full adjustment for VRF. To our knowledge, none of the other studies that have demonstrated the risks of low midlife cognition for later life dementia [1–5] also included midlife VRF. Thus while midlife cognition and midlife VRF are associated, they each represented distinct pathways that influenced later life cognitive outcomes. This unexpected result suggests that midlife cognitive status and VRF influence later life cognitive impairment through separate mechanistic pathways.

In models not including midlife cognitive status, African-American race was associated with DEM but not MCI prevalence. When V2 cognitive test scores were in the model, African American race appeared to be protective for MCI while the risk for DEM was attenuated.

Studies conducted on the differential quality of education of African American versus white children in Alabama [29] in the era of government-sanctioned segregation showed that African Americans had poorer educational opportunities. The elimination of the association between African American race and higher prevalence of MCI and DEM when V2 cognitive test scores were in the model occurred because the V2 cognitive test scores controlled (and perhaps over-controlled) for the various early life experiences including (but not limited to lower educational quality) between African- and European-Americans in the cohort.

More importantly though, there were no consistent differences between African-Americans and European-Americans on the relationship of VRF and midlife cognition to later life MCI or DEM (Tables 2, 3 and Supplemental Table 1). Race-specific associations of diabetes and hypertension for the outcomes of MCI plus DEM differed slightly, but the interaction was marginally significant only for diabetes. At this time, we cannot reconcile our finding of higher brain amyloid levels in African Americans [30] with the current observations on midlife VRF and cognition. For better or worse, neither race nor sex substantially influenced our principal findings with respect to VRF.

Female sex was protective against both MCI and DEM only when V2 cognition was not in the model, but when it was, the associations were diminished and no longer significant. At ARIC V2, women had higher scores on the cognitive tests than men [15] which might account for the latter observation. Men in the ARIC cohort experienced excess mortality (Table 1) so these comparisons, despite IPAW adjustment, may reflect some survival bias. Despite these various differences between men and women, we found similar ORs of VRF or midlife cognition for later life MCI or DEM in men and women.

Associations with APOE e4 genotype were significant for both MCI and DEM, but of larger magnitude for DEM (interaction $p<0.0001$). The APOE e4 associations with MCI and DEM were not attenuated by inclusion of V2 cognitive test scores in the model. The association of APOE e4 carriage and DEM was the only instance in our analyses where there was an interaction with race: African Americans had a lower risk of DEM attributable to APOE e4. This has been observed previously [31]. In contrast, the associations of APOE e4 with MCI were similar between African Americans and European Americans. We postulate that the etiological heterogeneity of MCI, and the lower probability of Alzheimer-related processes in MCI compared to DEM accounts for the lower associations of APOE e4 genotype with the former.

Results from this study of prevalent DEM are generally similar to those seen in ARIC incident DEM [18], but there were differences. For example associations with midlife diabetes and hypertension were observed in both analyses, but only in prevalent DEM in the current report were there associations with midlife elevated cholesterol and being underweight at midlife. The OR < 1 for DEM for low midlife exposure to cigarettes is almost certainly a consequence of competing mortality, as it was not evident in incident DEM in ARIC [30]. While examining incident dementia may be preferred for addressing competing mortality, the benefits of in-person evaluations are realized through more accurate diagnoses and, diagnoses of the mildest symptomatic impairment, ie MCI. In addition, differences in risk between MCI and DEM should be viewed with caution. Definitions of the

boundary between normality and MCI or between MCI and DEM are somewhat arbitrary, but our diagnostic methods are transparent so that others can compare their own results. The cognitive battery that was used in ARIC V2 was brief, and a more extensive battery might have allowed us to examine domain-specific functions.

In summary, we found that cognition and vascular risk factors assessed at midlife were potent and independent predictors of later life MCI and DEM. These observations suggest that midlife cognition and midlife vascular risk factors act on brain mechanisms pertinent to cognition through separate pathways.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix - Methodology

1. Details of ARIC V2 cognitive tests

The DWR [32] is a test of verbal learning and recent memory that requires the participant to recall 10 common nouns following a five-minute interval. In order to produce elaborative processing during the encoding stage of learning, individuals were required to make sentences incorporating the words presented. During the delay interval the digit symbol substitution test was given. After five minutes, free recall of the words was sought.

The DSS of the WAIS-R [33] is a paper and pencil task requiring timed translation of numbers to symbols using a key given at the top of the test page. The test was scored as the number of correct translations completed within 90 seconds.

The word fluency test [34] required the participant to generate as many words as possible, but not proper names or places, beginning with a particular letter of the alphabet within 60 seconds. Three separate one minute trial periods were used for the letters F, A, and S, respectively. The scores were summed.

2. Measurement of other cardiovascular risk factors

Plasma total cholesterol was determined by enzymatic methods in a laboratory standardized by the Centers for Disease Control.

Genotyping of the APOE polymorphisms was performed using the TaqMan assay (Applied Biosystems, Foster City, CA). Here we report only whether the e4 allele was carried or not carried.

BMI was calculated in kg/m^2.

Race, sex, age (birthdate), education level, and smoking status at V1 were self-reported. Cigarette-years was calculated as the average number of self-reported cigarettes smoked per day multiplied by the number of years smoked.

Prevalent stroke was defined as those strokes that were self-reported by subjects at V1.

Incident stroke prior to V5 was defined as a stroke meeting ARIC criteria, verified by an ARIC clinician through review of medical records [35, 36]. Incident stroke was given for descriptive purposes but not used in the current analyses.

3. Details of Clinical Diagnostic Assessment at ARIC V5

The neuropsychology test battery [37] administered at V5 included the following tests: Logical Memory immediate and delayed recall, and incidental learning from the Wechsler Memory Scale-III), Trail Making Test parts A and B, WAIS-R Digits Span Backwards), Boston Naming Test, Animal Naming. The Mini-Mental State Examination (MMSE) [38] was also administered. Robust age, race and education-specific normative data for most of the measures in the battery were developed within ARIC [37]. Comparable normative data for the Boston Naming Test and Digit Span Backwards were derived from data obtained from the National Alzheimer's Coordinating Center [39]. As previously reported [40], we constructed Z-scores for each of 4 cognitive domains (memory, psychomotor speed/executive functioning, language and visuospatial) by averaging the scores of tests within each domain, subtracting the domain mean and dividing by the domain standard deviation. A global composite Z-score was also derived from the three domain scores.

The algorithm used the following scores: MMSE, the sum of the 6 individual domain ratings in the Clinical Dementia Rating ("CDR sum of boxes") [23], z-scores from the ARIC V5 neuropsychological test battery, change scores from the serial 3-test ARIC cognitive assessments and the Functional Assessment Questionnaire [24].

Eight ARIC clinicians (4 physicians: DK, BGW, RFG and Guy McKhann MD, and 4 neuropsychologists: MA, TM, LC and Ola Selnes, PhD) comprised an expert dementia

classification committee who reviewed materials on the examinations that had been collected at each ARIC site. One physician and one neuropsychologist independently reviewed each participant whose algorithmic profiles were concordant or discordant for MCI or dementia. The reviewers then rendered syndromic and etiological diagnoses. A small number of profiles that were concordant for cognitive normality were also reviewed. Preliminary experience showed that participants whose algorithmic diagnosis was “normal or suspected normal cognition” were invariably viewed by the clinician reviewer panel as normal, and subsequently only one reviewer was assigned to review the data from those who were “normal or suspected normal” by the algorithm. For individuals in whom the two primary reviewers disagreed on cognitive syndrome, primary etiology or CVD etiology, a third reviewer (DK or MA) evaluated the participant’s case materials and rendered a deciding vote.

Research in Context

Systematic Review

We searched for articles relevant to midlife risk factors for mild cognitive impairment and dementia, as well as for the relationship of midlife cognition to later life mild cognitive impairment and dementia.

Interpretation

Midlife vascular risk factors and midlife cognition were independently and additively associated with later life mild cognitive impairment and dementia.

Future Directions

The ARIC study is an ongoing project that is now reexamining participants. This will allow us to examine the associations of mid-life vascular risk factors and cognition in relation to both incident mild cognitive impairment and dementia.

Highlights

- Cardiovascular risk factors and cognition were assessed in midlife in the ARIC cohort
- Mild cognitive impairment and dementia were assessed in later life 20–24 year later
- Midlife diabetes, hypertension, obesity and hypercholesterolemia were associated with later life MCI and DEM
- Compared to the highest midlife cognitive function score quartile, lower quartiles were associated with greater likelihood of later life MCI or DEM.
- Associations of midlife VRF and later life MCI and DEM were virtually identical whether midlife cognitive function was included or not included in the analytic model.

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Table 1

Demographic Characteristics of Participants Who Attended ARIC Visit 1 by Visit 5 Status

Total N = 15,680	**Deceased before V5**	**Alive, Did not attend V5**	**Normal**	**MCI**	**Dementia**
N	5030	4194	4743	1371	342
Median Follow-up (yrs)	14.55	24.04	23.65	23.71	23.79
Female (%)	45%	61%	61%	53%	57%
African-American (%)	33%	26%	23%	21%	42%
Age at Visit 1 (mean, SD)	56.9 (5.45)	54.1 (5.69)	51.4 (4.92)	53.4 (5.26)	55.9 (5.36)
Education					
< HS	34%	25%	14%	14%	38%
HS grad	38%	43%	41%	44%	34%
> HS	28%	32%	45%	41%	28%
V2 DWRT Z-score (mean, SD)	−0.29 (1.04)	0.02 (0.97)	0.26 (0.93)	−0.01 (0.91)	−0.32 (1.13)
V2 DSST Z-score (mean, SD)	−0.38 (1.01)	−0.00 (0.94)	0.38 (0.93)	0.01 (0.84)	−0.53 (1.07)
V2 WFT Z-score (mean, SD)	−0.19 (1.03)	−0.04 (0.97)	0.25 (0.97)	−0.08 (0.91)	−0.34 (1.05)
V1 BMI (%)					
Underweight	1%	1%	1%	1%	1%
Normal	28%	31%	38%	31%	25%
Overweight	38%	40%	39%	43%	43%
Obese	32%	28%	23%	25%	32%
V1 Smoking (%)					
Current	38%	24%	18%	17%	17%
Former	32%	31%	33%	35%	31%
Never	30%	44%	49%	48%	52%
V1 Median years smoked *	34	27	23	24	28
APOE ε4 1+ alleles (%)	32%	30%	26%	30%	46%
V1 Diabetes Mellitus (%)	22%	9%	5%	8%	13%
V1 HTN (%)					
Normal	25%	38%	50%	45%	26%
Pre-HTN	21%	24%	23%	22%	29%
HTN	54%	39%	27%	33%	45%

Total N = 15,680	Deceased before V5	Alive, Did not attend V5	Normal	MCI	Dementia
V1 TCH mg/dL (%)					
< 200	35%	36%	43%	34%	31%
200 to < 240	37%	38%	38%	40%	34%
>= 240	28%	27%	19%	26%	35%
V1 CHD (%)	11%	3%	2%	2%	4%
Stroke prior to V1 (%)	4%	1%	1%	1%	1%
Stroke prior to V5 (%)	17%	7%	3%	6%	14%

Note: V5 dementia status was either missing or unknown for an additional 64 participants, and 48 participants with race other than African-American or European American were excluded. Missing covariates are as follows: number missing at V1 (number missing of those with cognition classified at V5): education: 26 (11), V2 DWRT: 1582 (167), V2 DSST: 1632 (173), V2 WFT: 1602 (170), BMI 25 (4), smoking: 16 (8), years smoked: 194 (67), diabetes: 147 (50), HTN: 13 (4), TCH: 251 (83), CHD: 341 (127), V1 stroke: 44 (12). At V5, 1 or more covariates was missing for 461/6456 (7%), resulting in total N=5995. In addition, ApoE: was unknown for an additional 680 (267), These participants are included in analyses through coding as an additional ApoE category.

Abbreviations: V1=visit 1, V2=visit 2, V5 = visit 5, HS= High school, DWRT = delayed word recall test, DSST=digit symbol substitution test, WFT = word fluency test, HTN=hypertension, TCH= total cholesterol, CHD = coronary heart disease.

*Among current or former smokers at V1

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Table 2

Multinomial regression models of MCI or Dementia versus Normal cognitive function with IPW adjustment. V5 eligible cohort. Odds Ratios (95% CI)

	V2 cognitive scores excluded (N= 5995)		V2 cognitive scores included (N=5995)	
	MCI n = 1290 (w=1483)	**Dementia n = 312 (w=501)**	**MCI n = 1290 (w=1483)**	**Dementia n = 312 (w=501)**
Female			0.95 (0.83, 1.09)	
Black *†		**1.82 (1.44, 2.31)**		1.25 (0.97, 1.62)
Age at Visit 1 (reference: ages 44–49) *†				
50–54	**1.38 (1.16, 1.66)**	**2.23 (1.51, 3.31)**	**1.30 (1.09, 1.56)**	**2.16 (1.46, 3.21)**
55–59	**2.05 (1.72, 2.46)**	**5.14 (3.55, 7.45)**	**1.80 (1.50, 2.16)**	**4.70 (3.24, 6.83)**
60–66	**3.03 (2.52, 3.65)**	**10.63 (7.39, 15.29)**	**2.53 (2.09, 3.07)**	**9.36 (6.49, 13.50)**
Education (reference: > HS education) *†				
< HS	0.85 (0.71, 1.02)	**3.05 (2.32, 4.02)**		**1.81 (1.33, 2.46)**
HS grad	1.14 (0.99, 1.31)	**1.60 (1.22, 2.10)**		1.27 (0.96, 1.68)
V2 average cognitive score quartile (reference: 4th quartile) †				
1st quartile	--	--	**5.30 (4.18, 6.73)**	**3.84 (2.45, 6.01)**
2nd quartile	--	--	**2.99 (2.39, 3.73)**	**1.64 (1.04, 2.58)**
3rd quartile	--	--	**1.87 (1.49, 2.35)**	**1.65 (1.05, 2.60)**
V1 BMI (reference: normal BMI)				
Underweight	1.03 (0.48, 2.18)	**3.42 (1.30, 9.00)**	0.92 (0.43, 1.98)	**3.37 (1.28, 8.87)**
Overweight	**1.19 (1.02, 1.38)**	1.22 (0.94, 1.59)	1.11 (0.95, 1.30)	1.15 (0.88, 1.50)
Obese	**1.27 (1.07, 1.51)**	**1.39 (1.05, 1.85)**	**1.21 (1.02, 1.45)**	**1.36 (1.02, 1.81)**
V1 cig-years smoked (reference: non-smokers)				
1–500	0.90 (0.77, 1.04)		0.88 (0.75, 1.02)	
> 500	1.12 (0.95, 1.31)	0.99 (0.77, 1.28)	1.09 (0.93, 1.28)	1.01 (0.78, 1.30)
APOE4 (reference: no e4 alleles) *†				
1+ alleles	**1.38 (1.21, 1.58)**	**2.04 (1.65, 2.52)**	**1.43 (1.24, 1.64)**	**2.08 (1.68, 2.58)**

	V2 cognitive scores excluded (N= 5995)		V2 cognitive scores included (N=5995)	
	MCI n = 1290 (w=1483)	**Dementia n = 312 (w=501)**	**MCI n = 1290 (w=1483)**	**Dementia n = 312 (w=501)**
V1 Diabetes/HTN (reference: neither DM nor HTN) *†				
HTN only	1.11 (0.96, 1.28)	**1.41 (1.12, 1.77)**	1.12 (0.97, 1.30)	**1.45 (1.15, 1.83)**
Diabetes only	**1.49 (1.10, 2.03)**	**2.68 (1.74, 4.12)**	**1.46 (1.07, 2.00)**	**2.65 (1.72, 4.09)**
Both	**1.81 (1.40, 2.35)**	**1.87 (1.29, 2.71)**	**1.72 (1.32, 2.25)**	**1.83 (1.26, 2.66)**
V1 TCH (mg/dL) (reference: TCH <200)				
200 to <240	1.13 (0.98, 1.31)	0.88 (0.69, 1.13)	1.14 (0.99, 1.33)	0.89 (0.69, 1.14)
>= 240	**1.47 (1.25, 1.73)**	**1.52 (1.18, 1.96)**	**1.44 (1.22, 1.70)**	**1.48 (1.15, 1.91)**
V1 CHD *†	0.98 (0.71, 1.35)	**1.73 (1.15, 2.61)**	0.95 (0.69, 1.32)	**1.68 (1.11, 2.54)**
V1 prevalent stroke	1.44 (0.86, 2.42)	1.08 (0.51, 2.32)	1.24 (0.73, 2.09)	0.96 (0.45, 2.07)

Note: IPW adjustment is inverse probability weighting accounting for attrition from Visit 1 to Visit 5; w is the IPW weighted event count. V2 cognitive z-scores were averaged. 1st quartile is the lowest 25% of scores, 4th quartile is the highest 25% of scores. **Black bolded** values indicate increased risk with $p < 0.05$; **red bolded** values indicate decreased risk with $p < 0.05$.

Abbreviations: V1=visit 1, V2=visit 2, HS= High school, HTN=hypertension, TCH= total cholesterol, CHD = coronary heart disease.

*Excluding V2 cog scores: Comparison of ORs for MCI vs Dementia: race $p < 0.0001$, age $p < 0.0001$, education $p < 0.0001$, ApoE $p = 0.001$, Diabetes/HTN $p=0.034$, CHD $p=0.011$.

†Including V2 cog scores: Comparison of ORs for MCI vs Dementia: race $p < 0.0001$, age $p < 0.0001$, education $p < 0.0001$, average cognition score quartiles $p=0.021$, ApoE $p = 0.001$, Diabetes/HTN $p=0.030$, CHD $p=0.012$.

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Table 3

Logistic regression model of MCI+Dementia versus Normal cognitive function stratified by Quartiles of V2 average cognitive Z-scores with IPW adjustment. V5 NCS eligible cohort. Odds Ratios (95% CI)

		V2 average cognitive z-score quartiles			
Total N = 5995	**Overall n = 1602 w = 1984**	**1st quartile n = 605 w = 927**	**2nd quartile n = 454 w = 528**	**3rd quartile n = 342 w = 364**	**4th quartile n = 201 w = 165**
Female	0.91 (0.80, 1.04)	0.83 (0.67, 1.02)	1.09 (0.86, 1.40)	0.77 (0.58, 1.03)	1.10 (0.73, 1.65)
Black				0.69 (0.44, 1.07)	0.60 (0.27, 1.32)
Age at Visit 1 (reference: ages 44–49)					
50–54	**1.41 (1.19, 1.67)**	**1.62 (1.21, 2.17)**	**1.51 (1.09, 2.09)**	1.07 (0.73, 1.57)	1.37 (0.86, 2.17)
55–59	**2.14 (1.81, 2.54)**	**2.39 (1.80, 3.19)**	**1.86 (1.35, 2.58)**	**2.09 (1.45, 3.02)**	**2.08 (1.30, 3.33)**
60–66	**3.37 (2.82, 4.01)**	**3.90 (2.93, 5.20)**	**2.63 (1.87, 3.71)**	**3.38 (2.32, 4.93)**	**4.18 (2.43, 7.20)**
Education (reference: > HS education) *					
< HS		0.86 (0.65, 1.13)		1.05 (0.63, 1.76)	0.20 (0.02, 1.76)
HS grad	0.91 (0.79, 1.05)	1.07 (0.81, 1.41)	0.82 (0.64, 1.05)	0.89 (0.68, 1.17)	0.88 (0.60, 1.28)
V2 average cognitive score quartile (reference: 4th quartile)					
1st quartile	**4.97 (3.98, 6.20)**	--	--	--	--
2nd quartile	**2.64 (2.14, 3.25)**	--	--	--	--
3rd quartile	**1.80 (1.46, 2.23)**	--	--	--	--
V1 BMI (reference: normal BMI)					
Underweight	1.23 (0.63, 2.39)	1.53 (0.40, 5.89)	0.88 (0.28, 2.81)	3.09 (0.94, 10.16)	Unestimable
Overweight	1.11 (0.96, 1.28)	**1.30 (1.01, 1.66)**	1.13 (0.86, 1.49)	0.96 (0.70, 1.30)	0.95 (0.63, 1.43)
Obese	**1.24 (1.06, 1.46)**	1.16 (0.89, 1.52)	**1.68 (1.24, 2.28)**	1.03 (0.72, 1.48)	1.29 (0.82, 2.05)
V1 cig-years smoked (reference: non-smokers)					
1–500		0.83 (0.66, 1.05)	0.79 (0.59, 1.05)	0.87 (0.64, 1.19)	1.09 (0.73, 1.62)
> 500	1.06 (0.92, 1.23)	0.98 (0.77, 1.26)	1.09 (0.83, 1.44)	1.28 (0.92, 1.76)	0.85 (0.53, 1.36)
APOE4 (reference: no e4 alleles)					
1+ alleles	**1.57 (1.39, 1.79)**	**1.59 (1.29, 1.95)**	**1.30 (1.02, 1.67)**	**2.02 (1.53, 2.66)**	**1.59 (1.09, 2.33)**
V1 Diabetes/HTN (reference: neither DM nor HTN)					
HTN	**1.18 (1.03, 1.35)**	1.11 (0.89, 1.38)	1.16 (0.89, 1.51)	**1.42 (1.06, 1.91)**	1.26 (0.84, 1.89)
Diabetes	**1.67 (1.26, 2.22)**	**1.61 (1.03, 2.52)**	**2.35 (1.37, 4.00)**	1.08 (0.55, 2.10)	2.01 (0.78, 5.17)

	V2 average cognitive z-score quartiles				
Total N = 5995	**Overall n = 1602 w = 1984**	**1st quartile n = 605 w = 927**	**2nd quartile n = 454 w = 528**	**3rd quartile n = 342 w = 364**	**4th quartile n = 201 w = 165**
Both	**1.73 (1.36, 2.20)**	**1.79 (1.27, 2.53)**	**1.84 (1.14, 2.99)**	1.35 (0.74, 2.46)	2.72 (0.90, 8.22)
V1 TCH (mg/dL) (reference: TCH <200)					
200 to <240	1.08 (0.94, 1.24)	1.02 (0.81, 1.27)	1.15 (0.89, 1.49)	1.20 (0.90, 1.62)	1.02 (0.68, 1.54)
>= 240	**1.45 (1.25, 1.69)**	**1.50 (1.18, 1.90)**	**1.47 (1.10, 1.97)**	1.32 (0.94, 1.86)	**1.62 (1.04, 2.53)**
V1 CHD	1.11 (0.83, 1.49)	1.23 (0.78, 1.94)	1.19 (0.71, 2.01)	0.55 (0.25, 1.20)	1.72 (0.62, 4.73)
V1 prevalent stroke	1.13 (0.70, 1.84)	1.49 (0.76, 2.93)	1.04 (0.43, 2.48)	Unestimable	1.14 (0.11, 11.51)

Note: IPW = inverse probability weighting accounting for attrition from Visit 1 to Visit 5; V2 cognitive z-scores were averaged. 1st quartile is the lowest 25% of scores, 4th quartile is the highest 25% of scores; N is the sample size in the group, n is the number of people with MCI or dementia, and w is the IPW weighted event count. **Black bolded** values indicate increased risk with $p < 0.05$; **red bolded** values indicate decreased risk with $p < 0.05$.

Abbreviations: V1=visit 1, V2=visit 2, HS= High school, HTN=hypertension, TCH= total cholesterol, CHD = coronary heart disease.

* Interaction for education by V2 average cognitive score quartile = 0.018.

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