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Original Research Report

Vascular Health and Genetic Risk Affect Mild Cognitive Impairment Status and 4-Year Stability: Evidence From the Victoria Longitudinal Study

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Abstract

Objectives: Mild cognitive impairment (MCI) is a high-risk condition for progression to Alzheimer's disease (AD). Vascular health is a key mechanism underlying age-related cognitive decline and neurodegeneration. AD-related genetic risk factors may be associated with preclinical cognitive status changes. We examine independent and cross-domain interactive effects of vascular and genetic markers for predicting MCI status and stability.

Method: We used cross-sectional and 2-wave longitudinal data from the Victoria Longitudinal Study, including indicators of vascular health (e.g., reported vascular diseases, measured lung capacity and pulse rate) and genetic risk factors—that is, apolipoprotein E (*APOE*; rs429358 and rs7412; the presence vs absence of ε4) and catechol-O-methyltransferase (*COMT*; rs4680; met/met vs val/val). We examined associations with objectively classified (a) cognitive status at baseline (not impaired congnitive (NIC) controls vs MCI) and (b) stability or transition of cognitive status across a 4-year interval (stable NIC–NIC vs chronic MCI–MCI or transitional NIC–MCI).

Results: Using logistic regression, indicators of vascular health, both independently and interactively with *APOE* ε4, were associated with risk of MCI at baseline and/or associated with MCI conversion or MCI stability over the retest interval.

Discussion: Several vascular health markers of aging predict MCI risk. Interactively, *APOE* ε4 may intensify the vascular health risk for MCI.

Keywords: *APOE*—*COMT*—Mild cognitive impairment—Vascular health—Victoria Longitudinal Study

Accumulating evidence supports the view that the often lengthy and subtle preclinical changes linking normal aging and diagnosable late-onset Alzheimer's disease (AD) are continuous, detectable, and worthy of study as a classifiable phase of cognitive aging (Albert et al., 2011). The terms for this phase have generally consolidated around a semantically meaningful expression, mild cognitive impairment (MCI). As MCI is probabilistically linked to progression to AD, targeting predictors of MCI emergence or initial chronicity may facilitate the early identification of individuals at risk for the later development of dementia. Further, identifying risk factors for the early signs of cognitive impairment may lead to both improved theoretical understanding of the selective processes linking cognitive decline to dementia and the possibility of identifying and implementing early interventions to delay or arrest the

symptoms associated with neurodegeneration (Reinvang et al., 2010).

An extensive array of factors, including biological, genetic, health, environmental, functional, neurobiological, and lifestyle (e.g., Anstey, 2014), contribute to a wide range of normal and impaired cognitive changes. Recent research has examined a broad range of risk factors associated with cognitive changes in aging and dementia (e.g., Dolcos, MacDonald, Braslavsky, Camicioli, & Dixon, 2012; Fotuhi, Hachinski, & Whitehouse, 2009; Harris & Deary, 2011). Diverse predictors have been shown to exert differential influences on cognitive performance, thus a single causal factor of age-related decline seems unlikely, implicating dynamic and interacting multivariate approaches (Anstey, 2014).

Aging is associated with decremental changes in the vascular system. Vascular health factors play critical roles in many aging- and dementia-related diseases, such as cardiovascular disease, obesity, and diabetes (cf. DeCarlo, Tuokko, Williams, Dixon, & MacDonald, 2014). Recent research has demonstrated links between cognitive deficits and many vascular-related ailments, such as blood pressure (BP; Qiu, Winblad, & Fratiglioni, 2005), diabetes and stroke (Schneider et al., 2014), and an unhealthy body mass index (BMI; Gunstad, Lhotsky, Wendell, Ferrucci, & Zonderman, 2010), underscoring the important relationship between vascular health factors and cognitive health in aging.

Two potentially complementary genetic factors, apolipoprotein E (*APOE*) and catechol-O-methyl transferase (*COMT*), have been associated with vascular processes and implicated in (direct or indirect) mechanisms underlying late-life cognitive impairment and preclinical progression to AD (Harris & Deary, 2011). Correspondingly, the *APOE* protein, which is involved in cholesterol transport (Boyles et al., 1989), is implicated in many of the pathological events associated with AD, such as beta amyloid generation and neurofibrillary tangle formation (cf. Leoni, 2011). The *COMT* gene codes for an enzyme that degrades catecholamine neurotransmitters, such as dopamine, in the synaptic cleft. The Val allele results in higher enzymatic activity and subsequent dopamine degradation and therefore is considered a genetic risk factor for age-related cognitive deficits (e.g., Sapkota, Vergote, Westaway, Jhamandas, & Dixon, 2015). In the current project, we are merging two relevant lines of research. First, we observed significant independent associations between genetic risk factors (i.e., *APOE* and *COMT*) and early MCI status and stability (Dixon et al., 2014). Second, we found a significant interaction between a specific genetic polymorphism (insulin degrading enzyme [rs6583817]) and a particular vascular marker (pulse pressure) in predicting nondemented cognitive performance level and change (McFall et al., 2014). We now extend those findings and investigate whether multiple vascular health–related risk factors are independently and interactively with genetic risk factors associated with objectively classified status and stability profiles for a period of 4-year longitudinal interval. We hypothesize that markers reflecting theoretical causes and contributors of late-life cognitive impairment (i.e., vascular and genetic risk factors) may accurately and directionally predict cognitive change at early disease stages (i.e., MCI status, conversion to MCI, and MCI stability over time), as argued in detail elsewhere (DeCarlo et al., 2014).

We selected and assembled data from the Victoria Longitudinal Study (VLS). The VLS is well suited to analyze theoretically expected cross-domain, multifactorial contributions to cognitive status and change in late life. The present data set and approach are derived from the intersection of two larger established source subsamples: (a) the VLS genotyped subsample (McFall et al., 2013) and (b) the two-wave cognitive status stability sample only partially genotyped (Dolcos et al., 2012). As such, this is a second study in a planned program on biomarkers of early MCI emergence and initial stability, not including conversion to dementia (Dixon et al., 2014). We investigate four main research questions. First, we use concurrent baseline data to test whether indicators of vascular health—self-reported history of heart disease, high BP, stroke, atherosclerosis, and heart medication consumption as well as measured BMI, lung capacity, and pulse rate—uniquely differentiate between not impaired cognitive (NIC control group) and MCI adults from the VLS. The use of self-reported health has previously been shown to be useful for understanding the risk of mild cognitive disorders in adults (Sargent-Cox, Cherbuin, Sachdev, & Anstey, 2011). Second, using longitudinal data, we investigate whether vascular health indicators are independently associated with longitudinal stability of cognitive status. Third, using baseline data, we investigate whether genetic and vascular health risk factors interact to differentiate between initial NIC and MCI status. Fourth, using two-wave longitudinal data, we investigate whether the interactions between vascular and genetic risk factors are associated with MCI classification over the retest interval.

Method

Participants

This research was conducted under full, active, and continuous human ethics approval from prevailing Institutional Review Boards. Written informed consent was obtained from all participants. Participants were community-dwelling older adults from the VLS, originally recruited through advertisements in the public media and to community groups. The VLS is an ongoing multisample sequential investigation of multiple aspects (i.e., biological, cognitive, neuropsychological, health, and sensory) of human aging. Detailed background information on the VLS general design, measures, and procedures is available (e.g., Dixon & de Frias, 2004). The main source subsample for both the W1 (baseline) and the W1–W2 (longitudinal) groups for this study is a larger investigation of MCI and functional (nongenetic) biomarkers (Dolcos et al., 2012). We used the full genotyped subset of this source subsample to examine research questions involving genetic predictors (Dixon et al., 2014). Specifically,

the baseline and a two-wave longitudinal data set—mean retest interval for three outcome groups = 4.43 years (*SD* = 0.25)—combined data collected during the same time period across VLS Samples 1 and 2. The current Wave 1 (W1; *n* = 416) data were assembled from VLS Sample 1 (Wave 5) and VLS Sample 2 (Wave 3). The current Wave 2 (W2; *n* = 293) data were assembled from VLS Sample 1 (Wave 6) and VLS Sample 2 (Wave 4). Exclusion criteria at baseline included a history of AD, psychiatric disturbance (i.e., depression), and serious episodes of cardio/cerebrovascular disease (i.e., heart attacks, stroke, and heart surgery). The latter could directly result in cognitive deficits or impairment and not reflect emerging neurodegenerative conditions. Classification procedures are described below.

The first research question required the full cross-sectional baseline (W1) sample (Dolcos et al., 2012). The second research question required the full two-wave longitudinal data to examine independent vascular predictions of MCI stability groups. The third and fourth research questions required the genotyped subsample (Dixon et al., 2014). For longitudinal analyses (research questions 2 and 4), we focused on three of the four status stability groups: (a) the stable (and normal aging) NIC (NIC–NIC) group served as our standard reference subsample, (b) the corresponding transitional cognitive status (NIC–MCI; emerging MCI) group represented status decline over two waves, and (c) the stable MCI (MCI–MCI) group represented chronic and confirmed MCI status (a surrogate clinical outcome). The small "reversion" group (MCI–NIC) was classified but not included in these analyses, as it is conceptually ambiguous and we had no biomarker-related predictions (Dixon et al., 2014; Koepsell & Monsell, 2012). The genetic information was collected as a supplemental VLS activity during 2009–2011. We invited all active, noninstitutionalized, returning or potentially available VLS participants to ensure that the genotyped subsample was as representative as possible of the living participants. Approximately 90% of the identified participant pool agreed to donate biofluid (saliva) for genotyping in this period. Issues of selection, collection, and comparisons across subgroups are available (e.g., McFall et al., 2013; Sapkota et al., 2015). Of the W1 participants with genetic information, *n* = 136 were classified as NIC (age: *M* = 73.12, *SD* = 5.25; gender: 64% women; years of education: *M* = 15.21, *SD* = 2.94) and *n* = 101 met criteria for the initial MCI group (age: *M* = 73.75, *SD* = 5.55; gender: 59.4% women; years of education: *M* = 14.52, *SD* = 3.08). Of the returning W1 participants with genetic information, *n* = 101 met criteria for the stable NIC group (NIC-to-NIC: age *M* = 73.23, *SD* = 5.28; gender: 61.4% women; years of education *M* = 15.55, *SD* = 2.96), *n* = 25 met criteria for the status declining NIC group (NIC-to-MCI: age *M* = 72.64, *SD* = 5.30; gender: 72% women; years of education: *M* = 13.92, *SD* = 2.12), and 68 met criteria for the stable and chronic MCI group (MCI-to-MCI: age: *M* = 73.50, *SD* = 5.40; gender: 55.9% women; years of education: *M* = 14.32, *SD* = 3.00).

Cognitive Status Classification

The cognitive status classification was implemented with a standard, fully objective, multistep classification procedure. We applied it independently at both W1 and W2, as previously described (Dixon et al., 2014; Dolcos et al., 2012). To maximize the comparison distribution, we adopted the classifications from the source subsample, which was drawn from the VLS population base for research on MCI (Dolcos et al., 2012). In brief, the classification procedure emphasized objective and replicable assessments of cohort-relative performance on a set of five fundamental cognitive reference measures (Dixon et al., 2007; Dolcos et al., 2012). This battery includes measures that represent the theoretical domains of perceptual speed (digit symbol substitution), inductive reasoning (letter series), episodic memory (word immediate free recall), verbal fluency (controlled associations), and semantic memory (vocabulary). The five standard measures from the cognitive reference battery are widely available and used, and their psychometric properties have been regularly documented as acceptable according to conventional standards (e.g., Hultsch, Hertzog, Dixon, & Small, 1998). The first step is to stratify the sample by both age (64–73 or 74–95 years) and education (0–12 or 13+ years). The second step places each individual into one of four age × education cells. The third step is to calculate the mean performance for each of five cognitive reference measures. In the fourth step, these means serve as within-sample norms for cognitive status classification. In the fifth step, participants were classified as MCI if they scored one or more standard deviations (SDs) below their own age × education group means on one or more of the cognitive tasks; the 1 *SD* criterion was previously established and represented an approach that provided a degree of differentiation appropriate to the goal of detecting early or established signs of cognitive impairment (de Frias, Dixon, & Strauss, 2009; Dixon et al., 2007). At W1, the cognitive status classification procedure resulted in an NIC group and a classifiable MCI group. At W2, the independent cognitive status classification procedures revealed assignments in the same manner. When linked to W1 status, the following status stability groups were observed: a stable NIC (NIC–NIC) group, an NIC group transitioning to MCI (NIC–MCI), and a stable MCI (MCI–MCI) group. All participants were enrolled in both waves; transitions within the normal to impaired ranges could be ascertained, but no conversions to dementia were possible.

Vascular Health Markers

We utilized eight measures of baseline vascular health spanning self-reported and measured vascular risk factors. We chose relevant vascular factors that were both available and measured during the specific VLS samples and waves examined in this study. First, baseline peak expiratory flow (PEF) (L/min) was measured (MiniWright Peak

Flow Meter), wherein participants were asked to exhale as quickly and forcefully as possible (Dolcos et al., 2012). The score was the highest volume exhaled over three attempts. The PEF variable was divided into two levels (normal vs frail). Participants received a classification of "frail PEF" if the average score was below 311 L/min for women and below 341 L/min for men, consistent with the literature (Searle et al., 2008). Second, baseline BMI (kg/m^2) was calculated from concurrent measurements of weight and height. Similar to the PEF variable, the BMI variable was divided into two levels (normal vs unhealthy). A BMI greater than 30 kg/m^2 was considered unfavorable, consistent with the literature (Fitzpatrick et al., 2009; Searle et al., 2008) and the association between obesity, higher BMI, and MCI (Feng et al., 2012). Third, baseline mean pulse rate was calculated over eight readings across two testing sessions using a standard BP cuff. The pulse rate variable also had two levels, where those with an average rate between 40 and 80 beats per minute (BPM) were classified as healthy (*healthy* = "0") and those with an average rate higher than 80 BPM were classified as unhealthy (*unhealthy* = "1") for the purposes of this study. Fourth, history of taking medications for heart disease was indexed from a self-report measure (participants indicated whether they had ever consumed prescribed medications for heart trouble). A negative history of consuming heart medications was classified as healthy (*healthy* = "0"), whereas a positive history of heart medication consumption was classified as unhealthy (*unhealthy* = "1") for the purposes of this study. For the next four self-report measures, participants indicated whether they had ever been diagnosed with (a) heart disease, (b) atherosclerosis, (c) high BP, or (d) stroke, by a medical professional, regardless of disease/condition severity. Receiving a medical diagnosis of these diseases/conditions at any point in their life constituted an "*at risk*" state, and individuals were assigned a value of "1" for that specific condition (compared with 0 = *no risk*).

DNA Extraction and Genotyping

As described in detail elsewhere (e.g., McFall et al., 2013; Sapkota et al., 2015), genetic information was collected and processed following completion of the last testing session.

Procedure

Performance on the cognitive reference battery by both NIC and MCI groups was evaluated at both testing waves. Vascular factor measures were obtained only at baseline.

Data Analysis

All analyses were performed using SPSS Version 18 (IBM SPSS Statistics). For the initial cross-sectional analysis at baseline, we employed binary logistic regression to examine whether vascular health factors were independently associated with cognitive status (NIC vs MCI). For the corresponding longitudinal analyses, we employed multinomial logistic regression to examine whether vascular health factors were associated with cognitive status classification (stable NIC–NIC, transitional NIC–MCI, and chronic MCI–MCI) across the longitudinal retest interval (W1–W2). In addition to standard independent risk factor analysis, we also tested whether risk of MCI would be increased in the context of both vascular health and previously identified genetic risk factors (Dixon et al., 2014). Due to limited cell sizes, we restricted our focus to the computation of two-way interactions, each comparing the presence of both risk factors and genotypes (i.e., a vascular health risk factor along with a previously identified genetic risk factor) with all other possible combinations (i.e., at least one protective factor) for those particular factors (vascular and genetic). The genetic variables were referenced by the control alleles (*APOE* ε4 and *COMT* A/A). The reference outcome groups for main effects models are NIC (for W1 analyses) and NIC–NIC (for W1–2 analyses). The reference outcome groups for the interaction analyses are NIC (for W1 analyses) and no history of MCI status (for the W1–2 analyses). For the interaction analyses, logistic regression was employed to examine whether vascular factors in combination with genetic risk factors were associated with a risk of MCI classification across the longitudinal retest interval (from W1 to W2). Both *APOE* and *COMT* genotypes and their separate interactions with all eight vascular health markers were analyzed. Further, due to reduced sample sizes for the interaction analyses across cognitive status groups, the presence of MCI classification at any point within the testing interval (as opposed to stability of cognitive status classification, i.e., NIC–MCI or MCI–MCI groups) was the target outcome for these analyses. The goal was to assess whether vascular risk factors, with previously identified genetic risk factors in two-way combinations, increased the risk of stable or chronic MCI classification within the test interval. Given our a priori hypotheses regarding expected directional effects, we employed one-tailed tests for all analyses.

Results

We report results pertaining to the four major research questions. The frequencies of all genes were in Hardy–Weinberg equilibrium for the entire sample, as described by Dixon and colleagues (2014). Post hoc logistic regression power analyses (G*Power 3.1) indicate that the present study has sufficient power to detect independent and interactive effects both (a) at baseline (average baseline power, $M = 0.78$) and (b) over the retest interval (average longitudinal power, $M = 0.82$). Participant demographic characteristics and comparisons are reported in Table 1. We computed inferential tests of between-group differences with respect to the demographic variables. At baseline,

Table 1. Sample Demographics by Cognitive Status and Stability

Wave 1				Waves 1–2				
	NIC	MCI	p^1	NIC-NIC	NIC-MCI	p^2	MCI-MCI	p^3
N	220	196		134	36		95	
Age	74.77 (5.85)	76.24 (6.63)	.009	73.60 (5.24)	74.22 (6.26)	.275	74.71 (6.22)	.075
Gender (W)	65.5%	57.7%	.052	61.2%	77.8%	.035	58.9%	.366
Education	15.20 (2.94)	14.52 (3.17)	.013	15.39 (2.95)	14.19 (2.30)	.014	14.49 (3.01)	.014

Note: MCI = mild cognitive impairment; N = sample size; NIC = not impaired controls; p^1 = comparison between Wave 1 NIC and MCI groups; p^2 = comparison between NIC-NIC and NIC-MCI Waves 1-2 groups; p^3 = comparison between NIC-NIC and MCI-MCI Waves 1-2 groups. Age and education data are presented as average (standard deviation). For the two wave groups (Waves 1-2) the data presented refer to baseline (Wave 1) values.

participants belonging to the MCI group were significantly older (p = .009; one tailed), less educated (p = .013; one tailed), men (p = .052; one tailed) compared with the NIC group. Across waves, participants belonging to the NIC–MCI transition group or the MCI stability group were less educated (p = .014 and .014, respectively; one tailed) compared with the NIC–NIC stability group. There were more female participants in the NIC–MCI transition group compared with the NIC–NIC stability group (p = 0.035; one tailed). Chronological age, time in study, and years of education were entered into all analyses as covariates. Frequencies of reported and measured baseline vascular health according to cognitive status and stability group are reported in Tables 2 and 3.

Vascular Health Markers of Baseline Cognitive Status

As reported in Table 4, there are two vascular health factors that differentiate between NIC and MCI at baseline. Specifically, the presence of a frail PEF (p = .053; one tailed) and the consumption of heart medications (p = .025; one tailed) at baseline were associated with a 1.48- and 1.56-fold higher likelihood of MCI classification at baseline compared with the NIC group, respectively. Finally, a measured BMI of greater than 30 kg/m^2 was associated with a 43.8% lower odds [(1 – 0.562) × 100 = 43.8%] of being classified as MCI than the controls at baseline (p = .019; one tailed).

Vascular Health Markers of Two-Wave Stability of Cognitive Status

As reported in Table 2, there were four vascular health factors that were associated with either transition to or stability of MCI over the retest interval. Specifically, the presence of a history of heart disease (p = .017; one tailed), atherosclerosis (p = .030; one tailed), and stroke (p = .006; one tailed) at baseline were each associated with a 3.01-, 3.38-, and 7.73-fold higher likelihood of conversion from NIC to MCI status over the retest interval, respectively. In addition, the presence of a history of heart medication use at baseline was associated with a 1.56-fold higher likelihood of chronic MCI stability over the retest interval, compared with the stable NIC group (p = .005; one tailed). A history of high BP and a pulse rate of greater than 80 BPM were linked to a 63.9% and 69.0% lower odds, respectively, of being classified as stable MCI across the retest interval (p = .008 and .040; one tailed)].

Two-Way Interactions Between Vascular Health Factors and Genetic Risk

We previously demonstrated that the presence of at least one *APOE* ε4 allele conferred a 1.65-fold increase in risk of MCI status at baseline (Dixon et al., 2014). The two-way interactions between vascular health factors and genetic risk factors revealed that the presence of at least one *APOE* ε4 allele in combination with a self-report of high BP at baseline was associated with a 4.77-fold higher likelihood of MCI classification at baseline compared with the NIC group. This indicates that the addition of a vascular risk factor (i.e., high BP) to *APOE* risk increases baseline MCI prediction. Baseline MCI status was not associated with the interaction between vascular health factors and *COMT* G/G. Two-way interactions between vascular health factors and genetic risk factors did not reveal any statistically significant associations with transition to MCI or MCI stability over time.

Discussion

One significant area of aging research involves the identification of markers associated with transitions that occur early in a lengthy preclinical period of cognitive impairment (e.g., Albert et al., 2011; Anstey, 2014). Using both cross-sectional and two-wave longitudinal data, we examined whether vascular health risk factors operated independently and interactively with two genetic risk factors to

Table 2. Frequency of Vascular Factors at Wave 1, Stratified by Cognitive Status

Variable	N	NIC	N	MCI
Physiological functioning				
BMI	219		193	
18.5–30 kg/m^2		171 (78.4)		165 (87.3)
>30 kg/m		47 (21.6)		24 (12.7)
PEF	219		196	
Strong		179 (81.7)		145 (74)
Frail		40 (18.3)		51 (26)
HBP	168		122	
No history		111 (66.1)		90 (73.8)
Positive history		57 (33.9)		32 (26.2)
Pulse Rate	218		190	
40–80 BPM		195 (89.4)		175 (92.1)
>80 BPM		23 (10.6)		15 (7.9)
Vascular Disease factors				
Heart Disease	168		121	
No history		128 (76.2)		94 (77.7)
Positive history		40 (23.8)		27 (22.3)
Atherosclerosis	166		121	
No history		149 (89.8)		109 (90.1)
Positive history		17 (10.2)		12 (9.9)
Stroke	168		121	
No history		157 (93.5)		114 (94.2)
Positive history		11 (6.5)		7 (5.8)
Heart Medication	210		182	
No history		150 (71.4)		105 (57.7)
Positive history		60 (28.6)		77 (42.3)
APOE*HBP	109		68	
≥ 1 protective factor		101 (92.7)		59 (86.8)
Both risk factors		8 (7.3)		9 (13.2)

Note: BMI = body mass index; BPM = beats per minute; HBP = high blood pressure; MCI = mild cognitive impairment; N = sample size; NIC = not impaired controls; PEF = peak expiratory flow; data presented as frequency (percentage).

predict group membership in three clinically important situations: (a) baseline (W1) assessment, with NIC compared with MCI, (b) two-wave stability of MCI status, reflecting a chronic and stable condition (i.e., MCI–MCI), and (c) two-wave decline in NIC status, reflecting conversion to classified impairment (i.e., NIC–MCI). As our intended focus was on early and preclinical impairment and a critical aspect of our design required full participation, we did not evaluate transitions to dementia.

First, the presence of a frail PEF, according to gender-specific guidelines, was associated with a significantly higher risk of MCI status at baseline compared with the NIC group. A similar pattern was found in a related study in which impaired lung function was associated with poorer cognitive performance (Pathan et al., 2011). Although the link between cognition and lung function is well documented (Albert et al., 1995; MacDonald, Dixon, Cohen, & Hazlitt, 2004; MacDonald, DeCarlo, & Dixon, 2011) and related correlates such as cardiorespiratory fitness have been positively associated with executive function and episodic memory in older adults (Hayes, Forman, & Verfaellie, 2014), the precise mechanisms involved in this association are poorly understood. Pulmonary capacity is related to one's physical activity levels. Research in the area of physical fitness documents associations with various biological markers, such as brain-derived neurotrophic factor (BDNF; Cotman & Berchtold, 2002), inflammation (Kasapis & Thompson, 2005) and blood health–related genetic variants such as *RUNX1* and *FKBP7* in individuals with diabetes (Peter et al., 2013). These factors could conceivably influence and moderate cognitive functioning on the molecular level. The influence of PEF risk on MCI status, emergence, or chronicity was independent of the two genetic risk factors examined in this study. Future research may evaluate the potential for BDNF genotype to moderate the observed independent associations.

Second, the presence of reported high BP was not independently associated with risk of MCI classification at baseline or two-wave conversion to MCI (NIC–MCI). Contrary to expectation, a reported history of high BP was linked to a decreased risk of MCI stability over the retest interval. This could reflect the differential influences of both high and low BP on cognitive functioning (Qiu, Winblad, Fastbom, & Fratiglioni, 2003). Conceivably, this may reflect two important considerations. First, given the availability of universal health care, many of the present participants may be receiving treatment for BP abnormalities and may therefore experience a monitored or reduced vascular burden than might otherwise be associated with hypertension. Second, it is possible that high BP is a risk factor for early emergence of pre-AD conditions but not necessarily their continuation in this condition, especially if treated. Interestingly, the presence of reported high BP in individuals with at least one *APOE* ε4 allele significantly increased their risk of MCI classification at baseline. These findings extend to the preclinical period highlighted by previous research examining AD risk of genetically susceptible individuals with high systolic BP (Qiu, von Strauss, Fastbom, Winblad, & Fratiglioni, 2003). The results indicate that compromised vascular health may magnify the detrimental effects of *APOE* ε4 on cognitive status in late life, a finding consistent with the resource modulation hypothesis (Lindenberger et al., 2008) and recent empirical findings (McFall et al., 2013, 2014). Further, at least among informed older adults, reported BP levels could be a viable indicator of an individual's vascular health, as specific readings taken throughout a testing session may not be indicative of typical daily values or fluctuations in BP. Although reported BP, in concert with the *APOE* ε4 allele, was a predictive marker for cognitive status, a greater than 80 BPM pulse rate was not associated with risk of MCI at baseline or with conversion to MCI in the current study. Unexpectedly, a greater than 80 BPM pulse rate was linked to a reduced risk of MCI stability over time in the current study. Although higher pulse rate has been linked to

Table 3. Frequency of Vascular Factors Across the Retest Interval, Stratified by Cognitive Status Stability Group

Variable	N	NIC-NIC	N	NIC-MCI	N	MCI-MCI
Physiological functioning						
BMI	133		36		92	
18.5–30 kg/m²		102 (77.3)		29 (80.6)		78 (85.7)
>30 kg/m²		30 (22.7)		7 (19.4)		13 (14.3)
PEF	133		36		95	
Strong		112 (84.2)		27 (75.0)		74 (77.9)
Frail		21 (15.8)		9 (25.0)		21 (22.1)
HBP	105		27		60	
No history		67 (63.8)		19 (70.4)		50 (83.3)
Positive history		38 (36.2)		8 (29.6)		10 (16.7)
Pulse Rate	132		36		94	
40–80 BPM		119 (90.2)		30 (83.3)		90 (95.7)
Vascular Disease factors						
Heart Disease	105		27		59	
No history		86 (81.9)		18 (66.7)		49 (83.1)
Positive history		19 (18.1)		9 (33.3)		10 (16.9)
Atherosclerosis	104		27		59	
No history		96 (92.3)		22 (81.5)		57 (96.6)
Positive history		8 (7.7)		5 (18.5)		2 (3.4)
Stroke	105		27		59	
No history		102 (97.1)		22 (81.5)		56 (94.9)
Positive history		3 (2.9)		5 (18.5)		3 (5.1)
Heart Medication	126		35		87	
No history		96 (76.2)		25 (71.4)		50 (57.5)
Positive history		30 (23.8)		10 (28.6)		37 (42.5)
APOE*HBP	81		19		46	
≥ 1 protective factor		76 (93.8)		17 (89.5)		40 (87.0)

Note: ε4 = APOE ε4 allele; BMI = body mass index; BPM = beats per minute; HBP = high blood pressure; MCI = mild cognitive impairment; N = sample size; NIC = not impaired controls; PEF = peak expiratory flow; data presented as frequency (percentage).

declining cognitive function (Bohm et al., 2015), which could be conceivably mediated by poor physical fitness levels, heart rate can also be influenced by other factors, such as anxiety. To be sure, anxiety is common in older adults subjectively concerned about cognitive impairment (Forsell, Palmer, & Fratiglioni, 2003). It is possible that anxiety-related elevations in heart rate in individuals with chronic MCI could be naturally attenuated through the use of anxiolytics compared with healthy controls in a testing scenario, resulting in the current findings. However, investigation into the concomitant use of anxiety-reducing medication was beyond the scope of this study. Similar to pulse rate, a measured BMI of greater than 30 kg/m² was associated with a decreased risk of MCI status at baseline. Upon analysis of group composition, it was noted that 75% of participants in the *at risk* BMI category fell between 30 and 35 kg/m², thereby possibly indicating that BMI is an insensitive marker of vascular load in this study. However, protective effects of high BMI on cognitive functioning cannot be discounted, as literature suggests that higher BMI may be protective in some populations, such as in postmenopausal woman (e.g., Thilers, MacDonald, Nilsson, & Herlitz, 2010).

Third, a history of heart disease at baseline was associated with a significantly higher risk of conversion from NIC to MCI, compared with the stable NIC group. Similarly, a history of heart medication consumption was associated with a significantly higher risk of MCI classification at baseline compared with the NIC group, as well as associated with a significantly higher risk of chronic MCI classification compared with the stable NIC group. In general, cognitive deficits, especially in the domains of executive function, memory, language, and mental speed, are common in adults with chronic heart failure (Vogels et al., 2007). Moreover, some previous studies have revealed that heart failure is associated with an increased risk of MCI and dementia (Qiu et al., 2006), indicating that the presence of heart disease could be an early cardiovascular risk factor associated with changes in cognitive status. Our findings indicate that reported consumption of prescribed heart disease medications may be a sensitive indicator of early cognitive impairment at baseline and of chronicity in impaired status. Perhaps even manageable (and managed) heart conditions (i.e., requiring the use of medications) can reflect chronic vascular effects having an impact on cognitive performance in excess to that of typical cognitive decline.

Table 4. Statistical Results Relating Vascular Factors to Cognitive Status and Stability

Covariate	Wave	Status/Stability	Risk Factor	β	OR	95% CI	*p*
BMI	W1	MCI	>30 kg/m^2	-0.577	0.562	0.326–0.968	.019*
	W1-2	NIC-MCI	>30 kg/m^2	-0.143	0.867	0.338–2.220	.382
	W1-2	MCI-MCI	>30 kg/m^2	-0.474	0.623	0.300–1.292	.102
PEF	**W1**	**MCI**	**Frail**	**0.393**	**1.481**	**0.921–2.381**	**.053**
	W1-2	NIC-MCI	Frail	0.402	1.500	0.599–3.728	.195
	W1-2	MCI-MCI	Frail	0.339	1.281	0.640–2.567	.242
HBP	W1	MCI	History of HBP	-0.384	0.681	0.405–1.145	.074
	W1-2	NIC-MCI	History of HBP	-0.361	0.697	0.270–1.799	.228
	W1-2	MCI-MCI	History of HBP	-1.020	0.361	0.159–0.819	.008*
Pulse Rate	W1	MCI	>80 BPM	-0.227	0.797	0.399–1.592	.260
	W1-2	NIC-MCI	>80 BPM	0.685	1.983	0.667–5.899	.109
	W1-2	MCI-MCI	>80 BPM	-1.172	0.310	0.083–1.153	.040*
Heart Disease	W1	MCI	History of Heart Disease	-0.103	0.902	0.512–1.590	.360
	W1-2	**NIC-MCI**	**History of Heart Disease**	**1.103**	**3.012**	**1.090–8.322**	**.017**
	W1-2	MCI-MCI	History of Heart Disease	0.299	1.349	0.548–3.322	.258
Atherosclerosis	W1	MCI	History of Atherosclerosis	0.001	1.001	0.452–2.217	.499
	W1-2	**NIC-MCI**	**History of Atherosclerosis**	**1.217**	**3.377**	**0.953–11.969**	**.030**
	W1-2	MCI-MCI	History of Atherosclerosis	-0.585	0.557	0.111–2.799	.239
Stroke	W1	MCI	History of Stroke	-0.327	0.721	0.262–1.984	.263
	W1-2	**NIC-MCI**	**History of Stroke**	**2.045**	**7.726**	**1.579–37.801**	**.006**
	W1-2	MCI-MCI	History of Stroke	0.589	1.802	0.335–9.703	.247
Heart Medication	**W1**	**MCI**	**History of Heart Meds**	**0.444**	**1.558**	**0.998–2.435**	**.025**
	W1-2	NIC-MCI	History of Heart Meds	0.140	1.151	0.464–2.851	.381
	W1-2	**MCI-MCI**	**History of Heart Meds**	**0.841**	**2.319**	**1.221–4.405**	**.005**

Note: BMI = body mass index; HBP = high blood pressure; MCI = mild cognitive impairment; N = sample size; NIC = not impaired controls; OR = odds ratio; PEF = peak expiratory flow; W1 = Wave 1; W1-2 = Wave 1- Wave 2; p values are all presented as one-tailed; * = significant finding in the unexpected direction for BMI, HBP and pulse rate. The reference outcome groups are NIC (W1) and NIC-NIC (W1-2). For the self-reported variable analyses, the reference analysis groups consisted of those with no self-reported history. For the BMI, peak expiratory flow and pulse rate analyses, the reference analysis groups consisted of those with a normal range BMI, a normal range peak flow and a healthy pulse rate, respectively. Note, the same directionality was demonstrated for all analyses in the genotyped sample.

Notably, these cardiovascular factors were independent of genetic risk factors, at least for early MCI. Conceivably, the long-term effects could involve magnification of vascular risk by neurodegenerative-related genetic risk.

Fourth, a history of atherosclerosis at baseline was associated with a significantly higher risk of conversion from NIC to MCI, compared with the stable NIC group. Previous research has shown that clinical markers of atherosclerosis, such as carotid arterial intima-media thickness (Haley et al., 2007), pulse wave velocity (Waldstein et al., 2008), and low ankle-brachial index (Guerchet et al., 2011), are associated with normal cognitive decline in aging (e.g., McFall et al., 2014) and cognitive impairment or dementia. Recently, in a study measuring carotid artery thickness and cortical volume, independent of *APOE* status, subclinical carotid atherosclerosis was associated with cortical thinning of the parietal lobe (Cardenas et al., 2012), an area involved in the more advanced stages of AD. The authors suggest a "double hit" toward the development of AD when vascular risk factors are comorbid in individuals with incipient AD. Consistent with this view, recent research charts the association between increased white matter hyperintensities and MCI and AD but not with AD-related cerebral spinal fluid and magnetic resonance imaging biomarkers, indicating that the vascular contribution to AD-type dementia is likely additive and independent of the amyloid pathway (Lo, Jagust, & Alzheimer's Disease Neuroimaging Initiative, 2012). Unfortunately, it remains poorly understood whether vascular factors contribute to the underlying cause of the cognitive impairment (i.e., risk factors), accelerate the conversion to MCI (i.e., precipitating factors), or are indicative of separate disease processes underlying a more vascular-type dementia trajectory. Notably, at this phase of MCI, genetic risk factors did not significantly alter the effects of reported atherosclerosis on cognitive status classification at baseline or over the retest interval.

Fifth, a history of stroke at baseline was associated with a significantly higher risk of conversion from NIC to MCI, extending similar associations found in dementia patients (Rastas et al., 2007), with estimates that incident stroke is associated with a twofold greater increased risk of dementia (Reitz, Bos, Hofman, Koudstaal, & Breteler, 2008) and a more-rapid decline of AD (Regan et al., 2006). The association between history of stroke and risk of MCI could be based on stroke-induced brain atrophy. However, there is increasing evidence that cerebrovascular disease could

accelerate amyloid beta 40–42 production or accumulation and contribute to AD-specific pathology (Weller, Cohen, & Nicoll, 2004). Genetic risk factors did not significantly alter the effects of reported stroke on cognitive status classification at baseline or over the retest interval.

Several limitations should be acknowledged. First, although the present research is promising for delineating the breadth of vascular health influence on early MCI, other vascular health indicators and vascular impairment polymorphisms should be investigated. In addition, we did not have data available to examine related conditions such as inflammatory conditions, objectively measured or long-term emerging or worsening vascular factors, or potential causative environmental factors (e.g., nutrition; Anstey, 2014; Fotuhi et al., 2009). Second, our MCI classification procedures did not include clinical judgment (according to our standard fully objective system, e.g., de Frias et al., 2009; Dixon et al., 2007; Dolcos et al., 2012), and it is possible that the standard we set (1 *SD* below the appropriate group mean of a community-dwelling, educated group) may have included participants that could have been borderline or early transitional. Indeed, the aim was to examine the early preclinical normal-impairment phase. Importantly, the objective procedures produced high status stability rates (for both MCI and NIC) and may be transportable to other studies and clinics. Moreover, because we focused on relatively early conditions potentially emerging in a nondemented cohort, the data provided a conservative test of the hypotheses. Third, analyses of self-reported high BP did not differentiate between systolic and diastolic readings. As systolic and diastolic BP can have differing influences on risk of cognitive impairment (e.g., low diastolic has been associated with risk of dementia; Qiu, von Strauss, Winblad, & Fratiglioni, 2004), parsing out these differential influences in future analyses may help to better clarify the directional association between self-reported high BP and cognitive status and stability. Further, analyzing the differential influences on cognition of those with low BMI (<18.5 kg/m^2) versus high BMI (>30 kg/m^2) or utilizing an additional theoretically meaningful proxy for obesity, such as waist-to-hip ratio, may be useful steps in future analyses with larger sample sizes. Fourth, although it would have been interesting to identify individuals with diverse MCI subtypes (e.g., amnestic MCI), the present classification procedures and the sample size did not allow for this distinction. Future research should expand on the present approach. Fifth, the goal for generalizability would be restricted to that (growing) portion of older adults who are relatively educated with moderate-to-good health, and, regarding cognitive and neural integrity, likely to range from typical aging to early impairment—but not yet dementia.

Overall, the findings of this study reveal several interesting independent associations involving vascular and genetic risk factors for cognitive status both at baseline and over time. Recent evidence links poor vascular health to normative aging (van den Berg, Kloppenborg, Kessels, Kappelle, & Biessels, 2009) and AD-related risk (Clerici et al., 2012), indicating that vascular health likely contributes differentially to multiple cognitive trajectories. Importantly, comparing our findings with self-reported vascular conditions to previous findings (i.e., reported medicated hypertension, odds ratio of 1.86 in Tervo et al., 2004), we find that the magnitude of our self-reported vascular indices in individuals converting from NIC to MCI or with MCI stability tended to be higher, ranging from odds ratios of 1.6 to 7.73. This may reflect the importance of these self-report measures in identifying early cognitive impairment. Our findings also emphasize the importance of the interactive effects between vascular health and genetic risk factors; such magnification of effects was observed in a recent cross-domain (vascular-genetic) study in nonimpaired aging (e.g., McFall et al., 2014). The present findings represent a significant step forward in the identification of the complex mechanisms through which vascular health may influence cognitive status disruptions and early transitions from normal aging to clinically detectable cognitive impairment in late life.

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