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Independent and joint effects of vascular and cardiometabolic risk factor pairs for risk of all-cause dementia: a prospective population-based study

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Abstract

Objectives: To assess independent and joint effects of pairs of vascular and cardiometabolic risk factors (VCMRFs) in relation to risk of all-cause dementia.

Design: Population-based longitudinal cohort study of cognitive impairment. We used an algorithm to select pairs of VCMRFs and tested their joint effects in time-dependent Cox models. We used attributable proportions (AP) to measure the proportion of risk from interactions beyond any additive effect.

Setting: Economically depressed small-town population.

Participants: Adults age 65+ years with up to 10 yearly study visits (N=1701, median (Q1, Q3) age, 78 (71.0, 83.0), 62.3% female, 94.9% white).

Results: Among 1701 participants free from prevalent dementia with at least one follow-up visit, 109 developed incident all-cause dementia. In pairings of *APOE**4 with hypertension (HTN) and congestive heart failure (CHF), the variables contributed independently and additively to all-cause

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Descriptions of authors' roles

C. Shaaban formulated the research question, designed the analytic approach, analyzed the data, and wrote the manuscript. Y. Jia analyzed the data and provided critical revisions to the manuscript. C. Chang designed the analytic approach and provided critical revisions to the manuscript. M. Ganguli designed the cohort study, supervised data collection, and provided critical revisions to the manuscript.

Conflict of interest
None.

Supplementary material

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dementia risk. In pairings of *APOE**4 with stroke and stroke with CHF, the variables demonstrated independent contributions to all-cause dementia risk; their joint effects showed excess detriment demonstrating synergistic interactions (joint HR [95% CI]: 28.33 [6.74, 119.01] and 50.30 [14.57, 173.57] respectively, fully adjusted models). Physical activity (PA) was independently associated with lower all-cause dementia risk when paired with *APOE**4, stroke, and CHF in unadjusted models; these associations did not survive covariate adjustment. The joint effect of low PA and *APOE**4 was associated with additively increased all-cause dementia risk (joint HR [95% CI]: 4.61 [2.07, 10.23], fully adjusted model).

Conclusions: Reduction of VCMRFs, including low PA, could be valuable for dementia prevention, especially among *APOE**4 carriers.

Keywords

Alzheimer's disease (AD); apolipoprotein E (APOE); cerebral vascular disease (CVD); dementia; epidemiology

Introduction

Increasingly, vascular and cardiometabolic risk factors (VCMRFs) are recognized as vascular contributions to cognitive impairment and dementia (VCID) (Baumgart et al., 2015; Snyder et al., 2015). VCMRFs are associated with cerebral small vessel disease (cSVD) and other markers of poor cerebrovascular integrity (Jorgensen et al., 2018; Vemuri et al., 2017), which in turn increase risk for dementia (Kloppenburg et al., 2014; Pantoni et al., 2015; Prins et al., 2004). Co-occurrence of cerebrovascular lesions with Alzheimer's disease (AD), pathology nearly doubles dementia prevalence (Azarpazhooh et al., 2018).

How VCMRFs may co-occur to increase risk of dementia is of critical public health importance. As mortality rates decline, we are living longer with multiple chronic conditions. Most older adults present to their primary care practitioners with multimorbidity—the presence of two or more chronic health conditions (Salive, 2013). Understanding which VCMRFs co-occur to increase dementia risk, and whether they potentiate dementia risk, would allow us to better tailor preventions and treatments, the critical promise of precision medicine.

Here, our aim was to determine whether co-occurring VCMRFs operate independently and whether their joint effects are additive or synergistic over long-term follow-up in relation to incident all-cause dementia. Pairs of VCMRFs to be tested were selected based on an algorithm incorporating a review of the literature (Jorgensen et al., 2018) and univariable associations with incident all-cause dementia. We evaluated these relationships in a population-based cohort study with 10 years of follow-up.

Methods

Study participants

The Monongahela-Youghiogheny Healthy Aging Team (MYHAT) study is a longitudinal epidemiologic observational cohort study of cognitive impairment. Participants were

selected from voter rolls to be representative of the older adults in a socioeconomically depressed area of small former steel-manufacturing towns in southwestern Pennsylvania, USA. Participants were assessed either in their homes or in the study field office and had up to 10 yearly study visits. Study visits examined here took place between 3/20/2006 (first date of study visit 1) and 9/8/2017 (last date of study visit 10). The University of Pittsburgh Institutional Review Board reviewed and approved the study, and written informed consent was received from all participants before initiation of any study procedures.

DEMOGRAPHICS—In interviews with research staff, participants self-reported date of birth, sex (male or female), race, and education level at the baseline visit. Age was calculated based on the self-reported date of birth and treated as a continuous variable in the analyses reported here. Race was categorized as white or non-white. Education was categorized as less than high school, high school, or greater than high school.

VCMRFs—Four categories of VCMRFs were collected: physical exam measures, laboratory tests, chronic health conditions, and lifestyle factors.

PHYSICAL EXAM MEASURES—Systolic and diastolic blood pressure (SBP and DBP), apical pulse, and height, waist, and hip circumference in inches were measured by the examiner during the physical exam. Weight was self-reported by participants until visit 9 when it was measured by the examiner. Mean arterial pressure (MAP), a measure of organ perfusion, was estimated as: $MAP \cong \frac{SBP + (2 \times DBP)}{3}$. Pulse pressure (PP), a measure of pulsatility, was

calculated as $SBP - DBP$. Body mass index (BMI) was calculated as: $\frac{\text{weight in pounds}}{\text{height in inches}^2 * 703}$.

Waist to hip ratio (WHR) used as a measure of central obesity.

LABORATORY TESTS—Among those participants who consented to blood tests, the following markers were collected at study baseline or visit 2 if unsuccessful at baseline. ApoA1 and ApoB were measured, and the ratio of ApoB to ApoA1 was calculated. ApoB:ApoA1 is a measure of atherogenic to anti-atherogenic lipoprotein particles, and is a risk factor for cardiovascular disease (Walldius and Jungner, 2006). Hemoglobin A1C (glycosylated hemoglobin) is a running average measure of blood glucose within the past 3 months. Cystatin C is a marker of glomerular filtration which is related to cardiovascular disease (Ferguson et al., 2015). Homocysteine, an amino acid produced through methionine metabolism, has been correlated with cSVD (Vermeer et al., 2002; Wong et al., 2006). C-reactive protein was included as an inflammatory marker which has been related to cSVD (van Dijk et al., 2005). The *APOE*4* genotype was coded as *APOE*4* carrier or non-carrier. Finally, non-fasting total cholesterol and high-density lipoprotein cholesterol (HDL-C) were measured, and low-density lipoprotein cholesterol (LDL-C) was calculated as total cholesterol - HDL-C. The Chemistry and Nutrition Lab at the University of Pittsburgh Graduate School of Public Health completed these assays.

CHRONIC HEALTH CONDITIONS AND LIFESTYLE FACTORS—At study baseline, participants were asked whether they had *ever* been told by a health care provider that they have or had: a stroke, transient ischemic attack (TIA), diabetes, HTN, myocardial infarction (MI), high

cholesterol, CHF, irregular heartbeat (including atrial fibrillation or arrhythmia), depression, or anxiety (including “nerves”). At each follow-up visit, they were asked whether a health care provider had told them they have or had any of these conditions *since they were last seen* by the study. These variables were treated as dichotomous, yes/no. Study staff administered the modified Center for Epidemiologic Studies-Depression (mCESD) scale at each study visit (Ganguli et al., 1995). The score ranges from 0 to 20, representing the number of depression symptoms experienced during most of the preceding week. Ever and current smoking and drinking alcohol were self-reported by participants. At study baseline, participants were asked whether they had *ever* smoked cigarettes or had an alcoholic drink, and at each follow-up visit, they were asked whether they had smoked cigarettes or had an alcoholic drink *since they were last seen* by the study. These variables were treated as dichotomous, yes/no. Participants were asked if they exercise, and if yes, what kind of exercise they do. For these analyses, physical activity (PA) was assessed as the number of minutes per week spent walking specifically for exercise because walking is common, easy for older adults to engage in and requires no equipment or special training (Piercy et al., 2018; Rosano et al., 2017). This was calculated based on the product of the number of days per week and minutes per day the participant self-reported walking for exercise.

ALL-CAUSE DEMENTIA AND GLOBAL COGNITION—Incident all-cause dementia diagnosis was ascertained using the clinical dementia rating (CDR) score (Morris, 1993), without an etiological specification. The CDR was completed by research associates trained and certified in the CDR based on interview questions and observations during the evaluation with the participant and an informant, if available. All-cause dementia was defined as CDR

1. The Mini-Mental State Examination (MMSE) was administered by trained research associates as a measure of global cognition (Folstein et al., 1975).

Statistical analyses

Descriptive statistics of baseline characteristics were calculated as N (%) for categorical variables or median (Q1, Q3) for continuous variables due to non-normal distributions.

ALGORITHM TO SELECT THE VCMRF PAIRS OF INTEREST—We selected the variable pairs of interest using an algorithm based on the following criteria. First, based on the pairs having additive or synergistic effects identified in our previously published literature review (Jorgensen et al., 2018), we selected two pairs of interest, which could be tested in our population: *APOE*4*/HTN and HbA1c/SBP. For the candidate variable pair to be selected by the algorithm, the component variables had to be significantly related to incident all-cause dementia in univariable time-dependent Cox regression models (described below). Additional VCMRF pairs were selected based on the univariable associations between the VCMRFs and incident all-cause dementia; those variables significantly associated with dementia at $p < 0.05$ were ordered by effect size. If the variable was protective, the hazard ratio (HR) was inverted ($1/\text{HR}$) to format all effect sizes in the same direction. VCMRF pairs formed by those variables with the top three largest effect sizes were selected as candidate pairs to test. Thus, our final list of VCMRF pairs consisted of the following: any of the literature review-based candidates in which the component variables were also significantly

associated with incident all-cause dementia at $p < 0.05$ and VCMRF pairs formed by the three variables with the largest effect sizes.

PRIMARY ANALYSES—If VCMRF pairs were selected based on the algorithm, we evaluated their independent and joint effects on incident all-cause dementia using Cox regression models. We emphasize that here “effects” refers to statistical, rather than causal, associations. The risk set for incident all-cause dementia included all participants free from prevalent dementia at baseline ($CDR < 1$). We censored those who remained free from dementia at their last visit. For those who developed incident dementia, the visit at which they were first classified as $CDR = 1$ was designated as the event time. Given that VCMRFs may change in late-life over the years leading up to dementia (Wagner et al., 2018), accounting for these time-varying exposures is important for accurate risk assessment. We used time-dependent Cox models with the counting process format to deal with time-dependent covariates. The counting process format partitions the whole follow-up time interval into subintervals, allowing the covariates to change at each subinterval. Because this type of model incorporates time-dependent covariates, no assumption of proportional hazards is made. Continuous variables were standardized for analysis.

The independent contribution of the component variables of each pair was tested first, followed by a model testing the joint effects of the two variables on the additive scale. Variables in these additive models were coded as presence or absence for variable 1 and 2 as follows: variable 1 + /variable 2 –, variable 1 – /variable 2 +, and variable 1 + /variable 2 +. The absence of both variables (variable 1 – /variable 2 –) was set as the reference category. To test joint effects on the additive scale, variables must be coded in the direction of increased risk. Thus, any factor which was protective in univariable analysis was reverse coded for additive models. Synergistic interaction—contribution of the co-occurrence of the two variables beyond the expected additive amount—was tested using the attributable proportion (AP). The AP is a measure of the proportion of the total risk associated with the presence of both factors (variable 1 + /variable 2 +) that is due to the excess risk from interaction (Andersson et al., 2005). This is calculated as: $[HR(\text{variable 1 + /variable 2 +}) - (HR(\text{variable 1 + /variable 2 –}) - 1) - (HR(\text{variable 1 – /variable 2 +}) - 1) - 1] / HR(\text{variable 1 + /variable 2 +})$. Here, the 1s being subtracted represent the reference category (variable 1 – /variable 2 –). An AP different from 0 indicates the presence of a synergistic interaction. Both non-modifiable / demographic factors and VCMRFs are important for cerebrovascular health and dementia (Jorgensen et al., 2018; Larson, 2019). Therefore, significant unadjusted models were adjusted for non-modifiable factors including age, sex, race, education, and *APOE*4* and then further adjusted for additional confounders among the included VCMRFs—any variables significantly related to both the predictor and outcome, but not on the causal path. Thus, the confounders included in each model are specific to that model. The results of these analyses were adjusted for multiple comparisons using a False Discovery Rate (FDR) adjusted p-value and a cutoff of $p < 0.05$ (Benjamini and Hochberg, 1995). Results are presented as Hazard Ratios (HR) and APs and their 95% confidence intervals (CI). Analysis was carried out using SAS 9.4 (SAS Inst., 2013), the *survival* (Therneau, 2015) package in R (R Core Team, 2018), and the AP calculator of Andersson, et al. (Andersson et al., 2005), in Microsoft Excel 2016.

POST HOC ANALYSES—Using the same analytic approach as the primary analysis, we carried out additional tests not selected through our algorithm. We assessed whether the lifestyle VCMRF variable PA predicted dementia independently, additively, or synergistically when paired with the VCMRF variables with the three largest effect sizes from the primary univariable analyses. Continuous PA was dichotomized into low and high PA using a mean split for the joint effects models only. Given the exploratory nature of these analyses, we did not correct these results for multiple comparisons.

Results

Out of N=1982 total MYHAT participants, N=1959 were free from prevalent dementia at baseline, N=1701 had at least one follow-up visit, and N=109 developed incident all-cause dementia over the ten years (Supplementary Figure 1, published as supplementary material online attached to the electronic version of this paper at <https://www.cambridge.org/core/journals/international-psychogeriatrics>). Baseline descriptive statistics for the analytic study sample (N=1701) are shown in Table 1. Overall, participants were a median (Q1, Q3) age of 78.0 (71.0, 83.0) years old, 62.3% female, 94.9% white, and 86.9% had at least a high school education. VCMRF chronic health condition prevalence/history at baseline ranged from <5% for history of stroke to approximately 65% of participants for a history of having been diagnosed with hypertension.

PRIMARY ANALYSES

Hazard ratios (HR) and 95% confidence intervals (CI) for univariable relationships with incident dementia are shown in Table 2. All of the demographic variables except sex were significantly related to incident dementia in the expected direction. Among the VCMRFs, the three with the largest effect sizes were stroke HR [95% CI]: 9.90 [4.76, 20.58]; CHF: 2.91 [1.60, 5.31]; and *APOE**4: 2.02 [1.33, 3.05]. HTN, cardiac arrhythmia, and depression (both by history of diagnosis by a health care provider and number of depression symptoms by mCESD) were associated with increased risk of incident all-cause dementia, while larger BMI, self-reported high cholesterol, more PA minutes, and ever smoking were associated with decreased risk.

Four VCMRF pairs were selected based on our algorithm: *APOE**4/HTN based on the literature review and significant univariable associations as well as *APOE**4/stroke, *APOE**4/CHF, and stroke/CHF based on the three largest effect sizes in univariable analyses. HbA1c and SBP were not associated with all-cause dementia in univariable regression models, and therefore this pair was not algorithm-selected for further analyses. In all of the pairings tested, all variables remained significant independent predictors of all-cause dementia when simultaneously entered into the model with the paired variable, even after adjustment for multiple comparisons (20 total coefficients tested; 8 for independent effects models and 12 for joint effects models) and in models fully adjusted for non-modifiable factors and confounders (Table 3). The joint effects of *APOE**4 + /HTN +, *APOE**4 + /stroke +, *APOE**4 + /CHF +, and stroke + /CHF + were significant (Table 4). The joint effects of *APOE**4 + /HTN + and *APOE**4 + /CHF + contributed additively, while the joint effects of *APOE**4 + /stroke + and stroke + /CHF + contributed synergistically to

dementia risk. These results remained after adjustment for multiple comparisons and statistical adjustment for non-modifiable factors and confounders. The proportion of the total risk of all-cause dementia due to the excess risk of interaction was (AP [95%CI]: 0.67 [0.14, 1.20]) for *APOE**4 + /stroke + (Figure 1) and 0.89 [0.73, 1.06] for stroke + /CHF + (Supplementary Figure 2). Specifically, the joint effect of *APOE**4 and stroke would have had an HR of 9.31 (HR *APOE**4 (2.60) + HR stroke (7.71) – HR REF (1)) if they had a simply additive relationship with dementia risk. Instead, the HR associated with the presence of both was 28.33 [6.74, 119.01] (Table 4). Similarly, if stroke and CHF were solely additive, their joint HR would have been 5.36. However, it was 50.30 [14.57, 173.57] (Table 4).

POST HOC ANALYSES OF PA

In unadjusted models testing independent associations of PA with all-cause dementia in the presence of VCMRFs, greater minutes of PA were associated with lower risk of all-cause dementia (Supplementary Table 1). Upon covariate adjustment, the confidence intervals for these associations overlapped with an HR of 1.

As described in the methods, PA was dichotomized and reverse coded in order to test its joint effects with VCMRFs. The joint effect of low PA and *APOE**4 increased risk of all-cause dementia additively. In the model fully adjusted for age, race, sex, education, and current drinking, the HR [95% CI] for *APOE**4 + /low PA – was 3.43 [1.23, 9.56]; for *APOE**4 – /low PA + it was 1.84 [0.87, 3.88]; and the joint HR was 4.61 [2.07, 10.23]. As the AP in the unadjusted model was not significant at 0.02 [–0.61, 0.65], we did not examine it in adjusted models. For the model of stroke/low PA, the HR for stroke + /low PA – could not be estimated, and for the model of CHF/low PA, the HR for CHF + /low PA – could not be estimated; therefore, no coefficients are presented for these models.

Discussion

The primary purpose of this study was to identify pairs of vascular and cardiometabolic risk factors that operated independently, additively, and synergistically to increase risk of incident all-cause dementia. By additive, we mean that the hazard from two factors together was significantly associated with dementia, and their joint HR was approximately the sum of their individual HRs. By synergistic, we mean that the joint HR was more than the sum of the component variables' HRs, and the proportion of the joint HR that was excess risk due to interaction (the AP) was significantly different from 0. In the MYHAT cohort followed over ten years we found that *APOE**4, hypertension, stroke, and congestive heart failure were each independent risk factors for incident dementia. Examining them in the pairs *APOE**4/HTN, *APOE**4/stroke, *APOE**4/CHF, and stroke/CHF, their co-occurrence contributed significantly to all-cause dementia. The joint effects of *APOE**4+/HTN + and *APOE**4 + /CHF + were additive, while the joint effects of *APOE**4 + /stroke + and stroke + /CHF + were synergistic.

INDIVIDUAL RISK FACTORS

We found that the strongest individual risk factors for all-cause dementia are modifiable. Stroke was the strongest risk factor for dementia in our study. Our models of independent effects demonstrate a nearly 8 to 10-fold increased risk of all-cause dementia among those with vs. without stroke history, although risks from approximately 4 to 21-fold greater are compatible with our data. Most prior population-based studies report a doubling of risk of dementia among those with stroke (Ivan et al., 2004; Jin et al., 2006; Reitz et al., 2008). Our results are more in line with a medical records linkage analysis, which demonstrated up to a 9-fold increased risk of dementia in those with vs. without stroke (Kokmen et al., 1996). In our univariable model of incident all-cause dementia, CHF, the second strongest risk factor we identified, was associated with a nearly 3-fold increased risk. Results from several European population cohort studies suggest a link between CHF and dementia (Adelborg et al., 2017; Qiu et al., 2006; Rusanen et al., 2014).

Depression, a known dementia risk factor, but not anxiety, was a significant univariable predictor of all-cause dementia whether it was based on mCESD depressive symptoms or a self-reported diagnosis of depression by a health care professional (Diniz et al., 2013). Although depression was not selected by our algorithm for testing in conjunction with other VCMRFs, self-reported depression diagnosis had the next largest effect size following *APOE*4*. Given the strong association of depression with VCID (Diniz et al., 2013), future work should test whether its joint effects with other VCMRFs are additive or synergistic.

ADDITIVE RISK FACTORS

We found that the joint effects of *APOE*4* with HTN and *APOE*4* with CHF additively increase risk of all-cause dementia. While others have reported an interaction of *APOE*4* with HTN in relation to cSVD (de Leeuw et al., 2004) and cognitive trajectories (de Frias et al., 2014) such that *APOE*4* carriers with HTN have greater white matter hyperintensity burden and more rapid cognitive decline than non-carriers, we did not find a significant synergistic interaction of *APOE*4* + /HTN + in relation to dementia. Mid-life HTN vs. late-life HTN is more strongly associated with late-life cognitive impairment (Walker et al., 2017). It is possible that this association is amplified among *APOE*4* carriers—a three-way interaction of age, *APOE*4*, and HTN. Indeed, such a synergistic joint effect of *APOE*4* and mid-life HTN has been reported in relation to poor late-life cognitive function as measured by a screening test (Peila et al., 2001). As the youngest MYHAT participants entered the study at age 65, we have no mid-life data and were unable to study the effect of mid-life HTN in combination with *APOE*4* carrier status. In contrast to our results showing an increased risk of dementia for those with both *APOE*4* and CHF, CAIDE study investigators have reported that CHF may be associated with increased dementia risk among those who are *APOE*4* negative (Rusanen et al., 2014). Our results may be due to our increased sensitivity to detect dementia due to in-depth annual assessments for up to 10 annual visits vs. the use of medical records for some dementia case ascertainment and study visits which were 7–25 years apart.

SYNERGISTIC RISK FACTORS

We found that the joint occurrence of stroke and CHF increased dementia risk nearly 50 times vs. those without these factors, although HRs approximately 15–174-fold greater are compatible with our data. While this confidence interval is large, we note that it does not overlap with the predicted additive only HR of approximately 5. This indicates that contributions of stroke and CHF to dementia risk are beyond simply independent and additive, and there is good biological plausibility for this synergistic action. CHF is cross-sectionally associated with lower cerebral blood flow (Choi et al., 2006; Roy et al., 2017). Adding poor oxygen and nutrient delivery over and above parenchymal death from stroke is likely to overburden the brain's compensation abilities. CHF may be secondary to both MI and HTN. Long-term exposure to HTN causes left-ventricular hypertrophy, and poorer pumping capability. HTN, but not MI, was associated with greater risk of incident all-cause dementia in our univariable modeling. It is possible that this lack of association of MI with dementia risk is due to death or attrition among those with history of MI who suffer another MI over the course of study follow-up.

Similarly, we found that the joint effect of *APOE*4* and stroke was synergistic, with a joint risk approximately 28-fold greater than those without both of these factors. Although this HR is the best estimate given our data and statistical assumptions, HRs from approximately 7 to 119 are compatible with our data, and we note that this large confidence interval overlaps with the expected HR of 9 if the factors were purely additive. Others have demonstrated that the joint effect of *APOE*4* and stroke is additive for dementia risk, but have not found a synergistic relationship (Jin et al., 2008; Zhu et al., 2000). These studies were carried out in Sweden (Zhu et al., 2000) and Canada (Jin et al., 2008) and had follow-up time approximately half as long as in our study. Our results are concordant with a population representative study in the US, which did find a synergistic association of *APOE*4* and stroke in relation to dementia (Llewellyn et al., 2010). One plausible explanation for this synergism relates to the ability of *APOE*4* to damage the brain even prior to the presence of other neuropathology. ApoE4 protein operates through β amyloid ($A\beta$)-independent pathways to impair neurogenesis and synaptogenesis, and lead to phosphorylation of tau and mitochondrial dysfunction (Huang, 2010). Such damage could be present prior to stroke. Neuronal stress and ischemia induced by stroke then lead to increased ApoE production (Huang, 2010). Thus, the impact of stroke may be to potentiate the damaging impacts of ApoE4.

LIFESTYLE VCMRF: PHYSICAL ACTIVITY

We and others have previously reported the beneficial effects of physical activity (PA) on dementia-spectrum changes (Erickson et al., 2012; Erickson et al., 2010; Hughes et al., 2015; Intlekofer and Cotman, 2013; Rosano et al., 2017). Some have reported that PA may be more beneficial for *APOE*4* carriers than non-carriers (Etnier et al., 2007). We did not find such an interaction, but we did find that low PA was associated with additively increased all-cause dementia risk when paired with *APOE*4*, results that concur with those in the CAIDE study (Kivipelto et al., 2008). Taken together, this suggests that increasing PA could lower risk of all-cause dementia even among *APOE*4* carriers. We were unfortunately unable to draw conclusions about the joint effects of low PA with stroke and CHF due to the

inability of the model to estimate some of the HRs, and these relationships should be tested in other cohorts.

CLINICAL AND PUBLIC HEALTH IMPLICATIONS

An overarching pattern in our results is that *APOE*4*, a genetic and therefore non-modifiable VCMRF, combines with other modifiable VCMRFs including HTN, CHF, and low PA to increase dementia risk at least additively, and in the case of stroke, synergistically. Clinicians can use this knowledge to target individuals who are *APOE*4* positive for VCMRF prevention and reduction. Indeed, such a “precision medicine” approach to dementia prevention has been recently suggested (Berkowitz et al., 2018). From a public health perspective, active measures to target and reduce vascular multimorbidity should also be recognized as reducing dementia risk. Optimizing vascular and cardiometabolic health can promote cognitive well-being, especially in mid-life (Perales et al., 2018). Along with the fact that modifiable VCMRFs begin to accrue in early and mid-life, our findings suggest that related preventive efforts should be timed earlier rather than later, to have benefits in later life. The empowering message for the public might be that people can still reduce their risk of dementia despite a common genetic predisposition, by undertaking actions to reduce hypertension, heart disease, and stroke.

STRENGTHS AND LIMITATIONS

Strengths of our study include a well-characterized population-based cohort with yearly follow-up data for up to 10 years. This allowed us to test relationships of many VCMRFs, adjust for potential confounding, and test longitudinal associations accounting for varying exposure over time. Our primary analyses were robust to adjustment for multiple comparisons. Results demonstrating the importance of addressing modifiable risk factors are being reported in many countries (Perales et al., 2018; Yuan et al., 2018), and thus our findings likely have implications in other countries and populations. Nevertheless, our study cohort reflects the racial/ethnic proportions of the underlying older adult population and is largely white; replication is needed in other types of populations. Dementia ascertainment quality is a strength of our study, being based on an in-depth, multi-domain assessment with study participants. As this was not a clinical study, informants were not always available; however, the interviewers had seen the incident case participants during annual assessments in previous years, allowing them to detect change over time. Participant weight was self-reported in visits 1–9, so our estimate of the association of BMI with all-cause dementia may be biased. This would impact our key substantive conclusions only if the true effect size were stronger than our estimate and should have resulted in our algorithm selecting BMI for inclusion in our modeling of joint effects. We noted large confidence intervals with some of the joint effects HRs. This is likely due to the small number individuals with both risk factors of interest. Our conclusions regarding the synergistic nature of *APOE*4* with stroke and stroke with CHF would be strengthened by replication in cohorts with larger numbers of individuals with co-occurring risk factors. Our analysis was based on the cause-specific modeling. We fit a time-dependent Cox model for the all-cause dementia-specific hazards regression, where death was treated as censored. Given that we were interested in estimating the cause-specific Hazard Ratios for all-cause dementia rather than the probability of all-cause dementia, our estimates of dementia-specific HRs are valid estimates (Klein and

Moeschberger, 2003). Finally, our analyses of PA with other VCMRFs were post hoc and should be confirmed in other cohorts.

Conclusions

In summary, our data from a ten-year population-based longitudinal study validate and extend previous studies by demonstrating the additive or synergistic effects of certain combinations of vascular and cardiometabolic factors on the risk of developing dementia. These findings strongly suggest roles for timely and adequate management of vascular and cardiometabolic risk for the prevention of cognitive impairment and dementia in older adults.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Attributable proportion (AP) of *APOE*4*, stroke, and their excess risk due to interaction in relation to risk of all-cause dementia. Note: In the model fully adjusted for age at baseline, sex, race, education, hypertension, and physical activity minutes.

Table 1.

Baseline characteristics of MYHAT study participants free from prevalent dementia and with at least one follow-up visit

	TOTAL N	MEDIAN (Q1, Q3) OR N (%)
Demographics		
Age	1701	
65–74		602 (35.4)
75–84		789 (46.4)
85+		310 (18.2)
Female sex	1701	1060 (62.3)
White race	1701	1615 (94.9)
High school education	1701	1478 (86.9)
Vascular and cardiometabolic factors		
Physical exam measures		
Body mass index	1669	27.2 (24.2, 31.0)
Waist to hip ratio	1609	0.9 (0.8, 1.0)
Pulse	1693	68.0 (64.0, 76.0)
Systolic blood pressure	1691	132.0 (122.0, 142.0)
Diastolic blood pressure	1690	74.0 (70.0, 80.0)
Mean arterial pressure	1690	93.5 (87.3, 100.0)
Pulse pressure	1690	58.0 (50.0, 68.0)
Laboratory tests		
<i>APOE</i> *4 carrier	1569	330 (21.0)
Hemoglobin A1C	845	6.2 (5.9, 6.8)
Total cholesterol	901	188.0 (162.0, 220.0)
High density lipoprotein cholesterol	901	45.6 (37.6, 55.5)
Low density lipoprotein cholesterol	901	140.2 (115.5, 169.0)
ApoB:ApoA1 ratio	891	0.7 (0.6, 0.8)
Homocysteine	888	11.6 (9.6, 14.3)
Cystatin C	891	1.1 (0.9, 1.3)
C-reactive protein	891	1.9 (1.0, 3.9)
Chronic health conditions reportedly diagnosed by health care provider		

	TOTAL N	MEDIAN	(Q1, Q3) OR N (%)
History of stroke	1699		75 (4.4)
History of transient ischemic attack	1698		153 (9.0)
History of myocardial infarction	1699		243 (14.3)
History of hypertension	1698		1107 (65.2)
History of diabetes	1700		370 (21.8)
History of high cholesterol	1694		1041 (61.5)
History of congestive heart failure	1698		152 (9.0)
History of cardiac arrhythmia	1699		487 (28.7)
Behavioral factors			
Physical activity (min/week)	1700		0.0 (0.0, 90.0)
History of smoking (ever)	1699		889 (52.3)
Smoked in the past year	1697		120 (7.1)
Current smoking	1697		113 (6.7)
History of alcohol use (ever)	1700		1458 (85.8)
Current alcohol use (within past year)	1700		1129 (66.4)
Reported diagnosis of depression	1700		233 (13.7)
Number of depression symptoms (mCESD score)	1698		0.0 (0.0, 1.0)
History of anxiety	1700		176 (10.4)
Cognition and functioning			
Clinical dementia rating scale =0	1701		1259 (74.0)
Mini-Mental State Examination	1701		28.0 (26.0, 29.0)

Note: mCESD= modified Centers for Epidemiologic Studies-Depression scale

Table 2.

Univariable associations of variables with incident all-cause dementia

VARIABLES	HR	95% CONFIDENCE INTERVAL
Demographics		
Baseline age (78 y)	5.82 *	3.58 9.48
Sex, female	1.05	0.71 1.55
Race, white	0.38 *	0.21 0.67
Education		
<High school (ref)	–	–
High school	0.42 *	0.26 0.68
>High school	0.31 *	0.19 0.50
Vascular and cardiometabolic factors		
Physical exam measures		
Body mass index	0.58 *	0.43 0.77
Waist to hip ratio	0.84	0.67 1.04
Pulse	1.22	1.00 1.48
Systolic blood pressure	0.92	0.75 1.12
Diastolic blood pressure	0.83	0.68 1.01
Mean arterial pressure	0.85	0.69 1.03
Pulse pressure	1.02	0.84 1.25
Laboratory tests		
APOE*4 carrier	2.02 *	1.33 3.05
Hemoglobin A1C	0.99	0.74 1.34
Total cholesterol	0.79	0.59 1.07
High density lipoprotein cholesterol	0.85	0.63 1.16
Low density lipoprotein cholesterol	0.83	0.62 1.12
ApoB:ApoA1 ratio	0.97	0.70 1.35
Homocysteine	1.03	0.80 1.32
Cystatin C	1.13	0.84 1.52
C-reactive protein	0.93	0.63 1.37

VARIABLES	HR	95% CONFIDENCE INTERVAL
Chronic health conditions reportedly diagnosed by health care provider		
Stroke	9.90*	4.76 20.58
Transient ischemic attack	1.78	0.44 7.23
Myocardial infarction	0.80	0.11 5.71
Hypertension	1.64*	1.04 2.58
Diabetes	1.09	0.71 1.69
High cholesterol	0.61*	0.42 0.89
Congestive heart failure	2.91*	1.60 5.31
Cardiac arrhythmia	1.52*	1.01 2.30
Lifestyle and mood factors		
Physical activity (min/week)	0.65*	0.47 0.90
Ever smoked	0.62*	0.42 0.91
Smoked in the past year	0.88	0.36 2.16
Smoke now	0.95	0.39 2.34
History of alcohol use (ever)	0.58*	0.36 0.93
Current alcohol use (within past year)	0.30*	0.19 0.46
Reported diagnosis of depression	1.81*	1.08 3.04
Number of depression symptoms (mCESD score)	1.39*	1.26 1.53
Anxiety	1.24	0.64 2.37

Note:

* Confidence interval does not contain 1. mCESD= modified Centers for Epidemiologic Studies-Depression scale

Table 3.

Tests of independent associations of vascular and cardiometabolic risk factor pairs of interest with incident all-cause dementia

VARIABLES	MODEL 1		MODEL 2		MODEL 3	
	HR	95% CI	HR	95% CI	HR	95% CI
<i>APOE*4/HTN^a</i>						
<i>APOE*4</i>	2.04	1.35	3.09	2.58	1.68	3.96
HTN	1.65	1.02	2.65	1.43	0.88	2.31
<i>APOE*4/Stroke^b</i>						
<i>APOE*4</i>	2.08	1.37	3.15	2.61	1.70	4.00
Stroke	8.76	3.79	20.23	9.20	3.94	21.50
<i>APOE*4/CHF^c</i>						
<i>APOE*4</i>	2.09	1.38	3.16	2.62	1.70	4.04
CHF	3.37	1.84	6.17	2.33	1.26	4.28
<i>Stroke/CHF^c</i>						
Stroke	9.33	4.48	19.41	8.63	3.67	20.27
CHF	2.76	1.51	5.04	2.20	1.19	4.06

Model 1: variables of interest

Model 2: Model 1 + non-modifiable factors (baseline age, sex, race, education, *APOE*4*)

Model 3: Model 2 + vascular and cardiometabolic risk factors and behavioral factors that are confounders as follows:

^ahigh cholesterol, body mass index, PA minutes, current drinking, history of depression

^bHTN, PA minutes

^cPA minutes, HTN, high cholesterol, history of depression

Note: Bold=confidence interval does not contain 1; HTN=hypertension; CHF=congestive heart failure; PA=physical activity

Table 4.

Tests of joint effects of vascular and cardiometabolic risk factor pairs of interest with incident all-cause dementia

VARIABLES	MODEL 1		MODEL 2		MODEL 3	
	HR	95% CI	HR	95% CI	HR	95% CI
<i>APOE*4/HTN^a</i>						
<i>APOE*4 + HTN –</i>	2.04	0.86	4.86	1.04	6.00	2.64 0.76 9.14
<i>APOE*4 – HTN +</i>	1.65	0.91	2.98	1.41	0.77	2.55 1.00 5.36
<i>APOE*4 + HTN +</i>	3.36	1.75	6.45	3.66	1.88	7.12 6.60 2.61 16.70
<i>APOE*4/Stroke^b</i>						
<i>APOE*4 + Stroke –</i>	2.01	1.31	3.09	2.54	1.63	3.95 2.60 1.67 4.04
<i>APOE*4 – Stroke +</i>	7.38	2.66	20.44	8.09	2.89	22.67 7.71 2.74 21.64
<i>APOE*4 + Stroke +</i>	27.73	6.68	115.17	31.95	7.63	133.83 28.33 6.74 119.01
<i>APOE*4*CHF^c</i>						
<i>APOE*4 + CHF –</i>	2.20	1.43	3.40	2.69	1.72	4.21 2.86 1.83 4.48
<i>APOE*4 – CHF +</i>	3.86	1.97	7.56	2.49	1.26	4.92 2.46 1.24 4.87
<i>APOE*4 + CHF +</i>	4.67	1.13	19.07	4.81	1.16	20.05 4.78 1.15 19.86
<i>Stroke*CHF^c</i>						
<i>Stroke +/CHF–</i>	6.93	2.78	17.27	5.47	1.70	17.59 4.60 1.42 14.88
<i>Stroke –/CHF +</i>	2.31	1.17	4.59	1.83	0.91	3.66 1.76 0.88 3.55
<i>Stroke +/CHF +</i>	53.73	16.57	174.19	43.97	12.67	152.61 50.30 14.57 173.57

Model 1: variables and interaction of interest.

Model 2: Model 1 + non-modifiable factors (baseline age, sex, race, education, *APOE*4*)

Model 3: Model 2 + vascular and cardiometabolic risk factors and behavioral factors that are confounders as follows:

^a high cholesterol, body mass index, PA minutes, current drinking, history of depression

^b hypertension, PA minutes

^c PA minutes, HTN, high cholesterol, history of depression

Note: Bold=confidence interval does not contain 1; HTN=hypertension; CHF=congestive heart failure; PA=physical activity