ORIGINAL RESEARCH

Cardiovascular Risk Factors and Risk of Alzheimer Disease and Mortality: A Latent Class Approach

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BACKGROUND: Cardiovascular risk factors co-occur with one another, and little is known about the extent of their clustering and risk of Alzheimer disease (AD). We identify groups of cardiovascular risk factors in cognitively normal individuals and investigate between-group differences in incident AD and death.

METHODS AND RESULTS: Cognitively normal individuals were recruited from the National Alzheimer's Coordinator Center. A latent class analysis was conducted with hypertension, hypercholesterolemia, heart condition, stroke, smoking history, diabetes, and high body mass index. Between-group differences in the incidence of AD, mortality, and mortality-adjusted AD were investigated. This study included 12 412 cognitively normal individuals (average follow-up, 65 months). Three groups were identified: (1) low probabilities of cardiovascular risk factors (reference; N=5398 [43%]), (2) hypertension and hypercholesterolemia (vascular-dominant; N=5721 [46%]), and (3) hypertension, hypercholesterolemia, diabetes, and high body mass index (vascular-metabolic; N=1293 [10%]). Both vascular groups were significantly older, had more men, were slightly less educated, and were slightly more cognitively impaired than the reference group (all *P*<0.05). However, only the vascular-metabolic group had a significantly younger age of death compared with the reference group (84.3 versus 88.7 years, *P*<0.001). Only the vascular-dominant group had a greater incidence of AD (odds ratio [OR], 1.30; *P*<0.001) compared with the reference group. Mortality was greater in the vascular-dominant (OR, 3.26; *P*<0.001) and vascular-metabolic groups (OR, 1.84; *P*=0.02). Mortality-adjusted AD was greater in the vascular-dominant (OR, 1.54; *P*=0.02) and vascular-metabolic groups (OR, 1.46; *P*=0.04).

CONCLUSIONS: Three distinct cardiovascular risk factor groups were identified in cognitively normal elderly individuals. Only the vascular-dominant group was associated with a greater incidence of AD. Selective mortality may contribute to the attenuated association between the vascular-metabolic group and incident AD.

Key Words: Alzheimer disease ■ cardiovascular risk factors ■ epidemiology

Cardiovascular risk factors (CVRFs) are highly prevalent in the elderly population and have been associated with poor outcomes such as cognitive decline, functional decline, and progression to Alzheimer disease (AD).[1,2] However, the majority of evidence is based on longitudinal cohort studies investigating the impact of individual CVRFs only.[1] Because CVRFs are often comorbid with one another in the elderly population, studying the impact of individual CVRFs may not accurately reflect the real-world population. Studies investigating the interaction between individual CVRFs have reported an increased risk of AD in those with hypertension and diabetes,[3] and hypertension and stroke.[4,5] Several studies have investigated the impact of multiple

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CLINICAL PERSPECTIVE

What Is New?

- Three distinct groups of cardiovascular risk factors (CVRFs) were identified in cognitively normal elderly individuals: (1) low probabilities of CVRFs, (2) vascular-dominant group, and (3) vascular-metabolic group.
- Before accounting for mortality, only the vascular-dominant group was associated with incident Alzheimer disease (AD); however, after accounting for mortality, both the vascular-dominant and vascular-metabolic groups were associated with an increased incidence of AD.
- These findings support the multiple origins of CVRFs, and emphasize the importance of accounting for mortality when investigating the impact of CVRFs on AD.

What Are the Clinical Implications?

- Although the negative impacts of individual and multiple CVRFs on dementia and mortality have been well studied, they are unable to provide insight on how CVRFs co-occur with one another, and therefore are unable to guide clinical- and research-based decisions involving risk stratification.
- Deriving latent-class groups of CVRFs addresses the methodological limitations encountered by previous studies and provides the unique opportunity to determine the real-world impact of CVRFs on AD and mortality.
- This model can be used in future studies to investigate between-group differences in biological markers and treatment response, which may in turn identify group-specific treatment strategies for AD risk mitigation.

Nonstandard Abbreviations and Acronyms

CVRF	cardiovascular risk factor
LCA	latent class analysis
NACC	National Alzheimer's Coordinating Center

CVRFs as a marker of vascular burden, and have reported an increase in the risk of AD,[6] cognitive decline,[7,8] and AD-related biomarkers, with an increase in the number of CVRFs.[9,10] Although those studies support the negative impacts of CVRF multimorbidity, they are unable to elucidate distinct groups of CVRFs. The identification of CVRF groups would provide the opportunity to study between-group differences in the incidence of AD, which would inform the need to stratify patients for individualized treatment. Furthermore, the identification of CVRF groups would serve as a framework to design future studies aimed at investigating differences in AD-related outcomes between groups.

Of relevance, CVRFs have also been associated with mortality, a competing event for AD.[11] Mortality is an important outcome of consideration in longitudinal studies with elderly individuals given their advanced age, presence of comorbidities, and long-duration of follow-up. However, the majority of studies investigating the association between CVRFs and AD have not adjusted for mortality risk.[12] This may in part explain the mixed findings reported between CVRFs and AD-related outcomes. Accounting for mortality would limit bias and ensure accuracy when investigating differences in the incidence of AD between different CVRF groups.

Using data collected from the National Alzheimer's Coordinating Center (NACC) data set, we conducted a latent class analysis (LCA) with CVRFs in cognitively normal elderly individuals to identify distinct groups of CVRFs. We then investigated the risk of CVRF groups on (1) incident AD, (2) mortality, and (3) mortality-adjusted AD.

METHODS

Study participant data are available through the NACC (naccdata.org). Detailed data analysis plan and syntax will be made available upon request to the corresponding author.

Study Sample

The NACC data set includes clinical data from participants across 39 past and present Alzheimer disease research centers in the United States. Participants were included in this study if they were cognitively normal at baseline and were followed until loss to follow-up or death. All contributing Alzheimer disease research centers were required to obtain approvals from their respective institutional regulatory boards and informed consent from their participants before submitting data to the NACC.

Classification of AD

A diagnosis of AD was confirmed by a consensus team or physician using the results of a structured clinical history, neuropsychology testing, and validated assessments of symptoms and function. Dementia of AD type was diagnosed using the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association prior 2015, and National Institute on Aging and Alzheimer's Association after 2015. Participants were diagnosed with AD if it was the primary or contributing cause of cognitive impairment, which included participants who had probable or possible dementia of the AD type.

Latent Class Indicators and Analysis
CVRFs (Latent Class Indicators)

The presence/absence of a CVRF was based on the diagnosis from recent medical history or medication use. Seven CVRFs were investigated, which included 5 vascular CVRFs (hypertension, hypercholesterolemia, heart disease [atrial fibrillation, angina, heart attack, angiopathy, congestive heart failure, bypass, pacemaker/defibrillation, pacemaker, valve replacement], stroke [transient ischemic attack or stroke history], history of smoking), and 2 metabolic CVRFs (diabetes and high body mass index [$\geq 30\,kg/m^2$]).[13]

Latent Class-Derived CVRF Groups

An LCA is a structural equation modeling technique that uses a person-centered approach to derive an unobserved latent variable based on observed categorical variables. The categorical latent variable represents classes that can then be used to investigate differences in distal outcomes between groups.[14]

For the present study, an LCA with the 7 CVRF indicators collected at baseline was fit to 1 to 6 classes to determine an optimal class solution. Given the complex sampling design used to recruit participants, this LCA was conducted using a multilevel technique to account for the hierarchical data structure. The classes were formed using the MLR estimator, based on full information maximum likelihood estimation robust to nonnormal observed variables. The maximum number of iterations through which the algorithm was cycled was 100, and the maximum number of replications used to estimate the model was 400. Specifically, all individuals with at least 1 valid indicator were included in the formation of latent classes. The optimal model-class solution was chosen based on quantitative parsimony criteria, where the goal was to select a model that minimized the Akaike information criterion, Bayesian Information Criterion, and sample-size adjusted Bayesian Information Criterion. We also included the Lo-Mendell-Rubin adjusted likelihood ratio test and Vuong-Lo-Mendell-Rubin adjusted likelihood ratio test in our assessment, because these 2 tests are used to compare the k class from the k–1 class solution. A significant P value for the Lo-Mendell-Rubin adjusted likelihood ratio test and Vuong-Lo-Mendell-Rubin adjusted likelihood ratio test indicates superior fit of the k-class when compared with the k–1 class model. The entropy (range, 0–1) of each class model was computed to provide a measurement of class separation. An entropy value closer to 1 represents greater separation of classes. A moderate-to-high threshold probability of 0.5 or greater was used to identify CVRF class membership. Because each class is described using the probability of occurrence of each CVRF rather than its presence or absence, the CVRFs within each latent group are not mutually exclusive of one another.

Statistical Analysis
CVRF Multimorbidity

Separate multivariate logistic regressions, adjusted for baseline age, sex, Mini-Mental State Exam score, years of education, and apo E4 (apolipoprotein E4) allele presence were computed to assess the association between each of the 7 CVRFs. This analysis was conducted in R (version 4.0.2; R Foundation for Statistical Computing, Vienna, Austria) using the ISLR package.

Between-Group Comparisons in Study Demographics

A manual 3-step analytic approach was used to identify demographic differences between latent classes using the Bolck, Croon, and Hagenaars method.[15,16] This method computes the classification errors for each individual, whose inverse logits are then used as weights when investigating differences in outcomes between groups. Using this method, odds ratios (ORs) for categorical outcomes and mean differences for continuous outcomes were computed to quantify differences between groups. Using the extracted class membership in a classify–analyze approach would assume that there is negligible classification error in latent class assignment, which may consequently lead to biased results.

Between-Group Comparisons in AD and Mortality

The risk of CVRF groups on (1) incident AD, (2) mortality, and (3) mortality-adjusted AD were investigated using the Bolck, Croon, and Hagenaars method. Incident AD was based on a diagnosis at the final visit. Mortality-adjusted incident AD was determined by investigating the incidence of AD at the final visit in those who remained alive throughout the study. Using the Bolck, Croon, and Hagenaars method, baseline age, years of education, Mini-Mental State Exam score, sex, and apo E4 allele presence were included to ensure that computed ORs and mean differences were appropriately adjusted for relevant covariates. The LCA and comparisons between latent-derived CVRF groups were completed using Mplus (version 8.7).

RESULTS

This study included 12 412 elderly individuals who were cognitively normal. The mean duration of follow-up was 65 months. Baseline demographics, and medical and

medication history are included in Table 1. After adjusting for baseline age, sex, Mini-Mental State Exam score, years of education, and presence of the apo E4 allele, all CVRFs were significantly associated with one another, except smoking history, hypertension, and heart disease (Figure 1; Table S1).

Latent Class-Derived CVRF Groups
Latent Class Analysis With Baseline CVRFs

Model fitness metrics for 1 to 6 classes for baseline CVRFs are provided in Table 2. The 3-class model was selected because it had a lower Akaike information criterion and Bayesian Information Criterion compared with the 2-class model. Models with 4 or more classes were not considered, because fewer than 10% of participants were included in 1 or more groups.[17] Though the Vuong-Lo-Mendell-Rubin adjusted likelihood ratio test and Lo-Mendell-Rubin adjusted likelihood ratio test were not significant for the 3-class model compared with the 2-class model, the 3-class model identified a group with low probabilities of CVRFs (reference group) and 2 groups that were deemed clinically important, a group with moderate-to-high probabilities of vascular-dominant CVRFs and a group with moderate-to-high probabilities of vascular-metabolic CVRFs. The proportion of individuals allocated to each class are provided

in Table 3. Modal class posterior probabilities for the 3-class CVRF model are plotted in Figure 2.

Description of Latent Class-Derived CVRF Groups

Of the 3 latent groups identified, 1 included individuals with low probabilities of CVRFs (reference group, N=5398), because none of the CVRFs reached a loading threshold of 0.5. A second group included individuals with high probabilities of hypertension and hypercholesterolemia (vascular-dominant group, N=5721). A third group included individuals with high probabilities of hypertension, hypercholesterolemia, and the metabolic CVRFs, diabetes, and high body mass index (vascular-metabolic group, N=1293).

Demographic Comparisons Between Latent Class-Derived CVRF Groups

Compared with the reference group, the vascular-dominant and vascular-metabolic groups were significantly older, had fewer years of education, lower Mini-Mental State Exam scores, and had a greater proportion of men. Compared with the reference group, the vascular-dominant group also demonstrated slightly lower probabilities of apo E4 allele presence, and the vascular-metabolic group had a significantly younger age of death (Table 4). Given the differences in demographic characteristics between the CVRF groups, all baseline demographic variables were included as covariates when investigating risks

Table 1. Study Participant Demographics (N=12412)

Demographic	Value
Age, y	70.9 (10.5)
Sex, men	4358 (35%)
Education	15.9 (2.9)
MMSE	28.9 (1.4)
Cardiovascular risk factors	
Hypertension	6745 (54%)
Hypercholesterolemia	6136 (49%)
Smoking history	5237 (42%)
High BMI, ≥30 kg/m^2	2976 (26%)
Heart disease	1784 (14%)
Diabetes	1373 (11%)
Stroke/TIA	291 (2%)
Medication history	
Antidepressant use	2245 (18%)
Anxiolytic use	1365 (11%)
Antipsychotic use	70 (1%)
Other	
apo E4 allele	3341 (27%)
Incident AD	873 (7%)
Mortality	1812 (15%)
Mortality-adjusted incident AD	470 (4%)

Values are presented as mean (SD) or number (%). AD indicates Alzheimer disease; apo E4, apolipoprotein E4; BMI, body mass index; MMSE, Mini-Mental State Exam; and TIA, transient ischemic attack.
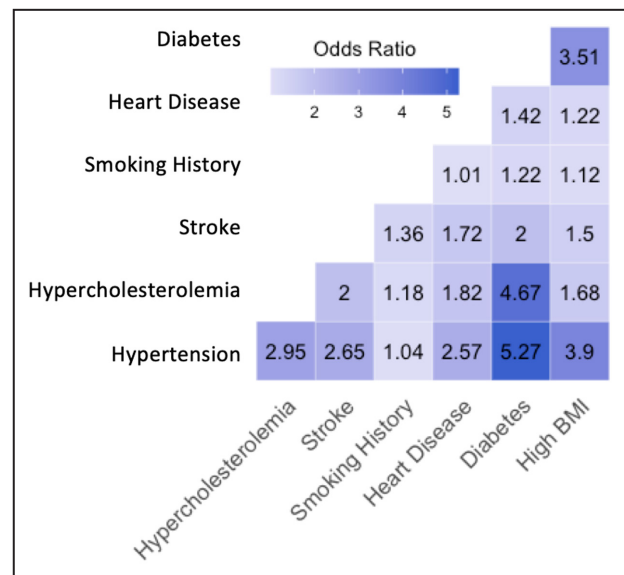

Figure 1. Adjusted odds ratios of association between each cardiovascular risk factor.
All: *P*<0.05, except between smoking history and hypertension, and smoking history and heart disease. BMI indicates body mass index.

Table 2. Model Fitness Characteristics for Baseline Cardiovascular Risk Factor Data (N=12 412)

Characteristic	1 class	2 classes	3 classes	4 classes	5 classes	6 classes
VLMRT	…	<0.001	0.191	0.533	0.460	0.626
LMRT	…	<0.001	0.193	0.535	0.461	0.636
AIC	85 928.591	82 923.199	82 685.362	82 624.443	82 602.016	82 601.102
BIC	85 980.576	83 034.595	82 856.169	82 854.662	82 891.646	82 950.144
ssaBIC	85 958.331	82 986.927	82 783.078	82 756.147	82 767.709	82 800.783
Entropy	…	0.524	0.692	0.505	0.517	0.554

AIC indicates Akaike information criterion; BIC, Bayesian Information Criterion; LMRT; Lo-Mendell-Rubin adjusted likelihood ratio test; ssaBIC, sample-size adjusted Bayesian Information Criterion; and VLMRT, Vuong-Lo-Mendell-Rubin adjusted likelihood ratio test.

on incident AD, mortality, and mortality-adjusted AD. Because age of death was not collected at baseline, this variable was not entered as a covariate.

Associations With Incident AD, Mortality, and Mortality-Adjusted AD

Incident AD

The incidence of AD was greatest in the vascular-dominant group, followed by the vascular-metabolic group, and the reference group. However, statistical significance was achieved when comparing the vascular-dominant group with the reference group only (Table 5).

Mortality

Mortality was greatest in the vascular-dominant group, followed by the vascular-metabolic group and the reference group. Both the vascular-dominant and vascular-metabolic groups had a significantly greater odds of mortality compared with the reference group (Table 6).

Mortality-Adjusted Incident AD

Compared with the reference group, the vascular-dominant and vascular-metabolic groups had a significantly greater incidence of AD while remaining alive throughout follow-up (Table 7).

DISCUSSION

This study identified 3 distinct groups of CVRFs in cognitively normal elderly individuals, which included low

probabilities of CVRFs (reference group), high probabilities of vascular-dominant CVRFs, and high probabilities of vascular-metabolic CVRFs. The vascular-dominant group had a significantly greater incidence of AD compared with the reference group, whereas the vascular-metabolic group did not. However, mortality was likely a competing risk that attenuated the association between the vascular-metabolic group and incident AD as in those who remained alive throughout the study; both CVRF groups had an increased incidence of AD compared with the reference group.

The negative effects of individual and multiple CVRFs on dementia and mortality have been well documented in epidemiological studies.[1,4,11] Although those studies emphasize the importance of identifying, preventing, and treating CVRFs, they do not provide insight on how CVRFs co-occur with one another, limiting their ability to guide clinical- and research-based decisions involving risk stratification. Furthermore, we determined that most CVRFs were significantly associated with one another, strongly supporting that the presence of comorbid CVRFs would confound the investigation of individual CVRFs on incident AD and lead to inaccurate estimates. Therefore, to evaluate the real-world impact of CVRFs on AD, CVRF multimordbidity must be considered. By using an LCA, we were able to avoid the methodological limitations encountered by previous studies and identify distinct groups of CVRFs that are reflective of the multiple origins of CVRFs.

The reference group included individuals who were comparatively healthier than either of the CVRF groups, because they had lower probabilities of CVRFs and had the lowest rates of mortality. Interestingly, the proportion of individuals allocated to the reference group

Table 3. Proportion of Individuals Within Each Class for Each Model

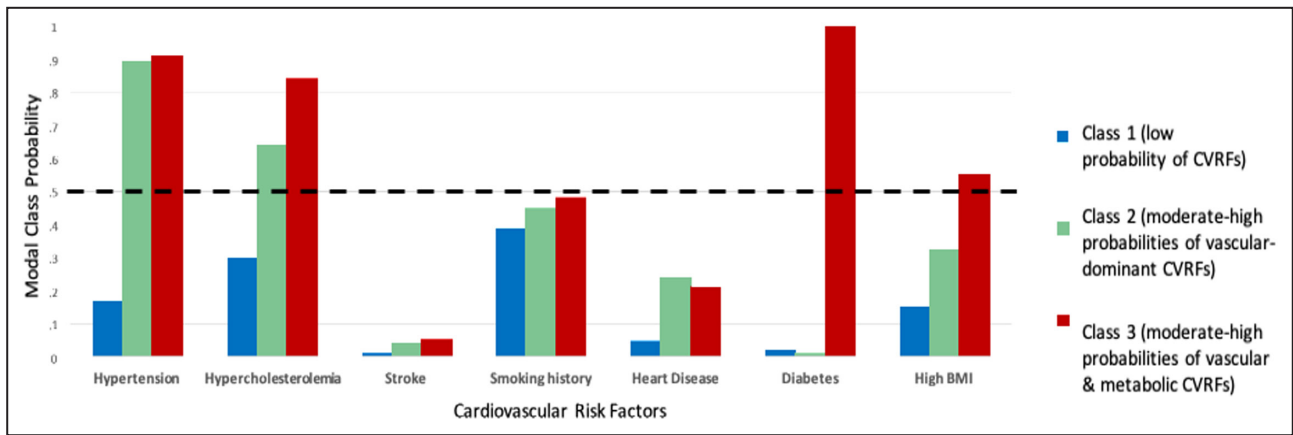| Class	1 class	2 classes	3 classes	4 classes	5 classes	6 classes
1	12 412 (100%)	5204 (42%)	5721 (46%)	830 (7%)	6698 (53%)	6693 (54%)
2		7208 (58%)	5398 (43%)	2021 (16%)	2896 (23%)	18 (0.1%)
3			1293 (11%)	2818 (23%)	824 (7%)	644 (5%)
4				6743 (54%)	645 (5%)	1722 (14%)
5					1349 (11%)	2907 (23%)

Figure 2. **Modal class posterior probabilities for the 3-class model solution with baseline cardiovascular risk factors (CVRFs).**
BMI indicates body mass index.

was greater than the proportion of individuals who reported having no CVRFs in population-based studies.[18–22] However, it is important to note that individuals in the reference group had low probabilities of CVRFs and were not completely void of CVRFs. In those who remained alive throughout the study, the incidence of AD was significantly greater in the vascular-dominant and vascular-metabolic groups compared with the reference group. Because the mortality-adjusted incidence of AD in the 2 CVRF groups were similar to one another, this suggests that both latent groups had similar risks of progression to AD. Because the vascular-dominant group had higher probabilities of 2 CVRFs, and the vascular-metabolic group had higher probabilities of 4 CVRFs, these findings contradict studies that have reported a dose-related increase in the risk of AD with an increase in the number of CVRFs.[6] This discrepancy may be attributable to the role of selective mortality, because the vascular-metabolic group had a significantly younger age of death compared with the vascular-dominant group and reference group. Therefore, individuals in the vascular-metabolic group may have been more likely to die before progressing to AD, and the risk of progression to AD in those with metabolic risk factors, such as diabetes, may have

been significantly underreported in previous studies. Differences in methodologies may have also contributed to the discrepancy between our findings and those reported in previous studies on the risk of AD. Specifically, previous studies have calculated a measurement of vascular burden by summing the number of CVRFs; however, this does not provide insight on the cause of the CVRFs and assumes that the risk of each CVRF on AD is the same. This contradicts biological studies reporting differential associations between individual CVRFs and AD-related outcomes.[23,24] Understanding the causation differences between the vascular-dominant and vascular-metabolic groups would assist in identifying group-specific treatments that can be used to reduce the risk of AD. For example, the presence of hypertension in the vascular-dominant group may be attributable to vascular causes such as poor regulation of the renin-angiotensin-aldosterone system,[25] renal artery stenosis,[26] or coarctation of the major aorta.[27] In the vascular-metabolic group, hypertension may be caused by underlying metabolic syndrome because of co-occurrence with diabetes and obesity.[28] Therefore, targeting the underlying cause of each vascular group may reduce their respective risks of progression to AD.

Table 4. **Demographic Differences Between Groups**

	Reference, N=5398	Vascular-dominant, N=5721	Vascular-metabolic, N=1293	Unstandardized coefficients	
				Vascular-dominant vs reference group	Vascular-metabolic vs reference group
Age, y	66.6 (1.2)	75.5 (0.7)	72.2 (0.6)	β, 8.90; SE, 1.17; P<0.001	β, 5.57; SE, 0.99; P<0.001
Age of death, y	88.7 (1.4)	89.7 (1.1)	84.3 (1.4)	β, 0.90; SE, 0.01; P=0.39	β, −4.40; SE, 0.01; P<0.001
Education	16.4 (0.1)	15.5 (0.2)	15.3 (0.3)	β, −1.20; SE, 0.27; P<0.001	β, −1.68; SE, 0.35; P<0.001
MMSE	29.2 (0.04)	28.7 (0.1)	28.5 (0.1)	β, −0.45; SE, 0.07; P<0.001	β, −0.67; SE, 0.12; P<0.001
Sex, men	1565 (29%)	2288 (40%)	504 (39%)	OR, 0.60; 95% CI, 0.75–0.97; P<0.001	OR, 0.63; 95% CI, 0.51–0.77; P<0.001
apo E4 allele	1727 (32%)	1659 (29%)	388 (30%)	OR, 0.85; 95% CI, 0.74–0.97; P=0.02	OR, 0.90; 95% CI, 0.78–1.04; P=0.17

β indicates β coefficient; MMSE, Mini-Mental State Exam; and OR, odds ratio.

Table 5. Between-Group Differences in Incident AD

Difference	Reference, N=5398	Vascular-dominant, N=5721	Vascular/metabolic, N=1293	Unstandardized coefficients	
				Vascular-dominant vs reference group	Vascular-metabolic vs reference group
Incident AD	269 (5%)	514 (9%)	91 (7%)	OR, 1.74; 95% CI, 1.28–2.36; *P*<0.001	OR, 1.30; 95% CI, 0.94–1.80; *P*=0.11

Values are presented as number (%) unless otherwise indicated. AD indicates Alzheimer disease; and OR, odds ratio.

Studies investigating the use of cardiovascular medications on cognitive function, risk of AD, and AD-related biomarkers would provide insight into potential treatments that may improve AD risk within each CVRF group. Although clinical trials have reported mixed findings or low effect sizes with antihypertensive[29] and cholesterol-lowering agents[30] on dementia risk, this may be attributable to short trial durations, the use of single tests to assess cognitive function, or heterogeneity within the study population. Although this prompts the need for high-quality clinical trials that consider those limitations, retrospective studies provide valuable insight into the potential cognitive and biological benefits associated with cardiovascular medications. Angiotensin receptor blockers, a class of antihypertensive medications that have the ability to cross the blood–brain barrier, have been associated with reduced cognitive decline and amyloid-β[31,32] and τ pathology.[32] Statins for hypercholesterolemia have been associated with a reduced risk of AD,[33] with potential benefits on amyloid-β and τ pathology.[34] Investigating whether the benefits of those medications are specific to each CVRF group would inform the need to stratify individuals to guide treatment decisions and monitor treatment response. With regard to antidiabetic medications, metformin use has been associated with greater memory function in cognitively normal individuals, whereas dipeptidyl peptidase-4 inhibitor use has been associated with slower rates of memory decline in individuals with AD.[35] Therefore, antidiabetic medications may offer cognitive benefits and reduce the risk of AD in the vascular-metabolic group. Physical activity has also been shown to improve cognitive and AD-related biomarker outcomes in those with CVRFs, and therefore may reduce the risk of AD.[36–38] However, the intensity, duration, and type of physical activity needed to obtain benefits within each CVRF group and lower vascular burden should be investigated further. The presence of hypoxia,[39] sleep apnea,[40] and physical inactivity[41] should also be investigated as potential latent indicators, because each have been associated with poor AD-related outcomes. We were not able to investigate the role of these risk factors, because they were not available in the NACC data set.

Future studies investigating biological differences between the CVRF groups would provide insight into potential mechanisms of association with AD. Studies investigating differences in AD-specific markers, such as amyloid-β and τ, would confirm a link between each CVRF group and AD. Preclinical and clinical studies have reported associations between hypertension and hypercholesterolemia and increased amyloid-β and τ pathology.[42–44] However, the association between metabolic risk factors and AD-specific markers have not been conclusive, suggesting the role of other potential markers.[45,46] Neuropathological studies comparing differences in AD, cerebrovascular disease, and other neurodegenerative disease pathologies, such as TDP-43 (TAR DNA-binding protein 43), frontotemporal lobar degeneration, and Lewy body disease, would provide insight into other contributing pathologies associated with progression to AD within each CVRF group, and would provide dementia diagnosis confirmation. Postmortem studies in individuals with AD strongly support the role of mixed pathology, particularly vascular pathology, in those with cardiovascular disease.[47] Therefore, findings from neuropathological studies would strengthen our understanding about the biological association between each CVRF group and AD.

Study strengths included a large sample size of sufficient power to conduct an LCA with several CVRFs and the inclusion of relevant covariates. Using an LCA, we were able to use a person-centered statistical approach that considered the distribution of our data, which was essential to investigating our study objectives. The NACC data set is a well-characterized data set with diagnoses determined by experienced clinicians, and included a thorough collection of medical and medication history that allowed us to identify the presence or absence of multiple CVRFs. This data set also had a long duration

Table 6. Between-Group Differences in Mortality

Difference	Reference, N=5398	Vascular-dominant, N=5721	Vascular-metabolic, N=1293	Unstandardized coefficients	
				Vascular-dominant vs reference group	Vascular-metabolic vs reference group
Mortality	130 (2%)	457 (8%)	52 (4%)	OR, 3.26; 95% CI, 2.40–4.43; *P*<0.001	OR, 1.84; 95% CI, 1.13–3.00; *P*=0.02

Values are presented as number (%) unless otherwise indicated. OR indicates odds ratio.

Table 7. Between-Group Differences in Those Who Died Without Progressing to AD and in Those Who Remained Alive and Progressed to AD

Difference	Reference, N=5398	Vascular-dominant, N=5721	Vascular-metabolic, N=1293	Unstandardized coefficients	
				Vascular-dominant vs reference group	Vascular-metabolic vs reference group
Alive with AD	151 (2.8%)	246 (4.3%)	53 (4.1%)	OR, 1.54; 95% CI, 1.09–2.12; P=0.02	OR, 1.46; 95% CI, 1.01–2.11; P=0.04

Values are presented as number (%) unless otherwise indicated. AD indicates Alzheimer disease; and OR, odds ratio.

of follow-up that allowed us to investigate the effect of latent-derived CVRF groups on the incidence of AD and mortality. Although the NACC used a complex sampling design by recruiting individuals from several Alzheimer disease research centers across North America, we were able to account for this by conducting our LCA within a multilevel design. This ensured that our results were not biased by the hierarchical data structure. We also used novel statistical methods to account for potential classification errors that are encountered by LCA models with an entropy below 0.90.[15] The consideration of mortality is also an important strength of this analysis given the advanced age of the study population and the long duration of follow-up. Without accounting for mortality, the reported risk of incident AD may have been underestimated, because individuals may not have survived long enough to progress to AD.

The findings of this study should be interpreted in the context of several limitations. As participants were recruited from urban specialist memory clinics, this study sample may not be representative of the general population. Furthermore, this study included individuals who were highly educated and who were primarily White, which may not be representative of low- or middle-income countries where it has been shown that low education is significantly associated with poor outcomes in those with cardiovascular disease.[11,48] Our study did not have an equal proportion of men to women. However, given the elderly study population, and the lower life expectancy of men compared with women,[49] the greater proportion of women in our study is expected. Nevertheless, we were able to account for sex, among other covariates, in our analyses. We were also unable to obtain information on the onset of each CVRF, and therefore cannot not infer conclusions based on the presence of midlife versus late-life presence of CVRFs.

In summary, we identified 3 groups of CVRFs using an LCA, a data-driven approach that overcomes the limitations of studies investigating individual CVRFs, or the sum of CVRFs. Using an LCA to cluster CVRFs identified meaningful groups that were further investigated for differences in incident AD and mortality. After accounting for mortality, the incidence of AD was significantly greater in the vascular-dominant and vascular-metabolic groups compared with the reference group. This classification model can be used in future studies to investigate between-group differences in biological markers and treatment response, which may in turn identify group-specific treatment strategies for AD risk mitigation.

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SUPPLEMENTAL MATERIAL

Table S1. Adjusted odds ratios between individual cardiovascular risk factors. Covariates included baseline age, sex, MMSE score, years of education, and presence of APOE E4 allele.

	Hypertension	Hyperchol-esterolemia	Stroke	Smoking History	Heart Disease	Diabetes	High BMI
Hypertension	-	-	-	-	-	-	-
Hypercho-lesteremia	OR: 2.95, 95%CI: 2.68-3.25 p<.001	-	-	-	-	-	-
Stroke	OR: 2.65, 95%CI: 1.87-3.76, p<.001	OR: 2.00, 95%CI: 1.51-2.65, p<.001	-	-	-	-	-
Smoking History	OR: 1.04, 95%CI: .95-1.14, p=.42	OR: 1.18, 95%CI: 1.08-1.29, p<.001	OR: 1.36, 95%CI: 1.04-1.78, p=.02	-	-	-	-

Heart Disease	OR: 2.57, 95%CI: 2.20-2.98, p<.001	OR: 1.82, 95%CI: 1.60-2.07, p<.001	OR: 1.72, 95%CI: 1.27-2.33, p<.001	OR: 1.01, 95%CI: .89-1.14, p=.88	-	-	-
Diabetes	OR: 5.27, 95%CI: 4.34-6.41, p<.001	OR: 4.67, 95%CI: 3.93-5.54, p<.001	OR: 2.00, 95%CI: 1.43-2.80, p<.001	OR: 1.22, 95%CI: 1.06-1.40, p=.006	OR: 1.42, 95%CI: 1.18-1.70, p<.001	-	-
High BMI	OR: 3.90, 95%CI: 2.92-3.71, p<.001	OR: 1.68, 95%CI: 1.52-1.87, p<.001	OR: 1.50, 95%CI: 1.11-2.03, p=.008	OR: 1.12, 95%CI: 1.01-1.25, p=.03	OR: 1.22, 95%CI: 1.06-1.42, p=.006	OR: 3.51, 95%CI: 3.03-4.07, p<.001	-