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A Novel Aging Phenotype of Slow Gait, Impaired Executive Function, and Depressive Symptoms: Relationship to Blood Pressure and Other Cardiovascular Risks

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Background. Our objectives were to investigate the existence of a group of nondemented elderly individuals who simultaneously have impairments in cognition, mobility, and mood, and to examine the association between being a member of this group and elevated blood pressure and other cardiovascular conditions.

Methods. The Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly of Boston study is an ongoing prospective observational study of community-dwelling individuals. We analyzed the cross-sectional data collected at baseline (N = 580, mean age = 77.8 years, 64% women, 14% African American, mean Mini-Mental State Examination = 27.2). Using latent profile analysis, we investigated the existence of a group of elderly participants with impairments in executive function (Trail Making Test Part B [TMT-B]), gait speed (two 4-m walk tests), and depressive symptoms (Center for Epidemiological Studies-Depression scale [CES-D]).

Results. We identified a group (n = 99 [17%]) with prolonged TMT-B, slow gait speed, and high CES-D scores. This group did not exist when we used a memory measure. Hypertension (p = .001), diabetes (p = .0002), congestive heart failure (p = .006), stroke (p = .005), and higher Framingham cardiovascular risk score (p = .0001) were associated with an increased likelihood of being a member in this group. This association with elevated systolic and pulse pressure, and stroke remained significant after multiple covariate adjustments.

Conclusions. There exists a group of elderly individuals in whom poor executive function, slow gait speed, and depressive symptoms occur simultaneously. Memory measures did not identify such a grouping. Elevated blood pressure and other cardiovascular diseases are independently associated with being a member of this group. Assessing these domains is an important part of the evaluation of the elderly patients with high vascular risk.

Key Words: Blood pressure—Cognitive function—Gait speed—Executive function—Depression—Vascular disease.

COGNITIVE impairment, mobility difficulties, and depressive symptomatology are common in aging. It is estimated that 17% of people older than 65 years have cognitive impairment with no dementia (1), 20%–24% have a gait speeds of less than 1 m/s (2), and 15% of older individuals have depressive symptoms without clinical depression (3). Prospective studies have demonstrated that lower executive function performance is associated with falling (4) and with disability in daily activities (5). Furthermore, there is an association between depressive symptoms and impairments in activities of daily living (6) and between slow gait speed and disability (7). There is increasing evidence that executive function impairments are most likely to be associated with disability (8), leading to loss of independence and institutionalization (2,9,10). Moreover, impairment in one of the three domains is associated with impairment in the other two domains. For example, depressive symptoms are associated with cognitive decline and lower physical functional performance, both of which in turn are associated with increased depressive symptoms (11,12). A similar bidirectional association has been reported between gait speed and cognitive function (13).

Despite these bidomain associations, no study has investigated whether there is co-occurrence of impairments in these three domains in a population of nondemented elderly people. Furthermore, no prior study has examined whether executive functions are more likely be part of this profile than other cognitive functions affected by aging, such as memory. If confirmed, such a symptom profile

would suggest the existence of a specific aging phenotype that is characterized by simultaneous impairment in these domains and yet distinct from the frequently studied cognitive, mood, and mobility disorders.

One possible pathophysiological mechanism for the co-occurrence of cognitive impairment, mobility difficulties, and depressive symptoms is microvascular disease affecting frontal subcortical regions of the brain, which may be a consequence of common vascular risk factors that accumulate with aging (14). Elevated blood pressure is one of the most common age-associated vascular risk factors, which is associated not only with cerebrovascular disease but also with lower scores on formal cognitive testing, clinical dementia syndromes (15,16), and depressive symptoms (17). Elevated blood pressure is also associated with disability in activities of daily living and impaired self-reported mobility (18). Both memory and executive functions are affected by hypertension, but the latter is more susceptible to elevated blood pressure. Seniors suffering from executive function problems have significant difficulty in following medical care advice (19). Among 7,717 elderly women, executive function but not overall global cognitive function was associated with worsening activities of daily living and mortality (20). We previously reported a dose–response association between systolic blood pressure (SBP) and impaired executive function, but not impairment of other cognitive domains (21). This evidence suggests that hypertension may be one common factor that links executive dysfunction with abnormalities in mood and mobility.

Therefore, our first objective was to determine if a group or cluster of elderly individuals exists who simultaneously have worse executive function, slower gait speed, and a greater burden of depressive symptoms. Our second objective was to investigate if being a member of this group is associated with elevated blood pressure and other cardiovascular risk factors and diseases. Finally, we intended to investigate if such a classification holds if we use a memory measure, rather than an executive function measure.

Methods

The Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly of Boston Study

The Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly of Boston study (MOBILIZE Boston) is a prospective observational study conducted at the Institute for Aging Research at Hebrew SeniorLife in Boston, Massachusetts, and funded through a National Institute on Aging program project grant. It is designed to investigate risk factors for mobility and falls in an elderly cohort living within a 5-mile radius from the study center. The details on the design and recruitment are described elsewhere (22). The Institutional Review Board at Hebrew SeniorLife approved this study and each participant provided written informed consent.

Participants

The recruitment process included a door-to-door recruitment of a probability sample from town lists capturing 90% of those aged 70 years or older listed in the most recent census located within 5 miles of the study center. Letters were sent to a random sample from the target recruitment area, followed by a home visit by the recruitment staff (22). Eligibility criteria included age 70 years or older, ability to speak and understand English, and plans to be living in the recruitment area for at least 2 years. Exclusion criteria included cognitive impairment defined as a Mini-Mental State Examination score less than 18 (23), hearing or visual impairment that interfered with communication, having a terminal illness (eg, receiving hospice services, metastatic cancer), and inability to walk 20 feet without assistance. Of the 5,655 households identified, 4,319 individuals were age eligible, 2,382 satisfied inclusion criteria, 1,616 agreed to be screened, and 765 were enrolled. Of those, 600 had available data at the time of this analysis (22).

Measures

Blood pressure was measured at the study center. Supine blood pressure and pulse were measured after the participant had been recumbent for at least 5 minutes using a standard sphygmomanometer. Two measurements were collected. The means of the two supine SBP and diastolic blood pressure readings were used in the analysis. Pulse pressure (PP) was defined as SBP minus diastolic blood pressure. Participants were considered hypertensive if they reported receiving antihypertensive medications or their average blood pressure was 140/90 mmHg or greater during the clinical examination. Controlled hypertensives were defined as those with a history of hypertension or receiving antihypertensives and their average blood pressure was less than 140/90 mmHg. A blood sample was collected for lipid profile. History of diabetes mellitus, presence or absence of heart disease including heart attacks or myocardial infarction, history of stroke, and congestive heart failure were collected using self-report.

Hopkins Verbal Learning Test–Revised (HVLT) (24) includes a 12-item list that was read to the participant three times. After each time, the participant was asked to list as many words as he or she can recall. A delayed recall was asked again few minutes later and list recognition was also conducted. In the latter, the participant was read a list of 24 words and was asked to recognize if the word was part of the original list. Three measures were calculated for the HVLT: immediate recall = sum of number of words recalled during the three trials; delayed recall = number of words remembered at the delayed trial; and recognition = number of correct identification if a word was present or absent on the recognition list. Each of these measures was standardized to a mean of 0 and standard deviation of 1. A cumulative memory score was calculated as the average of the three standardized measures. This measure was used as the overall memory assessment. Higher scores reflect better memory function.

Parts A and B of the Trail Making Test (TMT) (25) were also administered to the participants. TMT-A measures the time a participant needs to connect a series of numbers and TMT-B a series of alternating numbers and letters. Part A reflects the motor speed aspect of TMT and part-B the executive function aspect. Longer time reflects worse executive function. For consistency, we standardized TMT to a mean of 0 and standard deviation of 1.

The Short Physical Performance Battery was used to characterize mobility of the participants. It includes measures of standing balance (timing of tandem, semitandem, and side-by-side stands; test–retest correlation = .97), 4-m walking speed (.89), and ability and time to rise from a chair five times (.73) (26). Gait speed was measured according to the procedure reported by Guralnik and colleagues as the time it takes for the participants to walk 4 m at their normal pace, starting from an inactive standing position (7). Gait speed was computed in meters per second. Two trials were performed, and the maximum of the two trials was used in this analysis.

Depression symptomatology was measured using a modification of the revised 20-item Center for Epidemiological Studies-Depression scale (CES-D) (27). We calculated depressive symptom burden scores as the simple sum of item responses. In an initial sample of 600 MOBILIZE Boston study participants, the items that comprise the CES-D were highly internally consistent (coefficient $\alpha = .87$). Higher CES-D scores reflect greater burden of depressive symptoms. In addition, Mini-Mental State Examination was performed on all participants.

Information on age, gender, race–ethnicity, smoking and alcohol history, level of education, pain during walking, and activities of daily living, including bathing, showering, dressing, transferring from a bed or chair, using the toilet, and eating, was also collected. A medication inventory was performed during the home visit and included a thorough recording of prescription and over-the-counter medications used in the previous 2 weeks (28). Current use of antihypertensive medications was extracted from this inventory. Participants were also asked to rate their overall health (from poor to excellent) and if they have a physician that they see at least once a year. Height was measured using a stadiometer with the participants standing while holding a full breath. Weight was measured without shoes using a balance beam scale calibrated regularly.

Process of choosing variables for defining the group.—We were interested in identifying a group of individuals with poorer performance on measures of gait, depressive symptoms, and executive function. We identified the following set of measures to investigate if such a group existed: TMT-B (seconds), gait speed (seconds), and CES-D (score). Our justifications for selecting these measures were their evidence for reliability in the elderly population, ability to predict further physical and cognitive decline based on prior research (4–7), and ease of conduct in a busy clinical practice. Completing the three measures took about 10 minutes.

Statistical Analysis

To identify a group of participants with concurrent low performance on TMT-B, gait speed, and CES-D, we used latent profile analysis (LPA) to categorize individuals based on their performances. LPA is a type of latent class analysis that uses continuous measures to cluster individuals into classes or groups using posterior probabilities calculated by Bayes' theorem (29). The analysis operationalizes an assumption that an unobserved categorical latent variable is responsible for the covariation among the class indicators (cognitive functioning, gait speed, and depressive symptoms). Each participant was assigned to a latent class to which the largest posterior probability was calculated. Within LPA, the term *model* is used to compare *number of classes* or profiles of individuals with similar patterns of responses and performance on indicators of interest. Detailed criteria for determining the best-fitting model are described elsewhere (30,31). Briefly, the best-fitting model is the model with the lowest values for the following criteria: Akaike information criterion, Bayesian information criterion, and log likelihood. There are no a priori cutoffs for these measures of model fit and they are used in the relative comparisons between various models (lower values mean a better fit model). The Bootstrap likelihood ratio test compares two sequential LPA models, for example, the three-class versus the four-class model. The model with the lower p value means a better-fit model compared with the preceding one. To examine the accuracy of the LPA models for assigning individuals into classes, we noted the entropy values. Higher entropy values (closer to 1) means the model better explains the classification of individuals (30). For the clinical interpretation, we examined the mean level differences between classes across each LPA model. We conducted two LPAs, one with executive function (TMT-B) and the other with memory (HVLT). We used M-plus version 5 to perform this analysis.

Once we selected the best-fit model, we defined a discrete outcome variable based on each person's most likely class membership. We then proceeded to compare the latent classes on their demographics, social measures, comorbidities, and functional measures. We also investigated the association between blood pressure, elevated cholesterol, diabetes mellitus, stroke, and other cardiovascular diseases and the likelihood of being in the lower performance cluster. Using multiple logistic regression with the outcome being class membership, we examined the association of blood pressure, stroke, diabetes mellitus, and other cardiovascular diseases with membership in the three-symptom class after adjusting for age, race, body mass index, educational level, smoking, use of antihypertensives, osteoarthritis, and pain that interferes with walking. We used SAS (SAS Institute, Cary, NC) to conduct this analysis.

Table 1. Latent Profile Analysis on the Three Measures, With Mean ± Standard Error of Each Measure in Each Group and Model Fit Statistics

	2-Class Model		3-Class Model			4-Class Model			
	1	2*	1	2*	3	1	2*	3	4
n	483	97	468	83	29	459	99	17	5
TMT-B, s	110.3 ± 2.8	298.2 ± 12.2	110.4 ± 3.1	307.4 ± 15.6	175.7 ± 43.4	106.8 ± 2.3	280.5 ± 7.1	170.3 ± 44.6	559.6 ± 38
TMT-B, *z* score	–0.3 ± 0.02	1.8 ± 0.1	–0.4 ± 0.02	1.9 ± 0.1	0.4 ± 0.2	–0.4 ± 0.02	1.6 ± 0.05	0.4 ± 0.2	4.7 ± 0.5
CES-D	10 ± 1	16 ± 2	9 ± 1	11 ± 2	42 ± 6	9 ± 1	12 ± 1	46 ± 7	13 ± 4
Gait speed	1 ± 0.01	0.7 6 ± 0.03	1 ± 0.01	0.8 ± 0.03	0.77 ± 0.1	1 ± 0.01	0.78 ± 0.02	0.78 ± 1	0.7 ± 0.1
Model statistics									
Akaike's information criteria	11,612			11,472			11,367		
Bayesian information criteria	11,656			11,534			11,447		
Log likelihood	–5,796			–5,722			–5,665		
Likelihood ratio test *k* - 1 vs *k* classes	0.06			0.152			0.019		
Entropy	.85			.89			.91		

Notes: CES-D = Center for Epidemiological Studies-Depression scale; TMT = Trail Making Test. Lower model statistics indicate better model fit.
*The low-performance group.

Results

Of the 600 participants recruited, neuropsychological and gait speed data were available for 580 (97%). The mean age was 77.8 ± 0.2 years, 64% were women, and 80% were self-described as whites. In the overall sample, the mean TMT-B was 142.9 ± 3.7 seconds, gait speed 0.96 ± 0.1 m/s, and CES-D 10.9 ± 0.4.

Table 1 provides the results of the LPA using TMT-B as the cognitive measure. We compared two-, three-, and four-class models. Independent of the number of classes, we identified a group of participants with low performance on all three measures. Ninety-seven participants (17%) in the two-class model, 83 (14%) in the three-class model, and 99 (17%) in the four-class model belonged to the three-symptom group. Depending on the number of classes in the model, the mean gait speed of this group was 0.76–0.80 m/s, CES-D score 11–16, and TMT-B 1.6–1.9 *SD* units above the mean. We designated this group as the low-performance group.

As shown in Table 1, the four-class model had the best-fit statistics and high accuracy for classification of participants (entropy = .91). The three-class model did not differ significantly from the two-class model (p = .152 for the difference between the two-class and three-class models), and the four-class model was superior to the three-class model (p = .019). Therefore, we selected the four-class model (low-performance group: n = 99 [17%] and normative group: n = 459 [79%]) for our subsequent analyses. There were two additional small groups in the four-class model (n = 17 with high CES-D and n = 5 with prolonged TMT-B) that were excluded from subsequent analyses.

We then performed a similar LPA using HVLT (memory) instead of TMT-B (executive function) as the cognitive measure. Table 2 shows the results. This analysis did not reveal a distinct group with poor performance in cognition, mood, and gait as in the prior analysis. Although CES-D scores were different, the memory scores and gait speeds were almost identical in each group of the two-class and three-class models.

Table 3 provides the characteristics of the low-performance group versus the normative group. Members of the low-performance group were older (p < .0001), were more likely to be African American (p < .0001), had lower education (p < .0001), but had similar nonvascular comorbidities. They also reported poorer overall health (p < .0001), reported more overall disability in activities of daily living and instrumental activities of daily living (p < .0001 for both), and performed worse on the Short Physical Performance Battery (p < .0001). The difference in HVLT was statistically significant (p < .0001) but clinically small (0.7 *SD* units in the low-performance group vs 0.2 *SD* units in the normative group). Finally, the low-performance group had lower TMT-B score (p < .0001).

Tables 4 and 5 provide the results of the analysis comparing the two groups on blood pressure and other vascular diseases and risks. Among the members of the low-performance group, 93% were hypertensive and 34% had uncontrolled hypertension. They had higher SBP (p = .05) and PP (p = .001) but not diastolic blood pressure (p = .8) compared with the normative group. Members of the low-performance group were more likely to report a history of stroke (p = .005), congestive heart failure (p = .006), and diabetes (p = .0002). They also had a higher Framingham risk score (p = .0001). There were no differences in cholesterol levels, atrial fibrillation, or other heart diseases between the two groups.

In the multivariable models, SBP and PP remained significantly associated with being a member of the lower performance group after adjusting for age, race, education, gender, body mass index, smoking history, use of antihypertensives, and other cardiovascular diseases and risk factors. This was also true after adjusting for arthritis and having pain that interferes with walking. Similarly, stroke and low-density lipoprotein remained significantly associated with

Table 2. Latent Profile Analysis for Memory, Gait Speed, and Depressive Symptoms, With Mean ± Standard Error of Each Measure in Each Group

	2-Class Model		3-Class Model		
Classes	1	2	1	2	3
n	534	46	380	155	45
HVLT, *z* score	0.01 ± 0.11	−0.09 ± 0.12	0.36 ± 0.05	−0.81 ± 0.12	−0.04 ± 0.13
CES-D	9 ± 1	38 ± 4	8 ± 1	11 ± 1	39 ± 5
Gait speed	0.96 ± 0.01	0.84 ± 0.06	1.03 ± 0.02	0.80 ± 0.03	0.83 ± 0.07
Akaike's information criteria	6,296		6,222		
Bayesian information criteria	6,341		6,284		
Log likelihood	−3,139		−3,097		
Likelihood ratio test *k* - 1 vs *k* classes	0.03		0.03		
Entropy	.92		.72		

Note: CES-D = Center for Epidemiological Studies-Depression scale; HVLT = Hopkins Verbal Learning Test.

being a member of this group, independent of blood pressure and other covariates. Diabetes mellitus remained significantly associated with being member in this group after adjusting for SBP but not PP. Finally, congestive heart failure was not associated with membership in this group after multivariable adjustments. The association between uncontrolled hypertension and being in the low-performance group was not significant after these adjustments (odds ratio 3.13, 95% confidence

Table 3. Characteristics of the Overall Sample and the Two Groups of Participants With the Low- and Normative Performance Profiles in the Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly of Boston Study

	Total Sample	Low-Performance Group	Normative Performance Group	*p* Value
n (%)	580	99 (17)	459 (79)	
Age, y	77.8 ± 0.2	79.9 ± 0.6	77.3 ± 0.2	<.0001
Gender (% women)	64	67	63	.53
Race, %				
African American	14	36	9	<.0001
Other	6	8	5	
Body mass index, kg/m^2	27.3 ± 0.2	27.8 ± 0.5	27.1 ± 0.2	.19
No physician, %	3	3	3	.99
Smoking, %				
Current	4	2	4	.04
Past	52	43	55	
Alcohol (% none or <2 drinks per day)	93	98	91	.02
Education, % <12 y	9	32	3	<.0001
Self-reported comorbid illnesses, %				
Arthritis	45	42	44	.72
Kidney disease	6	9	5	.39
Anemia	21	20	20	.75
Cancer	23	21	23	.45
Depression	17	16	15	.88
Spinal stenosis or disc disease	20	14	21	.212
Parkinson's disease	1	1	1	.94
Overall health (% fair to poor)	14	31	8	<.0001
Cognitive function				
Mini-Mental State Examination	27.2 ± 0.1	24.3 ± 0.3	27.9 ± 0.1	<.0001
HVLT, overall *z* score	NA*	−0.6 ± 0.1	0.2 ± 0.1	<.0001
HVLT, recognition *z* score (pure memory test)	NA*	−0.7 ± 0.1	0.3 ± 0.1	<.0001
TMT-B (adjusted for motor speed using TMT-A)	88.2 ± 3.2	195.5 ± 5.9	60.7 ± 1.8	<.0001
TMT-B adjusted for trail A, z score	NA†	1.2 ± 0.1	−0.4 ± 0.1	<.0001
Functional measures				
Activities of daily living (% no impairment)	81	67	84	<.0001
Instrumental activities of daily living (% no impairment)	61	49	66	<.003
Short Physical Performance Battery	9.1 ± 0.1	8.1 ± 0.2	9.3 ± 0.1	<.0001
Pain interfere with walking, %				
No	46	43	47	.67
Mild	39	43	37	

Notes: HVLT = Hopkins Verbal Learning Test; TMT = Trail Making Test.

*This measure was standardized to an *M* of 0 and *SD* of 1.

†Total sample = 580 includes the two small groups of the four-class solution.

Table 4. Blood Pressure and Other Cardiovascular Risks and Diseases in the Overall Sample and in the Low- and Normative Performance Groups in the Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly of Boston Study

Cardiovascular Risk/Disease	All Sample	Low-Performance Group	Normative Performance Group	*p* Value
Systolic blood pressure, mmHg	130.8 ± 0.8	133.5 ± 2.0	130.8 ± 0.8	.05
Diastolic blood pressure, mmHg	70.2 ± 0.4	68.8 ± 1.0	70.5 ± 0.4	.08
Pulse pressure, mmHg	60.4 ± 0.7	64.7 ± 1.7	59.0 ± 0.7	.001
Total cholesterol, mg/dL	186.5 ± 1.8	186.0 ± 4.7	186.7 ± 1.9	.88
Low-density lipoprotein, mg/dL	108.4 ± 1.5	112.2 ± 4.1	108.1 ± 1.6	.31
Hypertension, %	78	93	75	.0001
Uncontrolled hypertension, %	26	34	23	.0004
Antihypertensives, %	68	82	64	.0008
Stroke, %	10	17	8	.005
Heart disease, %	27	29	26	.56
Atrial fibrillation, %	24	22	24	.62
Congestive heart failure, %	5	10	4	.006
Diabetes mellitus, %	17	30	14	.0002
Framingham score	10.9 ± 0.1	12.0 ± 0.3	10.6 ± 0.2	.0001

interval 0.90–10.88). We did not perform multivariable analysis for diastolic blood pressure because there was no difference between the two groups on bivariate analysis.

Discussion

This study demonstrates that there exists a group of elderly individuals with a unique phenotype of worse executive function, slow gait speed, and greater depressive symptoms compared with the general population. The prevalence of this phenotype is 17% of English-speaking ambulatory nondemented elders in the greater Boston area. Having this phenotype is independently associated with elevated SBP, PP, and other cardiovascular conditions. Memory indicators did not cluster with slow gait and depressive symptoms. Individuals with this phenotype are more likely to report limitations in function and perform poorly on physical performance measures.

To the authors' knowledge, this is the first study to identify a cluster of elderly individuals with simultaneous low performance on tests of executive function, gait speed, and depressive symptoms, and its association with high blood pressure and other vascular risk factors and diseases. Prior studies have reported that elevated blood pressure and diabetes are associated with cognitive impairment and depressive symptoms when assessed separately (15,21,32). These findings identify a potentially important but previously unexplored manifestation of elevated blood pressure and cardiovascular disease that may further explain the link between vascular disease and disability in late life (18).

SBP has been well documented as a more important risk factor for stroke and other cardiovascular diseases compared with diastolic blood pressure (33). In this study, we also demonstrate that SBP is more likely to be associated with poor functional performance than diastolic blood pressure. Finally, this is the first report of the association of PP with poor performance in the selected domains and confirms that PP is an important clinical measure that needs to be included in routine assessments.

Difficulties in executive function are critical mechanisms by which elders become disabled (34). Our study suggests that those with executive impairment are also more likely to have greater depressive symptoms and slower gait speed, offering an additional explanation for the association between executive function and disability. Additionally, the lack of clustering with measures of memory and the association of this profile with elevated blood pressure and vascular conditions suggest that executive function may be a more specific measure of vascular-related cognitive impairment.

From a clinical perspective, patients in the low-performance profile have a higher vascular load and worse performance on functional and disability measures. This raises the

Table 5. Odds Ratio Obtained From the Final Regression Models for the Association of Blood Pressure and Other Cardiovascular Conditions With Being a Member in the Cluster With the Low-Performance Profile (high-performance profile cluster as reference)

	Systolic Blood Pressure Model, OR* (95% CI)	Pulse Pressure Models, OR* (95% CI)
Blood pressure	1.01 (1.00–1.03)	1.03 (1.00–1.05)
Low-density lipoprotein	1.01 (1.00–1.02)	1.01 (1.00–1.02)
Diabetes mellitus	2.43 (1.00–5.89)	2.38 (0.98–5.82)
Stroke	5.12 (1.70–15.43)	4.97 (1.64–15.06)
Congestive heart failure	3.72 (0.75–18.50)	3.74 (0.75–18.74)

Notes: CI = confidence interval; OR = odds ratio. OR obtained from the logistic regression with class membership as the outcome.

*Model includes blood pressure, low-density lipoprotein, diabetes, stroke, congestive heart failure, demographics, education, smoking status, use of antihypertensives, osteoarthritis, pain upon walking, and body mass index.

need for measuring executive function as well as assessing gait speed and depressive symptoms in the routine assessments of high–vascular risk patients.

Our operational definition for the profile of executive, mood, and gait impairment can be easily applied in the clinical setting and is based on the upper or lower boundary of the 95% confidence intervals for the tests describing each of the symptoms in the triad. Those who *concurrently* have a gait speed of 0.85 m/s or less (range 0.71–0.85), a TMT-B score of 262 seconds or more, and a CES-D score of 8 or more meet our criteria. These criteria need to be validated in future studies of other populations. Until then, we recommend that vascular risk factors be assessed in individuals with these characteristics.

One possible explanation for our findings is that aging, blood pressure, and vascular risk factors tend to preferentially affect the frontal subcortical regions of the brain (21,35). Pathological processes that interfere with the integrity of circuits in these regions are associated with executive dysfunction, depressive mood, and motor "slowing" (35–37). The common convergence of abnormalities in these three domains may arise from damage to white matter association pathways interconnecting frontal and subcortical regions of the brain (14). In support of a cerebral microvascular etiology for this triad of symptoms, vascular risk factors, especially elevated blood pressure, reduce cerebrovascular vasoreactivity and cerebral blood flow, predisposing elderly individuals to greater risk of hypoperfusion in these anatomic areas (38,39).

The identification of the low-performance group and its association with vascular risk factors and cardiovascular diseases suggest that this may be a specific "vascular aging" phenotype. Elderly individuals with this phenotype are more likely to have impairments in activities of daily living, instrumental activities of daily living, and physical function compared with the remaining population. This phenotype is also prevalent in nondemented and relatively independent community dwellers, especially those with hypertension and other vascular risks and diseases.

Our study has several limitations. First, it is a cross-sectional study and therefore we cannot infer a temporal relationship between vascular disease and this phenotype. Nevertheless, it provides important information about manifestations of vascular disease in an aging population and offers one way to assess aging-related symptoms in future hypertension and other vascular-related studies. Second, we used self-reported comorbidities. Although this has been validated in population studies, there is still a risk of misclassification. Further, other nonvascular factors may be contributing to poorer performance on the selected tests. For example, arthritis and painful walking may limit gait speed measures. We have adjusted for these factors using multivariate analyses to the extent possible in our sample. Finally, we only explored the clustering of impairments in the three domains, and this does not preclude that those with impairment in two domains may also have high vascular risk.

Conclusions

In a representative cross-sectional sample of community-dwelling elderly individuals, there exists a cluster of individuals with a phenotype of poor executive function, slow gait speed, and greater depressive symptoms. Measures of memory were not associated with this constellation of symptoms. Elevated SBP and PP, stroke, and other cardiovascular conditions are independently associated with having this phenotype. Patients with impairments in executive function, mobility, and mood should be carefully assessed and treated for cardiovascular risk factors. Further studies are needed to validate this phenotype, determine its underlying mechanisms, and assess whether the amelioration of cardiovascular risk factors can prevent its development.

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Conflict of interest

The sponsor did not participate in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

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References

1. Graham JE, Rockwood K, Beattie BL, et al. Prevalence and severity of cognitive impairment with and without dementia in an elderly population. *Lancet*. 1997;349(9068):1793–1796.
2. Cesari M, Kritchevsky SB, Penninx BW, et al. Prognostic value of usual gait speed in well-functioning older people—results from the Health, Aging and Body Composition Study. *J Am Geriatr Soc*. 2005;53(10):1675–1680.
3. Beekman AT, Penninx BW, Deeg DJ, Ormel J, Braam AW, van Tilburg W. Depression and physical health in later life: results from the Longitudinal Aging Study Amsterdam (LASA). *J Affect Disord*. 1997;46(3):219–231.
4. Anstey KJ, von Sanden C, Luszcz MA. An 8-year prospective study of the relationship between cognitive performance and falling in very old adults. *J Am Geriatr Soc*. 2006;54(8):1169–1176.
5. Dodge HH, Kadowaki T, Hayakawa T, Yamakawa M, Sekikawa A, Ueshima H. Cognitive impairment as a strong predictor of incident disability in specific ADL-IADL tasks among community-dwelling elders: the Azuchi Study. *Gerontologist*. 2005;45(2):222–230.

6. Cronin-Stubbs D, de Leon CF, Beckett LA, Field TS, Glynn RJ, Evans DA. Six-year effect of depressive symptoms on the course of physical disability in community-living older adults. *Arch Intern Med*. 2000;160(20):3074–3080.
7. Guralnik JM, Ferrucci L, Pieper CF, et al. Lower extremity function and subsequent disability: consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. *J Gerontol A Biol Sci Med Sci*. 2000;55(4):M221–M231.
8. Kuo HK, Leveille SG, Yu YH, Milberg WP. Cognitive function, habitual gait speed, and late-life disability in the National Health and Nutrition Examination Survey (NHANES) 1999-2002. *Gerontology*. 2007;53(2):102–110.
9. Blaum CS, Ofstedal MB, Liang J. Low cognitive performance, comorbid disease, and task-specific disability: findings from a nationally representative survey. *J Gerontol A Biol Sci Med Sci*. 2002;57(8):M523–M531.
10. Penninx BW, Guralnik JM, Ferrucci L, Simonsick EM, Deeg DJ, Wallace RB. Depressive symptoms and physical decline in community-dwelling older persons. *JAMA*. 1998;279(21):1720–1726.
11. Apostolova LG, Cummings JL. Neuropsychiatric manifestations in mild cognitive impairment: a systematic review of the literature. *Dement Geriatr Cogn Disord*. 2008;25(2):115–126.
12. Raji MA, Ostir GV, Markides KS, Goodwin JS. The interaction of cognitive and emotional status on subsequent physical functioning in older mexican americans: findings from the Hispanic established population for the epidemiologic study of the elderly. *J Gerontol A Biol Sci Med Sci*. 2002;57(10):M678–M682.
13. Alfaro-Acha A, Al Snih S, Raji MA, Markides KS, Ottenbacher KJ. Does 8-foot walk time predict cognitive decline in older Mexicans Americans? *J Am Geriatr Soc*. 2007;55(2):245–251.
14. Pugh KG, Lipsitz LA. The microvascular frontal-subcortical syndrome of aging. *Neurobiol Aging*. 2002;23(3):421–431.
15. Reinprecht F, Elmstahl S, Janzon L, Andre-Petersson L. Hypertension and changes of cognitive function in 81-year-old men: a 13-year follow-up of the population study "Men born in 1914", Sweden. *J Hypertens*. 2003;21(1):57–66.
16. Launer LJ, Masaki K, Petrovitch H, Foley D, Havlik RJ. The association between midlife blood pressure levels and late-life cognitive function. The Honolulu-Asia Aging Study. *JAMA*. 1995;274(23):1846–1851.
17. Reiff M, Schwartz S, Northridge M. Relationship of depressive symptoms to hypertension in a household survey in Harlem. *Psychosom Med*. 2001;63(5):711–721.
18. Hajjar I, Lackland DT, Cupples LA, Lipsitz LA. Association between concurrent and remote blood pressure and disability in older adults. *Hypertension*. 2007;50(6):1026–1032.
19. Royall DR, Cordes J, Polk M. Executive control and the comprehension of medical information by elderly retirees. *Exp Aging Res*. 1997;23(4):301–313.
20. Johnson JK, Lui LY, Yaffe K. Executive function, more than global cognition, predicts functional decline and mortality in elderly women. *J Gerontol A Biol Sci Med Sci*. 2007;62(10):1134–1141.
21. Kuo HK, Sorond F, Iloputaife I, Gagnon M, Milberg W, Lipsitz LA. Effect of blood pressure on cognitive functions in elderly persons. *J Gerontol A Biol Sci Med Sci*. 2004;59(11):1191–1194.
22. Leveille SG, Kiel DP, Jones RN, et al. The MOBILIZE Boston Study: design and methods of a prospective cohort study of novel risk factors for falls in an older population. *BMC Geriatr*. 2008;8:16.
23. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189–198.
24. Shapiro AM, Benedict RH, Schretlen D, Brandt J. Construct and concurrent validity of the Hopkins Verbal Learning Test-revised. *Clin Neuropsychol*. 1999;13(3):348–358.
25. Gordon NG. The Trail Making Test in neuropsychological diagnosis. *J Clin Psychol*. 1972;28(2):167–169.
26. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol*. 1994;49(2):M85–M94.
27. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas*. 1977;1(3):385–401.
28. Psaty BM, Lee M, Savage PJ, Rutan GH, German PS, Lyles M. Assessing the use of medications in the elderly: methods and initial experience in the Cardiovascular Health Study. The Cardiovascular Health Study Collaborative Research Group. *J Clin Epidemiol*. 1992;45(6):683–692.
29. McCutcheon AL. Latent class analysis. In Niemi RG, ed. *Quantitative Applications in the Social Sciences*. Newbury Park, CA: Sage 2002:64.
30. Croudace TJ, Jarvelin MR, Wadsworth ME, Jones PB. Developmental typology of trajectories to nighttime bladder control: epidemiologic application of longitudinal latent class analysis. *Am J Epidemiol*. 2003;157(9):834–842.
31. Muthen B, Brown CH, Masyn K, et al. General growth mixture modeling for randomized preventive interventions. *Biostatistics*. 2002;3(4):459–475.
32. Stewart R. Hypertension and depression in late life. *Br J Psychiatry*. 2006;188:85.
33. Applegate WB. The relative importance of focusing on elevations of systolic vs diastolic blood pressure. A definitive answer at last. *Arch Intern Med*. 1992;152(10):1969–1971.
34. Royall DR, Palmer R, Chiodo LK, Polk MJ. Declining executive control in normal aging predicts change in functional status: the Freedom House Study. *J Am Geriatr Soc*. 2004;52(3):346–352.
35. Flint AJ, Eastwood MR. Frontal lobe syndrome and depression in old age. *J Geriatr Psychiatry Neurol*. 1988;1(1):53–55.
36. Alvarez JA, Emory E. Executive function and the frontal lobes: a meta-analytic review. *Neuropsychol Rev*. 2006;16(1):17–42.
37. Thompson PD. Gait disorders accompanying diseases of the frontal lobes. *Adv Neurol*. 2001;87:235–241.
38. Dai W, Lopez OL, Carmichael OT, Becker JT, Kuller LH, Gach HM. Abnormal regional cerebral blood flow in cognitively normal elderly subjects with hypertension. *Stroke*. 2008;39(2):349–354.
39. Cohen RA. Hypertension and cerebral blood flow: implications for the development of vascular cognitive impairment in the elderly. *Stroke*. 2007;38(6):1715–1717.

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