ABNORMALITY OF GAIT AS A PREDICTOR OF NON-ALZHEIMER'S DEMENTIA

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ABSTRACT

Background   Neurologic abnormalities affecting gait occur early in several types of non-Alzheimer's dementias, but their value in predicting the development of dementia is uncertain.

Methods   We analyzed the relation between neurologic gait status at base line and the development of dementia in a prospective study involving 422 subjects older than 75 years of age who lived in the community and did not have dementia at base line. Cox proportional-hazards regression analysis was used to calculate hazard ratios with adjustment for potential confounding demographic, medical, and cognitive variables.

Results   At enrollment, 85 subjects had neurologic gait abnormalities of the following types: unsteady gait (in 31 subjects), frontal gait (in 12 subjects), hemiparetic gait (in 11 subjects), neuropathic gait (in 11 subjects), ataxic gait (in 10 subjects), parkinsonian gait (in 8 subjects), and spastic gait (in 2 subjects). During follow-up (median duration, 6.6 years), there were 125 newly diagnosed cases of dementia, 70 of them cases of Alzheimer's disease and 55 cases of non-Alzheimer's dementia (47 of which involved vascular dementia and 8 of which involved other types of dementia). Subjects with neurologic gait abnormalities had a greater risk of development of dementia (hazard ratio, 1.96 [95 percent confidence interval, 1.30 to 2.96]). These subjects had an increased risk of non-Alzheimer's dementia (hazard ratio, 3.51 [95 percent confidence interval, 1.98 to 6.24]), but not of Alzheimer's dementia (hazard ratio, 1.07 [95 percent confidence interval, 0.57 to 2.02]). Of non-Alzheimer's dementias, abnormal gait predicted the development of vascular dementia (hazard ratio, 3.46 [95 percent confidence interval, 1.86 to 6.42]). Among the types of abnormal gait, unsteady gait predicted vascular dementia (hazard ratio, 2.61), as did frontal gait (hazard ratio, 4.32) and hemiparetic gait (hazard ratio, 13.13).

Conclusions   The presence of neurologic gait abnormalities in elderly persons without dementia at base line is a significant predictor of the risk of development of dementia, especially non-Alzheimer's dementia. (N Engl J Med 2002;347:1761-8.)

GAIT disorders become increasingly common with advancing age, occurring in 8 to 19 percent of elderly persons residing in the community.[1,2] Common causes of abnormal gait in elderly persons include neurologic diseases, arthritis, and acquired foot deformities. Neurologic diseases such as neuropathies, stroke, and parkinsonian syndromes account for 30 to 50 percent of cases in elderly patients who present for evaluation of abnormal gait.[2-5] Like the frequency of gait disorders, the prevalence of dementia also increases with age.[6] Although Alzheimer's disease is the most common type of dementia, vascular and other non-Alzheimer's dementias account for 30 to 50 percent of all cases of dementia.[6-9] The prevalence of vascular dementia is high worldwide and is particularly high in Asia.[6,9] Patients with vascular dementia may be more depressed, have greater functional impairment, and require different diagnostic and therapeutic approaches than patients with Alzheimer's disease.[10] Recent studies have focused on identifying persons who are at high risk for Alzheimer's disease, often with the use of cognitive tests.[11,12] Predictors of non-Alzheimer's dementia have been less well characterized.[13,14]

According to current criteria, the early appearance of abnormalities of gait makes a diagnosis of probable Alzheimer's disease unlikely.[15,16] In contrast, gait disorders are a well-known presenting feature of non-Alzheimer's dementias such as vascular and parkinsonian dementias.[17-21] Because gait abnormalities are often present at the onset of non-Alzheimer's dementia, we hypothesized that they may precede and predict diagnosis.

For 21 years, the Bronx Aging Study has conducted detailed clinical evaluations of a community-based cohort of subjects who did not have dementia at base line,[22,23] providing an opportunity to identify risk factors for non-Alzheimer's dementia. We examined the role of abnormal gait in predicting not only the risk of dementia, but also the risk of Alzheimer's disease as compared with non-Alzheimer's dementia.

METHODS

Study Population

Study design and recruitment methods for the Bronx Aging Study have been described previously.[22,23] Briefly, we enrolled English-speaking subjects between 75 and 85 years of age. Criteria for exclusion included a previous diagnosis of idiopathic Parkinson's disease, liver disease, alcoholism, or known terminal illness; visual or hearing impairment that interfered with completion of neuropsychological tests; and presence of dementia. The inception cohort

was middle-class, mostly white (90 percent), and largely female (64.5 percent). Subjects were screened to rule out dementia and were included if they made 8 or fewer errors on the Blessed Information–Memory–Concentration test (worst possible score, 32 errors).[24] This test has high test–retest reliability (0.86) and correlates well with the pathology of Alzheimer's disease.[25,26] Subjects were interviewed about their medical history with the use of structured questionnaires. Functional status was assessed with the subscale for activities of daily living from the Blessed Dementia Scale.[24] Whenever possible, a close friend or family member was also interviewed by a study clinician in order to confirm the history and assess functional status. Written informed consent was obtained at enrollment, and subjects were asked to consider eventual participation in an autopsy program. The local institutional review board approved the study protocol.

A total of 488 subjects were enrolled between 1980 and 1983, and the study period ended in 2001. In 1992, the Bronx Aging Study was incorporated into the Einstein Aging Study. Subjects had follow-up visits every 12 to 18 months, at which they underwent detailed neurologic and neuropsychological evaluations. We excluded 65 subjects who did not have a follow-up visit, either because they died, because they moved, or because they declined to return.[22,23] We excluded one subject both of whose legs had been amputated above the knee. After these exclusions, 422 subjects (86.5 percent) remained eligible for the study. Although 79 subjects subsequently dropped out of the study, the mean (±SD) follow-up was similar among the 8 subjects with abnormal gait who dropped out and the 71 without abnormal gait who dropped out (6.6±4.2 years vs. 7.2±5 years, P=0.70).

Assessment of Gait

Neurologic abnormalities affecting gait were diagnosed after clinical examination by board-certified neurologists.[2,3,27] Gait impairments due solely to nonneurologic causes such as arthritis were not classified as abnormal gait. Gait abnormalities were subclassified as unsteady, ataxic, frontal, parkinsonian, neuropathic, hemiparetic, or spastic.[2,3,27] Examples of the first six types of gait abnormalities are shown in videos in Supplementary Appendix 1 (available with the full text of this article at http://www. nejm.org). Gait was classified as unsteady if two or more of the following features were present: marked swaying, loss of balance, or falls while the subject was walking, walking in a straight line placing one foot directly in front of the other, or turning. Ataxic gait (resulting from cerebellar ataxia) is a wide-based gait with other features associated with cerebellar disease, such as heel-to-shin incoordination or intention tremor. Frontal gait is characterized by short steps, a wide base, and difficulty in picking the feet up off the floor (magnetic response). Elderly persons with parkinsonian gaits take small, shuffling steps, have a flexed posture, do not swing their arms, make en bloc turns, exhibit festination, and have postural instability. Patients with neuropathic gaits have unilateral or bilateral foot drop and other neuropathic signs such as a "stocking"-pattern sensory loss and an absence of deep-tendon reflexes. Patients with hemiparetic gait swing their legs outward and in a semicircle from the hip (circumduction). They usually have a history or other clinical signs of stroke. In spastic gait, both legs circumduct, and when this abnormality is severe, the legs cross in front of one another (scissoring).

To assess the reliability of the evaluations of gait, we compared assessments performed a year apart at the first and second study visits. We excluded subjects whose scores on the Blessed Information–Memory–Concentration test increased by more than two points in order to eliminate persons with changes in gait that might be related to progressive neurodegenerative disease. For the remaining 189 subjects, there was 89 percent agreement between the two assessments in the classification of gaits as neurologically normal or abnormal (kappa, 0.61).[28] We have previously reported good interrater reliability for retrospective abstraction of data (kappa, 0.57 to 0.90).[29]

Neuropsychological Evaluation

A battery of neuropsychological tests was administered at study visits in order to assess the following cognitive domains: general cognitive status, assessed by the Blessed Information–Memory–Concentration test[24] and the verbal and performance IQ according to the Wechsler Adult Intelligence Scale[30]; attention, assessed by the Digit Span subtest of the Wechsler Adult Intelligence Scale[30]; executive function, assessed by the Digit–Symbol Substitution subtest of the Wechsler Adult Intelligence Scale[30]; memory, assessed by the Fuld Object-Memory Evaluation[31] and the five-item Blessed memory phrase subtest[30] (the selective reminding test, an extensively validated memory test, was not administered at the first visit, and results on this test are not reported here); visual–perceptual processing, assessed by Raven's Progressive Matrices, Set A,[32] and by the Object-Assembly subtest of the Wechsler Adult Intelligence Scale[30]; motor skills, assessed by the Purdue Pegboard test[33]; language skills, assessed by the Category Fluency Test[34]; and mood, assessed by the self-rating Zung depression scale.[35]

Diagnosis of Dementia

Subjects in whom dementia was suspected on the basis of clinical and neuropsychological evaluations, worsening scores on the Blessed Information–Memory–Concentration test, or the observations of study investigators underwent a workup.[22,23] The presence or absence of gait impairment was not used to trigger evaluation. The workup included computed tomographic scanning and blood tests (complete blood count, routine chemical screen, liver-function and thyroid-function tests, measurement of vitamin B_{12} and folate levels, and serologic testing for syphilis) and did not vary with gait status. Diagnoses of dementia were assigned according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, third edition (DSM-III),[36] at case conferences attended by at least one study neurologist, a neuropsychologist, and a geriatric nurse or social worker. Beginning in 1986, the criteria of the revised edition of the DSM-III (DSM-III-R) were used to diagnose dementia.[37] Alzheimer's disease was diagnosed according to the criteria for probable disease detailed by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.[15] Vascular dementia was diagnosed according to the criteria of the DSM-III and DSM-III-R[36,37] and by a Hachinski Ischemic Score of more than 2 on the modified 12-point scale.[17]

At the original case conferences, clinicians had access to clinical data, including gait status, which created the potential for circularity in diagnosis. In addition, criteria for diagnosing subtypes of dementia were published after the study began.[18-20] To avoid such circularity and to ensure that uniform diagnostic criteria would be used for subtypes of dementia, all cases were reassessed in 2001 by a neurologist and a neuropsychologist who were unaware of the subjects' gait status and who had not participated in the original case conferences. Clinical details were abstracted from clinical records and functional-assessment questionnaires[24] and were presented to the diagnostic team by an assistant in neuropsychology who omitted all references to gait, use of canes or walkers, and limitations on activities of daily living because of poor mobility. Dementia was diagnosed according to the criteria of the DSM-III-R,[37] and the subtype was determined according to standard criteria for probable or possible Alzheimer's disease,[15] vascular dementia (according to the criteria for probable, possible, or mixed disease defined by the State of California Alzheimer's Disease Diagnostic and Treatment Centers),[18] and dementia with Lewy bodies (according to the revised consensus criteria for probable or possible disease).[20] Disagreements between raters were resolved by consensus after the presentation of the case to a second neurologist who was also blinded to gait status. Since our aim was to define the role of abnormal gait in predicting dementias other than Alzheimer's disease, we analyzed pure and mixed vascular dementias together.

Statistical Analysis

We used either the t-test for independent samples or the Mann–Whitney nonparametric test for comparisons of continuous variables and chi-square or Fisher's exact tests, as appropriate, for comparisons of categorical variables. To determine the effect of any neurologic gait abnormality and the effects of specific subtypes of gait abnormalities on the development of dementia, we used Cox proportional-hazards regression analysis to estimate hazard ratios with 95 percent confidence intervals, with adjustment for potentially confounding demographic, medical, and cognitive-status variables.[38] The time to an event was calculated from enrollment to the date of a diagnosis of dementia, or to the final contact or visit in subjects in whom dementia did not develop. Kaplan–Meier survival plots were generated to represent graphically the effect of base-line gait status on the development of dementia.

RESULTS

Demographics

Of the 422 subjects, 85 (20.1 percent) had neurologic gait abnormalities at base line. During 2609 person-years of follow-up (median follow-up, 6.6 years), dementia developed in 125 subjects, of whom 37 had abnormal gaits and 88 had normal gaits at enrollment. A total of 70 cases of dementia were subclassified by blinded raters as Alzheimer's disease, and 55 were classified as non-Alzheimer's dementia (47 of them as vascular dementia and 8 as other types of dementia). After the end of this study, all cases were reviewed by raters with full knowledge of subjects' gait and mobility status. There was good agreement between the assessments by blinded observers and those by unblinded observers, with only one additional case of dementia diagnosed and five cases of Alzheimer's disease reclas-

sified as mixed dementias as a result of the unblinded assessment. There were no significant differences in demographic or medical variables according to base-line gait, except for age and a history of stroke, which was more common in subjects with abnormal gait (Table 1).

Neuropsychological Testing

Subjects' performance on the neuropsychological tests is summarized in Table 2. Subjects with neurologic gait abnormalities had a significantly lower mean performance IQ (P=0.001) but not a significantly lower mean verbal IQ (P=0.34).[30] Subjects with abnormal gait also had significantly worse performance on tests of visual–perceptual processing (Raven's Progressive Matrices and the Object-Assembly test),[30,32] motor skills (Purdue Pegboard test),[33] and language skills (Category Fluency test).[34] There were no significant differences in scores on the Blessed Information–Memory–Concentration test[24] or the Zung depression scale.[35] Subjects with abnormal gait had significantly lower scores on the Fuld Object-Memory Evaluation[31] but not on the Blessed Memory Phrase test.[24]

Abnormal Gait

There was no significant difference in the incidence of Alzheimer's disease according to base-line gait status (Table 3). However, subjects with abnormal gaits were more likely to have a non-Alzheimer's dementia, such as vascular dementia.

Subjects with abnormal gaits had an increased risk

TABLE 1. CLINICAL CHARACTERISTICS OF STUDY SUBJECTS ACCORDING TO GAIT STATUS AT BASE LINE.*

VARIABLE	SUBJECTS WITH NORMAL GAIT (N=337)	SUBJECTS WITH ABNORMAL GAIT (N=85)	P VALUE
Age — yr	78.93±3.03	79.97±3.11	0.005
Female sex — no. (%)	219 (65)	52 (61)	0.53
White race — no. (%)	303 (90)	81 (95)	0.28
High-school education — no. (%)	162 (48)	36 (42)	0.50
Remote history of head injury — no. (%)	31 (9)	12 (14)	0.23
Diabetes mellitus — no. (%)	33 (10)	11 (13)	0.43
Ischemic heart disease — no. (%)	86 (26)	23 (27)	0.78
Myocardial infarction — no. (%)	44 (13)	9 (11)	0.71
Cancer — no. (%)	43 (13)	8 (9)	0.43
Hypertension — no. (%)	167 (50)	44 (52)	0.80
Depression — no. (%)	72 (21)	25 (29)	0.15
Chronic lung disease — no. (%)	103 (31)	22 (26)	0.42
Thyroid disease — no. (%)	43 (13)	6 (7)	0.18
Arthritis — no. (%)	219 (65)	63 (74)	0.12
Previous stroke — no. (%)	17 (5)	11 (13)	0.01

*Plus–minus values are means ±SD.

of dementia (hazard ratio, 1.96; 95 percent confidence interval, 1.30 to 2.96) (Table 4), particularly non-Alzheimer's dementia (hazard ratio, 3.51; 95 percent confidence interval, 1.98 to 6.24), but did not have an increased risk of Alzheimer's disease (hazard ratio, 1.07; 95 percent confidence interval, 0.57 to 2.02), after adjustment for potential confounders. The effect of gait on the risk of non-Alzheimer's dementia is, in large part, accounted for by the association between abnormal gait and vascular dementia (hazard ratio, 3.46; 95 percent confidence interval, 1.86 to 6.42).

Adjustment for neuropsychological variables in addition to base-line scores on the Blessed Information–Memory–Concentration test[24] had minimal effects on the association between gait and dementia. For instance, the hazard ratio for the development of dementia was 1.82 (95 percent confidence interval, 1.20 to 2.75) after adjustment for the results on the Fuld Object-Memory Evaluation[31] and 2.03 (95 percent confidence interval, 1.27 to 3.53) after adjustment for base-line performance IQ scores.[30] The cumulative risk of dementia (Fig. 1A) and the cumulative risk of vascular dementia (Fig. 1B), but not the cumulative risk of Alz-heimer's disease (Fig. 1C), were influenced by the base-line gait status.

Types of Abnormal Gait

A total of 31 subjects had unsteady gait at base line, 12 had frontal gait, 11 had hemiparetic gait, 11 had neuropathic gait, 10 had ataxic gait, 8 had parkinso-nian gait, and 2 had spastic gait. Unsteady gait was associated with an increased risk of vascular dementia (hazard ratio, 2.61; 95 percent confidence interval, 1.14 to 5.99), as was frontal gait (hazard ratio, 4.32; 95 percent confidence interval, 1.26 to 14.83) and hemiparetic gait (hazard ratio, 13.13; 95 percent con-fidence interval, 4.81 to 35.81) (Table 4).

Pathology

Autopsies were performed in 48 of the 330 study subjects who died (14.5 percent). Postmortem exam-inations were performed by persons who were unaware of subjects' clinical status, and diagnoses were assigned according to established criteria.[39] The final diagno-sis included 4 cases of Alzheimer's disease, 5 cases of mixed dementia, 11 cases of vascular dementia, 4 cases

TABLE 2. BASE-LINE PERFORMANCE ON NEUROPSYCHOLOGICAL TESTS.*

TEST	SUBJECTS WITH NORMAL GAIT	SUBJECTS WITH ABNORMAL GAIT	P VALUE	ABNORMAL SCORES†
	score			
Blessed Information–Memory–Concentration test	2.4±2.1	2.7±2.1	0.16	>8
Verbal IQ	110.3±15.2	108.0±16.6	0.34	<80
Performance IQ	105.3±12.8	99.5±15.0	0.001	<80
Zung depression scale	46.6±10.4	48.4±9.7	0.19	>50
Digit Span test	9.7±2.0	9.6±1.8	0.66	<4
Blessed memory phrase test	1.3±1.3	1.2±1.2	0.2	>3
Fuld Object-Memory Evaluation	7.4±1.3	6.8±1.4	0.002	<5
Digit–Symbol Substitution test	30.5±12.0	25.5±14.4	0.008	<7
Object-Assembly test	17.4±7.4	15.1±5.8	0.002	<7
Purdue Pegboard test	12.3±2.0	10.9±2.2	0.003	<9
Raven's Progressive Matrices, Set A	8.6±1.9	7.9±1.9	0.004	<10
Category Fluency Test	49.6±11.1	44.3±12.3	0.001	<29

*Plus–minus values are means ±SD. Not all tests were administered to all subjects at base line: the total number of subjects with normal gait tested ranges from 271 to 337; the total number of subjects with abnormal gait tested ranges from 76 to 85. Scores on the Blessed Information–Memory–Concentration test range from 0 to 32, with higher scores indicating worse general cognitive status. Normal IQs range from 85 to 115. Scores on the Zung depression scale range from 0 to 100, with higher scores indicating greater depression. Scores on the Digit Span test range from 0 to 17, with higher scores indicating better attention. Scores on the Blessed memory phrase subtest range from 0 to 5, with higher scores indicating worse memory. Scores on the Fuld Object-Memory Evaluation range from 0 to 10, with higher scores indi-cating better memory. Scores on the Digit–Symbol Substitution test range from 0 to 90, with higher scores indicating better executive function. Scores on the Object-Assembly test range from 0 to 44, with higher scores indicating better vis-ual–perceptual processing. Scores on the Purdue Pegboard test range from 0 to 25, with higher scores indicating better motor skills; for each subject, we used the mean score for three one-minute trials. Scores on the Raven's Progressive Matrices, Set A, range from 0 to 12, with higher scores indicating better visual–perceptual processing. Normal scores on the Category Fluency Test range from 26 to 46, with higher scores indicating better language skills.

†The cutoffs for abnormal scores for the Blessed Information–Memory–Concentration test, the Digit Span test, the Blessed memory phrase subtest, the Fuld Object-Memory Evaluation, the Purdue Pegboard test, and the Category Fluency Test were derived from the base-line evaluations in our study.

TABLE 3. INCIDENCE OF DEMENTIA AMONG 337 SUBJECTS WITH NORMAL GAIT
AND 85 SUBJECTS WITH ABNORMAL GAIT AT BASE LINE.

CLINICAL DIAGNOSIS	NO. OF SUBJECTS WITH DIAGNOSIS		INCIDENCE PER 100 PERSON-YEARS OF FOLLOW-UP		UNADJUSTED RELATIVE RISK (95% CI)*
	NORMAL GAIT	ABNORMAL GAIT	NORMAL GAIT	ABNORMAL GAIT	
Any dementia	88	37	4.07	8.28	2.03 (1.39–2.99)
Alzheimer's disease	57	13	2.64	2.91	1.10 (0.60–2.01)
Non-Alzheimer's dementia	31	24	1.43	5.30	3.75 (2.20–6.38)
Vascular	26	21	1.20	4.70	3.91 (2.20–6.94)
Other	5	3	0.23	0.67	2.90 (0.69–12.14)

*CI denotes confidence interval.

TABLE 4. HAZARD RATIOS FOR ANY DEMENTIA, NON-ALZHEIMER'S DEMENTIA,
AND VASCULAR DEMENTIA, ACCORDING TO TYPE OF ABNORMAL GAIT AT BASE LINE.*

TYPE OF GAIT	NO. OF SUBJECTS	ANY DEMENTIA (N=125)	NON-ALZHEIMER'S DEMENTIA (N=55)	VASCULAR DEMENTIA (N=47)
Any abnormal	85	1.96 (1.30–2.96)	3.51 (1.98–6.24)	3.46 (1.86–6.42)
Unsteady	31	1.68 (0.94–3.01)	2.43 (1.13–5.23)	2.61 (1.14–5.99)
Frontal	12	2.36 (0.85–6.59)	3.45 (1.03–11.55)	4.32 (1.26–14.83)
Hemiparetic	11	5.53 (2.49–12.27)	11.66 (4.45–30.54)	13.13 (4.81–35.81)
Neuropathic	11	0.93 (0.29–3.05)	0.66 (0.90–5.01)	0.79 (0.10–6.02)
Ataxic	10	0.93 (0.32–2.66)	0.62 (0.08–4.84)	0.57 (0.07–4.51)
Parkinsonian	8	1.02 (0.32–3.31)	1.36 (0.31–5.99)	0.75 (0.10–5.72)

*Hazard ratios were derived by Cox proportional-hazards regression analysis, with adjustment for demographic variables (age, educational level, and sex), medical conditions (stroke, cardiac disease, hypertension, diabetes, and head injury), and base-line cognitive status (as assessed by the Blessed Information–Memory–Concentration test). Hazard ratios for spastic gait (in two subjects) could not be calculated because the number of observations was insufficient.

of dementia with Lewy bodies, and 2 cases of argyrophilic grain disease.[40] The remaining 22 subjects in whom autopsies were performed did not have dementia. Vascular dementia was more common in subjects with abnormal gait than in those with normal gait, affecting 45 percent of subjects with abnormal gait in whom dementia was confirmed at autopsy. Antemortem diagnosis of vascular dementia had a sensitivity of 70 percent and a specificity of 100 percent. The frequencies of lacunes, stroke, hippocampal sclerosis, and leukoencephalopathy did not differ significantly according to gait status, although microinfarctions were somewhat more common among subjects with abnormal gait (31 percent vs. 9 percent, P=0.07).

DISCUSSION

In this cohort of elderly persons residing in the community who did not have dementia at base line, subjects with neurologic gait abnormalities were at increased risk for the development of dementia. The presence of neurologic gait abnormalities strongly predicted non-Alzheimer's dementia, especially vascular dementia, but not Alzheimer's disease. The association between gait status and the risk of non-Alzheimer's dementia remained strong even after adjustment for demographic, medical, and base-line cognitive variables. Our findings are supported by a previous study, which found that elderly persons with a combination of cognitive, vascular, and extrapyramidal features including abnormal gait were at increased risk of progression to dementia over a three-year period.[41]

Specific subtypes of abnormal gaits were associated with an increased risk of dementia. Videos showing representative examples of six of these gait abnormalities appear in Supplementary Appendix 1. Elderly persons are at high risk for dementia after stroke, especially if they already have a degenerative disease.[14,42] It is not surprising that subjects with hemiparetic gait had

A Any Dementia

B Vascular Dementia

C Alzheimer's Disease
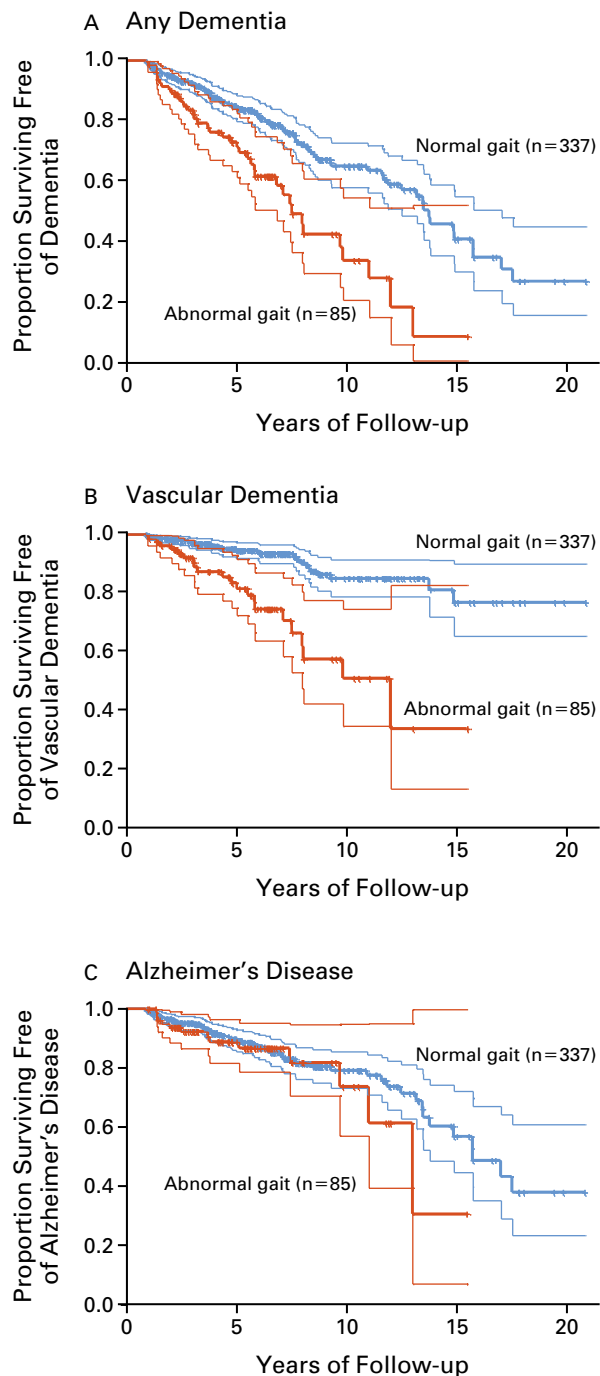
Figure 1. Kaplan-Meier Curves for the Cumulative Risk of Any Dementia (Panel A), Vascular Dementia (Panel B), and Alzheimer's Disease (Panel C) According to Gait Status at Enrollment. Dotted lines represent 95 percent confidence intervals.

the highest risk of vascular dementia. Frontal gait in the elderly may result from cerebrovascular disease.[27] On the other hand, the predictive role of unsteady gait in the elderly is intriguing. Unsteady gait may have many causes, resulting from both age-related and disease-related changes at various neuroanatomical sites. Unsteady gait may be a marker of cerebrovascular lesions, accounting for the association with dementia. However, further study in this area is required.

An unexpected finding of our study was that the presence of abnormal gaits predicted the risk of non-Alzheimer's dementia well into the future. Although an abrupt onset of dementia might be expected after stroke, our findings suggest a long prodrome, in which incremental lesions or interactions between vascular risk factors may set in motion processes that lead to dementia. These brain processes may produce abnormal gait early in their course and only much later manifest as dementia.[43,44] Elderly men with *APOE* ε4 genotype and white-matter lesions visible on neuroimaging have been reported to be at high risk for immobility and dementia, because of impaired brain-repair mechanisms or an increased susceptibility to brain injury in persons with this genotype.[45]

We found a distinct neuropsychological profile involving impairment in performance IQ but sparing verbal IQ in subjects with abnormal gaits, suggesting possible functional and anatomical correlates. Persons with vascular dementia may have better verbal memory than those with Alzheimer's disease but greater impairment of executive functioning.[46] Other non-Alzheimer's dementias, such as dementia with Lewy bodies,[20] are also associated with distinct profiles that may provide clues to their natural history.

Our study has several limitations. First, the subjects were volunteers who resided in the community; white persons and subjects older than 75 years of age who might have a greater burden of chronic disease were overrepresented, potentially limiting the generalizability of our results. Second, assignment of subtypes of dementia is fallible. Although the diagnoses were made according to standardized criteria by a well-established procedure, some misclassification is inevitable. We used blinded assessments to avoid circularity in diagnosis, but reanalysis using diagnoses determined by unblinded observers did not alter the association of gait with dementia. Third, abnormal gait would not be predictive of Alzheimer's disease even if cases of mixed dementia were analyzed together with cases of Alzheimer's disease (hazard ratio, 1.61 [95 percent confidence interval, 0.94 to 2.78]), suggesting that gait influences risk of vascular dementia and not Alzheimer's disease in the mixed cases. Fourth, although experienced clinicians assessed gait, quantitative analysis of gait might be more reliable. Fifth, attrition is a major issue of concern in any longitudinal study, but we had

relatively complete follow-up over a long observational period, reducing potential selection bias.

Clinical and pathological definitions of vascular dementia are controversial.[47,48] Current clinical criteria are criticized for being either too sensitive or too specific.[47,48] Dementia can follow cortical strokes, lacunar infarctions, or diffuse ischemic lesions.[14,18,19] Thus, there are several subtypes of vascular dementia, which vary in their causes, pathogenesis, and clinical phenotypes. There is substantial overlap in pathology between vascular dementia and Alzheimer's disease on autopsy,[49] and vascular mechanisms are implicated in the pathogenesis of both Alzheimer's and vascular dementias.[13] Among subjects with dementia in our autopsy series the prevalence of vascular pathology increased with age.[50]

Our study provides a clinical profile for elderly persons at high risk for non-Alzheimer's dementia, particularly vascular dementia. The high-risk group defined at base line accounts for almost a third of subjects in whom vascular dementia eventually developed and identifies such subjects with a specificity of 84 percent. If replicated, these findings would provide a strategy for identifying a group at very high risk for vascular dementia and would facilitate the introduction of preventive interventions designed to reduce the incidence of non-Alzheimer's dementia, especially vascular dementia.

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