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Motoric Cognitive Risk Syndrome and the Risk of Dementia

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Background. Despite growing evidence of links between gait and cognition in aging, cognitive risk assessments that incorporate motoric signs have not been examined. We sought to validate a new Motoric Cognitive Risk (MCR) syndrome to identify individuals at high risk of developing dementia.

Methods. We evaluated 997 community residing individuals aged 70 and older participating in the Einstein Aging Study over a median follow-up time of 36.9 months. MCR syndrome was defined as presence of cognitive complaints and slow gait (one standard deviation below age- and sex-specific gait speed means) in nondemented individuals. Cox models were used to evaluate the effect of MCR syndrome on the risk of developing dementia and subtypes.

Results. Fifty-two participants met criteria for MCR syndrome at baseline with a prevalence of 7% (95% CI: 5–9%). Prevalence of MCR increased with age. Participants with MCR were at higher risk of developing dementia (hazard ratio [HR] adjusted for age, sex, and education: 3.27, 95% CI: 1.55–6.90) and vascular dementia (adjusted HR: 12.81, 95% CI: 4.98–32.97). The association of MCR with risk of dementia or vascular dementia remained significant even after accounting for other confounders and diagnostic overlap with "cognitive" mild cognitive impairment syndrome subtypes.

Conclusions. A motor-based MCR syndrome provides a clinical approach to identify individuals at high risk for dementia, especially vascular dementia, to target for further investigations and who may benefit from preventive interventions.

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STRONG links have been described between cognition, gait, and vascular disease in aging (1–3). Slow gait has been reported to predict ischemic strokes in older women (4). Clinical gait abnormalities as well as slow gait also predicts risk of dementia even after accounting for confounders such as age, sex, education, medical illness, or cognitive status (3,5). Older adults with mild cognitive impairment (MCI) syndrome walk slower than healthy controls (6). Gait speed was reported to slow a decade before diagnosis of MCI and preceded declines in tests of cognitive function (7). These observations suggest that gait slowing may be an early clinical marker of dementia and provide a novel strategy to identify high-risk individuals independent of cognitive test performance.

We proposed to validate a Motoric Cognitive Risk (MCR) syndrome in nondemented older individuals with cognitive complaints but without significant functional impairment building on current operational definitions for MCI (8,9). MCI does not account for all individuals converting to dementia (8). Individuals diagnosed with MCI may remain clinically stable or even revert to normal (9). Hence, further research and alternate strategies are required to expand detection of individuals at high risk for dementia. Establishing this new high-risk MCR syndrome might not only provide a clinical approach to identify a larger pool of high-risk individuals to target preventive interventions but also spur research to discover new pathways leading to dementia.

Methods

Study Population

We undertook a prospective cohort study based in the Einstein Aging Study (EAS [10]). The goal of the EAS is to identify risk factors for dementia. Study design has been reported (5,10). In brief, potential participants (aged 70 and older) identified from Bronx County population lists were contacted by letter explaining the purpose and nature of the study and then by telephone. Participants who gave verbal consent on the telephone were invited for evaluations at our research center. Exclusion criteria included

severe audiovisual loss, bed bound, and institutionalization. Additional exclusion criteria for this study included presence of dementia at baseline (5). Comprehensive in-person assessments were completed at baseline and annual visits.

Written informed consents were obtained prior to enrollment from all participants and study evaluations followed protocols approved by the Committee on Clinical Investigations of the Albert Einstein College of Medicine.

Gait Speed

Gait speed (cm/s) during normal pace walking was measured by research assistants using a computerized walkway with embedded pressure sensors (GAITRite, CIR systems [11]). The GAITRite system is widely used in clinical and research settings and has excellent validity and reliability (5). Participants were asked to walk on the walkway at their usual pace in a quiet well-lit room wearing comfortable footwear and without any attached monitors. Reliability for gait speed on two consecutive trials in our cohort was excellent (r = .96 [12,13]). Participants walked for two trials at their normal pace on a walkway with 15 feet (457.2 cm) recording surface till July 2008. Following which, assessments were done for one trial on a walkway with 20 feet (609.6 cm) recording surface. Correlation for gait speed measured on the two walkways in 20 participants was excellent (r = .94 [13]).

Additional Assessments

Presence of depression, diabetes, heart failure, hypertension, angina, myocardial infarction, strokes, Parkinson's disease, chronic lung disease, and arthritis was used to calculate a summary illness index (5). A neuropsychological test battery validated in our and other aging populations was administered at all visits to all participants (14). We examined performance on the following tests: general cognition—Blessed-Information-Memory-Concentration test (15), memory—Free and cued selective reminding test, executive function—Digit symbol substitution, attention—Digit span, visuospatial ability—Trail making test version B, language—Category fluency test, and mood—15-item Geriatric Depression Scale (GDS). Study clinicians did neurological examinations (10) and completed the Clinical Dementia Rating (CDR) scale (16).

Motoric Cognitive Risk

MCR was diagnosed if participants met all four criteria below, operationalized using information obtained at baseline evaluations. We built on current MCI operational definitions (8,9), substituting the cognitive impairment criterion with slow gait:

1. Cognitive complaints were assessed with the 15-item Consortium to Establish a Registry for Alzheimer's Disease (CERAD) questionnaire, a yes/no rating scale of current functioning in several cognitive domains (17,18). Study clinicians' observations during clinical interviews were also used to determine presence of cognitive complaints or concern regarding change in cognition (17). As many EAS participants lived alone (17), informant reports were not used. In 33 MCR cases with an informant, cognitive complaints were confirmed in 58%.
2. Slow gait defined as gait speed one standard deviation (*SD*) or more below age- and sex-appropriate mean values established in the same cohort (see Table 1 [11]).
3. Preserved activities of daily living assessed by a scale developed for assessing function in community-residing older adults (19) as well as study clinicians' interviews.
4. Absence of dementia (see later).

We have reported using a similar procedure for diagnosing MCI subtypes (6,9). Nondemented participants with cognitive complaints but without functional limitations were classified as amnestic MCI if the memory domain was impaired (1.5 *SD* below age-adjusted mean on free recall scores) or nonamnestic MCI if there was impairment on nonmemory domains (1.5 *SD* below age-adjusted means).

All available clinical (except gait speed) and neuropsychological data for all participants were reviewed at consensus case conferences attended by study neurologists and neuropsychologist (3,5). Research assistants who measured gait speed did not participate in the conferences. Dementia diagnosis was assigned using the *Diagnostic and Statistical Manual of Mental Disorders*, *Fourth Edition* criteria (20) and was subtyped using standard criteria for Alzheimer's disease (AD [21]) as well as probable, possible, or mixed vascular dementia (VaD [22]). The *State of California Alzheimer's Disease Diagnostic and Treatment Centers* criteria used in EAS for probable VaD require presence of dementia with evidence of two or more ischemic strokes (on history, neurological examination, or imaging) or occurrence of a single stroke with a clearly documented temporal relationship to the onset of dementia. For a stroke to be considered temporally related to dementia, it had to precede onset of dementia by no more than 3 months or cause abrupt worsening of cognitive function in patients with prior cognitive deficits. We reviewed study evaluations to document focal neurologic signs

Table 1. Gait Speed Cutscores for Defining Slow Gait for the Motoric Cognitive Risk (MCR) syndrome*

Age group (y)	Men	Women
70–74	80.7	77.8
75–79	79.1	71.4
80–84	74.1	66.2
85 or older	65.9	57.5

Note: *Gait speed (cm/s) values at or below the cutscores (one standard deviation [SD] below age and sex means) previously established in the study cohort (11) were used to define slow gait.

such as hemiparesis. Alzheimer's Disease Diagnostic and Treatment Centers' criteria require evidence of infarction on neuroimaging study for a diagnosis of probable (but not possible) VaD (22,23). Although actual scans were not available, neuroimaging study reports (available in 76% of cases) were reviewed. Mixed dementia is diagnosed when there was a clear relationship between cognitive symptoms and cerebrovascular disease, but clinical course or cognitive testing indicated possible AD (22,23). We have good clinicopathological agreement between clinical diagnoses of dementia and VaD in our cohort (3,24–26).

Data Analysis

Two-sample *t* test or Wilcoxon's rank–sum test for continuous variables and χ^2 tests or Fisher's exact test for categorical variables were used to test differences in MCR status. Crude outcome rates were calculated per 1000 person-years. Cox proportional hazard models were used to assess hazard ratios (HRs) for the association of MCR with dementia and VaD adjusting for age, sex, and education as well as in fuller models that also adjusted for medical illness index (5) and Blessed test score (15). Time to event was from enrollment to interview at which dementia was diagnosed or to final study contact. Proportional hazards assumption was tested using methods based on scaled Schoenfeld residuals. To account for diagnostic misclassification, we repeated the analysis in the primary model excluding participants who developed dementia in the first 2 years of follow-up. All analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC).

We conducted sensitivity analyses to account for diagnostic overlap of MCR with "cognitive" MCI subtypes. First, we excluded participants who also met criteria for either amnestic MCI or nonamnestic MCI from the MCR group. Second, we examined mutually exclusive high-risk groups adapting current hierarchical MCI criteria (9). In this analysis, the priority was to assign a diagnosis of amnestic MCI first, followed by nonamnestic MCI, and lastly MCR. "Pure" MCR, hence, has no overlap with other "cognitive MCI" subtypes. Finally, we conducted analysis to establish the independent effects of amnestic MCI, nonamnestic-MCI, and MCR to predict dementia and subtypes by jointly modeling all three groups together.

Results

Study Population

This study began on February 2002 when quantitative gait evaluations were introduced in the EAS and follow-up ended April 2011. Of the 997 EAS participants enrolled during this period, 41 with dementia at baseline, 187 without follow-up, and 2 with missing data were excluded. Main reasons for exclusion from the longitudinal analysis were new enrollees awaiting follow-up and death. The remaining 767 participants were eligible. Eligible and excluded participants were similar in terms of age, sex, education, and Blessed scores (15).

Motoric Cognitive Risk

Fifty-two participants met MCR criteria at baseline (average age 79.9 years). There were 21 men (40%) and 31 women (60%) with MCR. Table 1 compares baseline characteristics by MCR status. There were no group differences on age, gender, and education. MCR participants had higher proportion of black ethnicity, CDR scores of greater than or equal to 0.5, and gait abnormalities (10). They also had higher illness index as well as higher prevalence of hypertension, diabetes, and arthritis. Gait speed, cognitive test scores, and depressive symptoms were worse in MCR.

The overall prevalence of MCR was 7%. Table 2 presents MCR prevalence rates by age, sex, and education. During 2704 person-years follow-up (median: 36.9 months, range: 8.2–109.7 months), 70 participants developed dementia (41 AD [21], 21 VaD [22], and 8 other). Eight (15%) MCR and 62 (9%) non-MCR participants developed dementia. Subtypes in eight MCR participants who converted to dementia were AD ($n = 1$) and VaD ($n = 7$). Incidence rate of dementia was 66 per 1000 person-years in MCR and 24 per 1000 person-years in non-MCR participants.

Table 3 shows that participants with MCR had increased risk of dementia (HR: 3.27, 95% CI: 1.55–6.90). MCR did not predict AD (HR: 0.66, 95% CI: 0.09–4.84) but strongly predicted VaD (HR: 12.81, 95% CI: 4.98–32.97). MCR syndrome provides incremental validity over its individual components. For instance, slow gait (irrespective of cognitive complaints) did not predict dementia (HR: 1.7, 95% CI: 0.8–3.2) but did predict VaD with a smaller magnitude than MCR (HR: 4.5, 95%: CI 1.8–11.4) in our cohort. After excluding 13 mixed dementia cases, MCR still predicted "possible or probable" VaD (HR: 31.20, 95% CI: 7.03–138.54, $p < .001$).

After excluding 31 participants who developed dementia (11 VaD) in the first 2 years, MCR syndrome still predicted risk of VaD (HR: 14.54, 95% CI: 3.66–57.72) but not dementia (HR: 3.14, 95% CI: 0.96–10.29), though the direction of the association was similar.

Previous MCI studies have used different cutscores to define the objective cognitive impairment criterion (27). Using a 1.5 *SD* cut to define slow gait lowers the prevalence of MCR from 7% to 3% in our cohort. This alternate MCR definition was not significantly associated with risk of dementia (HR adjusted for age, sex, and education: 2.97, 95% CI: 0.93–9.53, $p = .07$) but predicted VaD (HR adjusted for age, sex, and education: 10.48, 95% CI: 2.99–36.81, $p < .001$).

Survival plots show disease-free probabilities for any dementia (Figure 1A) and VaD (Figure 1B) based on MCR status.

Table 2. Baseline Characteristics by Presence or Absence of Motoric Cognitive Risk (MCR) syndrome status

Variables	MCR (n = 52)	Not MCR (N = 715)	p value
Age	79.9 ± 5.9	79.7 ± 5.4	.711
Sex (women), %	60	61	.846
Education years	13.7 ± 3.6	14.0 ± 3.4	.399
Mean follow-up, months	27.9 ± 20.5	43.4 ± 27.4	<.001
Cognitive complaints, %	100	39	<.001
Slow gait, %	100	9	<.001
Race, %			
White	56	71	.025
Black	44	25	.002
Medical illness index (range 0–10)	1.9 ± 1.2	1.2 ± 1.0	<.001
Strokes, %	15	9	.135
Coronary artery disease, %	15	9	.128
Previous myocardial infarction, %	8	5	.352
Congestive heart failure, %	4	2	.296
Hypertension, %	75	60	.035
Diabetes, %	31	14	.001
Depression, %	15	11	.341
Parkinson's disease, %	2	1	.297
Chronic obstructive pulmonary disease, %	10	5	.182
Arthritis, %	13	4	.012
Clinical gait abnormality, %	85	34	<.001
Neurological gait abnormality, %	31	9	<.001
Non-neurological gait abnormality, %	29	12	<.001
CDR score ≥0.5, %	60	26	<.001
Gait speed, cm/s	59.5 ± 13.1	96.9 ± 21.8	<.001
Blessed test score (range 0–32)	3.3 ± 2.3	2.1 ± 2.2	.001
Free recall (range 0–48)	28.7 ± 6.5	31.3 ± 6.0	.002
Digit symbol substitution test	33.7 ± 14.4	42.8 ± 13.9	<.001
Digit span total	12.9 ± 2.9	14.1 ± 3.5	.017
Category fluency test	31.3 ± 8.1	37.5 ± 8.9	<.001
Letter fluency test	28.5 ± 10.7	36.4 ± 12.6	<.001
Trail making test B	169.6 ± 69.3	128.7 ± 56.5	<.001
Geriatric depression scale (range 0–15)	3.5 ± 2.7	2.1 ± 2.2	<.001

Note: CDR = Clinical Dementia Rating scale.
Values are means ± *SD* unless otherwise noted.

Table 3. Prevalence of Motoric Cognitive Risk (MCR) Syndrome in Overall Cohort As Well As by Age, Sex, and Education

	MCR (N)	Not MCR (N)	Prevalence % (95% CI)	p value
Overall	52	715	6.8 (5.0–8.6)	
Age				
70–79	24	401	5.7 (3.5–7.8)	.164
80 and older	28	314	8.2 (5.3–11.1)	
Sex				
Men	21	279	7.0 (4.1–9.9)	.846
Women	31	436	6.6 (4.4–8.9)	
Education				
Less than high school	26	288	8.3 (5.2–11.3)	.169
High school or higher	26	427	5.7 (3.6–7.9)	

Motoric Cognitive Risk and Mild Cognitive Impairment

In sensitivity analysis, excluding 18 MCR cases who also met nonamnestic MCI criteria, association of the remaining MCR cases with dementia (HR: 4.33, 95% CI: 1.96–9.58, p < .001) and VaD (HR: 15.80, 95% CI: 5.83–42.82, p < .0001) was significant. After excluding 10 overlapping amnestic MCI cases from MCR, the association with dementia became nonsignificant (HR: 1.47, 95% CI: 0.46–4.70, p = .518), but the association with VaD remained (HR: 6.88, 95% CI: 1.92–24.69, p = .003).

There were 69 amnestic and 79 nonamnestic MCI cases. Using a mutually exclusive hierarchical definition, all three groups predicted dementia and VaD (Table 4). HR for 24 "pure MCR' cases (no overlap with MCI) with risk of VaD was 11.47 (95% CI: 2.33–56.35).

When all three subtypes were jointly modeled to establish their independent effects (Table 5), the association of the 52 "any MCR" cases with VaD was significant (HR: 8.88). Amnestic MCI (p < .001) but not nonamnestic MCI (p = .138) predicted VaD.

Discussion

This study proposed a new MCI subtype, MCR, in nondemented older adults. Our observations confirm that MCR is a high-risk clinical syndrome with strong

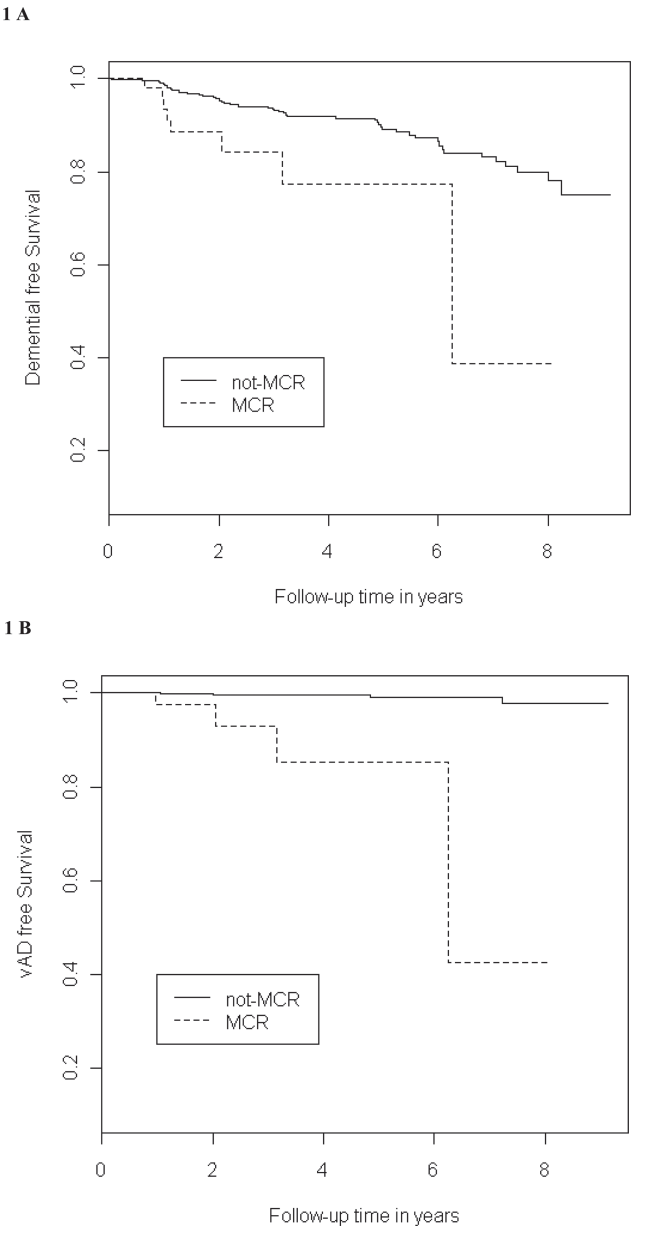

Figure 1. Survival plots show the cumulative risk of developing any dementia (**A**) and vascular dementia (VaD) (**B**) based on baseline motoric cognitive risk (MCR) syndrome status.

predictive validity for dementia, especially VaD. Older individuals who met MCR criteria had an over threefold risk of developing dementia and an over 12-fold risk of VaD. The association of MCR with dementia and VaD remained robust after adjustments for potential confounders including demographic factors, illness burden, and cognitive status as well as accounting for diagnostic misclassification by excluding incident dementia cases in the first 2 years of follow-up. These findings are in line with our previous observations; neurological gait abnormalities predicted non-Alzheimer's dementia in the Bronx Aging Study (3) and slow gait predicted cognitive decline in the EAS (5). The 7% prevalence of MCR syndrome is comparable to that reported for MCI subtypes in community samples (9).

Although our choice of slow gait was based on extensive research supporting its role as an early clinical marker (2,3,5,28), we do not discount the possibility that other motoric signs might improve predictive validity of MCR syndrome for dementia. Our intention is to provide a conceptual framework (as for MCI) whose operational definitions can be refined if better motoric markers are described. However, it should be noted that the MCR syndrome based on slow gait predicted dementia with an adjusted HR of 3.3 and the secondary outcome of VaD with a HR of 12.8. In contrast, we reported that clinical gait abnormalities such as frontal gait (HR 4.3) but not parkinsonian gait predicted VaD in the Bronx Aging Study (3). Any one of frontal, parkinsonian, or unsteady gaits predicted VaD with a lower HR of 2.7 in the same cohort (2). Clinical gait assessments are dependent on examiner's expertise and there is no one universally accepted classification, which is a major limitation for developing MCR criteria based on clinical gait abnormalities. In the Sydney Older Persons Study, clinical extrapyramidal signs alone did not predict dementia (29). Other neurological signs such as tone or strength were not predictive of dementia in our cohort. MCR syndrome provides incremental validity over its individual components. None of the participants with slow gait but no cognitive complaints at baseline developed VaD further supporting the utility of the MCR definition. Future studies should examine MCR in other populations and test other motoric signs.

MCR is conceptualized as a high-risk transitional state for dementia akin to MCI and can complement current MCI definitions. The MCR criteria differ from MCI criteria only in the substitution of the cognitive impairment criterion by a motoric criterion (8,9). MCR provides incremental validity for predicting dementia over MCI subtypes. Given the association with VaD, the main comparison of MCR may be with nonamnestic MCI. Of the 52 MCR cases, 35% met criteria for nonamnestic MCI and 19% had amnestic MCI. The association of MCR with VaD was significant after

Table 4. Risk of Dementia and Vascular Dementia Associated With Motoric Cognitive Risk (MCR) syndrome

	MCR (n = 52)	Non-MCR participants (n = 715)	Model 1*	Model 2**
	N	N	HR (95% CI), p value	HR (95% CI), p value
Dementia	8	62	3.27 (1.55–6.90), .002	2.72 (1.24–5.97), .013
Vascular dementia	7	14	12.81 (4.98–32.97), <.001	11.10 (4.00–30.82), <.001

*Cox model 1 is adjusted for age, sex, and education.
**Cox model 2 is for covariates in model 1 as well as illness index and Blessed test scores.

Table 5. Risk of Dementia and Vascular Dementia associated With Motoric Cognitive Risk (MCR) Syndrome and Mild Cognitive Impairment (MCI) Subtypes

MCI subtypes	Dementia HR (95% CI), *p* value	Vascular dementia HR (95% CI), *p* value
Model A: Hierarchical diagnosis		
Pure amnestic MCI	11.74 (6.64–20.75), <.001	10.60 (3.51–31.98), <.001
Pure nonamnestic MCI	2.84 (1.43–5.67), .003	4.85 (1.48–15.92), .009
Pure MCR	2.91 (0.69–12.28), .146	11.47 (2.33–56.34), .003
Model B: Joint modeling		
Any amnestic MCI	10.53 (5.97–18.57), <.001	6.13 (2.11–17.79), <.001
Any nonamnestic MCI	2.47 (1.23–4.94), .011	2.40 (0.75–7.61), .138
Any MCR	2.04 (0.95–4.41), .069	8.88 (3.26–24.20),<.001

Note: Hazard ratios (HR) with 95% confidence interval (CI) derived from Cox models adjusted for age, sex, and education. MCI subtypes are mutually exclusive in Model A and examined jointly in Model B (see Methods).

excluding participants who also met criteria for "cognitive" MCI subtypes. "Pure" MCR predicted VaD using a stringent hierarchical definition where diagnoses of amnestic or nonamnestic MCI were assigned before MCR. MCR was also an independent predictor of VaD when jointly modeled with MCI subtypes.

Walking requires a complex interplay of sensory, cognitive, and motor functions, and these systems may be impacted early in dementias (5,30). Slow gait results from neurological and nonneurological diseases (10). The predictive validity of MCR for dementia and VaD supports the use of a gait-based phenotype (irrespective of etiology) to identify high-risk individuals (5,28). White matter lesions and subcortical infarcts are associated with slow gait in aging (1). Although it is tempting to ascribe the predictive validity of MCR for dementia solely to vascular pathology, given the occurrence of slow gait early in other neurodegenerative diseases such as parkinsonian syndromes (29), we acknowledge that MCR may also predict other non-Alzheimer's dementias.

Strengths of the study include the relatively large and well-characterized cohort with longitudinal assessments, standardized study measures and outcome ascertainments, and assignment of dementia diagnoses blinded to gait speed. We used instrumented methods to measure gait as part of our study protocol (5). However, gait speed can be measured over a fixed distance using a stopwatch. The distances could be standardized or corrections applied for gait speed measured over different distances (31).

The lack of single diagnostic criteria for VaD is a limitation. Multiple criteria are in use leading to variable rates of VaD (32). Although it is reassuring that MCR predicted VaD even after excluding mixed dementia cases, our findings need to be verified using other VaD criteria as well as by conducting clinicopathological studies. The MCR syndrome did not predict AD, which most likely reflects lack of power. MCR may have low utility as an AD risk prognosticator since large number of participants would have to be screened. Although differences in prevalence of racial groups were noted between MCR and non-MCR participants, we lacked power to examine race interactions in our models. Gait speed cutscores (such as 70 cm/s) are used to predict adverse outcomes (33). However, these cutscores are not usually derived from population norms (33) and bias against oldest age groups with lower mean gait speed (11). Using a more stringent 1.5 *SD* cutscore to define slow gait in MCR lowers prevalence without improving predictive validity in our cohort. The need for instrumented methods will limit the use of gait variables other than speed to diagnose MCR in clinical settings (5). Although more detailed studies such as vascular testing or neuroimaging will reveal underlying disease processes, time and resource constraints will not permit screening all patients using these tests to define MCR or MCI in clinical settings. However, the MCR syndrome can help streamline patients for more elaborate testing.

This study provides preliminary support for a motor-based MCR syndrome that identifies older individuals at high risk for transitioning to dementia, especially VaD. To our knowledge, a high-risk gait-based phenotype for dementia that builds and complements the MCI concept has not been previously validated and could complement current MCI definitions. If the MCR syndrome is validated by other studies, clinicians and researchers could apply this approach to improve diagnostic approaches, plan investigations and management, and recruit participants for clinical trials.

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