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Motoric Cognitive Risk Syndrome: Multicountry Prevalence and Dementia Risk

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Motoric cognitive risk syndrome

Multicountry prevalence and dementia risk

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Supplemental data at Neurology.org

ABSTRACT

Objectives: Our objective is to report prevalence of motoric cognitive risk syndrome (MCR), a newly described predementia syndrome characterized by slow gait and cognitive complaints, in multiple countries, and its association with dementia risk.

Methods: Pooled MCR prevalence analysis of individual data from 26,802 adults without dementia and disability aged 60 years and older from 22 cohorts from 17 countries. We also examined risk of incident cognitive impairment (Mini-Mental State Examination decline ≥4 points) and dementia associated with MCR in 4,812 individuals without dementia with baseline Mini-Mental State Examination scores ≥25 from 4 prospective cohort studies using Cox models adjusted for potential confounders.

Results: At baseline, 2,808 of the 26,802 participants met MCR criteria. Pooled MCR prevalence was 9.7% (95% confidence interval [CI] 8.2%–11.2%). MCR prevalence was higher with older age but there were no sex differences. MCR predicted risk of developing incident cognitive impairment in the pooled sample (adjusted hazard ratio [aHR] 2.0, 95% CI 1.7–2.4); aHRs were 1.5 to 2.7 in the individual cohorts. MCR also predicted dementia in the pooled sample (aHR 1.9, 95% CI 1.5–2.3). The results persisted even after excluding participants with possible cognitive impairment, accounting for early dementia, and diagnostic overlap with other predementia syndromes.

Conclusion: MCR is common in older adults, and is a strong and early risk factor for cognitive decline. This clinical approach can be easily applied to identify high-risk seniors in a wide variety of settings. ***Neurology*® 2014;83:718–726**

GLOSSARY

aHR = adjusted hazard ratio; **CI** = confidence interval; **H-EPESE** = Hispanic Established Populations for Epidemiologic Studies of the Elderly; **HR** = hazard ratio; **InCHIANTI** = Invecchiare in Chianti; **MAP** = Memory and Aging Project; **MCI** = mild cognitive impairment; **MCR** = motoric cognitive risk syndrome; **MMSE** = Mini-Mental State Examination; **ROS** = Religious Orders Study.

Predementia syndromes based on cognitive tests, biomarkers, or neuroimaging have been proposed to identify dementia risk in older adults,[1,2] but have limitations in many settings. For instance, an estimated two-thirds of persons with dementia live in low- and middle-income countries where there is often no access to complex neuropsychological testing or neuroimaging.[2,3] Hence, there is a need to optimize and increase accessibility of clinical dementia risk assessments in order to institute preventive measures and curtail health care costs.

There is increasing evidence that gait slowing occurs early in dementia and may precede declines in cognitive tests.[4–6] Hence, incorporating gait into dementia risk assessments is a novel approach that can be used even in resource poor settings.[7] The motoric cognitive risk syndrome (MCR), a recently described predementia syndrome characterized by cognitive complaints and slow gait, avoids the need for complex cognitive tests or other burdensome investigations.[7,8]

Our goal is to report prevalence of MCR in 26,802 older adults from 17 countries. We predicted that participants with MCR would have higher disease burden and worse cognitive status than non-MCR participants.[8] Older adults with MCR in our validation study[8] were at increased risk of dementia even after accounting for potential confounders and diagnostic overlap with

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mild cognitive impairment (MCI) syndrome. To further explore this finding, we studied the association of MCR with risk of cognitive decline in 4,812 cognitively normal individuals without dementia and with Mini-Mental State Examination (MMSE) scores ≥25 from 4 well-established cohorts.

METHODS The MCR consortium includes data from 22 cohorts from 17 countries: 7 North American,[9–15] 6 European,[16–19] 5 Asian,[15,20–22] 2 African,[15] 1 Israel,[23] and 1 Australia.[24] Sixteen studies were community-based, 4 memory clinics, and 2 recruited from clinic and community. Eligible cohorts contained baseline information on cognitive complaints, gait speed, cognitive tests, mobility disability, and dementia. Main features are summarized in table 1. From 62,215 available individuals, we excluded 27,882 who were younger than 60 years because our focus was the geriatric population, and few studies enrolled younger participants. From the remaining 34,333 participants, we excluded those missing gait speed (n = 4,508) and cognitive complaints (n = 517). We also excluded 881 participants with mobility disability (inability to ambulate with or without assistive devices) and 1,625 with clinically adjudicated dementia at baseline. Table 1 lists diagnostic procedures in individual studies. After exclusions, the final sample included 26,802 individuals aged 60 years and older.

Standard protocol approvals, registrations, and patient consents. The institutional review board of the Albert Einstein College of Medicine approved this analysis. Each site obtained approval from their local ethics committee.

MCR. MCR diagnosis builds on MCI criteria,[1] and is defined as presence of cognitive complaints and slow gait in older individuals without dementia or mobility disability.[8] Table e-1 on the

Table 1 MCR consortium: Summary of studies, procedures, and tests

Study, inception year	No., total/eligible	Age range, y	Gait assessment	Cognitive complaint	Dementia diagnosis
Australia (TASCOG), 2005	426/413	61–86	GAITRite	GDS[a]	Clinical[b]
Belgium, 2010	171/82	62–90	GAITRite	Self-report	*DSM-IV*[c]
Canada, 2007	92/87	63–93	GAITRite	Self-report	*DSM-IV*
China (SAGE), 2007	15,050/6,539	60–94	4-m walk	Self-report	Clinical
France (GAIT), 2009	355/354	63–90	GAITRite	Self-report	*DSM-IV*
Ghana (SAGE), 2007	5,858/2,382	60–114	4-m walk	Self-report	Clinical
India (KES), 2011	391/271	60–94	10-ft walk	GDS	*DSM-IV*
India (SAGE), 2007	12,198/3,377	60–105	4-m walk	Self-report	Clinical
Israel (2 cohorts), 2003	285/224	69–94	10-m walk	GDS	*DSM-IV*
	786/239	60–90	GAITRite	GDS	*DSM-IV*
Italy (InCHIANTI), 1998	1,453/975	60–96	4-m walk	Disability Scale	*DSM-IV*
Japan, 2008	591/514	74–95	6-m walk	Self-report	*DSM-IV*
Korea (KLoSHA), 2005	1,000/549	65–102	4-m walk	Self-report	*DSM-IV*
Mexico (SAGE), 2007	5,448/1,442	60–96	4-m walk	Self-report	Clinical
Russia (SAGE), 2007	4,947/1,708	60–101	4-m walk	Self-report	Clinical
South Africa (SAGE), 2007	4,227/1,743	60–113	4-m walk	Self-report	Clinical
Switzerland, 2007	1,921/344	60–113	GAITRite	GDS	*DSM-IV*
United Kingdom, 2007	189/173	61–90	GAITRite	GDS	*DSM-IV*
United States (LonGenity, 2006)	852/510	61–94	GAITRite	GDS	*DSM-IV*
United States (CCMA), 2011	359/326	65–96	GAITRite	GDS and AD8	*DSM-IV*
United States (MAP), 1997	1,505/1,371	60–100	8-ft walk	Self-report	*DSM-III-R*
United States (ROS), 1994	1,061/1,041	62–100	8-ft walk	Self-report	*DSM-III-R*
United States (H-EPESE), 1994	3,050/2,138	65–108	9-ft walk	IADL	Clinical

Abbreviations: AD8 = cognitive screening instrument; CCMA = Central Control of Mobility in Aging; *DSM-III-R* = *Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised*; *DSM-IV* = *Diagnostic and Statistical Manual of Mental Disorders, 4th edition*; GAIT = Gait and Alzheimer Interactions Tracking Study; GDS = Geriatric Depression Scale; H-EPESE = Hispanic Established Populations for Epidemiologic Studies of the Elderly; IADL = Instrumental Activities of Daily Living Scale; InCHIANTI = Invecchiare in Chianti; KES = Kerala-Einstein study; KLoSHA = Korean Longitudinal Study on Health and Aging; MAP = Memory and Aging Project; MCR = motoric cognitive risk syndrome; ROS = Religious Orders Study; SAGE = Study on Global Ageing and Adult Health; TASCOG = Tasmanian Study of Cognition and Gait.

[a] Cognitive complaint coded present if self-report elicited on cognitive questionnaires or if there was a positive response on the geriatric depression item: "Do you feel you have more problems with memory than most?"

[b] Clinical diagnosis of dementia at baseline was done by self-report, review of medical history, cognitive testing, and/or clinical interview, followed by interview of proxy if available.

[c] *DSM-III-R* or *DSM-IV* was done with consensus diagnostic case conference procedures in the individual studies.

Neurology® Web site at Neurology.org lists tests and procedures in individual cohorts. Cognitive tests were not used to assign MCR. Presence of cognitive complaints was ascertained by participant responses on standardized questionnaires administered by interviewers (table e-1).[8] Informant reports were not used because no cohort had this as a requirement. Gait speed (cm/s) was measured quantitatively or timed over a fixed distance. Slow gait was defined as walking speed 1 SD below age- and sex-specific means individualized to each cohort (table e-1).[8]

To account for population and procedural differences, we examined an alternate MCR definition by deriving global slow gait cutscores pooling gait data from all sites. We also examined MCR prevalence in 2,753 individuals (10.2%) from 9 studies in which gait speed was measured with similar equipment (GAITRite[25]; CIR Systems, Inc., Sparta, NJ) (table 1) and walking protocols.

Other covariates. Scores on tests of global mental status, memory, attention, executive function, and depressive symptoms in each cohort were standardized to facilitate comparisons. Because not all studies diagnosed MCI,[1] we classified participants as MCI if they had cognitive complaints and memory or nonmemory test scores 1.5 SDs below age- or sex-specific means in each cohort.[1]

Presence of self-reported vascular diseases (any one of angina, hypertension, diabetes, and strokes), depression, and arthritis was recorded. Information on myocardial infarctions, TIA, and Parkinson disease was available for <15% of the sample, and is not reported.

Cognitive outcomes. Incident cognitive impairment was defined as a change during follow-up in MMSE scores of ≥4, a reliable indicator of significant cognitive decline.[26] Four studies with 4,812 participants with longitudinal data were included. The Chicago-based Memory and Aging Project (MAP) is a clinical-pathologic aging study (mean age 79.9 years, 74.0% women, 93.1% Caucasian, 6.2% African American).[14] The Religious Orders Study (ROS) is also based in Chicago, but enrolled religious clergy from across the United States (mean age 75.1 years, 69% women, 91.7% Caucasian, 7.2% African American).[11] The Hispanic Established Populations for Epidemiologic Studies of the Elderly (H-EPESE) is a representative sample of community-dwelling Mexican American elderly from 5 southwestern US states (mean age 72.3 years, 56% women).[12] The Invecchiare in Chianti (InCHIANTI) Study is a representative population-based study in Chianti, Italy (mean age 74.1 years, 55% women).[17]

Dementia was diagnosed prospectively using individual study procedures (tables 1 and e-1) in MAP,[14] ROS,[11] and H-EPESE cohorts,[12] and examined as a secondary cognitive outcome.

Analysis. Random-effects meta-analysis was used to pool individual and summary estimates. Heterogeneity between studies was tested using the χ^2 test and quantified by the I^2 statistic. We report MCR prevalence by age and sex. Associations with 95% confidence intervals (CIs) of MCR with medical and cognitive variables were examined using linear regression for continuous variables and logistic models for binary variables, adjusted for age, sex, and education.

To confirm MCR as a dementia risk factor, we used Cox models to compute hazard ratios (HRs) with 95% CIs adjusted for age, sex, education, cohort source, baseline MMSE scores, and vascular disease for developing cognitive impairment and dementia. All participants were clinically adjudicated to be dementia-free at baseline using individual study procedures (table 1). In addition, we excluded participants with MMSE scores <25. We examined associations in the pooled sample using meta-analysis. We conducted sensitivity analyses to account for early dementia and diagnostic overlap with MCI.

RESULTS The ages of the 26,802 participants ranged from 60 to 114 years (mean 71.6), with 55.7% women, and mean education 6.9 years. Mean gait speed was 81.8 ± 32.7 cm/s. Participants with MCR had worse performance on all cognitive tests than participants without MCR (table 2). Participants with MCR had higher prevalence of vascular and nonvascular diseases. High education (≥12 years) was associated with reduced risk of MCR (estimate −0.47, 95% CI −0.65 to −0.29, $p < 0.001$). Older age (≥75 years) had a borderline association (estimate 0.14, 95% CI −0.00 to 0.28, $p = 0.05$) and sex was not associated with MCR (estimate 0.03, 95% CI −0.06 to 0.11, $p = 0.55$).

Prevalence. Of the 26,802 participants, 2,808 met MCR criteria. Pooled MCR prevalence among individuals aged 60 years and older was 9.7% (95% CI 8.2%–11.2%). Age- and sex-adjusted pooled MCR prevalence was 9.6% (95% CI 8.7%–10.6%). MCR prevalence in 6 low- or middle-income countries with 14,011 participants ranged from 5.3% to 15.5% (figure 1). MCR prevalence was higher in the 8,651 individuals aged 75 years and older (10.6%, 95% CI 9.0%–12.3%) than in the 18,151 individuals aged 60 to 74 years (8.9%, 95% CI 7.1%–10.7%). Prevalence of MCR was similar in 11,881 men (9.5%, 95% CI 7.9%–11.1%) and 14,921 women (9.6%, 95% CI 7.8%–11.3%).

MCR prevalence using alternate criteria (global slow gait cutscores) was 9.2% (95% CI 7.7%–11.0%, I^2 90.0%). MCR prevalence in 2,753 individuals with similar GAITRite walking protocols[25] was 8.0% (95% CI 5.0%–1.1%, I^2 80.1%). MCR prevalence was similar in the 11 studies that used similar assessments for gait speed (timed walk) and cognitive complaint (self-report questionnaire): 9.0% (95% CI 8.1%–10.7%, I^2 65.0%).

Figure 1 shows MCR prevalence in the individual cohorts (I^2 94.2%). The lowest MCR prevalence was seen in the Australian (2%) and UK (2%) studies that recruited ambulatory seniors with high walking speeds.[18,24] The highest MCR prevalence was in French (16%) and Indian (15%) cohorts, which enrolled seniors with cognitive complaints.[19,20] When these 4 outliers with lowest and highest prevalence rates were excluded, pooled MCR prevalence was 10.0% (95% CI 8.7%–11.3%). When the Canadian, French, and Belgian cohorts that only enrolled participants with cognitive complaints were excluded,[10,19] MCR prevalence was 9.1% (95% CI 7.5%–10.8%).

Cognitive outcomes. Mean follow-up varied from 5.1 to 9.3 years. MCR predicted incident cognitive

Table 2 Motoric cognitive risk syndrome (MCR) baseline characteristics

	Sample, n	MCR	No MCR	*p* Value
No.	26,802	2,808	23,994	
Age, y	26,802	73.6 ± 8.2	71.4 ± 7.5	<0.001
Women, %	26,802	57.0 ± 0.5	56.0 ± 0.5	0.145
Education, y	25,668	6.2 ± 6.0	7.0 ± 6.0	<0.001
Gait speed, cm/s	26,802	47.8 ± 20.0	85.8 ± 31.5	<0.001
Medical illness, %				
Angina	22,236	16.2 ± 3.7	12.1 ± 3.3	<0.001[a]
Hypertension	26,543	75.9 ± 4.3	71.5 ± 4.5	<0.001[a]
Diabetes	26,429	15.2 ± 3.6	11.4 ± 3.2	<0.001[a]
Strokes	26,458	8.7 ± 2.8	4.4 ± 2.3	<0.001[a]
Depression	26,653	9.0 ± 2.9	6.0 ± 2.4	<0.001[a]
Arthritis	22,690	32.4 ± 4.7	26.6 ± 4.4	<0.001[a]
Cognitive tests, *z* score				
Global mental score	25,828	−0.36 ± 1.06	0.06 ± 0.98	<0.001[a]
Memory	22,111	−0.29 ± 0.97	0.04 ± 1.00	<0.001[a]
Attention	22,155	−0.21 ± 1.04	0.04 ± 0.98	<0.001[a]
Executive function	23,215	−0.23 ± 0.96	0.04 ± 1.00	<0.001[a]
Depressive symptoms	8,767	0.38 ± 1.14	−0.05 ± 0.97	<0.001[a]

[a] Adjusted for age, sex, and education.
Values are means ± SD.

impairment in all cohorts with adjusted HRs (aHRs) ranging from 1.48 in the H-EPESE to 2.74 in InCHIANTI (table 3).

To examine whether MCR mainly identifies individuals with early dementia, we repeated the analysis excluding 668 participants who met incident cognitive impairment criteria in the first 3 years. MCR still predicted incident cognitive impairment in this subgroup (aHR 1.71, 95% CI 1.31–2.24). MCR also predicted incident cognitive impairment when the analysis was restricted to 3,289 participants with baseline MMSE scores ≥28 (aHR 1.65, 95% CI 1.36–2.01). The results were similar in individual cohorts (data not shown).

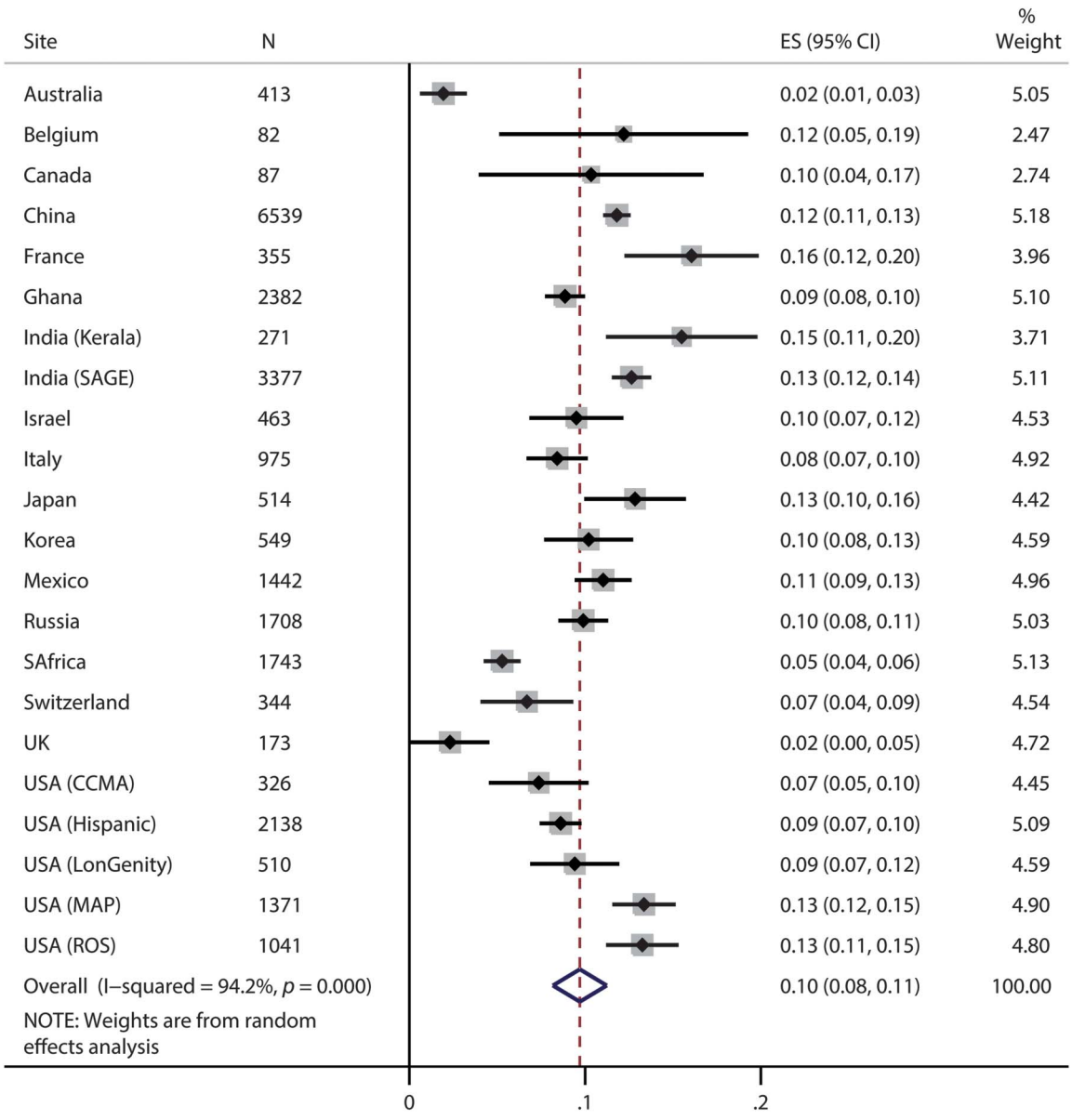
While MCR is diagnosed independent of cognitive tests used to define MCI, 39% of individuals with MCR also met MCI criteria.[1] Both MCR (aHR 1.63, 95% CI 1.39–1.89) and MCI (aHR 1.36, 95% CI 1.19–1.56) predicted cognitive impairment when examined together in the same model.

There were 212 incident dementias in MAP, 265 in ROS, and 417 in H-EPESE. MCR predicted dementia in MAP (aHR 2.10, 95% CI 1.43–2.09), ROS (aHR 1.98, 95% CI 1.44–2.74), and H-EPESE (aHR 1.79, 95% CI 1.31–2.44) cohorts as well as in the pooled sample (aHR 1.93, 95% CI 1.59–2.35). MCR was associated with increased risk of Alzheimer disease dementia[11,14,27] in MAP (aHR 2.21, 95% CI 1.49–3.28) and ROS (aHR 1.97, 95% CI 1.41–2.74) cohorts. There were insufficient cases of vascular dementia to examine as an outcome. Dementia subtyping was not done in H-EPESE.

Figure 2A graphically presents risk of incident cognitive impairment over 12 years' follow-up associated with MCR (HR adjusted for age, sex, education, and cohort source 1.69, 95% CI 1.44–1.98), slow gait alone (aHR 1.40, 95% CI 1.20–1.65), and self-reported cognitive complaints alone (aHR 1.09, 95% CI 0.94–1.27) compared with healthy controls with neither subjective cognitive complaints nor slow gait. Figure 2B shows risk of dementia over 12 years' follow-up associated with MCR (aHR 2.47, 95% CI 1.93–3.17), slow gait alone (aHR 1.77, 95% CI 1.38–2.27), and cognitive complaints alone (aHR 1.27, 95% CI 0.99–1.63) compared with healthy controls.

DISCUSSION In this multicountry study of 26,802 older adults, pooled prevalence of MCR was 9.7%. MCR prevalence was higher in persons aged 75 years and older, paralleling the greater prevalence of cognitive complaints and dementia in this age segment. There were no sex differences in MCR prevalence. Our findings show that MCR criteria can be easily

Figure 1 Prevalence of motoric cognitive risk syndrome



Prevalence estimates (ES) for each study are graphically represented by small diamonds and 95% CIs by horizontal bars. Gray boxes surrounding the diamonds graphically represent study weighting in the analysis, which is also shown in the last column. The large diamond is the pooled prevalence estimate. Pooled effect estimate was similar for random- and fixed-effects model. The vertical dotted line represents the prevalence estimates of the pooled result. CCMA = Central Control of Mobility in Aging; CI = confidence interval; MAP = Memory and Aging Project; ROS = Religious Orders Study; SAGE = Study on Global Ageing and Adult Health.

applied in clinical settings with simple questions about cognitive complaints and timing gait; 90% of participants had walking timed over fixed distances without requiring major resource commitments.

MCR was associated with a 2-fold increased risk of developing incident cognitive impairment (aHR 2.0) in 4,812 participants without dementia and MMSE scores ≥25, even after accounting for vascular disease and baseline cognitive status.[8] MCR predicted dementia in our current (aHR 1.9) and previous (aHR 3.3) analyses.[8] MCR was a stronger predictor of cognitive outcomes than its individual components of cognitive complaints or slow gait in the current and previous validation study.[8] The association of MCR with cognitive impairment remained even when the analysis was conservatively restricted to participants with baseline MMSE scores ≥28 or when incident cognitive impairment cases in the first 3 years were excluded. These findings support MCR as an early clinical marker for cognitive decline.

MCR predicted vascular dementia in our validation cohort.[8] However, MCR predicted Alzheimer disease dementia in more than 2,000 participants from 2 cohorts in this study.[11,14] This finding may

Table 3 Motoric cognitive risk syndrome and risk of cognitive impairment

				Cognitive impairment	
Country (study)	Eligible sample, n	Follow-up, y, mean ± SD	Incident cases, n	Unadjusted HR (95% CI), *p* value	Adjusted HR (95% CI), *p* value
United States (H-EPESE)	1,562	6.04 ± 2.06	826	1.65 (1.30–2.10), <0.001	1.48 (1.16–1.88), 0.002
United States (MAP)	1,280	5.08 ± 3.61	377	1.61 (1.17–2.21), 0.003	1.49 (1.08–2.07), 0.015
United States (ROS)	1,013	9.28 ± 5.38	374	2.19 (1.67–2.88), <0.001	1.90 (1.44–2.51), <0.001
Italy (InCHIANTI)	700	7.23 ± 3.21	180	3.54 (2.05–6.12), <0.001	2.74 (1.54–4.86), 0.001

Abbreviations: CI = confidence interval; H-EPESE = Hispanic Established Populations for Epidemiologic Studies of the Elderly; HR = hazard ratio; InCHIANTI = Invecchiare in Chianti; MAP = Memory and Aging Project; ROS = Religious Orders Study.
Associations are reported as HRs with 95% CIs unadjusted as well as adjusted for age, sex, education, baseline Mini-Mental State Examination scores, and presence of vascular disease. Cognitive impairment was defined as a 4-point or more change in Mini-Mental State Examination scores over follow-up.

be explained by the higher frequency of mixed brain pathology with advancing age.[28] Alternatively, Alzheimer pathology can manifest in early gait dysfunction as suggested by reports of gait slowing in the years leading to MCI.[4–6,29] The association of MCR with clinical dementia subtypes needs to be further verified. The inverse association noted between education and MCR needs further scrutiny to gain insights into potential interventions. Three of 4 cohorts in the cognitive analysis were from the United States, as was our initial study.[8] While insights into dementia gained from these 4 well-established cohorts have been generalizable to other populations,[8,11,12,14,25,30] MCR findings should be cross-validated in other countries.

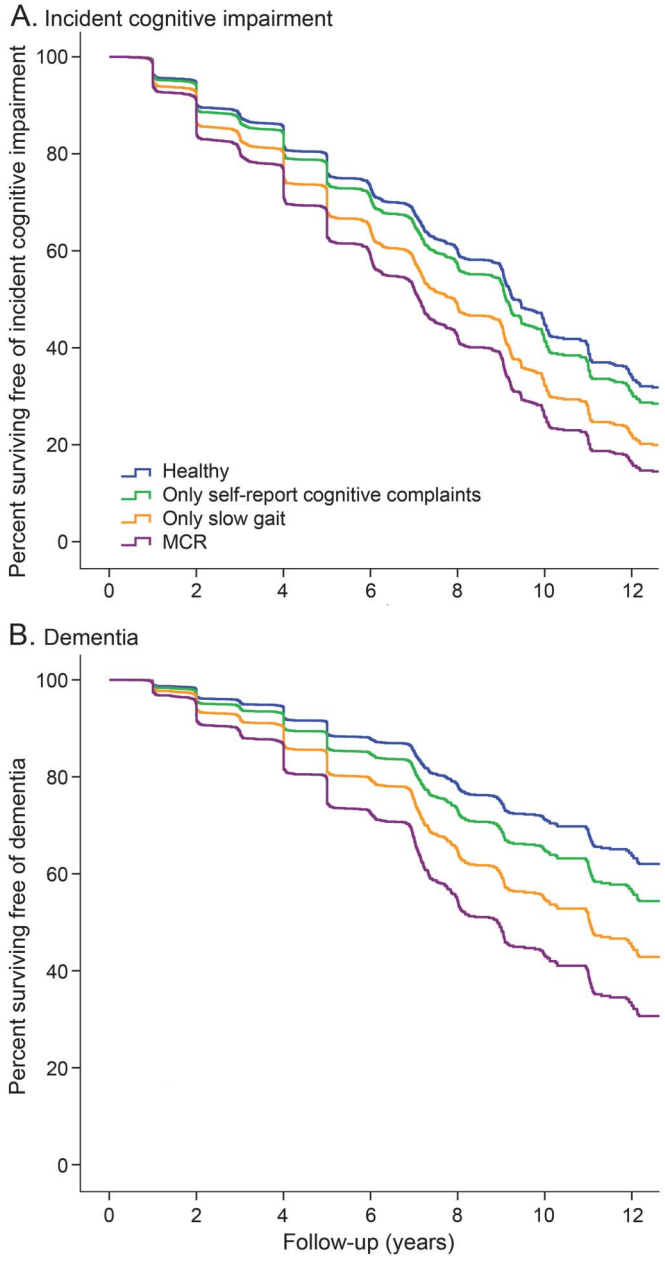
The gait-based MCR offers several benefits in detecting cognitive risk. Gait speed has a common metric, high reliability between different protocols, and excellent validity in predicting health outcomes.[12,25,31,32] A universal test or metric is lacking for cognitive test–based predementia syndromes, and may account for variance in reported prevalence.[1,33] Unlike MCR criteria that can be easily and inexpensively applied, neuropsychological tests to diagnose MCI or laboratory and imaging tests for biomarker-based predementia syndromes may not be practical in many settings.[1,2] MCR is diagnosed independent of cognitive tests minimizing diagnostic circularity in using the same test to define predementia and dementia syndromes.

A key strength is that our study is based on well-established cohorts with reliable cognitive and motor protocols from multiple nations, 52% from low- or middle-income countries. Because MCR is newly proposed, there are no other comparative studies.[8] There are few global studies of predementia syndromes, and fewer still in low- or middle-income countries.[33] A low prevalence of amnestic MCI was reported in 15,376 seniors from 8 low- or middle-income countries: from 0.8% in China to 4.3% in India.[33] Lack of specificity in MCI criteria was proposed to account for the low prevalence.[33] MCR prevalence was higher in the 14,011 participants from our 6 low- or middle-income countries. HRs for cognitive impairment were similar for MCR and MCI.

To our knowledge, this is one of the largest prevalence studies of a predementia syndrome, yet it shares limitations of prior studies in not being global.[33] While representing all countries may not be feasible, MCR needs to be examined elsewhere because etiologies for core criteria such as cognitive complaints and slow gait might vary regionally. Then again, modifiable risk factors for cardiovascular disease and strokes,[34,35] major contributors to gait and cognitive declines, were remarkably consistent globally. Although detailed vascular or neuroimaging studies may reveal underlying etiologies for MCR, resource constraints will not permit screening all patients with these tests. The MCR approach can help streamline high-risk individuals for further investigations, especially in resource-poor settings.

Because the inception of our studies antedated the MCR concept,[8] heterogeneity is not unexpected given clinical and methodologic diversity. While some might preclude pooling data due to heterogeneity, we believe the summary data provide a global perspective on MCR. The variance in MCR prevalence in our different sites is in accord with the variability in MCI and dementia prevalence globally.[1,33] Moreover, our estimates show the same direction of effect in multiple sites, an equally important consideration in meta-analyses.[36] The high agreement in MCR prevalence defined multiple ways and excluding subgroups is reassuring. There was no significant heterogeneity in longitudinal analyses. Reasons for heterogeneity are not explained by subgroup analyses, but might include differences in methods. Memory complaints are subject to cultural bias,[33] a limitation of MCR common with MCI and dementia definitions.[1,27] However, exclusion of cohorts that recruited only participants with memory complaints or restriction to cohorts that used similar cognitive complaint

Figure 2 MCR and risk of incident cognitive impairment (A) and dementia (B)



Kaplan-Meier survival curves with 95% confidence interval over 12 years' follow-up in pooled samples. MCR = motoric cognitive risk syndrome.

ascertainment did not change the MCR prevalence estimates. Refinements of cognitive complaint ascertainment should be pursued to increase the specificity of the MCR criteria.

Given differences in source populations, sample sizes, and protocols, variability in gait cutscores is not unexpected. This situation is not unique to gait; cognitive test norms also vary by population. We used insular slow gait cutscores in each cohort, reflected in the relatively narrow MCR prevalence range of 7% to 13% in 17 studies (81% of sample). Furthermore, MCR prevalence rates were not materially changed when an alternate secular definition using global slow gait cutscores was used or when examined in the subgroup with uniform instrumented gait protocols, although heterogeneity remained high. However, global slow gait cutscores or arbitrary cutscores will not account for regional variations and bias against the oldest age groups. The slow gait criterion was age- and sex-adjusted, which accounts for similarity in the adjusted and unadjusted MCR prevalence. As is done for cognitive tests, we recommend developing local slow gait norms.

Gait speed may not be the strongest motoric predictor of dementia,[25] but there is limited information on comparative predictive validity of other motoric signs for dementia.[8,25] Substituting motoric signs such as tone or strength for slow gait in MCR did not improve dementia prediction.[8] Gait markers, such as variability or rhythm, predict declines on specific cognitive domains.[25] The need for instrumentation will restrict accessibility of these quantitative markers by nonspecialists or in community settings.[7,8] Nonetheless, other motoric markers should be investigated in research settings to improve MCR definition to gain insights into early stages of dementia. Given the scale of data collection and retrospective design, a more limited analysis than is possible in single-population studies was done. For instance, *APOE* genotype information that may have shed light on cognitive and gait decline was not available.[37,38] Dementia prevalence may be underestimated with criteria used in our participating studies, particularly in low- and middle-income countries.[3] However, informant reports and functional scales needed to apply alternate dementia criteria were not available in all of our cohorts.[3] The agreement in predictive validity of MCR for cognitive outcomes in different well-established cohorts and after accounting for early dementia or overlap with MCI is reassuring.

This multicountry study supports MCR as a high risk of dementia phenotype that can be easily applied and identified in a variety of settings by clinicians. Further validation studies are required so that clinicians and researchers may utilize this clinical approach to improve dementia risk assessments, plan management, and develop novel interventions to prevent cognitive decline worldwide.

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AUTHOR CONTRIBUTIONS

Verghese was responsible for study concept, acquisition of data, initial draft, and analysis of data. Ayers and Wang were responsible for revising draft for content and analysis of data. Annweiler, Barzilai, Beauchet, Bennett, Bridenbaugh, Buchman, Callisaya, Camicioli, Capistrant, Chatterji, De Cock, Ferrucci, Giladi, Guralnik, Hausdorff, Holtzer, Kim, Kowal, Kressig, Lim, Lord, Meguro, Montero-Odasso, Muir-Hunter, Noone, Rochester, and Srikanth were responsible for acquisition of data, interpretation of data, and revising draft for content.

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DISCLOSURE

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