ORIGINAL ARTICLE

Risk factors, neuroimaging correlates and prognosis of the motoric cognitive risk syndrome: A population-based comparison with mild cognitive impairment

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Abstract

Background and purpose: This study was undertaken to compare risk factors, neuroimaging characteristics and prognosis between two clinical prodromes of dementia, namely, the motoric cognitive risk syndrome (MCRS) and mild cognitive impairment (MCI).

Methods: Between 2009 and 2015, dementia-free participants of the population-based Rotterdam Study were classified with a dementia prodrome if they had subjective cognitive complaints and scored >1 SD below the population mean of gait speed (MCRS) or >1.5 SD below the population mean of cognitive test scores (MCI). Using multinomial logistic regression models, we determined cross-sectional associations of risk factors and structural neuroimaging markers with MCRS and MCI, followed by subdistribution hazard models, to determine risk of incident dementia until 2016.

Results: Of 3025 included participants (mean age = 70.4 years, 54.7% women), 231 had MCRS (7.6%), 132 had MCI (4.4%), and 62 (2.0%) fulfilled criteria for both. Although many risk factors were shared, a higher body mass index predisposed to MCRS, whereas male sex and hypercholesterolemia were associated with MCI only. Gray matter volumes, hippocampal volumes, white matter hyperintensities, and structural white matter integrity were worse in both MCRS and MCI. During a mean follow-up of 3.9 years, 71 individuals developed dementia and 200 died. Five-year cumulative risk of dementia was 7.0% (2.5%–11.5%) for individuals with MCRS, versus 13.3% (5.8%–20.8%) with MCI and only 2.3% (1.5%–3.1%) in unaffected individuals.

Conclusions: MCRS is associated with imaging markers of neurodegeneration and risk of dementia, even in the absence of MCI, highlighting the potential of motor function assessment in early risk stratification for dementia.

INTRODUCTION

Dementia is a complex syndrome with gradual and permanent loss of multiple brain functions, severe enough to interfere with activities of daily living. Aside from cognitive complaints, affected individuals may experience functional decline, resulting in loss of mobility and independence [1]. Increasing evidence suggests that motor function impairment [2], particularly reduced gait speed [3], is an important marker of imminent cognitive decline [4]. To this end, motoric cognitive risk syndrome (MCRS) was proposed as a dementia prodrome [5], integrating slow gait and cognitive complaints. MCRS may capture a wide range of (neuro)pathology [6] and has been related to risk of dementia [7], as well as mortality [8]. However, it remains undetermined to what extent the etiology and prognosis diverge from the widely used concept of mild cognitive impairment (MCI), which thus far only regards cognitive abilities [9].

MCRS is likely to carry additional prognostic value when the pathophysiological substrates captured by this construct, at least in part, differ from MCI. Some studies have linked MCRS predominantly to vascular dementia [5], whereas MCI is typically associated with Alzheimer dementia (AD) [9]. In separate studies, cardiovascular risk factors such as hypertension and diabetes have been associated with both MCRS and MCI [10], but comparison of effect estimates in a single population are lacking. Similarly, a meta-analysis of four neuroimaging studies reported that gray matter atrophy and lacunar infarcts predispose to MCRS, but these studies did not account for concurrent MCI [11,12]. Better understanding of discrepancies between associations with MCRS versus MCI would help to gauge the potential clinical value of MCRS in general, and gait speed in particular, for settings where comprehensive cognitive assessments required for MCI are not feasible. However, direct comparisons between MCRS and MCI of either clinical outcome or neuroimaging markers remain limited.

We therefore investigated disparities in risk factors and structural neuroimaging markers of MCRS and MCI, and compared their prognosis with respect to dementia and mortality in a population-based setting.

METHODS

Study population

This study was embedded in the Rotterdam Study, a large population-based cohort in the Netherlands that recruited inhabitants from Ommoord, a suburb of Rotterdam [13]. In brief, the study was initiated in 1990 with a study population of 7983 participants aged ≥55 years. The cohort was subsequently expanded twice, first in 1999 including an additional 3011 individuals who had reached the eligible age or had moved into the study area, and again in 2005 with 3932 individuals from the same area aged 45 or older. Participants partake in extensive interviews and examinations at a dedicated research facility every 4 years.

An extensive neuropsychological test battery was introduced in the Rotterdam Study in 2002. From 2005 onward, participants were routinely invited to undergo brain magnetic resonance imaging (MRI) in a research scanner at the facility. Gait assessment was incorporated during the fifth wave of the Rotterdam Study, from 2009 onward. For the present study, we included all dementia-free participants aged ≥60 years, who attended the fifth wave between 2009 and 2015, and did not use any walking aids. Of 3197 eligible participants in this examination round, 3025 (94.6%) participants with complete data on subjective cognitive complaints, gait, and cognitive assessment were included in the current study. Participants were classified with no prodrome of dementia, MCRS, MCI, or both, after which all were uniformly followed up for incident dementia and/or death.

Assessment of subjective cognitive complaints

Subjective cognitive complaints were assessed by interview and considered present if a participant confirmed having at least one problem, either with memory or daily functioning. For memory, the questions were: "Do you have more difficulty to remember things?", "Are you frequently on your way to do something and then forget what you had intended to do?", and "Do you experience difficulty to find the right words when speaking?" For daily functioning, the questions were: "Do you have difficulty managing finances?", "Do you experience any problems using a telephone?", and "Do you have difficulty getting dressed?" Mobility problems are considered exclusion criteria for MCRS; therefore, the last question was not part of its case definition.

Assessment of gait

A sensor-based 5.79-m-long electronic walkway (GAITRite Platinum, CIR Systems; 4.88-m active area, 120-Hz sampling rate) was used to assess gait. The reliability and validity of the GAITRite have previously been described [14,15]. Per protocol, participants were requested to perform eight normal walks. Gait velocity was determined as the average speed of seven normal walks in m/s, excluding the first "practice" walk.

Assessment of cognitive function

The extensive neuropsychological test battery of the Rotterdam Study protocol [16] included a letter–digit substitution task, Stroop

test, verbal fluency test, and 15-word verbal learning test based on Rey's recall of words. We used these tests to create cognitive domain scores for memory function, information-processing speed, and executive function, as previously described in detail [17].

Definition of MCRS and MCI

Slow gait was defined as a walking velocity of ≤1 SD below the age- and sex-specific population mean. Consistent with standard definitions of MCRS [5,7], individuals were classified with MCRS in case of ≥1 subjective cognitive complaint and slow gait in the absence of mobility disability [7]. Based on previously defined criteria for MCI [9], individuals were classified with MCI if they had a subjective cognitive complaint in combination with a score < 1.5 SD of the age- and education-adjusted population means on any of the three cognitive domains [17].

Neuroimaging protocol

The complete neuroimaging protocol has been published previously [18]. MRI of the brain was performed on a 1.5-T scanner (General Electric Healthcare) using an eight-channel head coil. Imaging acquisition included a high-resolution axial T1-weighted sequence, a fluid-attenuated inversion recovery sequence, a proton density-weighted sequence, and a T2*-weighted gradient echo sequence. Details about the sequences, preprocessing, and classification algorithm have been described elsewhere [18]. A k-nearest neighbor tissue classification algorithm was implemented for quantification of total brain volume, gray matter, normal-appearing white matter, and white matter hyperintensities (WMHs). [19] Hippocampal volumes (HVs) were segmented using FreeSurfer 6.1 [20]. All segmentation results, except HVs, were visually inspected and manually corrected if needed.

From March 2006 onward, a diffusion-weighted imaging sequence was incorporated in the scan protocol [21]. A standardized pipeline for preprocessing of the diffusion data started with eddy current and head motion correction on the acquired data, followed by the fitting of diffusion tensors to compute mean fractional anisotropy (FA) and mean diffusivity (MD) in the normal-appearing white matter. Lower FA and higher MD values are indicative of worse structural connectivity.

Neuroimaging data within 1 year of gait and cognitive assessments (median of time interval = 0.001 years, interquartile range = 0.001–0.002 years) were available for a subset of 2999 individuals. We excluded scans for which segmentations were unreliable due to, for example, movement artifacts, leaving 2553 participants for the imaging analyses.

Dementia screening and surveillance

Ascertainment methods for dementia have previously been described [22]. During baseline and follow-up center visits, participants were screened for dementia using the Mini-Mental State Examination (MMSE) and the Geriatric Mental Schedule (GMS) organic level, with further assessment and informant interview for those with MMSE < 26 or GMS > 0. In addition, computerized linkage of the study database with medical records from general practitioners and the regional institute for outpatient mental health care allowed continuous surveillance of the entire cohort for incident dementia. All cases suspect for dementia were also reviewed by a consensus panel, including a consultant neurologist, which applied standard criteria for dementia (Diagnostic and Statistical Manual of Mental Disorders III-R) and AD (National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association) to come to a final diagnosis. Follow-up until 1 January 2016, was near complete (96.1% of potential person-years), and participants were censored within this follow-up period at date of dementia diagnosis, date of death, date of loss to follow-up, or 1 January 2016, whichever came first.

Mortality ascertainment

Vital status of participants was established by a bimonthly check of municipal records. Mortality data were complete until 1 January 2016.

Covariates

Information on educational attainment, current smoking habits, medical history, and medication use was obtained during home interviews using questionnaires, with verification in medical records if applicable. Participants were asked about their highest attained education level, after which their educational attainment was harmonized according to the United Nations Educational, Scientific, and Cultural Organization International Standard Classification of Education [23] into primary (primary education), or further (lower/intermediate general education, lower vocational education, intermediate vocational education, or higher general education) and higher education (higher vocational education or university level). Smoking habits were assessed by the following questions: "Did you ever smoke?" and "Do you currently smoke?", with follow-up questions if applicable. Subsequently, participants were categorized into never-smokers or ever-smokers. Blood pressure was measured twice in a sitting position, using a random-zero sphygmomanometer on the right arm. We used the average of two measurements to define hypertension as blood pressure ≥ 140/90 mmHg or use of blood pressure-lowering drugs. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Blood samples were taken at center visit to acquire information on serum total cholesterol and high-density lipoprotein cholesterol. Hypercholesterolemia was defined as a total cholesterol value of ≥6.2 mmol/L in serum or use of lipid-lowering medication. Type 2 diabetes was defined as a fasting serum glucose level ≥ 7.0 mmol/L

(126 mg/dl), or a nonfasting serum glucose level ≥ 11.1 mmol/L (200 mg/dl), and/or the use of blood glucose-lowering medication. *APOE* genotype was determined using polymerase chain reaction on coded DNA samples (RS-I) and biallelic Taqman assays (RS-II and RS-III; TaqMan Gene Expression Assays, Thermo Fisher Scientific; rs7412 and rs429358). For the analysis, *APOE* genotype was stratified in carriers and noncarriers of the *APOE*-ε4 allele.

Statistical analysis

Missing data on covariates (maximum = 5.5%) were imputed by the mean of fivefold multiple imputation using Markov chain Monte Carlo method, yielding similar distributions before and after imputation. WMH volume was log-transformed, because of its left-skewed distribution. All MRI measures were standardized to facilitate comparison. We used multinomial logistic regression to examine associations between risk factors or neuroimaging markers with MCRS, MCI, or both. Model I was adjusted for age, sex, and subcohort, whereas Model II was additionally adjusted for *APOE*-ε4 carriership, education, smoking, BMI, hypertension, diabetes, and hypercholesterolemia. Neuroimaging models were additionally adjusted for total intracranial volume, and models with WMHs, FA, and MD were also corrected for normal-appearing white matter. We performed Fine and Gray regression for prognostic associations of MCRS and MCI to obtain subdistribution hazard ratios and cumulative incidences, accounting for the competing risk between dementia and death.

In exploratory analyses, we (i) determined neuroimaging associations with separate subcomponents of MCRS and MCI to disentangle the contribution of slow gait and objective cognitive deficits from subjective cognitive complaints, and (ii) examined the prognostic associations of slow gait and objective cognitive deficits on risk of dementia and death. In sensitivity analyses, we (i) excluded participants with cortical infarcts on brain MRI, as cortical infarcts may render segmentations less reliable; and (ii) excluded participants with a BMI ≥ 30 kg/m^2 to verify associations were not solely driven by slower gait in obese individuals.

Analyses were done using R version 3.6.1 (packages tidyr, dplyr, lubridate, foreign, mlogit, riskRegression, cmprsk) and SPSS Statistics version 24.0 (IBM).

RESULTS

Baseline characteristics of all 3025 participants are presented in Table 1. The median age of the study population was 70.4 years, and 54.7% were female. Of all participants, 231 individuals met criteria for MCRS (7.6%), 132 individuals met criteria for MCI (4.4%), and 62 (2.0%) fulfilled criteria for both MCRS and MCI. Baseline characteristics of the subset of participants with brain MRI were similar to the overall population (Table 1). The characteristics per prodrome are presented in Table S1.

**TABLE 1** Baseline characteristics of the study population

Characteristic	Total, n = 3025	MRI subsample, n = 2553
Age, years, median [IQR]	70.4 [64.9–76.5]	69.9 [64.8–75.7]
Sex		
Male	1369	1176
Female	1656	1377
Gait velocity, m/s (SD)	1.18 (0.20)	1.19 (0.19)
Educational attainment		
Primary	239	199
Further or higher	2753	2354
Body mass index, kg/m^2 (SD)	27.4 (4.0)	27.3 (3.9)
Smoking		
Never	970	820
Former or current	2050	1733
Hypertension	1850	1548
Hypercholesterolemia	1718	1458
Diabetes	501	433
APOE-ε4 carrier	771	686
MMSE, median [IQR]	28 [27–29]	28 [27–29]
Subjective cognitive complaints	1887	1588
Objective cognitive deficits	275	226
Slow gait	432	345

Note: Unless specified otherwise, mean values and SD are displayed for continuous measures and absolute numbers are presented for categorical values. Data were missing for educational attainment (1.1%), body mass index (0.1%), smoking (0.2%), systolic blood pressure (0.3%), diastolic blood pressure (0.3%), blood pressure lowering medication (0.1%), *APOE* ε4 carriership (5.4%), total cholesterol (2.6%), lipid-lowering medication (0.1%), and diabetes (1.2%). Presented data for the MRI subsample were virtually complete.

Abbreviations: *APOE* = apolipoprotein E; IQR = interquartile range; MMSE = Mini-Mental State Examination; MRI, magnetic resonance imaging; *n* = number of participants.

Persons with either prodrome were more likely to be older and have lower educational attainment than unaffected individuals. They were more often carriers of an *APOE*-ε4 allele, more often smoked, and more often had hypertension or diabetes. Of these risk factors, diabetes (odds ratio [OR] = 2.05, 95% confidence interval [CI] = 1.16–3.61) and hypertension (OR = 2.43, 95% CI = 1.22–4.84) were also more prevalent in individuals who were classified with both prodromes. A higher BMI was associated with an increased prevalence of MCRS, but not MCI, whereas male sex and hypercholesterolemia were only associated with increased prevalence of MCI (Figure 1).

Most of the neuroimaging markers were associated similarly to MCRS and MCI, such as, smaller gray matter and hippocampal volumes, more white matter hyperintensities, and worse white matter structural integrity. A discrepancy was noted for smaller white matter volume, which was particularly associated with MCI, rather than MCRS. In accordance, total brain volume showed stronger associations with MCI

Risk factor associations:
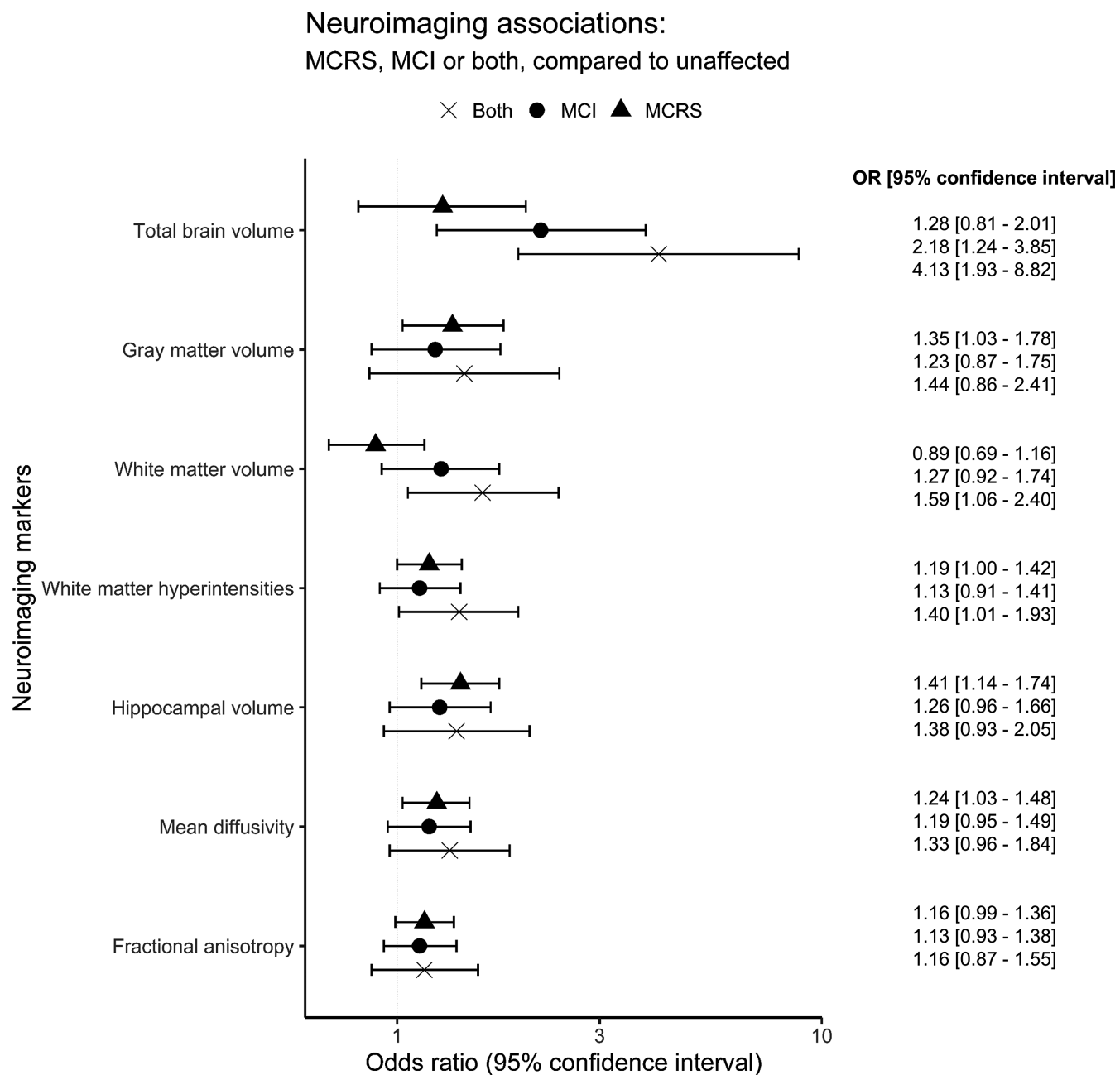### MCRS, MCI or both, compared to unaffected

✕ Both ● MCI ▲ MCRS
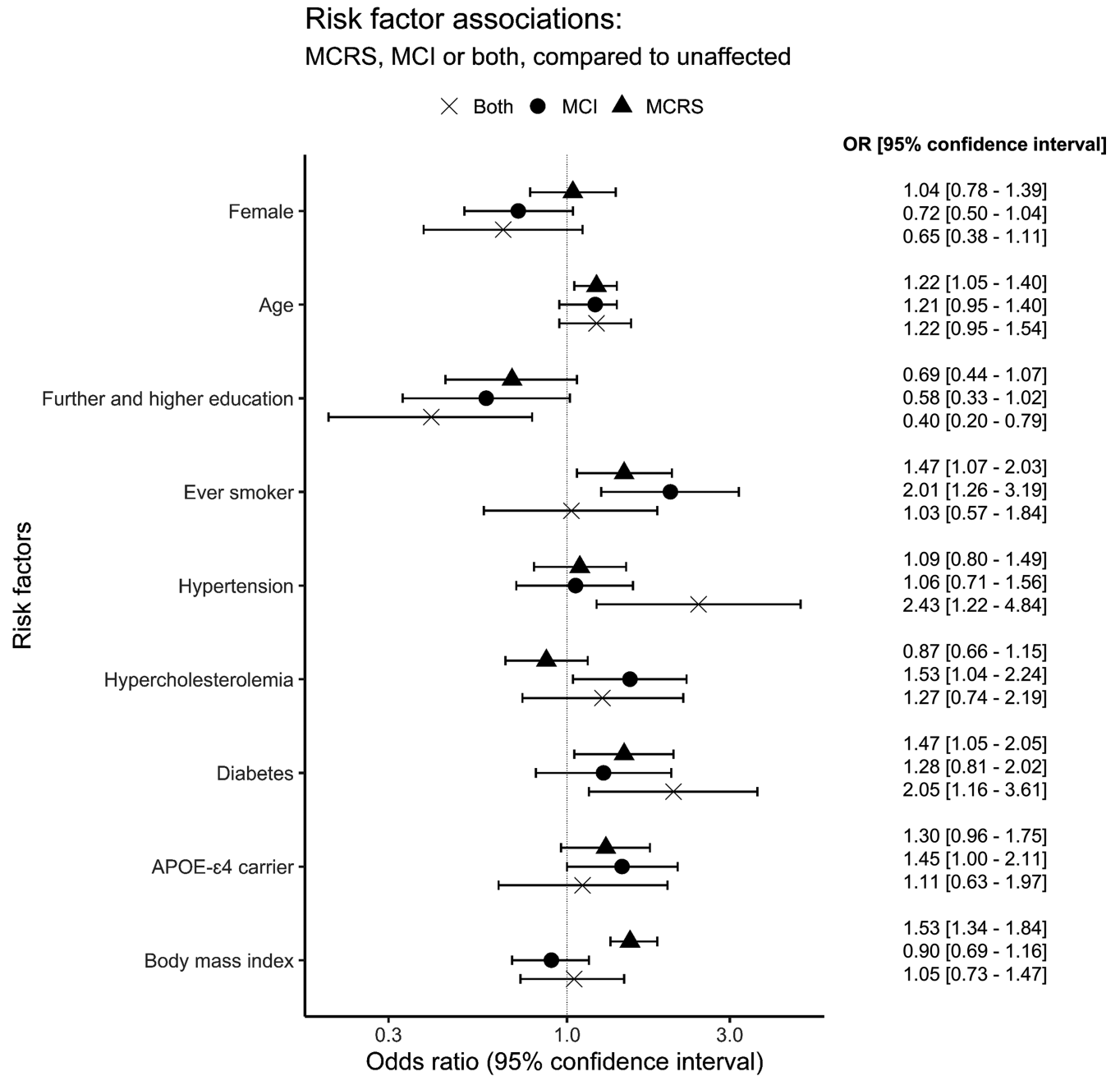
FIGURE 1 Associations of risk factors with motoric cognitive risk syndrome (MCRS), mild cognitive impairment (MCI), and both, compared to unaffected subjects. X-axis is displayed in log10 scale. This model is adjusted for age, sex, study cohort, *APOE*-ε4 carriership, education, smoking, body mass index, hypertension, diabetes, and hypercholesterolemia. Reference levels: females versus males, age per 5-year increase, further and higher education versus primary education, ever-smoker versus never-smoker, hypertension versus no hypertension, hypercholesterolemia versus no hypercholesterolemia, diabetes versus no diabetes, *APOE*-ε4 carrier versus not a carrier, body mass index per 5-kg/m^2 increase. OR, odds ratio

than MCRS (Figure 2). This was observed regardless of obesity and remained similar when individuals with cortical infarcts were excluded (Figures 3 and 4). Exploratory analyses showed that neuroimaging associations were primarily driven by objective cognitive complaints and slow gait, rather than subjective cognitive complaints (Figure 5).

During a mean follow-up of 3.9 (±1.4) years, 71 individuals developed dementia and 200 died. Compared to unaffected individuals, risk of dementia was highest with MCI (subdistribution hazard ratio = 6.95 [95% CI = 3.78–12.75]), followed by MRCS (3.55 [1.91–6.60]) and individuals classified with both prodromes (2.03 [0.49–8.43]). After 5 years of follow-up, cumulative risk of dementia was highest for individuals with MCI (cumulative incidence = 13.3% [95% CI = 5.8%–20.8%]), followed by MCRS (7.0% [2.5%–11.5%]) and the co-occurrence of both prodromes (3.8% [0%–9.0%]), whereas unaffected individuals (2.3% [1.5%–3.1%]) had the lowest risk (Figure 6a). However, individuals with

Neuroimaging associations:
MCRS, MCI or both, compared to unaffected

FIGURE 2 Associations of neuroimaging markers with motoric cognitive risk syndrome (MCRS), mild cognitive impairment (MCI), and both, compared to unaffected subjects. X-axis is displayed in log10 scale. This model is adjusted for age, sex, study cohort, *APOE-ε*4 carriership, education, smoking, body mass index, hypertension, diabetes, hypercholesterolemia and intracranial volume. Models of white matter hyperintensities, mean diffusivity and fractional anisotropy were also corrected for (normal appearing) white matter. All associations are displayed per SD decrease, except for white matter hyperintensities and mean diffusivity (per SD increase). OR, odds ratio

MCRS and individuals with simultaneous presence of both prodromes were at increased risk of death (14.2% [8.5%–20.0%] and 15.8% [5.5%–26.1%], respectively) compared to individuals with MCI (6.9% [2.1%–11.7%]) or those unaffected (6.5% [5.2%–7.8%]; Figure 6b). Excluding participants with a BMI < 30 kg/m² did not affect these results (data not shown).

Risks of dementia and death were markedly increased when the same subjects were reclassified into those with objective deficits only or slow gait only, respectively (Figure 7).

DISCUSSION

In this study, we found that the clinical risk factor profile and neuroimaging characteristics of MCRS were mostly similar with MCI, with the exception of differences in sex, hypercholesterolemia, BMI and white matter volumes. Individuals with MCRS were at increased risk of incident dementia and death, even when MCI was absent, which was mainly associated with reduced gait speed.

Neuroimaging associations (without cortical infarcts):
MCRS, MCI or both, compared to unaffected

✕ Both ● MCI ▲ MCRS

Neuroimaging markers

OR [95% confidence interval]

Total brain volume
1.28 [0.80 - 2.06]
1.99 [1.09 - 3.65]
3.02 [1.27 − 7.17]

Gray matter volume
1.31 [0.98 - 1.74]
1.30 [0.90 - 1.88]
1.95 [1.10 − 3.46]

White matter volume
0.92 [0.70 - 1.20]
1.15 [0.82 - 1.62]
1.11 [0.67 − 1.82]

White matter hyperintensities
1.24 [1.03 - 1.48]
1.14 [0.91 - 1.43]
1.04 [0.72 - 1.51]

Hippocampal volume
1.42 [1.13 - 1.77]
1.28 [0.96 - 1.70]
1.22 [0.79 − 1.89]

Mean diffusivity
1.23 [1.02 - 1.49]
1.21 [0.95 - 1.53]
1.11 [0.75 - 1.62]

Fractional anisotropy
1.20 [1.02 - 1.41]
1.16 [0.94 - 1.42]
1.09 [0.79 - 1.52]

Odds ratio (95% confidence interval)

FIGURE 3 Associations of neuroimaging markers (without cortical infarcts) with motoric cognitive risk syndrome (MCRS), mild cognitive impairment (MCI), and both, compared to unaffected subjects. X-axis is displayed in log10 scale. This model is adjusted for age, sex, study cohort, APOE-ε4 carriership, education, smoking, body mass index, hypertension, diabetes, hypercholesterolemia and intracranial volume. Models of white matter hyperintensities, mean diffusivity and fractional anisotropy were also corrected for (normal appearing) white matter. All associations are displayed per SD decrease, except for white matter hyperintensities and mean diffusivity (per SD increase). OR, odds ratio
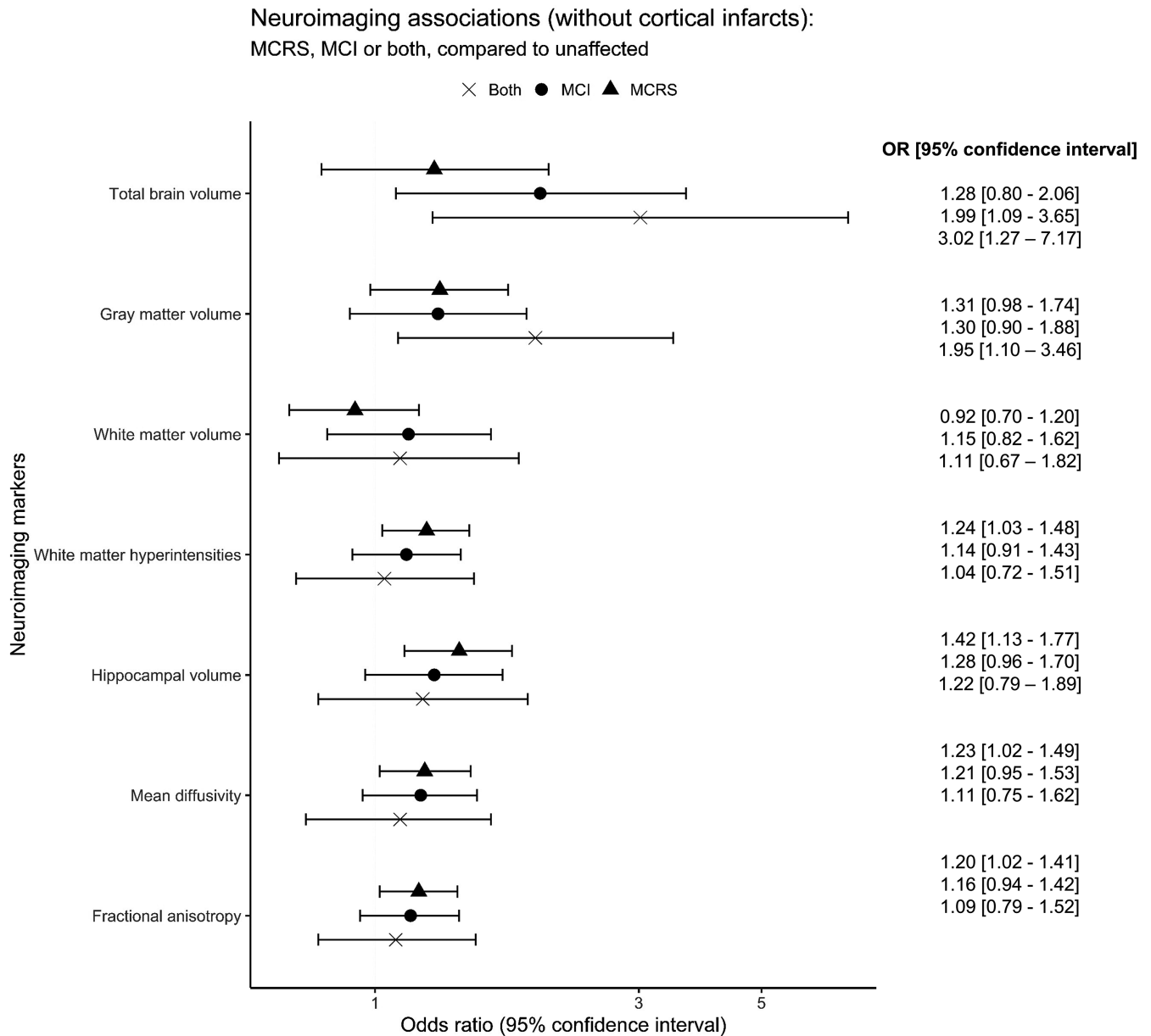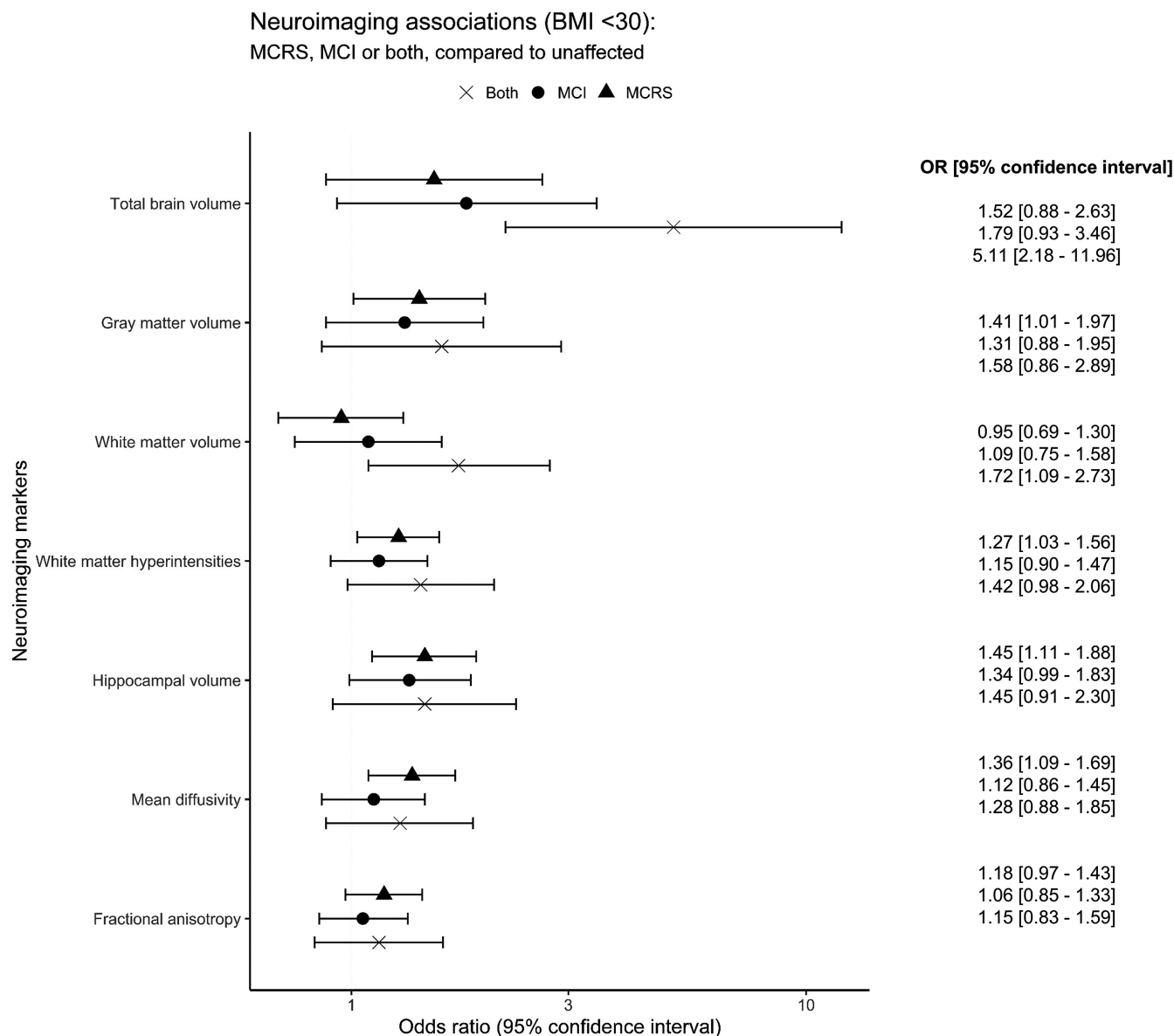
Some cardiovascular and genetic risk factors for dementia (smoking, hypertension, diabetes, and APOE-ε4 carriership) were shared between MCRS and MCI, which adds to emerging evidence for common underlying neuropathologic substrates for gait disturbances and cognitive deficits [24]. It is presumed that the APOE-ε4 allele modulates cortical gait control in cognitively normal older adults and those with MCI, by stimulating regional and global Aβ-related depositions in the brain, extending to regions responsible for motor function [25]. Similarly, well-recognized cardiovascular risk factors such as smoking, hypertension, and

diabetes contribute to large artery and small vessel disease, including microinfarcts, and cerebral amyloid angiopathy. Such manifestations can occur as early as midlife, often go unrecognized [26], and particularly when coupled with APOE-ε4 carriership [25], may have implications for both gait and cognition [27], as reflected in both prodromes. Meanwhile, perhaps due to an enhanced brain reserve, higher educational attainment serves as a protective factor for both MCRS and MCI.

We observed that associations with BMI were stronger with MCRS than MCI, whereas the opposite was observed for

Neuroimaging associations (BMI <30):
MCRS, MCI or both, compared to unaffected

✕ Both   ● MCI   ▲ MCRS

OR [95% confidence interval]

Total brain volume
1.52 [0.88 - 2.63]
1.79 [0.93 - 3.46]
5.11 [2.18 - 11.96]

Gray matter volume
1.41 [1.01 - 1.97]
1.31 [0.88 - 1.95]
1.58 [0.86 - 2.89]

White matter volume
0.95 [0.69 - 1.30]
1.09 [0.75 - 1.58]
1.72 [1.09 - 2.73]

White matter hyperintensities
1.27 [1.03 - 1.56]
1.15 [0.90 - 1.47]
1.42 [0.98 - 2.06]

Hippocampal volume
1.45 [1.11 - 1.88]
1.34 [0.99 - 1.83]
1.45 [0.91 - 2.30]

Mean diffusivity
1.36 [1.09 - 1.69]
1.12 [0.86 - 1.45]
1.28 [0.88 - 1.85]

Fractional anisotropy
1.18 [0.97 - 1.43]
1.06 [0.85 - 1.33]
1.15 [0.83 - 1.59]

*Neuroimaging markers* (y-axis)   Odds ratio (95% confidence interval) (x-axis: 1, 3, 10)

FIGURE 4 Associations of neuroimaging markers (only individuals with body mass index [BMI] < 30) with motoric cognitive risk syndrome (MCRS), mild cognitive impairment (MCI), and both, compared to unaffected subjects. X-axis is displayed in log10 scale. This model is adjusted for age, sex, study cohort, *APOE-ε4* carriership, education, smoking, BMI, hypertension, diabetes, hypercholesterolemia and intracranial volume. Models of white matter hyperintensities, mean diffusivity and fractional anisotropy were also corrected for (normal appearing) white matter. All associations are displayed per SD decrease, except for white matter hyperintensities and mean diffusivity (per SD increase). OR, odds ratio

hypercholesterolemia. Unlike waist circumference, BMI does not reflect the distribution of body fat. Age-related decline in lean body mass, subsequent rise in body fat and its distribution could be more strongly related to MCRS [28], whereas dyslipidemia via mechanisms attributed to apolipoprotein (*APOE*) may have a more prominent role in MCI [25]. Polygenic risk scores for BMI have been associated with MCRS [29], but pleiotropic effects of single nucleotide polymorphisms related to both obesity and dementia (for instance in the *FTO* gene) may have limited the causal inference. Alternatively, the differential association of BMI with MCRS relative to MCI may indicate extracranial pathology, such as peripheral vascular disease [30] or locomotor disorders [6].

Our results suggest that sex differences might exist in the prodromal phase leading toward dementia, as men more commonly had MCI and women more often had MCRS. It is postulated that men experience a faster decline in verbal memory than women, despite having similar levels of Aβ deposition, metabolic deficits, and hippocampal atrophy [31], which might precipitate an increased risk for MCI in men. Women, compared to men, experience a steeper decline of lean muscle mass during aging [32], which may contribute to a higher BMI, physical frailty, and subsequent decline in motor function in women. This underlines the importance of using sex-specific cutoffs for gait speed in clinical assessments.
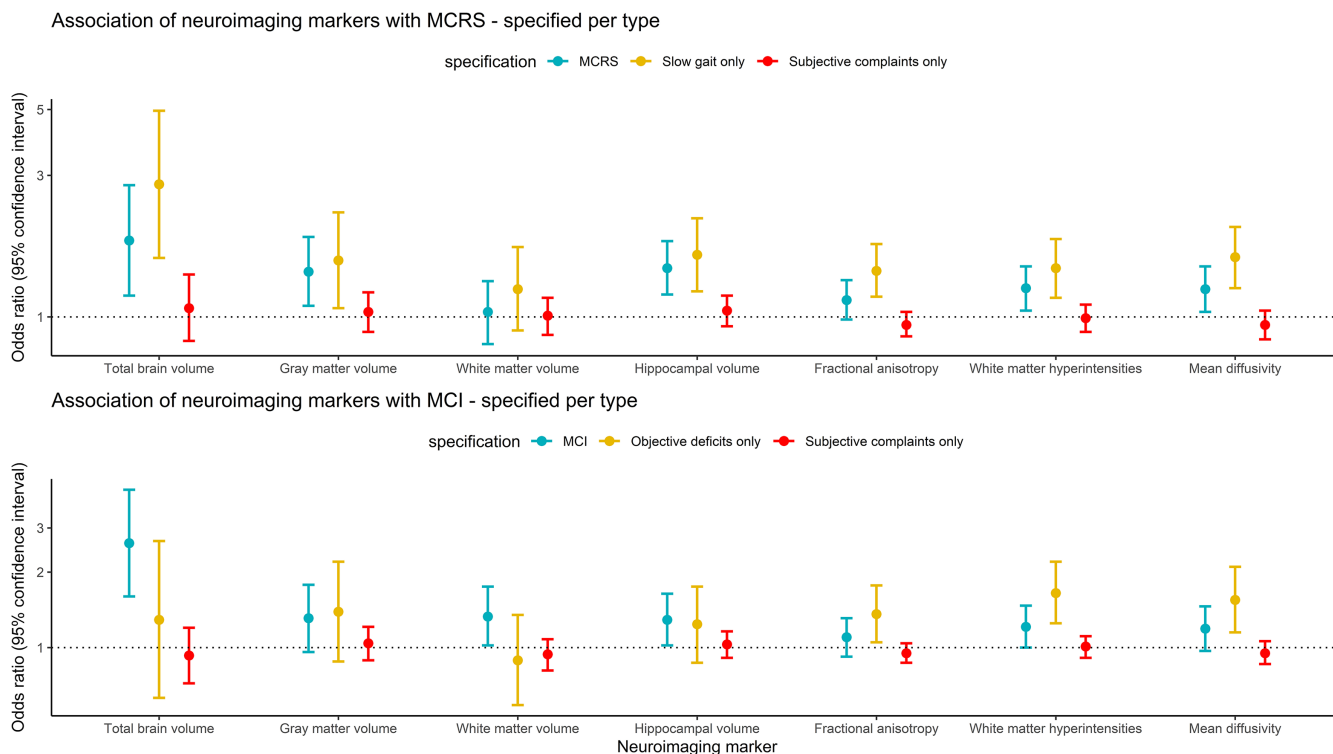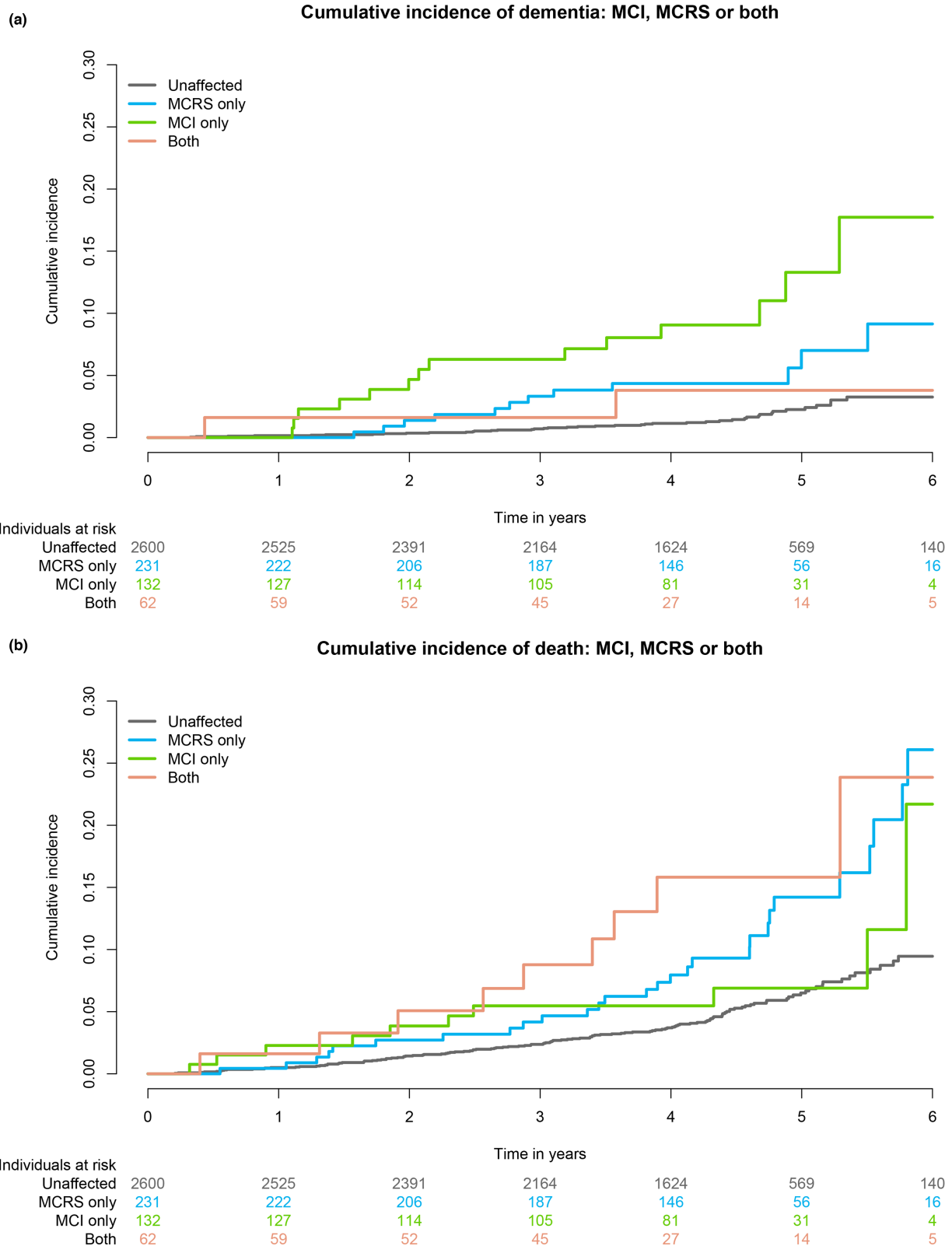
FIGURE 5 Neuroimaging associations, per subcomponent of mild cognitive impairment (MCI) and motoric cognitive risk syndrome (MCRS). Odds ratios are presented with 95% confidence intervals on a log10 scale. Associations are displayed per SD decrease in volume for all neuroimaging markers, except for white matter hyperintensities and mean diffusivity (per SD increase) [Colour figure can be viewed at wileyonlinelibrary.com]

Smaller brain tissue volumes, more WMHs, and a diminished white matter structural integrity were associated with MCI as well as MCRS. In accordance with white matter atrophy, total brain atrophy was more pronounced for individuals with MCI, compared to MCRS. This observation may reflect various underlying mechanisms, such as Wallerian degeneration, white matter rarefaction and myelin breakdown, predisposing to MCI [33]. Hippocampal atrophy [34] and WMHs [17] are commonly associated with MCI, but did not show a significant association with MCRS in a prior meta-analysis of four small studies [11]. Data from the relatively large sample of this study implicate that hippocampal atrophy and small vessel disease markers such as WMHs also confer an increased risk for MCRS, aside from the well-known relation to gray matter atrophy [11]. It is speculated that hippocampal atrophy may be a risk factor for motor dysfunction [24], due to its apparent role in sensorimotor integration during spatial navigation [35]. Both hippocampal and gray matter atrophy are strongly associated with dementia risk [36], and as such implementing clinical motor function assessments besides cognitive assessments may be valuable.
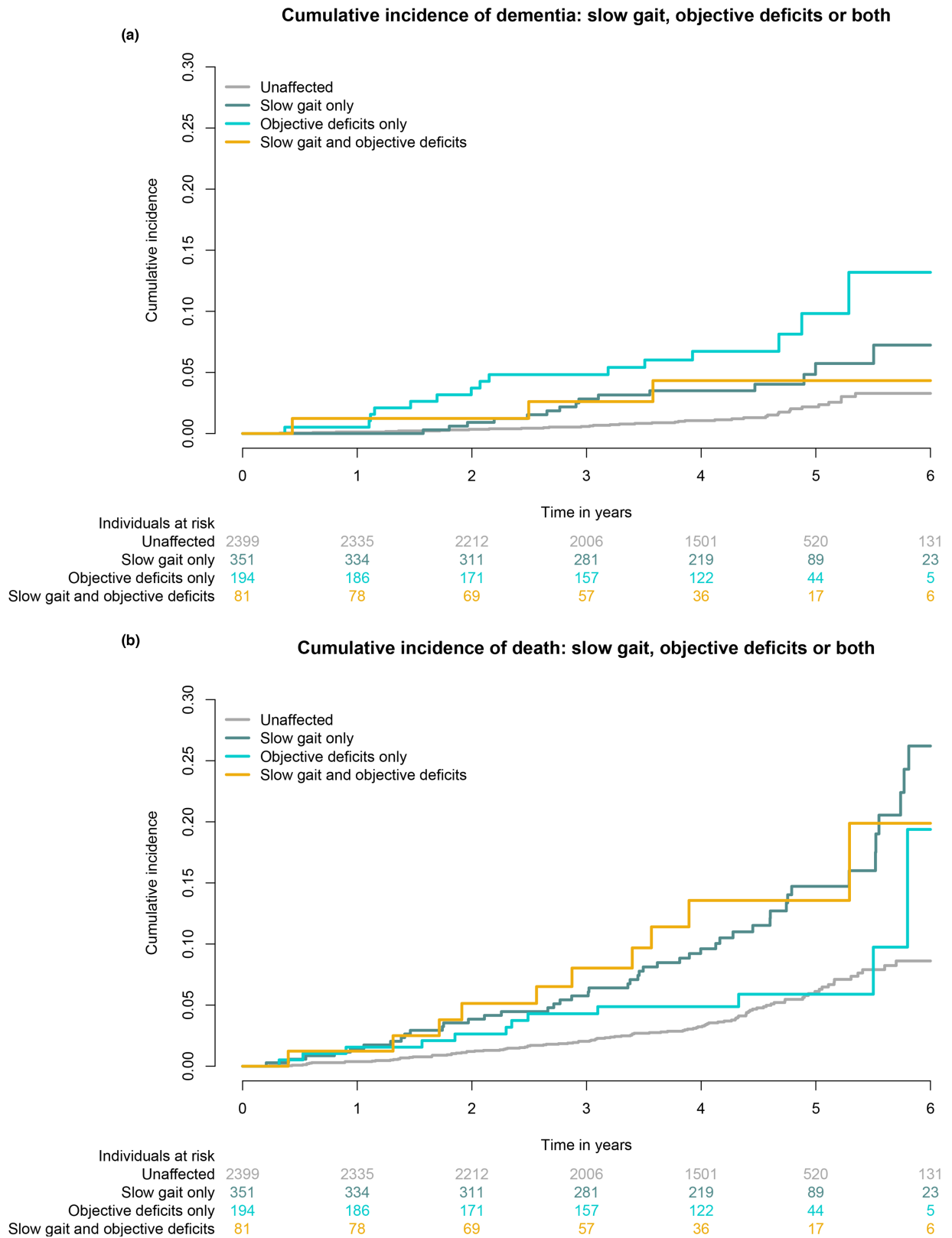
The MCRS construct has been explored in different populations, which verifies its external validity [37]. Previous studies have demonstrated that MCRS is associated with an increased risk of cognitive impairment [38], such as decreased processing speed and executive functioning [39]. The risk factors, neuroimaging correlates, and prognosis of MCRS without MCI in this single population, as well as the decomposition of these prodromes in explorative analyses, suggest that particularly the slow gait component of MCRS warrants further

consideration in clinical risk assessment of dementia. When competing risks are accounted for, individuals with only MCRS, as well as those with both MCI and MCRS, were at increased risk of death, compared to those with MCI only, which suggests that slow gait may reflect an advanced state of neurodegeneration and frailty [40], that may include extracranial pathology [30]. Due to limited data, however, causes of death could not be distinguished in this study population. It should be noted that similar to other neurodegenerative disorders, pathology of dementia is widespread and not confined to the cognitive domain. Gait speed measures are accessible and scalable motor assessments, for instance by using telehealth devices or smartphones, which makes them valuable in settings where serial assessments are preferred and comprehensive cognitive assessments are not feasible. Currently, the concept of MCRS includes gait speed only, but this could easily be expanded, for example, with other components of gait abnormality [41] and manual dexterity [42], as well as dual-task gait assessments [43]. Altogether, our findings exemplify the potential of motor assessments in population-based risk stratification for dementia, beyond the clinically implemented concept of MCI, which can be explored in future studies.

Strengths of this study include a comprehensive evaluation of MCI and MCRS with standardized assessment of risk factors and neuroimaging data, in a large population of community-dwelling older adults, whom we followed prospectively for the onset of dementia and death. Limitations include firstly, the cross-sectional nature of the imaging and risk factor analyses, which hampered inference about temporality. Secondly, the relatively small group of persons

(a)

Cumulative incidence of dementia: MCI, MCRS or both

Individuals at risk						
Unaffected	2600	2525	2391	2164	1624	569	140
MCRS only	231	222	206	187	146	56	16
MCI only	132	127	114	105	81	31	4
Both	62	59	52	45	27	14	5

(b)

Cumulative incidence of death: MCI, MCRS or both

Individuals at risk						
Unaffected	2600	2525	2391	2164	1624	569	140
MCRS only	231	222	206	187	146	56	16
MCI only	132	127	114	105	81	31	4
Both	62	59	52	45	27	14	5

FIGURE 6 Cumulative incidence of dementia (a) and death (b) for unaffected individuals and those with motoric cognitive risk syndrome (MCRS), mild cognitive impairment (MCI), or both. Derived from competing risk regression models. Risk table denotes total number of individuals at risk (*n*) at each time point. Whereas 42 incident dementia cases were identified in unaffected individuals (reference), risk of dementia was highest with MCI (subdistribution hazard ratio [95% confidence interval] = 6.95 [3.78–12.75], *n* = 14/132), followed by MRCS (3.55 [1.91–6.60], *n* = 13/231) and individuals classified with both prodromes (2.03 [0.49–8.43], *n* = 2/62). Although 142 unaffected individuals died (reference), risk of death was highest in individuals classified with both prodromes (subdistribution hazard ratio [95% confidence interval]: 3.75 [2.03–6.90], *n* = 11/62), followed by MRCS (2.47 [1.65–3.71], *n* = 32/231) and MCI (1.54 [0.80–2.94], *n* = 15/132) [Colour figure can be viewed at wileyonlinelibrary.com]

(a)

Cumulative incidence of dementia: slow gait, objective deficits or both

Individuals at risk							
Unaffected	2399	2335	2212	2006	1501	520	131
Slow gait only	351	334	311	281	219	89	23
Objective deficits only	194	186	171	157	122	44	5
Slow gait and objective deficits	81	78	69	57	36	17	6

(b)

Cumulative incidence of death: slow gait, objective deficits or both

Individuals at risk							
Unaffected	2399	2335	2212	2006	1501	520	131
Slow gait only	351	334	311	281	219	89	23
Objective deficits only	194	186	171	157	122	44	5
Slow gait and objective deficits	81	78	69	57	36	17	6

FIGURE 7 Cumulative incidence plot of dementia (a) and death (b), per domain: unaffected, slow gait only, objective deficits only, or both. Data are derived from competing risk regression models. Risk table denotes total number of individuals at risk (*n*) at each time point. Whereas 37 cases of incident dementia were identified in unaffected individuals (reference), risk of dementia was highest for individuals with objective deficits only (subdistribution hazard ratio [95% confidence interval] = 5.22 [2.86–9.54], *n* = 15/194), followed by those with slow gait only (3.00 [1.67–5.39], *n* = 16/351) and those with both (2.44 [0.75–7.98], *n* = 3/81). Subsequently, 118 unaffected individuals died (reference), and risk of death was highest in individuals with both slow gait and objective deficits (3.44 [1.90–6.24], *n* = 13/81), followed by those with slow gait only (3.08 [2.19–4.33], *n* = 52/351) and those with objective deficits only (1.38 [0.76–2.52], *n* = 17/194) [Colour figure can be viewed at wileyonlinelibrary.com]

with both MCRS and MCI limited our power to detect associations in this group, which may be particularly vulnerable to selection bias. In addition, we lacked statistical power to evaluate dementia subtypes such as clinical AD and vascular dementia. Third, the questions for defining presence of subjective cognitive complaints are not standardized in literature, which limits their external validity. Fourth, the cutoffs used to classify individuals for MCRS and MCI depend on age, sex, and educational attainment, and may thus differ across studies depending on the reference population that is used [7,9]. For instance, the mean gait speed (1.18 m/s) of this study population was either lower [3,28] or higher [4,44] compared to estimates provided in previous literature; the development of age- and sex-specific absolute cutoffs for slow gait may facilitate use of gait assessment in clinical practice. Finally, the results from this predominantly White population are not necessarily generalizable to other ethnicities.

CONCLUSIONS

In this study, MCRS captured early features of dementia in the absence of MCI. Although MCRS and MCI share many risk factors and neuroimaging correlates, differences in gender, hypercholesterolemia, BMI, and cerebral white matter volumes suggest in part different pathophysiological substrates. The increased risk of dementia and death in MCRS without MCI suggests a prominent role for motor function assessments in risk stratification for dementia.

CONFLICT OF INTEREST
The authors declare that they have no conflicts of interests.

AUTHOR CONTRIBUTIONS
Amber Yaqub: Data curation (supporting), formal analysis (lead), methodology (equal), visualization (lead), writing–original draft (lead). **Sirwan K. L. Darweesh:** Data curation (supporting), methodology (equal), writing–review & editing (supporting). **Lisanne J. Dommershuijsen:** Data curation (supporting), writing–review & editing (supporting). **Meike W. Vernooij:** Data curation (lead), writing–review & editing (supporting). **M. Kamran Ikram:** Data curation (lead), writing–review & editing (supporting). **Frank J. Wolters:** Conceptualization (lead), methodology (equal), supervision (lead), writing–review & editing (lead). **M. Arfan Ikram:** Conceptualization (lead), methodology (equal), supervision (lead), writing–review & editing (lead).

ETHICAL APPROVAL
The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus University Medical Center (registration number MEC 02.1015) according to the Population Screening Act, executed by the Dutch Ministry of Health, Welfare, and Sport (license number 1071272-159531-PG). All participants provided written informed consent.

DATA AVAILABILITY STATEMENT
Reasonable requests for data access will be considered. Such requests can be addressed to the management team of the Rotterdam Study (secretariat.epi@erasmusmc.nl). Due to privacy concerns, regulations, and informed consent provided by participants, this data cannot be uploaded to a freely accessible public repository.

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